Research Article

EVALUATING THE ANTI-CANCER POTENTIAL OF *LAUNAEA PROCUMBENS* (ROXB.) BY COMPARATIVE MOLECULAR DOCKING ANALYSIS AGAINST ABL KINASES

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Article Received on: 04/01/19 Approved for publication: 02/02/19

DOI: 10.7897/2230-8407.1003105

ABSTRACT

Phytochemicals have been used as drugs since long time and many of the medicinal plants have been characterized for secondary metabolite and their possible use in the chemotherapy including cancer. The most important and commonly targeted compounds in the search of anticancer molecules are tyrosine kinases. 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. The scope of present study is based on the aim to determine possible use of plant *Launaea procumbens* in the field of therapeutics for cancer studies by performing *in-silico* docking analysis of isolated flavonoid compound from *Launaea procumbens* on two most conserved domains SH3 and SH2 of each tyrosine protein kinase ABL 1 and ABL 2 in comparison with approved anti-cancer drugs such as Imatinib, Dasatinib, Daunorubicin, and Doxorubicin. The present investigation elucidated that the flavonoid compound which is isolated and identified from plant, *Launaea procumbens*, acted as potential anticancer agent for the target proteins. Further, its physicochemical detailing comparison with approved drugs, it was found that the isolated flavonoid constituent has high possibilities to be an anticancer drug, if utilized further with systematic approaches.

Keywords: *Launaea procumbens*, Molecular Docking, Flavonoid, Tyrosine Protein Kinase ABL

INTRODUCTION

Cancer chemoprevention has become an appealing strategy to combat the dogma associated with increasing cases of cancers worldwide. One of the most important and versatile phytochemicals found in plant in variable proportions is the flavonoid¹. Flavonoids constitute one of the most characteristic classes of compounds in higher plants². The possible uses of isoflavonoids on human health are also extensively investigated, especially in the prevention of breast cancer³, and colon cancer⁴. Herbal medication in general was applied as a combination therapy with the conventional chemotherapy to hopefully increase the therapeutic benefit and quality of life as well as to decrease the side effects or complications^{5,6}. The most important and commonly targeted compounds in the search of anticancer molecules are the tyrosine kinases⁷.

Tyrosine kinases integrate multiple signalling networks in cells, including growth, survival, invasion and angiogenesis during tumour initiation and progression. Various forms of drug discovery efforts in cancer therapy have therefore focused on the tyrosine kinase inhibition⁸. Non-receptor protein tyrosine kinases shows an important role in regulation of gene expression, either by activating the signal transducer and activator of transcription or by inhibition of cell growth via stimulation of nuclear tyrosine kinases, such as Abl, resulting in transcription factor activation^{9,10}.

The Abelson (Abl) kinase family members include; Abelson kinase 1 (Abl-1) and 2 (Abl-2) encoded by ABL 1 and ABL 2 gene respectively, which are considered as most conserved domains in human genome¹¹. ABL 1 was first discovered as oncogene in the Abelson murine leukaemia virus and later identified as an oncogene associated with chromosome translocations in human leukaemia¹². An example of Oncogenic activation of the ABL kinases can be observed in the Philadelphia positive (Ph+) human leukaemia containing a fusion gene called BCR-ABL 1 gene. This gene codes for a hybrid protein: a tyrosine kinase signalling protein that is “always on”, causing the cell to divide uncontrollably¹³. Each of ABL protein contains an SH3-SH2 domain cassette, which confers auto regulated kinase activity and is common among the non-receptor tyrosine kinases¹⁴. Therefore with all due studies and involvement in cancer regulations, ABL has become a very interesting molecule of choice to analyze for the new potential anticancer agents.

Imatinib, the wonder drug, was identified in the late 1990s by Dr. Brian J Druker, which is a small molecule kinase inhibitor used to treat certain types of cancer. Imatinib is a tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase. It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Ph+ CML¹⁵. Dasatinib, at nanomolar concentrations, inhibits tyrosine protein kinases including Bcr-Abl, SRC family and others. Based on the modelling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase¹⁶. Daunorubicin and Doxorubicin are antineoplastic in the anthracycline class

possessing antimitotic and cytotoxic activity through a number of proposed mechanisms of action. Doxorubicin is widely used for the treatment of several solid tumors while daunorubicin is used exclusively for the treatment of leukaemia¹⁷.

Hence, in the present study, authors tried to evaluate the flavonoid constituent isolated from plant *Launaea procumbens* against SH2 and SH3 domains of both ABL-1 and ABL-2 kinases and compared its potential with these selected anticancer drugs viz., Imatinib, Dasatinib, Daunorubicin and Doxorubicin.

