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MOLECULAR DOCKING STUDY OF POTENTIAL PHYTOCHEMICALS OF MERREMIA EMARGINATA AND THEIR ANTI INFLAMMATORY EFFECT ON THE P38 MITOGEN ACTIVATED PROTEIN KINASE ENZYME

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ABSTRACT

Merremia emarginata Burm.f (Convolvulaceae) is a perennial, much-branched herb present throughout India. There are multiple pharmacological effects of Merremia emarginata has been reported. As the structures of more and more proteins and nucleic acids become available, molecular docking is increasingly considered for lead discovery. In this study the structures of the ligands were generated in the CDX format using the tool Chem Draw ultra-version 8.0. The Maestro suite 2021-4 was used to perform molecular docking. MD simulation was performed using Macro model Version 9.0. ADMET prediction for the top docking hits was calculated by using the Qikprop module of the Schrodinger suite program. The present investigation helped in recognizing the role of some lead molecules such as quercetin and chlorogenic acid. Results from the in-silico study revealed that many of the phytoconstituents of *Merremia emarginata* may be used fully against MAPK14 and produce anti-inflammatory action.

Key words: Molecular docking, Merremia emarginata, MAPK14, Anti-inflammatory.

INTRODUCTION

Natural products used in traditional herbal medicine can be an important source for the search for novel medicinal compounds [1]. Herbal medicines are complex compounds with multiple synergistic mechanisms of action that modulate physiological functions [2].*Merremia emarginata* Burm.f (Convolvulaceae) is a perennial, much-branched herb. It is found widely distributed all over India [3].The biological properties of chemical components were reported as antioxidant[4], Anti-arthritis, Analgesic[5], Anti urolithiyatic[6],Anti

inflammatory[7],Diuretic [8],Anti pyretic [9],Anti diabetic[10]. Anti-inflammatory is a property of a substance or treatment that reduces inflammation or swelling [11]. However, unregulated inflammation often results in chronic inflammation, consequently leading to the development of various chronic cardiovascular and pulmonary diseases [12].As the structures of more and more proteins and nucleic acids become available, molecular docking is increasingly considered for lead discovery [13]. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization[14].Mitogen-activated protein kinase 14 (MAPK 14), also called p38α MAPK is an enzyme that in humans is encoded by the MAPK 14 gene [15]. Cytokines and growth factors activate the **Mitogen-activated protein (MAP**) kinase pathways [11].

MATERIALS AND METHODS

PROTEIN PREPARATION

The crystal structure of protein Human **MITOGEN ACTIVATED PROTEIN KINASE(MAPK14)** (PDB ID: 1A9U) also called p38 at 2.50A^{o}was downloaded from the Protein Data Bank (PDB) and was usedto model the order to structure in this study. In general, the protein structures are refined for their bond orders, formal charges and missing hydrogenatoms, topologies incomplete and terminal amide groups.The water molecules beyond 5A^{o}of the hetero atom were removed. The possible ionization states were generated for the heteroatom present in the protein structure and the most stable state was chosen. The hydrogen bonds were assigned and orientations of the retained water molecules were corrected.[16]

LIGAND PREPARATION

The structures of the ligands were generated in the CDX format using the tool Chem Draw ultra-version 8.0. These ligands were then converted to the mol2 format and subjected to the LigPrep module of Maestro in the Schrodinger suite 2019-4. They were converted from 2D to 3D structures by including stereochemical, ionization, and tautomeric variations, as well as energy minimization and optimized for their geometry, desalted, and corrected for their chiralities and missing hydrogen atoms. The bond orders of these ligands were fixed, and the charged groups were neutralized. The ionization and tautomeric states were generated between a pH of 6.8 to 7.2 using the Epik module. In the final stage of LigPrep, compounds were minimized using Optimized Potentials for Liquid Simulations-2005(OPLS-2005) force field in the Impact package of Schrodinger until a root mean square deviation of 1.8A^{o} was achieved. Steepest descent algorithm was used for minimization, followedby the conjugate gradient method. A single low-energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis.[17]

