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Identification and screening of *Aegel marmelos* compounds against viral infection

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ABSTRACT

Advanced medicines and pills have become such an important part of people`s lives that Ayurveda seems to have vanished from the picture completely. But Ayurveda contains some medicinal plants and herbs which can effectively treat and cure multiple health problems and can be great for your overall health. These Plants have been a part of our lives since our existence and have been used for various medicinal purposes since ancient times. Medicinal plants and herbs like Basil leaves, Bael Tree, Aloe Vera, Tulsi, etc. One of the best and well know medicinal plant is Bael Tree 'A.marmelos'. Various phytoconstituents like alkaloids, coumarins and steroids have been isolated and identified from different parts of the Bael tree such as leaves, fruits, wood, root and bark. It will help to cure the viral infections like Dengue, HIV, and Hepatitis etc. Hence the present study carried out to uncover the basic molecular properties of potent bioactive compounds of *A.marmelos* and analyse their drug likeliness and ADMET properties using bioinformatics tools and databases.

Keywords: Aegel Marmelos, Viral Infection, Bael Tree, Phyto-Compounds.

I. INTRODUCTION

Aegle marmelos Linn. Of family Rutaceae is commonly called as 'Beal' is the well-known Indian medicinal plant of therapeutic importance. Beal tree is commonly found in Hindu sacred grooves (12). Aegle marmelos, a plant indigenous to India has been used by the inhabitants of the Indian subcontinent for over 5000 years. The leaves, bark, roots, fruits and seeds are used extensively in the Indian traditional system of medicine the Ayurveda and in various folk medicine to treat myriad ailments. Bael fruits are also used in the treatment of chronic diarrhea, dysentery, and peptic ulcers, as a laxative and to recuperate from respiratory affections in various folk medicines. Scientific studies have validated many of the ethnomedicinal uses and reports indicate that the fruit possesses broad range of therapeutic effects that includes free radical scavenging, antioxidant, inhibition of lipid peroxidation, antibacterial, antiviral, anti-diarrheal, gastroprotective, anti-ulcerative colitis, hepatoprotective, anti-diabetic, cardioprotective and radio protective effects. For the first time, this review critically assesses the nutritional

values, phytochemistry and preclinical pharmacological properties of the bael fruit. Attempts are also made at emphasizing the dietary and pharmaceutical potential of bael fruit that has been largely underutilized and neglected (15).

Since ancient times, plants are used as source of medicine. Aegle marmelos is a pharmacologically varied medicinal plant. The various parts of Aegle marmelos, precisely fruit, have an immense range of medicinal uses in folk medicine and used for the healing of different disease. The numerous phytochemical constituents of this plant have been exposed namely, marmeline, Agelin, aegelenine, marmeline, dictamine, fragrine, inulin, proteins, carbohydrates, alkaloids, cardiac glycosides and flavonoids. Researchers reported pharmacological potential of various parts such as fruits, leaves, and stems of Aegle marmelos as antioxidant, antimicrobial, hypoglycemic, anti-inflammatory, analgesic, nephroprotective, hepatoprotective etc.

II. METHODS AND MATERIAL

- **Collection of Phyto Compounds:**
  - Collection of the information of *Aegle marmelose* (Bael) tree compounds from the literature. These compounds from based literature on bael tree fruit, leaves and bark.
- **Virtual screening for drug likeness properties:**
  - The utility of drug ability from a medicinal chemistry standpoint has been summarized by the rule of five (Lipinski rule, Ro5) and its extension. The compounds shows there drug likeness in bioinformatics tool drug bank database. The drug likeness was evaluated through the drug bank database.
- **Toxicity analysis:**
  - For the detection of toxicity of these compounds we screened these compounds by using the ADMET software bioinformatics tool. To check the four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug.
- **Designing of standard ligands structures:**
  - The ligands were re-designed by Marvin's sketch software.
- **Molecular docking:**
  - The ligands were docked with receptor protein by using Autodock tool.
- **Visualisation of structures:**
  - The docked molecules visualised by Pymol and Discovery studio 2021 is bioinformatics visualisation software's.