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. 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 fine powder and stored in the air tight 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., and was subjected to initial screening of flavonoids through the thin layer chromatography¹⁷. After successful formation of 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. The isolated component of fraction was then analyzed using UV-Vis Spectrophotometer showing single peak². 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 for molecular docking analysis

The PDB structures of SH3 and SH2 domains for each ABL kinase namely ABL1-SH2 Domain (1ab2), ABL1-SH3 Domain (5oaz), ABL2-SH2 Domain (2ecd) and ABL2-SH3 Domain (5np3) was retrieved from Research Collaboratory for Structural Bioinformatics Protein Data Bank. The identified flavonoid (FRC-1) was searched on chemical databases and the PDB structure of compound was downloaded from Pubchem website with id CID546821, while the PDB structures of other four known compounds reported to show anti-cancer property viz., Imatinib (DB00619), Dasatinib (DB01254), Daunorubicin (DB00694), and Doxorubicin (DB00997) were downloaded from Drugbank website.

Analysis of physicochemical properties

The physicochemical descriptions of ligands as well as ADME parameters were analyzed using SwissADME web tool¹⁹, developed and maintained by the Molecular Modeling Group of the Swiss Institute of Bioinformatics (SIB), while the physicochemical properties of proteins were evaluated and compared using the ExPASy's ProtParam tool.

Preparation of Protein and Ligand Structure

The PDB protein structures and ligand structures were processed with the Protein Preparation Wizard and LigPrep tools in the Schrodinger suite respectively²⁰. 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 performed²¹.

Analysis of Target Active Binding Sites

Active binding site pockets of protein targets were identified using CASTp server²². CASTp is used to verify the ligand binding sites of a protein. It includes annotated functional information of specific residues on the protein structure²³.

Molecular Docking Analysis

Docking analysis of target proteins and ligands were done using the online program PatchDock²⁴. The PDB format of both proteins and ligands was sent to PatchDock server for docking maintaining clustering RMSD at default 4.0 and complex type as default. A conformational analysis of docking was also performed using AutoDock Vina as stated by Rauf et al.²⁵ and macromolecules were docked separately with the ligand molecules²⁶. Detailed visualization and comparison of the docked sites of target proteins and ligands was done by PyMol²⁷ and LigPlot²⁸.

RESULTS AND DISCUSSION

Isolation of Flavonoid Constituent and Characterization

The confirmation of flavonoid component in leaf extracts of *Launaea procumbens*, and its further isolation was carried out by following the procedure of Mishra et. al.^{2, 18} and named the fraction as FRC-1. The fraction collected, FRC-1, was then subjected for further characterization studies by identifying the specific component present in it by GC-MS analysis. The GC-MS analysis 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 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.

Analysis of Physicochemical Properties

The 3D structure of all the proteins and ligands including FRC-1 is visualized using PyMOL (Fig. 1), while the physicochemical properties of proteins were calculated using the ExPASy's ProtParam web tool²⁹ (Table 1) and the physicochemical details and pharmacokinetic properties of FRC-1 and other ligands were analyzed using the SwissADME web tool (Table 2). The analysis of physicochemical properties of FRC-1 (Table 2) shows that it is comparatively a small molecule, which increases its permeation rate. Studies report that increase in molecular weight and rotatable bond count has a negative effect on the permeation rate of drugs and therefore it should be preferably less than 450 g/mol and 10 respectively³⁰. The number of H-bond acceptors and donors in FRC-1 are also less which depicts the better solubility of compound, as the higher number of H-bond donors lead to low fat solubility so that the drug cannot penetrate the cell membrane to reach inside the cell³¹. The topological surface area (TPSA) of

FRC-1 was also calculated to be 29.46 Å². This shows that it is having a very high permeating property in the cells, as molecules having polar surface area greater than 140 Å² tend to be poor at permeating cell membranes and for molecules to penetrate the blood brain barrier, a polar surface area less than 90 Å² is usually needed³².

To access the chance for a molecule to become an oral drug with respect to bioavailability, the properties such as druglikeness and medicinal chemistry properties of compounds were also calculated and compared (Table 3). The druglikeness properties of compound provides five different rule based filters; originate from analyses by major pharmaceutical companies aiming to improve the quality of their proprietary chemical collections such as; The Lipinski (Pfizer)³³, The Ghose (Amegen)³¹, Veber (GSK)³⁰, Egan (Pharmacia)³⁴ and Muegge (Bayer)³⁵. FRC-1 in the studies clearly passes all the filters with only one Lipinski rule of five violations, where MLOGP value is 4.38 while it should not be more than 4.15³³.