VALIDATION OF THE DOCKING PROGRAM

The accuracy of the docking procedure was determined by finding how closely the lowest energy pose (binding conformation) of the co-crystallized ligand predicted by the object scoring function, Glide score (G Score), resembles an experimental binding mode as determined by X-ray crystallography. Extra precision Glide

docking procedure was validated by removing the co-crystallized ligand from the binding site of the protein and redocking the ligand with its binding site. The hydrogen bonding interactions and the root mean squaredeviation (RMSD) between the predicted conformation and the observed X-ray crystallographic conformation were used for analyzing the results.[16]

RECEPTOR GRID GENERATION

The ligand ANP (Phosphoraminophosphonic acid adenylate ester) was retained in the crystal structure of the prepared protein which was used for the receptor grid construction. The binding box dimensions (within which the centroid of a docked pose is confined) of the protein were set to 14A^o x 14A^o x 14 A^o. [18]

MOLECULAR DOCKING ANALYSIS

The Maestro suite 2021-4 was used to perform molecular docking and utilized to prepare the input PDB file CYSLT1R (PDB ID: 6RZ5). Molecular docking uses the computational simultion predicts the ligand preferred orientation to a receptor when interact each other to form a higher stability complex. Molecular docking was performed by docking the prepared ligand on the selective site of the protein using the Glide molecule. The result was analyzed based on the docking score and molecular interaction formed between the ligand and the protein molecule.[19]

Molecular Dynamic Simulation

MD simulation was performed using Macro model Version 9.0 (a Schrodinger module).41The OPLS_2005 force field was used for the energy calculation. The constant temperature was 300 K and in the integration step, 1.0 fs was given. Run the MD simulations for complex structures. MD simulation with position restraints was carried out for a period of 4000 PS to allow the accommodation of the water molecules in the system. Finally, Root Mean Square Deviation (RMSD) was calculated for checking the stability of 6RZ5 protein with their native motion. All the coordinate file was saved every 1000psupto4 ns and the result was analyzed by Scatter Plot.[20]

RESULTS AND DISCUSSION

Table -1 Glide Docking Studies for Phytocompounds of *M.emarginata* with MAPK14

COMPOUNDS	Glide cpu time	Docking score	Glide XP HBond	Glide evdw	Glide ecoul	Glide energy	Glide einternal	Glide emodel
n-Hexadecanoic acid	94.49	-2.49213	-2	-18.9874	-6.43223	-25.4196	4.72818	-26.6647
1,3,4,5-Tetrahydroxy-cyclohexanecarboxylic acid	49.22	-4.95264	-2.27	-15.2837	-11.3774	-26.661	2.8008	-29.7455
Octadecanoic acid, ethyl ester	130.92	-1.54889	-0.35	-26.4774	-3.61159	-30.0889	4.1477	-34.5491

Neophytadiene	159.7	-1.40184	0	-27.1642	0.320125	-26.844	5.83185	-29.4865
Hexadecanoic acid, ethyl ester	127.59	-0.72428	-0.53975	-26.5594	-2.45755	-29.017	6.70875	-32.6667
sec-Butyl nitrite	13.56	-1.23738	0	-13.5711	-0.48935	-14.0605	1.44619	-16.1005
Ethyl octanoate	145.33	1.96614	-0.31574	-30.0534	-2.96347	-33.0168	4.28613	-37.5121
(-)-Loliolide	4.52	-4.80527	-0.9975	-18.2588	-5.99404	-24.2529	1.41394	-25.5716
8-Pranylnaringenin	46.1	-4.76389	-1.53	-31.4924	-5.32064	-36.8131	2.9994	-49.7228
5-chlorodecanoic acid	79.61	-3.52774	-0.7	-22.1791	-2.60731	-24.7864	4.71705	-27.3099
Alpha-Tocopherol-beta-D-mannoside	198.68	-6.82483	-2.89342	-31.8778	-14.3294	-46.2071	6.95771	-63.7819
Chlorogenic Acid	71.08	-7.80676	-3.85294	-35.7978	-12.3295	-48.1273	5.21149	-53.6585
Quercetin	45.55	-3.97998	-2.73994	-31.4668	-7.39153	-38.8583	3.33186	-45.9693
.9,12-Octadecadienoic acid	73.18	-2.54117	-1.49224	-23.5826	-4.88437	-28.467	7.92772	-32.9799
Scopoletin	6.55	-4.79572	-1.53	-17.2695	-6.2142	-23.4837	0.124595	-30.6374
Ethyl(9Z,12Z)-9,12-Octadecadienoate	557.57	-7.05727	-3.39247	-49.5581	-9.28945	-58.8475	27.1344	-57.615
Stigmasterol	36.33	-3.30428	-0.60003	-27.5595	-2.35594	-29.9154	3.30358	-35.9735
S-[2-[N,NDimethylamino]ethyl] N,Ndimethylcarbamoyl thiocarbonyl Hydroxamate	13.62	-1.52711	-0.6778	-25.0902	-5.15294	-30.2431	9.93202	-29.162
Co ligand	43.27	-6.50428	-0.81805	-38.6431	-4.92242	-43.5655	1.43568	-60.3784