III. RESULTS AND DISCUSSION

- **Collection of Phyto Compounds:**
- The collection the information of medicinal compounds of *Aegle marmelose* (Bael tree) from the literature. The medicinal compounds from based on literature which are bael tree fruit, leaves and bark as shown in table.no.01, 02, and 03.
- **Virtual screening for drug likeness properties:**
  - The utility of drug ability from a medicinal values has been summarized by the rule of five (Lipinski rule, Ro5) and its extension. Drug Bank database, it shows SMILES and Molecular weight, Accession Id's, Chemical Formula of the compounds as shown in table. No.04 and table No.5. Shows the Drug ability screening of compounds on the basis of Lipinski Rule of five .
- **Toxicity analysis:**
  - For the detection of toxicity of these compounds we screened these compounds by using the ADMET software bioinformatics tool. Some properties in that compounds like Absorption, Distribution, metabolism, and excretion. 22 compounds were predicted, Blood Brain Barrier (BBB), HIA (Human Intestinal Absorption), ADME Toxicity, Carcinogenicity. These compounds as shown in table.no.06.
- **Designing of standard ligands structures:**

- The ligands were re-designed by Marvin's sketch software, which was collected by Drug bank database.

- **Molecular docking:**

- The 22 ligands were tested for docking studies by using Auto dock tool. 18 ligands were docked with receptor (DC-SIGN) and computed their binding energies, residues involved, and hydrogen bonds and interactions like Van der Waals, Conventional Hydrogen Bond, Carbon hydrogen bond, Carbon bond, Alkyl bond, PI-DONOR of compounds which shows interaction with receptor, 15 ligands show strong bonding with receptor, shown in table no.7.

- **Visualisation of docking:**

- The docked molecules were visualised by Pymol and Discovery studio 2021 are bioinformatics software's use to visualise molecules docked structures and their interactions, as shown in figures no. 1, 2, 3, 4, 5, 6, 7, and 8.

Table.No.1 .Compounds Collected from Bael tree fruit.

Sr. No.	Fruit
1.	Angeline
2.	Dictamine
3.	Fragrine
4.	O-isopentenylhalfordinol
5.	Marmelosin
6.	Imperatorin
7.	Methyl ether
8.	Xanthotoxol
9.	Psoralen
10.	Marmelide
11.	N-2-(4-3,3-dimethylallyloxy phenyl)ethyl cinnamide
12.	N-2-hydroxy-2-(4-3-3-dimethylallyloxy phenyl)ethyl cinnamide
13.	O-3-3-dimethylallyl halofordinol
14.	N-2-ethoxy-2-(4-methoxy phenyl) ethyl cinnamide
15.	N-2-methoxy-2-(4-3-3-dimethylalloxy)phenyl ethyl cinnamide
16.	N-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamid.
17.	Naringenine
18.	Rutin
19.	Fisetin

Table.No.2. Compounds Collected from Bael tree Bark.

Sr.No.	Leaves
1.	Pentadecenoic acid
2.	Hexadecenoic acid(methyl ether)
3.	g.octadecenoic acid
4.	Octa-catrienoic acid(methyl ether)
5.	cis-g-Hexadecenal,octadecenoic acid
6.	Benzenoic acid (4-ethaoxy ethyl ester)
7.	2-propanol (1, 1, 2 ethanedyl).

Table No 3 Compounds collected from Bael tree Leaves

Sr.No.	Leaves
1.	Pentadecenoic acid
2.	Hexadecenoic acid(methyl ether)
3.	g.octadecenoic acid
4.	Octa-catrienoic acid(methyl ether)
5.	cis-g-Hexadecenal,octadecenoic acid
6.	Benzenoic acid (4-ethaoxy ethyl ester)
7.	2-propanol (1, 1, 2 ethanedyl).

Table No.4 Molecular weight and Chemical formula, Accession id of compounds by Drug Bank database.

