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COMPARATIVE MOLECULAR DOCKING ANALYSIS OF FLAVONOID COMPONENT FROM *LAUNAEA PROCUMBENS* (ROXB.) AGAINST TYROSINE-PROTEIN KINASE FYN

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Keywords:

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ABSTRACT: Plants have been studied since ages for their therapeutic uses. In the earlier time, not much was known about the phytocompounds, but today the constituents of the different plants have been extracted and isolated for the use in the name of medicines or drugs. Flavonoid is one of the most characteristic classes' of compounds in higher plants known to play several important roles including therapeutic uses in cancer treatment. The activation of oncogenes in the cancer cells can be regulated by the selective tyrosine kinases inhibitors, and therefore it can be considered as a promising approach for the targeted therapeutic development. Hence, in the present study, the authors tried to combine the knowledge of using plant *Launaea procumbens* in traditional medicine by analyzing and identifying the specific phytocompounds, especially flavonoids, and evaluating its anticancer potential. The scope of the present study is based on the aim to determine the possible use of plant *Launaea procumbens* in the field of therapeutics for cancer studies by performing *in-silico* docking analysis of isolated flavonoid compound on Tyrosine-protein kinase Fyn in comparison to Methotrexate, Imatinib, Clofarabine, and Daunorubicin. Based on the molecular drugs docking and binding affinities of the target proteins with an isolated flavonoid constituent from the plant, and its physicochemical detailing, it was found that the isolated flavonoid constituent has high possibilities to be an anticancer drug if utilized further with systematic approaches.

INTRODUCTION: Plants have been studied since ages for their therapeutic uses. In the earlier time, not much was known about the phytocompounds but beliefs set to be used as the life-saving remedy. While today the constituents of the different plants have been extracted and isolated for the same use in the name of medicines or drugs [1].

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Several diseases such as malaria, diarrhea, dysentery, bacterial and fungal infections, epilepsy and many more have been managed traditionally using the medicinal plants [2, 3]. The scope of using plants in the treatment of cancer is also now reported in many parts with versatile phyto-compounds [4-10].

Herbal medication in general, therefore, was applied as a combination therapy with the conventional chemotherapy to increase the therapeutic benefit and quality of life hopefully as well as to decrease the side effects or complications [11, 12]. The plant *Launaea procumbens* belongs to the family Asteraceae and traditionally used as folk

medicine in the treatment of rheumatism, kidney and liver dysfunctions, skin diseases, dysentery and eye diseases [13]. The use of the plant in cytotoxic evaluations has also been reported and showed the anticancer activity against Leukemia, Cervical Cancer, Pancreatic Cancer and Breast Cancer [14].

Cancer has diverse classifying approaches, and one of them is including Sarcoma and Carcinoma. Carcinoma is considered a malignant tumor originating from the epithelial cells, while sarcoma is cancer that arises from transformed cells of mesenchymal origin. It refers to cancer that originates in supportive and connective tissues such as bones, tendons, cartilage, muscle and fat [15].

In 1911, Francis Peyton Rous purified a substance from chickens that were later shown to be a sarcoma-causing virus (Rous sarcoma virus), and the responsible oncogene was called v-Src [16, 17]. Later, in 1976, J. M. Bishop and H. E. Varmus discovered a related gene in chickens, which showed a striking resemblance to v-Src and this normal cellular counterpart, called cellular Src or c-Src or Src was the first proto-oncogene to be identified [17, 18]. Src belongs to a family of nonreceptor tyrosine kinases that includes nine members divided into 3 sub-families. The first subfamily, SrcA, includes Src, Yes, Fyn and Fgr; the second subfamily, SrcB, includes Lck, Hck, Blk and Lyn; while the third subfamily is composed of Frk in its own subfamily [19]. Tyrosine kinases are important mediators of signal transduction process in the cell, leading to cell proliferation, differentiation, migration, metabolism and programmed cell death [20-23].

The Fyn member of the Src family is ubiquitously expressed and known to function in T-cell signaling and differentiation [24, 25], entry into mitosis [26] and cell adhesion [27]. It has also been reported using the cell lines model of blast crisis CML, that over-expression of constitutively active Fyn caused increased aneuploidy and genomic alterations, suggesting that a balance of Fyn expression and activity exist to regulate cell growth [28]. Reviews on the Fyn reports that pharmacologic developments of Src family kinases inhibitors have focused upon inhibition of c-Src rather than other Src family kinases that may be more relevant to human diseases such as Fyn [29].