Table – 2 In-silico ADMET screening for compounds *M.emarginata* Phytoconstituents with MAPK14

COMPOUNDS	**Mol. MW**	**Donor HB**	**Accept HB**	**QPlog Khsa**	**QPlog P o/w**	**#metab**	**Rule Of Five**	**% Human Oral Absorption**
n-Hexadecanoic acid	256.428	1	2	0.535	5.251	1	1	87.187
1,3,4,5-Tetrahydroxy-cyclohexane carboxylic acid	192.168	5	7.85	-0.981	-1.244	4	0	38.341
Octadecanoic acid, ethyl ester	312.535	0	2	1.406	7.073	1	1	100
Neophytadiene	278.52	0	0	1.712	9.701	1	1	100
Hexadecanoic acid, ethyl ester	284.481	0	2	1.158	6.273	1	1	100

Sec-Butyl nitrite	103.121	0	2.5	-0.858	0.327	0	0	85.829
Ethyl octanoate	340.588	0	2	1.677	7.86	1	1	100
(-)-Loliolide	196.246	1	4.7	-0.4	0.939	1	0	86.729
8-Prenylnaringenin	340.375	2	4	0.454	2.982	8	0	84.285
5-chlorodecanoic acid	255.184	0	2	0.425	4.422	1	0	100
Alpha-Tocopherol-beta-D-mannoside	592.855	4	10	1.1	6.227	8	2	79.675
Chlorogenic Acid	354.313	6	9.65	-0.913	-0.229	5	1	16.78
Quercetin	302.24	4	5.25	-0.348	0.368	5	0	51.987
9,12-Octadecadienoic acid	280.45	1	2	0.536	5.291	4	1	87.542
Scopoletin	192.171	1	4	-0.481	0.854	2	0	82.085
Ethyl(9Z,12Z)-9,12-Octa Decadienoate	1029.968	7	28.1	-2.572	2.469	9	3	0
Stigmasterol	412.698	1	1.7	2.169	7.737	5	1	100
S-[2-[N,NDimethylamino]ethyl]N,Ndimethylcarbamoylthio-carbohydroxamate	219.301	0	6.7	-1.177	0.048	1	0	71.052
Co ligand	377.435	1	7	0.342	3.81	3	0	81.416
Recommended value	130.0-725.0	0-6	2-20	-2-8.5	-2-6.5	1-8	Max 4	>80% Is High <25% Is Poor

MW- Molecular weight of the molecule,

DonorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.

Accept HB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution

QPlogKhsa- Prediction of binding to human serum albumin.

QPlogPo/w - Predicted octanol/water partition coefficient.

#metab- Number of likely metabolic reactions.

Rule of Five Number of violations of Lipinski's rule of five.

%Human oral absorption- Predicted human oral absorption ona 0 to 100% scale.

ADMET

ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction for the top docking hits was calculated by using the Qikprop module of the Schrodinger suite program running in normal mode. Qikprop generates physically relevant descriptors, and the toxicity of a ligand is considered important for the ligand to act as an effectual drug discovery of new drug development. These entire processes were used by Schrodinger software.