Compounds Names	DB Accession Id	Molecular weight	Chemical Formula
9-Octadecenoic acid	DB13171	356.5	$C_{21}H_{40}O_4$
Encainide	DB01228	352.4699	$C_{22}H_{28}N_2O_2$
Hexadecenal	DB03381	240.4247	$C_{16}H_{32}O$
Rutin	DB01698	610.5175	$C_{27}H_{30}O_{16}$
Glycerin	DB09462	92.0938	$C_3H_8O_3$
Narginine	DB03467	272.2528	$C_{15}H_{12}O_5$
Methyl ether	DB02342	302.4079	$C_{19}H_{26}O_3$
Hexaden	DB09494	242.44	$C_{16}H_{34}O$
Cineole	DB03852	154.2493	$C_{10}H_{18}O$
Eugenol	DB09086	164.2011	$C_{10}H_{12}O_2$
Hesperetein	DB01094	302.2788	$C_{16}H_{14}O_6$
Dictamine	DB09085	264.3633	$C_{15}H_{24}N_2O_2$
Hexadecenoic acid	DB04257	254.4082	$C_{16}H_{30}O_2$
Psoralen	DB04571	228.2433	$C_{14}H_{12}O_3$
Marmelide	DB00778	837.0465	$C_{41}H_{76}N_2O_{15}$
Xanthotoxol	DB00553	216.1895	$C_{12}H_8O_4$
Phenyl ethyl cinnamide	DB09364	---	$C_{28}H_{41}HgN_3O_9$
Dihydroxy methyl	DB01838	426.05	$C_{16}H_{10}Br_2O_4$
Propenoic acid	DB02579	72.0627	$C_3H_4O_2$
Butanol	DB02606	74.12	$C_4H_{10}O$
Tetramethyl	DB01637	298.5	$C_{20}H_{42}O$

Table No. 5 Drug ability screening of compounds Hydrogen Acceptor count, Hydrogen donor count and Rotatable bond count

No	Names	HAC	HDC	RBC	Water Sol(mg/ml)	Log P
1	9-Octadecenoic acid	3	2	19	0.00151	5.61
2	Encainide	3	1	6	0.004.1	4.49
3	Hexadecenal	1	0	14	5.88	6.1
4	Rutin	16	10	6	125	-0.87
5	Glycerin	3	3	2	1170.0	-1.8
6	Narginine	5	3	1	0.214	2.84
7	Methyl ether	3	2	1	0.00968	3.59
8	Hexaden	1	1	14	0.000181	6.14
9	Cineole	1	0	0	3500	2.35
10	Eugenol	2	1	3	1.44	2.61
11	Hesperetein	6	3	2	0.138	2.68
12	Dictamine	3	1	9	0.555	2.79
13	Hexadecenoic acid	2	1	13	0.000447	5.89
14	Psoralen	1	0	0	0.0627	2.95
15	Marmelide	16	5	13	0.187	3
16	Xanthotoxol	2	0	1	0.164	1.78
17	Phenyl ethyl cinnamide	7	1	14	3.43	0.83
18	Dihydroxy methyl	4	2	1	0.0196	4.29
19	Propenoic acid	2	1	1	123.0	0.53
20	Butanol	1	1	1	195.0	0.78
21	Tetramethyl	1	1	14	2.31	7.29

Table.No.6 Predicted ADMET Properties

Sr.No	Compounds	BlBB	HIA	Carcino-genicity	AMES toxicity
1.	Octadecenoic acid	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
2.	Dioxybicyclo	BBB-	HIA+	Non-carcinogens	Non-AMES toxic
3.	Butanol	BBB+	HIA+	Carcinogens	Non-AMES toxic
4.	Propenoic acid	BBB+	HIA+	Carcinogens	Non-AMES toxic
5.	Hexadecenal	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
6.	Hexadenen	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
7.	9-Octadecenoic acid	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
8.	Hexadecenoic acid	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
9.	Tetradecenol acid	BBB+	HIA+	Carcinogens	Non-AMES toxic
10.	Dihydroxy methyl	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
11.	Xanthotoxol	BBB+	HIA+	Non-Carcinogens	AMES toxic
12.	Marmelide	BBB-	HIA-	Non-Carcinogens	Non-AMES toxic
13.	Psoralen	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
14.	Dictamine	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
15.	Hesperetin	BBB-	HIA+	Non-Carcinogens	Non-AMES toxic
16.	Eugenol	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
17.	Cineole	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
18.	Naringenin	BBB+	HIA+	Non-AMES toxic	18.
19.	Glycerin	BBB-	HIA+	Non-Carcinogens	Non-AMES toxic
20.	Rutin	BBB-	HIA+	Non-Carcinogens	Non-AMES toxic
21.	Encainide	BBB+	HIA+	Non-Carcinogens	Non-AMES toxic
22.	Phenyl ethyl cinnamide	BBB-	HIA-	Non-Carcinogens	Non-AMES toxic