Hence, in the present study, authors tried to combine the knowledge of using *Launaea procumbens* in traditional medicine by analyzing and identifying the specific phyto-compounds, especially flavonoids, and evaluating its anticancer potential by *in-silico* molecular docking studies.

MATERIALS AND METHODS:

Collection of Samples: Fresh plants were collected from, Shree Bapalal Vaidhya Botanical Garden, located in the Veer Narmad South Gujarat University Campus, Udhna Magdalla Road, Surat, Gujarat, India. Taxonomic identities of the plant were confirmed by the Taxonomists in Department of Biosciences, Veer Narmad South Gujarat University, Surat, Gujarat, India, and the specimen voucher collection were preserved in the herbarium of the Department vide herbarium no. The leaves from the plants were separated, washed under the running tap water and dried at 45 °C in the oven. The dried leaves were then homogenized to a fine powder and stored in the airtight container for future use.

Isolation of Flavonoids and Characterization: Methanolic extract of the stored powdered plant material was prepared according to the procedure stated by Mishra *et al*., 2012 [30], and was subjected to initial screening of flavonoids through the thin layer chromatography [31]. After successful formation of a clear band of flavonoid and identification through chemical analysis, the preparative high-performance thin layer chromatography was performed and the minute proportion of the flavonoid component was collected [30].

The isolated component of the fraction was assigned with code FRC1 and analyzed further using UV-Vis Spectrophotometer showing single peak [30]. The confirmation of single compound believed to be from the family of flavonoids was done by the IR Spectroscopy, and then the fraction was sent for GC-MS analysis at Central Salt and Marine Chemical Research Institute (CSMCRI), Bhavnagar, Gujarat, India.

Retrieval of Protein and Ligand Structures from Database for Molecular Docking Analysis: The three dimensional structures of protein, playing an important role in cancer development namely

Tyrosine-protein kinase Fyn was retrieved from Research Collaboratory for Structural Bioinformatics Protein Data Bank (http://www. rcsb.org/pdb/home/home.do), with the PDB ID: 1G83.

The identified flavonoid FRC-1 was searched on the chemical database, and three dimensional structure of the compound was downloaded from the PubChem website with id CID546821 (https://pubchem.ncbi.nlm.nih.gov/compound), while the other known compounds reported being used in cancer therapy *viz*., Methotrexate with id; DB00563, Imatinib with id; DB00619, Clofarabine with id; DB00631 and Daunorubicin with id; DB00694 were downloaded from Drugbank website (https://www.drugbank.ca/drugs).

Analysis of Physicochemical Properties: The physicochemical descriptions of all the compounds as well as ADME parameters were analyzed using SwissADME web tool [32], developed and maintained by the Molecular Modeling Group of the Swiss Institute of Bioinformatics (SIB) (http://www.swissadme.ch/index.php). While the physicochemical properties of protein were evaluated and compared using the ExPASy's Prot-Param tool (https://web.expasy.org/protparam/).

Preparation of Protein and Ligand Structure: The PDB protein structure and ligand structures were processed with the Protein Preparation Wizard and LigPrep tools in the Schrodinger suite respectively [33]. All the interacting heavy atoms, crystallographic water molecules, other unwanted ligand, metal ions are removed and added with hydrogen atoms using Schrodinger suite. Then, the protein was subjected to energy minimization, and on the final stage, addition of hydrogen atoms to the target protein molecule before docking was performed [34].

Analysis of Target Active Binding Sites: Active binding site pockets of target protein were identified using CASTp (Computed Atlas of Surface Topography of proteins) server (http://sts.bioe.uic. edu/castp/calculation.html) [35].

CASTp is used to verify the ligand binding sites of a protein, and it includes annotated functional information of specific residues on the protein structure [36, 37].