MM-GBSA

The best ligands molecule was selected and subjected to the MM-GBSA and induced fit docking. Selected ligand and protein structures were considered for performing the MM-GBSA calculation. This calculation helps in calculating the relative binding affinity of the ligand toward the selected protein.

Table-3Binding free energy calculation using Prime/MM-GBSA approach

COMPOUNDS	MM-GBSADGBind	MM-GBSA DGBind Column	MM-GBSA DGBind covalent	MM-GBSA DGBind Hbond	MM-GBSADGBindLipo	MM-GBSADG_Bind_vdW
n-Hexadecanoic acid	-55.3714	4.236057	5.938914	-2.4336	-5.69644	-7.72561
1,3,4,5-Tetrahydroxy-cyclohexane carboxylicacid(quinic acid)	-34.6689	195.1767	-9.46729	-3.70973	-11.4488	-33.1883
Octadecanoic acid, ethyl ester	-83.336	-34.056	-2.55085	1.749419	-22.0609	-43.5347
Neophytadiene	-66.038	19.34009	-12.504	2.236027	-21.5314	-32.4304
Hexadecanoic acid, ethyl ester	-36.8374	66.35723	-14.5336	-2.98934	-0.18423	2.177097
sec-Butyl nitrite	-35.0348	-5.11839	-6.21986	1.352614	-2.52584	6.598009
Ethyl octanoate	-39.3251	-0.00393	4.333418	-0.5644	-9.5032	-15.4377

(-)-Loliolide	-57.6216	-25.2944	-1.06318	-2.16555	-8.74908	-10.3604
8-Pranylnaringenin	-0.86399	-28.0322	6.138154	-0.74647	-1.30514	-19.057
5-chlorodecanoic acid	-52.5415	-11.3726	-1.38252	0.170944	-9.61591	-22.7178
Alpha-Tocopherol-beta-D-mannoside	-39.7324	-17.8869	-2.12131	1.626048	-9.7163	-8.86662
Chlorogenic Acid	-19.3159	47.03992	2.592757	1.037258	-5.29311	-1.06706
Quercetin	-9.77981	40.72236	11.30855	1.168628	-5.55332	-9.1672
.9,12-Octadecadienoic acid	-37.8803	31.56372	-21.7136	4.408193	-9.13497	-11.4829
Scopoletin	-27.0268	-39.871	2.0585	-0.89655	-0.07254	2.784735
Ethyl(9Z,12Z)-9,12-Octadecadienoate	-39.6844	14.55358	-4.69006	3.203206	-13.5128	-16.3359
Stigmasterol	-24.2498	-43.2058	14.18678	-1.61752	-3.25557	-5.02638
S-[2-[N,NDimethylamino]ethyl]N,Ndimethylcarbamoyl thiocarbonyl Hydroxamate	-45.3069	-16.7402	1.51852	1.779204	-9.39279	-8.45639
Co ligand	-19.0669	34.13228	-6.7073	3.286368	-12.3517	-7.08802