Table No. 7. Docking properties of compounds

No	Ligands	Binding energy	Residues involved	Hydrogen bonds	Interactions
1	Butanol	-2.97	A:PRO337, A: SER338, A: PHE339, A: GLN341 A:	ARG312: HH21	Van der Waal
2	Cineole	-4.87	A: GLN341, A: SER338, A: PHE339, A:PRO337, LYS340, A: TYR342	A: ASN322: HD22	Van der Waals, Bump
3	Dictamine	-4.74	A: TYR342, A: GLN341, A :SER338	A: GLN274: HE21, A: TRP260: HE1, B: TRP260: HE1	Conventional Hydrogen Bond, Unfavourable Bump
4	Eugenol	-4.45	A: PHE339, A: SER338, A: LYS340,	A: PHE313: HN, A: PHE374: HN	Van der Waals

			A: GLN341, A:PRO337		
5	Glycerin	-2.76	A: GLN341, A: SER388	D: ARG309: HH22, E: LEU355: HN	Unfavourable bump
6	Hexadecenal	-3.49	NOT BOND WITH	J: GLY361: HN	NOT INTERACTED
7	Hexadecenoic acid	-3.48	A: GLN354, A: ASN365, A:ASP366, A: VAL351, A: ASN349, A: GLU347, A: GLY361, A: ASN311, J: GLU354	A: LYS379:H22	Van der Waals, Conventional Hydrogen bond, Carbon hydrogen bond
8	Marmelide	-4.93	A: GLN341, A: SER338, A: ALA297, A: TYR342	B: GLN274, A: PHE262	Van der Waals
9	Methoxy ethyl	-6.65	A: GLN341, A: PHE339, A: LEU336, A: SER338, A:PRO337	NO Hydrogen bonds form	Carbon bond
10	Methyl ether	-2.3	Residues involved	A: ASN322: HN	NOT INTERACTED
11	Naringenin	-5.95	A: TYR342, A: GLN341, A: LYS340, A: PHE339, A:PRO337, A: SER338	NO Hydrogen bonds form	Van der Waals, Conventional Hydrogen bond
12	Octadecenoic	-2.86	A: LYS340, A: PHE339, A: LEU336, A: SER338, A:PRO337	A: ARG345: HN	Bump, Alkyl bond
13	9 Octadecdenoic acid	-6.02	A: GLN341, A: SER338, A: ALA297, A: TYR342	No Hydrogen bonds form	Van der Waals, unfavourable Bump
14	Phenyl ethyl cinnamide	-5.14	A: GLN341	A: TRP258: HN, A: TRP260: HE1	PI-DONOR
15	Propenoic	-3.96	A: GLN341, A: SER338	A: ASN322: HN, A: ASN322: HD22	NOT INTERACTED
16	Psoralen	-6.26	A: GLN341	A: ASN322: HN	Conventional Hydrogen Bond
17	Rutin	-2.03	A:GLN34	A:ASN301:HD21	Conventional Hydrogen Bond
18	Xanthotoxol	-5.88	A: GLN341, A: SER338	A: ARG: HH12	Carbon Hydrogen Bond, Conventional Hydrogen Bond

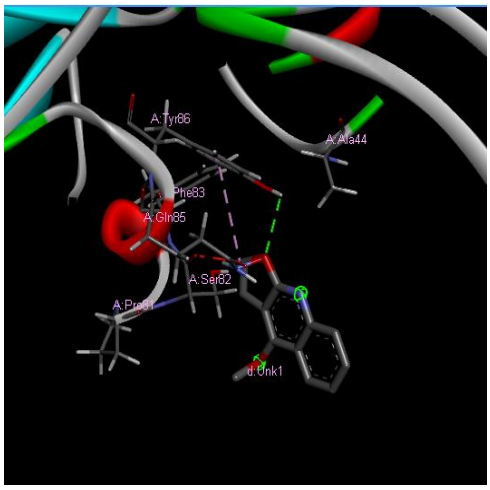

Fig. 1 Dictamine docked structure visualized by Discovry studio 2021.