Further the bioavailability score of FRC-1 (Table 3) shows it to be a good permeant compound for oral absorption³⁶. Also the medicinal chemistry properties show that FRC-1 does not pose any objectionable alerts such as PAINS (Pan Assay Interference Compounds) or Brenk, where molecules containing substructures showing potent response in assays irrespective of the protein target yielding false positive biological output³⁷. The synthetic accessibility is also one of the major factors to be considered where virtual molecules can be synthesized for biological assays depending on the size and complexity such as macrocycles, chiral centres, or spiro functions³⁸. The synthetic accessibility score range from 1 (very easy) to 10 (very difficult), and this shows that FRC-1 with a score of 4.49 can be moderately easy to synthesize.

Analysis of Target Protein Active Sites

Analysis of protein structures for binding site pockets is an important and often the starting point considered in the protein-ligand docking studies. In the present study, CASTp server is used to identify the possible active binding sites for ligand in the respective proteins. CASTp server predicted 16 active sites of protein 1AB2, 6 active sites of protein 5OAZ, 28 active sites of protein 5NP3 and 18 active sites of protein 2ECD. The area and volume of computed proteins along with total amino acids and residues are shown in Table 4 respectively, while the 3D representation of pockets is shown in Figure 2 with largest pocket in blue color and other pockets in 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 structures³⁹. To study the binding mode of FRC-1 in the binding site of ABL Kinases, docking studies were performed and compared with the standard drugs marketed using one online tool and one offline tool. The online docking studies were carried out by PatchDOCK server (Table 5), while the offline analysis was done by Autodock Vina (Table 6). In both the programs, energy values were calculated from the docked conformations of the protein-inhibitor complexes in order to find out how likely the compound binds to the target proteins based on the negative binding affinity values⁴⁰. Docking studies yielded crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. Comparison of minimum binding energy of FRC-1 and other selected drug molecules with both the kinases indicated that both the ABL Kinases were successfully docked with FRC-1 and showed a good binding affinity.

In the molecular docking paradigm, the ligand with more negative binding energy is considered more successful and more potent than to the one with less or positive binding energy. In the present study, results from PatchDock analysis revealed that the binding affinity of FRC-1 is significant in comparison of other drug molecules. The binding affinity score of FRC-1 with both the ABL kinases is much better than the other drugs (Table 5). The percentage energy of minimization with respect to the area of binding is -97.02% and -73.47% for SH3 and SH2 domain of ABL-1, while it is -53.50% and -36.77% for SH2 and SH3 domain of ABL-2 respectively. Following the PatchDock analysis for molecular docking of compounds, an offline analysis for molecular docking of compounds was also performed to compare and confirm the results using AutoDock Vina. The affinity of ligands was calculated in Vina and showed in the Table 6. The results of Vina also confirm that FRC-1 is the most successful ligand to bind with both the ABL kinases. The binding energy of FRC-1 with SH2 and SH3 domain of ABL-1 is -14.1 Kcal/mol and 13.2 Kcal/mol, while that with SH2 and SH3 domain of ABL-2 is -11.9 Kcal/mol and -16.1 Kcal/mol respectively, which is much better in comparison to the other ligands used in the study (Table 6).

Thus the results of PatchDock and Vina, supports the consideration that FRC-1 is much better compound in the comparison of insilico molecular docking analysis with available drug molecules and also shows very prominent binding affinity with all the four ABL kinase domains (Fig. 3 & 4), which makes the molecule to be considered as much better competitor in the arena of ABL kinase inhibitors for cancer treatment.

Table 1: Physicochemical properties of Proteins by ExPASy's ProtParam Tool

Properties	ABL-1 SH2 Domain (1AB2)	ABL-1 SH3 Domain (5OAZ)	ABL-2 SH2 Domain (2ECD)	ABL-2 SH3 Domain (5NP3)
Number of Amino acids	109	63	119	61
Molecular Weight	12139.38	7004.73	12781.10	6760.52
Theoretical pI	9.06	4.70	8.11	6.77
Extinction coefficient, M ⁻¹ cm ⁻¹ @ 280 nm in water	15930	15470	15930	15470
Estimated half life (N-terminal is Gly)	30 hrs (Mammalian reticulocytes, in vitro) >20 hrs (Yeast, in vivo) >10 hrs (E.coli, in vivo)	30 hrs (Mammalian reticulocytes, in vitro) >20 hrs (Yeast, in vivo) >10 hrs (E.coli, in vivo)	30 hrs (Mammalian reticulocytes, in vitro) >20 hrs (Yeast, in vivo) >10 hrs (E.coli, in vivo)	30 hrs (Mammalian reticulocytes, in vitro) >20 hrs (Yeast, in vivo) >10 hrs (E.coli, in vivo)
Instability index	46.46 (Unstable)	14.06 (Stable)	45.50 (Unstable)	19.44 (Stable)
Aliphatic index	75.14	71.11	73.70	76.56
Grand average of hydropathicity (GRAVY)	-0.635	-0.530	-0.398	-0.446