2D ligand interaction for phytoconstituents of *Merremia emarginata* with MAPK14

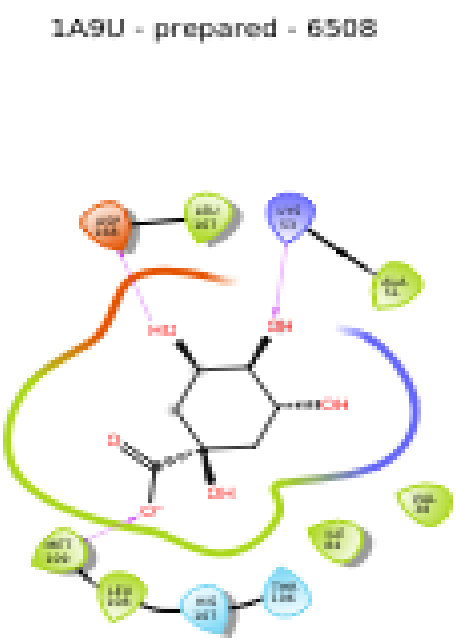


Fig:1

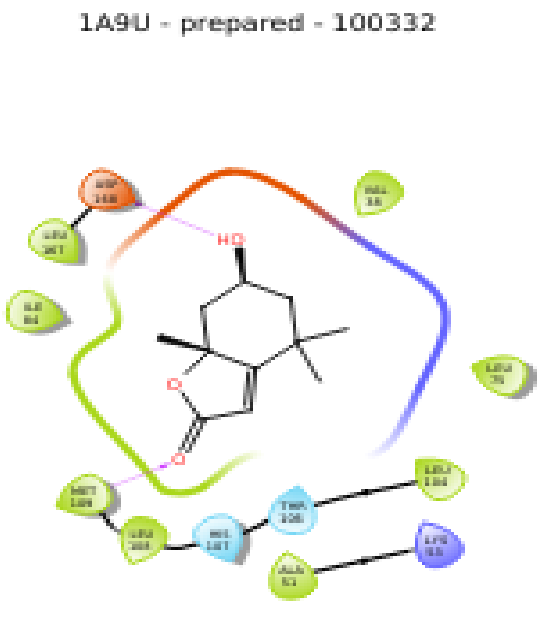


Fig:2

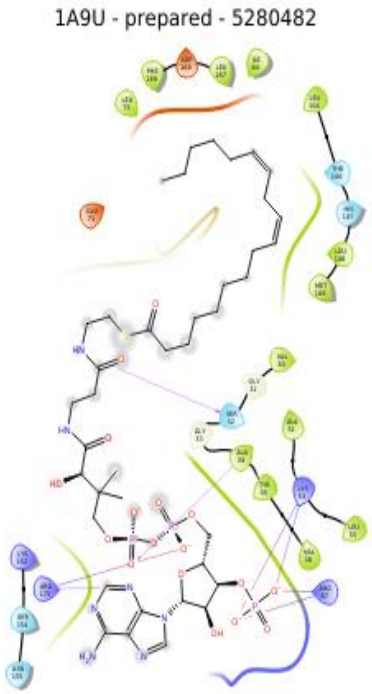


Fig:3

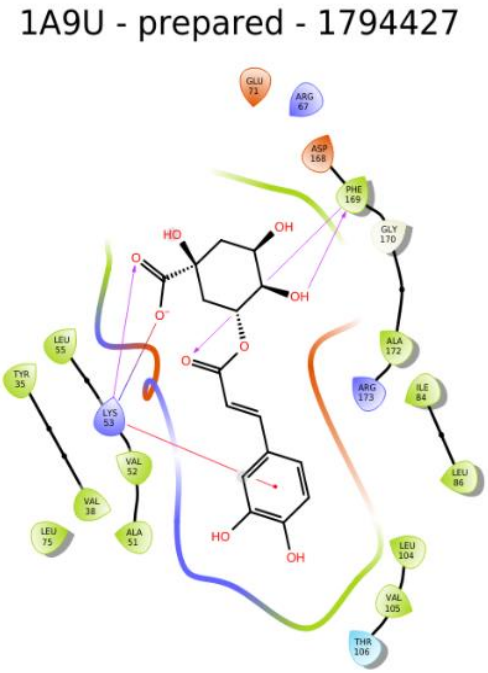


Fig:4

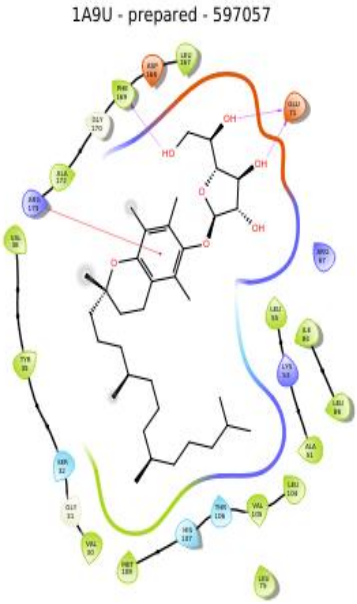
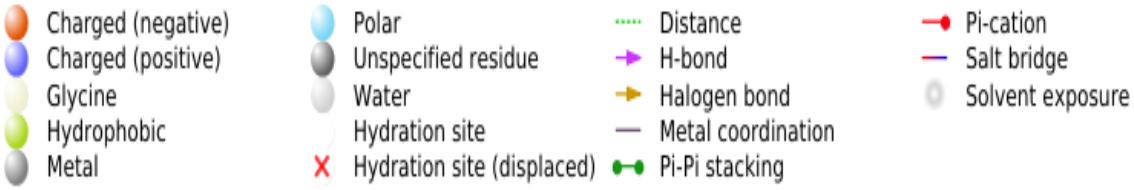