Molecular Docking Analysis: Docking analysis of target protein and ligands were done using the online program PatchDock [38, 39]. The PDB format of both proteins and ligands was sent to PatchDock server for docking (http://bioinfo3d.cs.tau.ac.il/ PatchDock/) maintaining clustering RMSD at default 4.0 and complex type as default. Conformational analysis of docking was also performed using AutoDock Vina as stated by Rauf *et al*., 2015 [40] and macromolecules were docked separately with the ligand molecules in AutoDock Vina [41, 42]. Detailed visualization and comparison of the docked sites of target proteins and ligands were done by PyMol [43].

RESULTS AND DISCUSSION:

Isolation of Flavonoid Constituent and Characterization: The presence of flavonoid constituent in the leaf extract of *Launaea procumbens* was confirmed using the procedure and protocol-stated by Mishra *et al*., 2014 [31]. Further isolation and confirmation of the isolation of flavonoid constituent were done using the procedure stated by Mishra *et al*., 2012 [30]. The FRC-1 component collected by the preparative HPTLC process was then subjected for the identification of component present in it. The fraction was sent to CSMCRI lab at Bhavnagar for GC-MS analysis and revealed one major peak with two minor peaks.

The major peak constitutes of 80.03% area with retention time at 17.985, and the IUPAC name of the compound was interpreted as "1, 4-Epoxy-naphthalene-1(2H)-methanol, 4, 5, 7-tris (1, 1-dimethyl)-3,4 dihydro" from the library search. The compound was searched on various chemical databases for structure identification and found on PubChem Database with ID: CID546821 (https:// pubchem.ncbi.nlm.nih.gov/compound/546821).

Analysis of Physicochemical Properties: In this present study, the interactions between the tyrosine protein kinase Fyn (target) with FRC-1 and standard drugs (Ligands) was studied to explore their binding mode. Docking study was performed using the online program PatchDock. Tyrosine-protein kinase Fyn (PDB ID: 1G83) structure was derived from RCSB Protein Data Bank and used as a target for docking simulation. The physicochemical details and pharmacokinetic

properties of FRC-1 and standard drugs (Methotrexate with id; DB00563, Imatinib with id; DB00619, Clofarabine with id; DB00631 and Daunorubicin with id; DB00694) are mentioned in **Table 1** and **Table 2** respectively. The 3D structure of protein and ligands were visualized using PMV tool by MGL [44] and Rasmol as shown in **Fig. 1** and **Fig. 2** respectively.

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF COMPOUNDS

Properties	DB00563	DB00619	DB00631	DB00694	FRC-1
Formula	$C_{20}H_{22}N_8O_5$	$C_{29}H_{31}N_7O$	$C_{10}H_{11}ClFN_5O_3$	$C_{27}H_{29}NO_{10}$	$C_{23}H_{36}O_2$
Mol. weight (g/mol)	454.44	493.60	303.68	527.52	344.53
XLOGP3	-1.85	3.52	0.66	1.83	5.73
No. of heavy atoms	33	37	20	38	6
Rotatable bonds	10	8	2	4	4
H-bond acceptors	9	6	7	11	2
H-bond donors	5	2	3	5	1
Molar refractivity	118.40	154.50	66.57	131.50	106.09
TPSA (A°)	210.54	86.28	119.31	185.84	29.46

TABLE 2: PHARMACOKINETIC PROPERTIES OF COMPOUNDS

Properties	DB00563	DB00619	DB00631	DB00694	FRC-1
GI absorption	Low	High	High	Low	High
BBB permeate	No	No	No	No	Yes
P-gp substrate	Yes	Yes	No	Yes	Yes
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	No	Yes	No	No	No
CYP2C9 inhibitor	No	Yes	No	No	No
CYP2D6 inhibitor	No	Yes	No	No	Yes
CYP3A4 inhibitor	No	Yes	No	No	No
Log K_p (skin permeation)	-10.39	-6.81	-7.68	-8.22	-4.33