Table 2: Physicochemical and Pharmacokinetic properties of Ligands by SwissADME

Properties	Imatinib (DB00619)	Dasatinib (DB01254)	Daunorubicin (DB00694)	Doxorubicin (DB00997)	FRC-1 (CID546821)
1. Physicochemical Properties:					
Formula	C29H31N7O	C22H26ClN7O2S	C27H29NO10	C27H29NO11	C23H36O2
Molecular weight	493.60 g/mol	488.01 g/mol	527.52 g/mol	543.52 g/mol	344.53 g/mol
No. of heavy atoms	37	33	38	39	25
No. of aromatic heavy atoms	24	17	12	12	6
No. of rotatable bonds	8	8	4	5	4
No. of H-bond acceptors	6	6	11	12	2
No. of H-bond donors	2	3	5	6	1
Molar refractivity	154.50	138.63	131.50	132.66	106.09
TPSA (Å ²)	86.28 Å ²	134.75 Å ²	185.84 Å ²	206.07 Å ²	29.46 Å ²
2. Lipophilicity Properties:					
iLOGP	4.04	3.37	2.94	2.58	4.07
XLOGP3	3.52	3.59	1.83	1.27	5.73
WLOGP	3.19	2.36	0.70	-0.32	5.32
MLOGP	2.15	1.35	-1.35	-2.10	4.38
3. Pharmacokinetic Properties:					
GI absorption	High	High	Low	Low	High
BBB permeant	No	No	No	No	Yes
P-gp substrate	Yes	No	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	Yes	Yes	No	No	No
CYP2C9 inhibitor	Yes	Yes	No	No	No
CYP2D6 inhibitor	Yes	Yes	No	No	Yes
CYP3A4 inhibitor	Yes	Yes	No	No	No
Log K _p (skin permeation)	-6.81 cm/s	-6.73 cm/s	-8.22 cm/s	-8.71 cm/s	-4.33 cm/s

Table 3: Druglikeness and Medicinal Chemistry properties of selected ligands

Properties	Imatinib (DB00619)	Dasatinib (DB01254)	Daunorubicin (DB00694)	Doxorubicin (DB00997)	FRC-1 (CID546821)
1. Druglikeness:					
Lipinski	Yes; 0 violations;	Yes; 0 violations;	No; 2 violations; MW>500; NorO>10	No; 3 violations; MW>500; NorO>10; NHorOH>5	Yes; 1 violation; MLOGP>4.15
Ghose	No; 2 violations; MW>480; MR>130	No; 2 violations; MW>480; MR>130	No; 2 violations; MW>480; MR>130	No; 2 violations; MW>480; MR>130	Yes
Veber	Yes	Yes	No; 1 violations; TPSA>140	No; 1 violations; TPSA>140	Yes
Egan	Yes	No; 1 violations; TPSA>131.6	No; 1 violations; TPSA>131.6	No; 1 violations; TPSA>131.6	Yes
Muegge	Yes	Yes	No; 2 violations; TPSA>150; H-acc>10	No; 3 violations; TPSA>150; H-acc>10	No; 1 violation; XLOGP3>5
Bioavailability score	0.55	0.55	0.17	0.17	0.55
2. Medicinal Chemistry:					
PAINS	0 alert	0 alert	1 alert; Quinone A	1 alert; Quinone A	0 alert
Brenk	0 alert	0 alert	1 alert; Hydroquinone	1 alert; Hydroquinone	0 alert
Leadlikeness	No; 3 violations; MW>350; Rotors>7; XLOGP3>3.5	No; 3 violations; MW>350; Rotors>7; XLOGP3>3.5	No; 1 violation; MW>350	No; 1 violation; MW>350	No; 1 violation; XLOGP3>3.5
Synthetic accessibility	3.78	3.83	5.77	5.81	4.49