Fig:5



MD SIMULATION

The molecular dynamics simulation was carried out for the protein MAPK14 and Alpha-Tocopherol-beta-D-mannoside. For evaluate the structural constancy of those molecules with the help of Desmond. The final

trajectory files were taken for calculating the RMSD of the complex structures. At the same time as running MD simulation for MAPK14 protein and Alpha-Tocopherol-beta-D-mannoside for 10 ns, the RMSD (Root Mean Square Deviation) plot shows the stability of the complex structures. The period and the constant potential energy stable at 1.2 ns to 10 ns. In addition, when performing the simulation for 10 ns, and it makes the stability of the complex structure during the entire simulation time up to 10 ns Figure 6

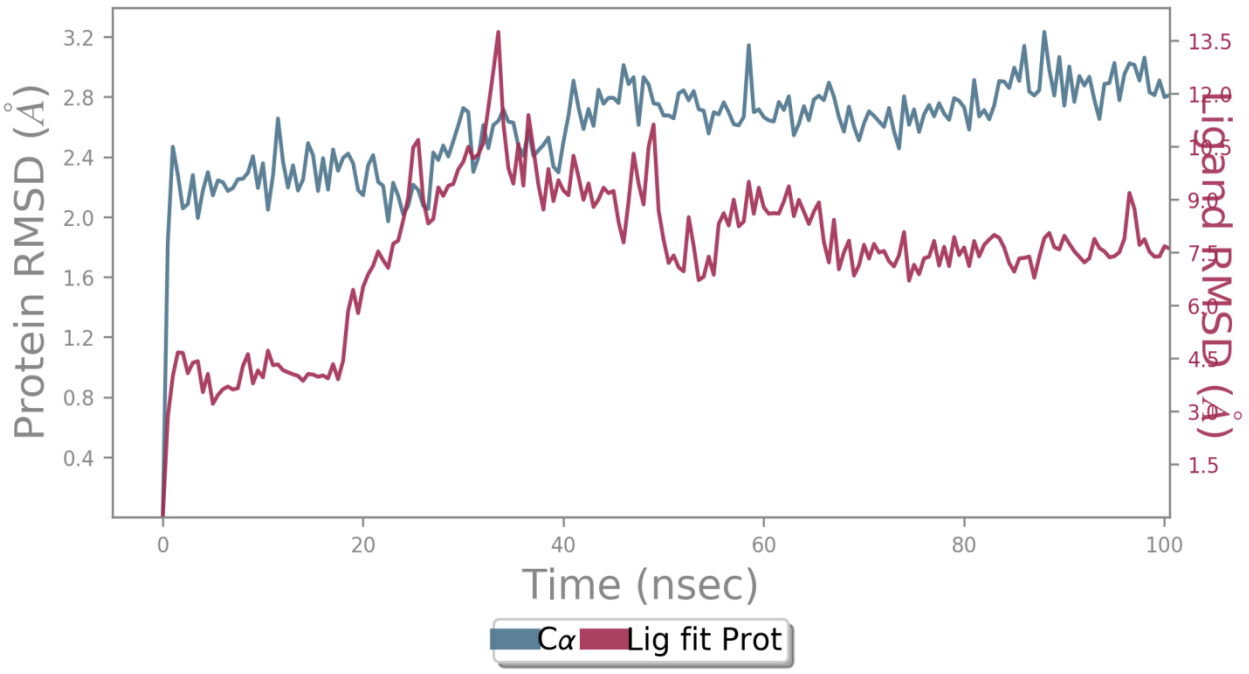


FIG :6 Protein-Ligand RMSD

RESULTS AND DISCUSSION

Results are summarized in Tables 1, 2, and 3 and Figs. 1, 2, 3, and 4. The results revealed that the MAPK14 inhibitory property of the compounds of *Merremia emarginata*(Burm.F) greatly depended on the chemical nature of the substituents. The chemical structures of selected major bioactive constituents of *Merremia emarginata*(elikathukeerai). The docking studies of the ligands to protein active sites were performed by an advanced molecular docking program Glide module of Schrodinger suite 2019 Maestro-12.2 version for determining the binding affinities of the compounds. The designed analogs were docked towards the MAPK14 P38 Kinases (PDB ID;1A9U) to ascertain their inflammatory activity. The analogs have a meansquare difference (RMSD) value of 0.2. The results are summarized in Table 1. Almost all the compounds are docked in the same binding pocket. The 2D-ligand interaction diagrams of quinicacid,(-)-Loliolide,alpha-Tocopherol-beta-D-mannoside,Ethyl(9Z,12Z)-9,12-Octadecadienoate,chlorgenic acid with MAPK14 P38 kinases (PDB ID 1A9U) are given in Fig. 1. From the molecular docking study, it was revealed that the ligands have shown Glide G score values from –0.72kcal/mol (hexadecenoic acid, ethyl ester) to–7.80 kcal/mol (Chlorogenic acid).The ligands have shown agreeable Glide scores of 7.80 kcal/mol (chlorogenic acid),-7.05 kcal/mol (ethyl 9,12,-octadecadienoate), -6.82(alpha-Tocopherol-beta-D-mannoside),-3.97kcal/mol(quercetin)when compared to the other phytoconstituents. Molecular docking was additionally assessed MMGBSA-free restricting vitality which

is identified with the post-scoring approach forMAPK14 P38 Kinases (PDB ID 1A9U) target and the values are shown in Table 3.