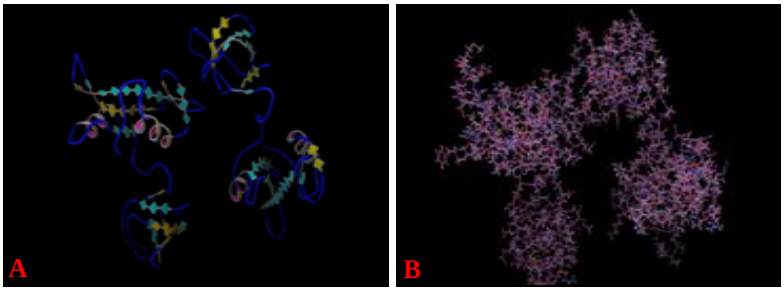

FIG. 1: 3D STRUCTURE OF 1g83 USING PMV TOOL BY MGL

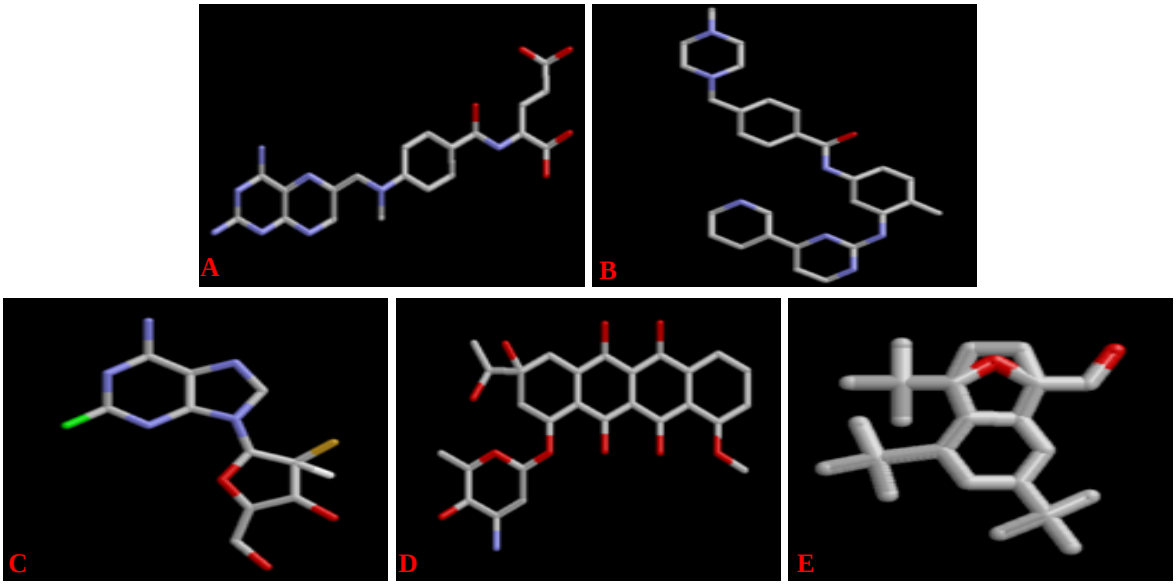

FIG. 2: 3D STRUCTURE OF A) DB00563, B) DB00619, C) DB00631, D) DB00694 AND E) FRC-1 USING RASMOL

All the physicochemical properties of target proteins were calculated using the ExPASy's ProtParam web tool **Table 3**. The parameters computed by ProtParam include the molecular weight, theoretical pI, amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index and grand average of hydropathicity (GRAVY). Molecular weight and theoretical pI are calculated as in Compute pI/Mw [45].

TABLE 3: PHYSICOCHEMICAL PROPERTIES OF TARGET PROTEIN BY ExPASy's PROTPARAM TOOL

Properties	Tyrosine Protein Kinase Fyn (1g83)
Number of Amino acids	330
Molecular Weight	37755.91
Theoretical pI	5.59
Total No. of Negatively charged residues (Asp + Glu)	48
Total No. of Positively charged residues (Arg + Lys)	40
At. Composition (C,H,O,N,S)	1692, 2570, 521, 460, 2
Total No. of atoms	5245
Extinction coefficient, M^{-1} cm^{-1} @ 280 nm in water	73800
Estimated half-life (N-terminal is Gly)	7.2 h (Mammalian reticulocytes, *in-vitro*), >20 h (Yeast, *in-vivo*), >10 h (*E. coli*, *in-vivo*)
Instability index	33.75 (Stable)
Aliphatic index	72.12
Grand average of hydropathicity (GRAVY)	-0.645

Analysis of Target Protein Active Sites: Analysis of protein structures for binding site pockets is important and often the starting point considered in the protein-ligand docking studies. In the present study, the CASTp server is used to identify the possible active binding sites for the ligand in the tyrosine protein kinase Fyn. CASTp server predicted 37 active sites of the target protein. The area computed for the pocket 1 is the largest with a value of 230.239 and volume with a value of 250.224. Pocket 1 being the largest is comprising of 18 amino acid residues viz., VAL88, ALA89, LEU90, TYR91, LYS105, GLY106, ASN136, VAL138, ALA139, GLN145, ALA146, GLU147, GLU148, TYR150, PHE151, GLY152, LYS153, and GLU177, is shown with blue color while others with red color in the **Fig. 3**.