Table 4: CASTp result of the proteins

Protein	Area	Volume	Amino Acids	Residues
1AB2	329.05	313.50	16	GLY3, ASN4, GLU7, HIS9, SER10, TRP11, TYR12, HIS13, GLY14, PRO15, VAL16, ALA20, ALA21, LEU24, LEU25, SER32, PHE33, LEU34, ARG50, PRO100, ALA101, PRO102, LYS103, ARG104, ILE106, HIS107 & ARG108
5OAZ	163.33	297.66	7	ASP77, ASN78, THR79, GLU101, GLN108, GLY109 & TRP110
2ECD	346.73	468.01	23	SER5, SER6, GLY7, THR8, PRO9, VAL10, ASN11, SER12, GLU14, LYS15, HIS16, SER17, TYR19, HIS20, ALA108, PRO109, LYS110, CYS111, ASN112, GLY115, PRO116, SER117 & SER118
5NP3	148.76	174.38	12	TYR70, ASP71, SER75, GLY76, ASP77, ASN78, THR79, LYS84, ASN94, GLN95, TRP99 & TRP110

Table 5: PatchDock results

Ligand	Protein	Domain	Code	Score	Area	ACE	ACE (%)
IMATINIB (DB00619)	ABL1	SH2	1AB2	6456	866.7	-347.19	-40.06
		SH3	5OAZ	5552	777.8	-384.62	-49.45
	ABL2	SH2	2ECD	6804	867.9	-376.54	-43.39
		SH3	5NP3	5926	730.0	-167.37	-22.93
DASATINIB (DB01254)	ABL1	SH2	1AB2	5358	636.0	-253.22	-39.81
		SH3	5OAZ	5512	699.5	-300.4	-42.94
	ABL2	SH2	2ECD	6084	772.7	-302.35	-39.13
		SH3	5NP3	5818	703.2	-208.79	-29.69
DAUNORUBICIN (DB00694)	ABL1	SH2	1AB2	5374	597.7	-209.76	-35.09
		SH3	5OAZ	5130	642.0	-253.98	-39.56
	ABL2	SH2	2ECD	5972	793.4	-270.56	-34.10
		SH3	5NP3	5068	643.4	-52.08	-8.09
DOXORUBICIN (DB00997)	ABL1	SH2	1AB2	5188	604.4	-229.21	-37.92
		SH3	5OAZ	5316	665.5	-223.5	-33.58
	ABL2	SH2	2ECD	5950	815.7	-284.58	-34.89
		SH3	5NP3	5132	611.3	6.16	1.01
FRC-1	ABL1	SH2	1AB2	2636	313.3	-230.19	-73.47
		SH3	5OAZ	2452	252.5	-244.98	-97.02
	ABL2	SH2	2ECD	2696	294.7	-157.67	-53.50
		SH3	5NP3	2948	346.1	-127.27	-36.77

Table 6: AutoDock Vina results

Ligand	Affinity (Kcal/Mol)			
	1AB2	5OAZ	2ECD	5NP3
IMATINIB (DB00619)	-8.2	-7.7	-7.9	-9.2
DASATINIB (DB01254)	-6.8	-7.4	-7.2	-7.6
DAUNORUBICIN (DB00694)	-8.4	-8.0	-9.2	-9.4
DOXORUBICIN (DB00997)	-8.8	-8.1	-9.3	-9.3
FRC-1	-14.1	-13.2	-11.9	-16.1

Figure 1: 3D structure of Proteins and Ligands using PyMOL

Figure 2: CASTp result showing major pocket in blue color and other pockets in red color

Figure 3: Binding model of PatchDock results for FRC-1 with SH2 & SH3 domains of ABL-1 & ABL-2

Figure 4: Binding model of Vina results for FRC-1 with SH2 & SH3 domains of ABL-1 & ABL-2

CONCLUSION

In the present *in-silico* investigation, we elucidated one finding that the flavonoid compound (FRC-1) which is isolated and identified from plant (*Launaea procumbens*) shows very high binding affinity against the selected domains of ABL kinases. It can therefore be considered as potential anticancer agent for the target proteins, namely, Abelson tyrosine protein kinase 1 and Abelson tyrosine protein kinase 2. 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 proteins with FRC-1 and its physicochemical detailing, it was found that the flavonoid, FRC-1, has high possibilities to be an anticancer 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 on the basis of 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 phytochemical (FRC-1). This compound shows a significant and very high potential in anticancer property in *insilico* 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.

ACKNOWLEDGEMENT

The authors highly acknowledge the support and facilities provided by the Department of Biosciences, Veer Narmad South Gujarat University, Surat and Department of Chemistry, Towson University, Maryland, USA for the entire research program.

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Cite this article as:

Gaurav J. Mishra et al. Evaluating the anti-cancer potential of *Launaea procumbens* (Roxb.) by comparative molecular docking analysis against ABL kinases. Int. Res. J. Pharm. 2019;10(3):200-207 <http://dx.doi.org/10.7897/2230-8407.1003105>

Source of support: Nil, Conflict of interest: None Declared

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