The ADMET screening for the molecules can be predicted in-silico by using the qikprop module of the Schrodinger suite 2019-4. The results of the ADMET properties for compounds are shown in Table-2. FromTable-2, Insilco ADMET screening results of most of the compounds are within the recommended values. The molecular weight is between 103.1 and 1029.9. The evaluated number of hydrogen bond donors of the molecules is in the range of 1-7. The evaluated number of hydrogen bond acceptors of most of the compounds is in the range of 1–28.1.Most of the compounds have QPlogP valuesbetween -1.24 and 9.70. Several likely metabolites of the compounds are in the range of 0-9. The number of violations of Lipinski's rule of five is 0-3. The compounds have % Human oral absorption in the scope of 0-100%.So, from the in-silico ADMET screening results of most the compounds are within the recommended values except few parameters of some compounds. Molecular docking was additionally assessed with MM-GBSA free restricting vitality which is identified with the post-scoring approach for MAPK14 (PDB ID: 1A9U) target and the values are shown in Table 3. The accuracy of docking is confirmed by examining the lowest energy poses predicted by the scoring function. The Glide score and MM-GBSA free energy retained by the docking of ligands into the coupling pocket are more stable. In the results of docking the compound chlorogenic acid have the highest Gscore(-7.80) but its human oral absorption rateislow (16.78 %) and another compound Ethyl(9Z,12Z)-9,12-Octadecadienoate also has ahigh'sGscore (-7.05) but its oral absorption rate is 0%.By the results of molecular docking shown intable-1and 2, the quercetin compounds have shown anGscore (-3.97kcal/mol) and human oral absorption rate (51.9%) the Alpha-Tocopherol-beta-D-mannosidehave shown the most agreeable Gscore(-6.8kcal/mol) and also showedresults in between the recommended value.

CONCLUSION

The results of the docking study that the phytoconstituents of *Merremia emarginata* demonstrated better arrangement at the dynamic site of the MAPK14 P38 Kinase. The in-silico structuring strategy embraced in the present investigation helped in recognizing some lead molecules such as quercetin and chlorogenic acid and determination like in vivo and in vitro assessments. Results from the in-silico study revealed that many of the phytoconstituents of *Merremia emarginata* may be used fully against MAPK14 and produce anti-inflammatory action.

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