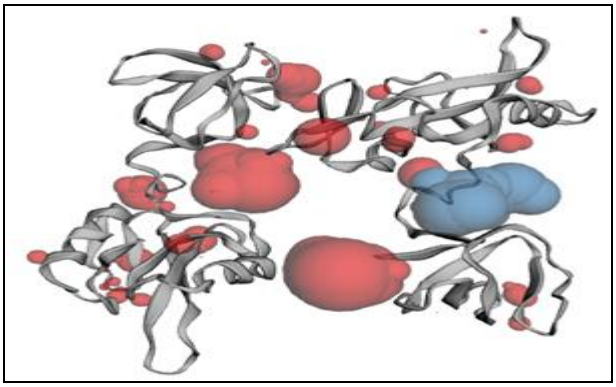

FIG. 3: CASTp RESULT SHOWING POCKETS IN 1g83: POCKET1 WITH BLUE COLOR AND OTHERS WITH RED COLOR

Molecular Docking Analysis: The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known 3D structures [46]. To study the binding mode of FRC-1 in the binding site of Tyrosine-protein kinase Fyn, docking studies were performed, and energy values were calculated from the docked conformations of the protein-inhibitor complexes.

The target protein with FRC-1 and known compounds *viz*., Methotrexate (DB00563), Imatinib (DB00619), Clofarabine (DB00631) and Daunorubicin (DB00694), was docked using an automated molecular docking server PatchDock in order to find out how the chemical compounds inhibit the target proteins structure based on the negative binding affinity values [47] as shown in **Table 4**.

Docking studies yielded crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. The minimum binding energy indicated that the Tyrosine-protein kinase Fyn was successfully docked with FRC-1 as showed in **Table 4**.

Further confirmation of the docking was also carried out using Autodock Vina tool and results confirmed the PatchDock results, showing successful binding of FRC-1 with the Tyrosine-protein kinase Fyn target protein **Table 5**.

TABLE 4: PATCHDOCK RESULTS FOR TOP 3 SOLUTIONS FOR EACH COMPOUND AGAINST 1g83 PROTEIN

Compound	Sol. no.	Score	Area	ACE	Transformation
DB00563	2221	2278	635.0	-422.32	-2.20 0.49, 2.60 36.41, -28.99 35.65
	2338	2092	539.3	-392.88	2.18 -0.73, -0.30 19.49, -19.64 46.93
	2532	1626	516.9	-380.40	1.93 0.33, -0.90 8.41, -6.00 -9.00
DB00619	3563	2050	806.1	-550.18	2.68 1.32, -2.12 32.00, -23.77 28.68
	2378	3390	623.2	-450.33	-2.80 0.54, 0.30 14.29, -11.76 25.45
	3497	2204	699.3	-446.97	1.14 -0.35, 2.07 35.64, -32.49 40.03
DB00631	769	1856	384.7	-249.53	-0.01 -0.65, -2.17 28.06, -9.02 33.73
	850	1238	343.8	-228.26	-0.47 -0.13, -2.86 29.02, -10.98 28.79
	853	1164	370.8	-226.29	-0.51 -0.05, 0.48 7.53, -17.39 -3.11
DB00694	1371	2980	682.3	-397.27	-1.69 -1.08, -0.91 26.93, -19.36 45.69
	1640	2606	646.3	-388.26	-0.23 -0.54, 1.42 12.29, -20.22 0.06
	1879	2198	560.1	-379.98	1.94 1.30, 2.29 6.02, -8.97 -11.83
FRC-1	103	1898	206.3	-329.01	-0.31 0.55, 1.62 23.48, -16.02 27.23
	5	2472	270.2	-307.15	0.09 0.66, -0.40 25.51, -13.52 28.47
	8	2428	253.8	-296.45	1.06 -0.39 -0.25 12.59, -13.73 -4.66