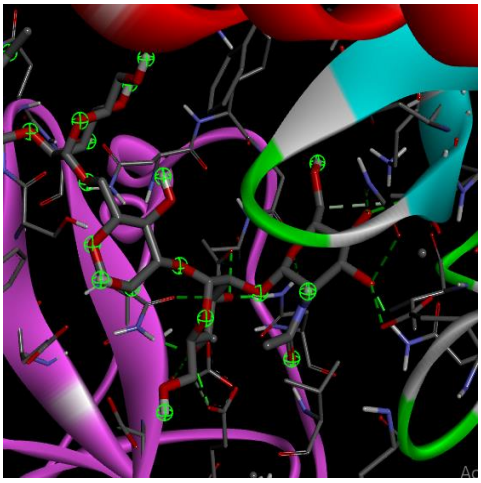

Fig.2 Hexadecenoic acid docked structure visualized by Discovry studio 2021.

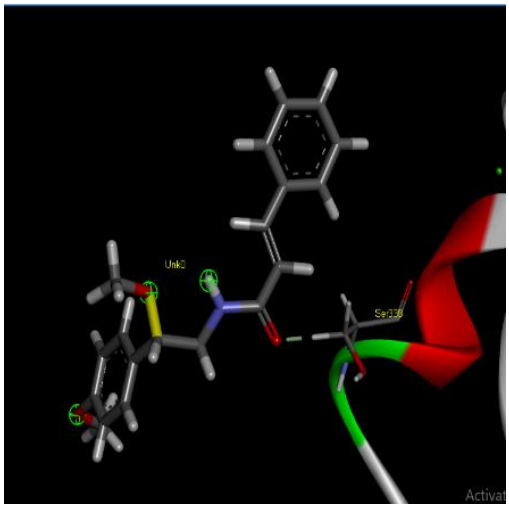

Fig. 3 Methyl ethyl docked structure visualized by Discovry studio 2021.

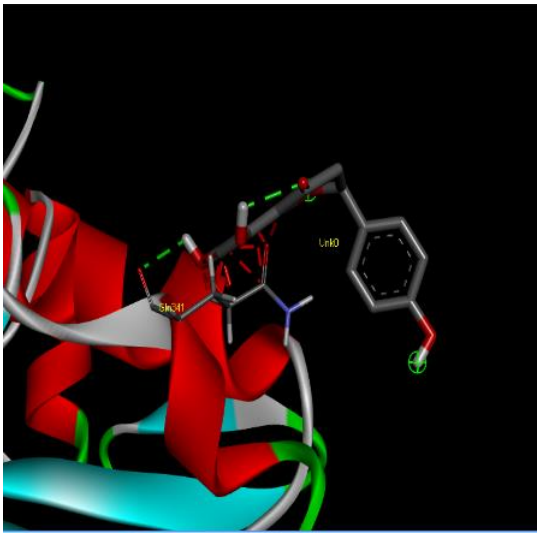

Fig. 4 Naringenin docked structure visualized by Discovry studio 2021.

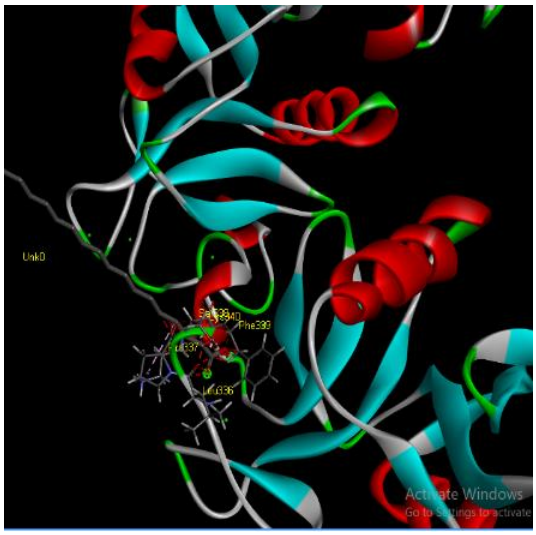

Fig. 5 Octadecenoic docked structure visualized by Discovry studio 2021.

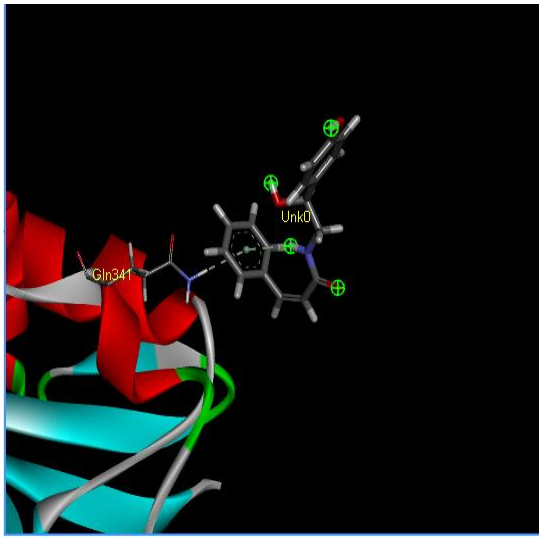

Fig. 6 Phenyl ethyl cinnamide docked structure visualized by Discovry studio 2021.