TABLE 5: AUTODOCK VINA RESULTS FOR TOP 3 CONFORMATIONS OF EACH COMPOUND AGAINST 1g83 TARGET PROTEIN

Ligand	Mode	Affinity (Kcal/Mol)	Distance from best mode	
			RMSD L.B	RMSD U.B
DB00563	1	-6.4	0.000	0.000
	2	-6.2	20.720	24.936
	3	-6.1	20.286	24.166
DB00619	1	-8.2	0.000	0.000
	2	-7.8	2.604	10.862
	3	-7.8	3.533	11.260
DB00631	1	-6.0	0.000	0.000
	2	-6.0	2.534	3.323
	3	-6.0	3.727	6.547
DB00694	1	-8.5	0.000	0.000
	2	-8.1	3.949	10.215
	3	-8.1	2.256	2.615
FRC-1	1	-10.5	0.000	0.000
	2	-9.8	0.799	2.326
	3	-9.8	1.691	3.173

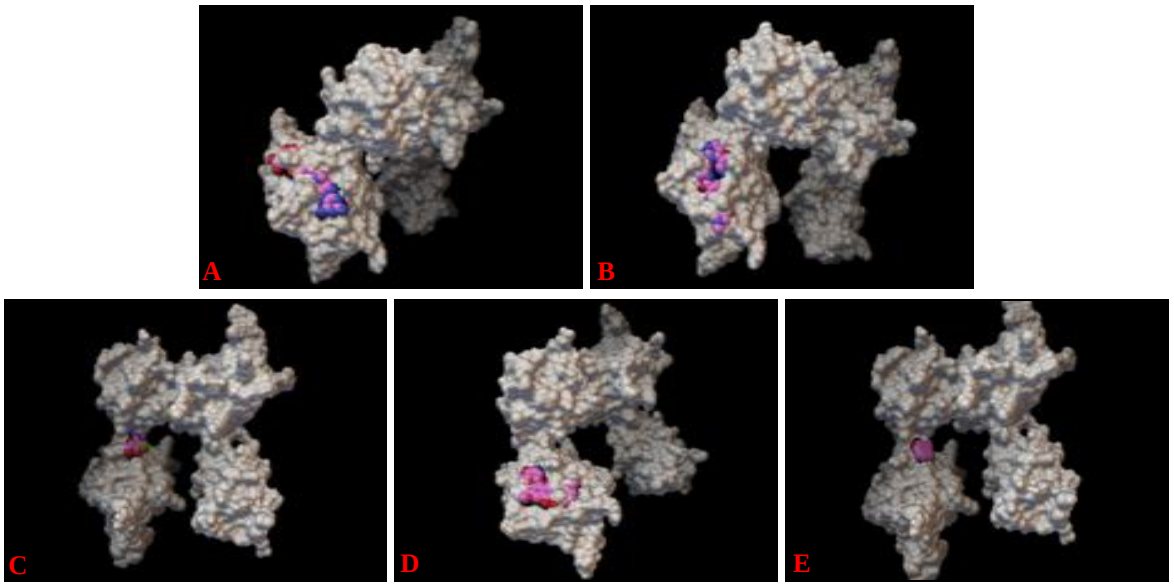

FIG. 4: PATCHDOCK RESULT OF (A) DB00563-1g83, (B) DB00619-1g83, (C) DB00631-1g83, (D) DB00694-1g83 AND (E) FRC1-1g83

The molecular docking results clearly show that the binding affinity of FRC-1 with target protein is very good. PatchDock results show that the binding value of FRC-1 with 1g83, is -329.01 which is very good for a compound to show binding conformation with that protein **Table 4**. While comparing the binding affinity of FRC-1 with other compounds, it should not be overlooked that the other compounds are much bigger than compared to FRC-1 and therefore may give a higher binding affinity value. Although, it is very much clear from the PatchDock results that, the binding affinity value of FRC-1 is much better in context to the potent drug inhibitor of 1g83, further confirmations of docking score is carried out.

The confirmation of docking scoring is therefore carried out by AutoDock Vina, and the results also supported PatchDock output. Moreover, FRC-1 determines to be the most prominent compound giving the highest binding affinity values with tyrosine protein kinase Fyn **Table 5**.

Finally as the FRC-1 shows most promising high negatively binding values than compared to Methotrexate (DB00563), Imatinib (DB00619), Clofarabine (DB00631) and Daunorubicin (DB00694), and also the successful binding of compounds to the target proteins pockets **Fig. 4 and Fig. 5**, it can be considered as one potential inhibitor of Tyrosine-protein kinase Fyn.

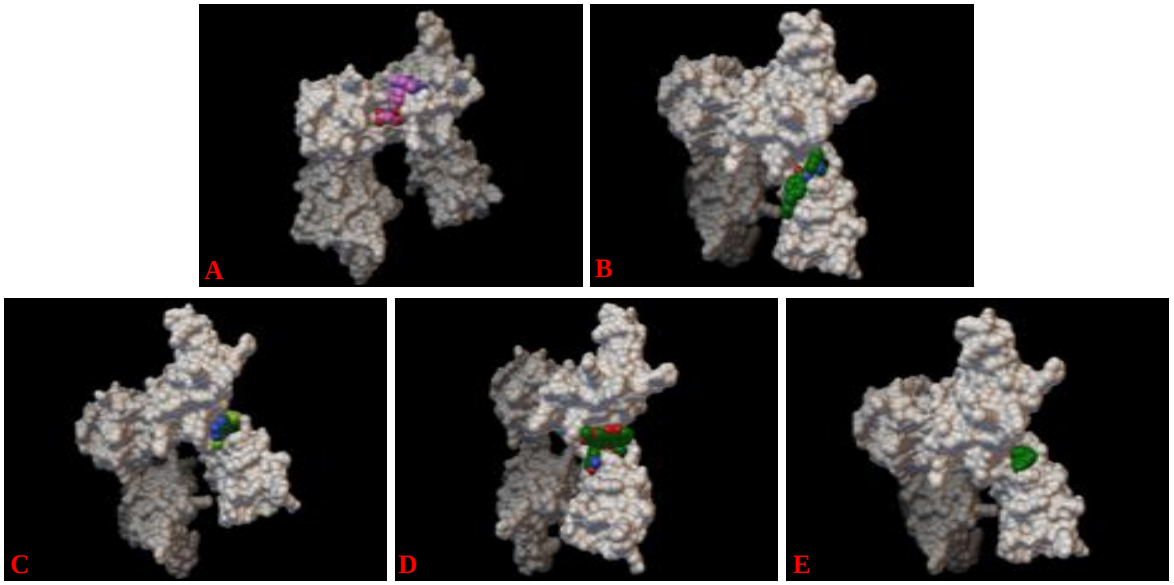

FIG. 5: AUTODOCK VINA RESULT FOR (A) DB00563-1g83, (B) DB00619-1g83, (C) DB00631-1g83, (D) DB00694-1g83 AND (E) FRC1-1g83

CONCLUSION: In the present *in-silico* investigation, we elucidated one finding that the flavonoid compound (FRC-1) which is isolated and identified from the plant (*Launaea procumbens*) acted as potential anticancer agent for the target protein, Tyrosine-protein kinase Fyn. Analysis of ligand binding interaction with the target proteins can be useful for new preventive and therapeutic drug for cancer. Based on the molecular drugs docking and binding affinities of the target protein with FRC-1 and its physicochemical detailing, it was found that the flavonoid, FRC-1, has high possibilities to be an anti-cancer drug if utilized further with systematic approaches.

The results obtained from this study would be useful in both understanding the inhibitory mode as well as in rapidly and accurately predicting the activities of new inhibitors by docking scores to narrow down and finalize the lead compounds. The results are also helpful for the design and development of novel drug having better inhibitory activity against various types of cancer. Finally, from this study, we conclude that plant *Launaea procumbens* contains a very remarkable phytocompound (FRC-1). This compound shows a significant and very high potential in anticancer property in *in-silico* studies and therefore can be one of the possible compound to provide anticancer property to plant for which it is used as traditional herbal medicine in leukemia. This potential drug candidate can, therefore, be further validated in wet lab studies for its proper function.

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CONFLICT OF INTEREST: Authors report there is no conflict of interest in the present study.

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