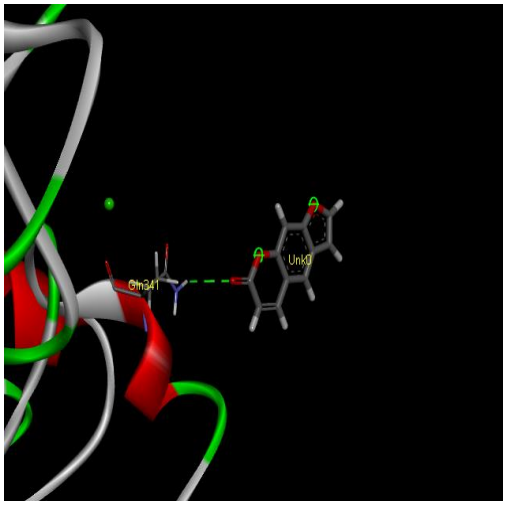

Fig.7 Psoralen docked structure visualized by Discovry studio 2021.

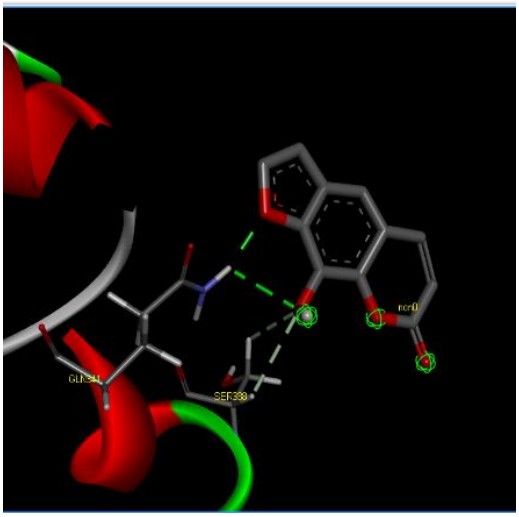

Fig. 8 Xanthotoxol docked structure visualized by Discovry studio 2021.

IV. CONCLUSION

Aegle marmelos is one of the most important medicinal plants of India, Bael is reported to have number of coumarins, alkaloids, steroids, and essential oils. Root and fruits contain coumarins such as scoparone, scopoletin, umbellliferone, marmesin and skimming. It seems that Bael has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents, which usually act in the later stages of viral replication and have potent side effect. Scientist has long known the importance of the plants and chemicals they produce in overcoming disease. The screening of Phyto compounds from Bael tree suggests that out 38 compounds collected, 22 compounds were screened for ADMET and toxicity in which all 22 compounds passed the screening parameters and found potent to be used as drugs for the treatment of Dengue infection upon interaction studies with the selected target protein (DC-SIGN), Dengue infection is a mosquito-borne tropical disease caused by the dengue virus. Symptoms typically begin three to fourteen days after infection. This may include a high fever, headache, vomiting, muscle and joint pain, and a characteristic skin rash. DC-SIGN is a C-type lectin and has a high affinity for the ICAM3 molecule. It binds various microorganisms by recognizing high-mannose-containing glycoproteins on their envelopes and especially functions as receptor for several viruses such as Dengue, HIV and Hepatitis C. Binding to DC-SIGN can promote Dengue, HIV and Hepatitis C virus to infect T-cell from dendrite cells. Thus, binding to DC-SIGN is an essential process for Dengue infection. Hence the present investigation mainly deals with the understanding of detailed molecular features of DC SIGN protein to uncover its key role in the infection of Dengue by retrieving its protein sequence information, analysis of physicochemical properties, secondary structure, conserved domains and tertiary structure. The analysis reveals that the protein is highly stable with helix dominating secondary structure. These docked analog complexes analyzed upon their interaction such as hydrogen, ionic and hydrophobic interactions. All the analogs showed good interactions with the target protein DC-SIGN but the analog 8 showed the best interaction with the target.

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