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In Silico Identification of Promising IL-6 Inhibitors Among Natural Derivatives: A Docking, MM-GBSA and ADMET Study

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KEYWORDS

Docking, ADMET, MMGBSA, Tubericidin

ABSTRACT:

Interleukin-6 (IL-6) is recognized as a B cell stimulation factor that promotes the transformation of effector B cells into antibody-producing cells. The association between the disruption of IL-6 signalling and the onset of several illnesses, such as psoriasis, has been established. Presently, therapeutic agents that suppress IL-6, such as siltuximab, have been identified and are used to manage several persistent inflammatory disorders. Notwithstanding the well-documented advantages linked to monoclonal antibody treatment, it is crucial to recognize that these biological agents also exhibit significant limitations, such as their high prices. Objectives: The objective of this study was the identification of natural derivatives that exhibit strong binding affinity against IL-6. Methods: In order to achieve the objective, docking, MMGBSA, and ADMET investigations were conducted. Molecular docking was performed on the library of natural derivatives using Schrodinger's Glide tool, explicitly targeting IL-6. The Prime-MMGBSA approach was used to determine the binding free energy of selected natural derivatives. In-silico ADMET profiling was performed using the pkCSM web server. Results: Several natural derivatives had exceptional docking scores, suggesting their potential to serve as anti-IL-6 agents. Our result indicated Shikimic acid, Indole-3-butyric acid, and Tubericidin exhibited docking scores below -5.2. Additionally, these compounds exhibited exceptional drug-like features. Conclusions: This work identifies the possible inhibitory effects of several natural derivatives on IL-6. Shikimic acid, Indole-3-butyric acid and Tubericidin have a high binding affinity and favourable ADMET profile, thus making them potential potent inhibitors of IL-6. However, further in-vitro and in-vivo study is required.

1. Introduction

Inflammation plays a crucial role in eliminating pathogens and safeguarding against infection. Consequently, pro-inflammatory cytokines serve as regulators of the host's reactions to infection, inflammation, and trauma. However, it is essential to note that these cytokines also exacerbate illness in pathological settings [1]. The pro-cytokines include tumour necrosis factor (TNF), interleukin (IL)-1, IL-6, and interferon (IFN)-γ [2].

In 1986, IL-6 was recognized as a B cell stimulation factor that promotes the transformation of effector B cells into antibody-producing cells, sometimes referred to as IFN-β2 [3]. IL-6 is a 22 kDa polypeptide consisting of 185 amino acids [4]. IL-6 is produced primarily by immune cells, such as dendritic cells, macrophages, and mast cells, along with B cells. Furthermore, some CD4 effector T helper (Th) cells also contribute to the production of IL-6 to a lesser degree. IL-6 is also produced by a diverse range of non-leukocytes, including endothelial cells, astrocytes, fibroblasts and epithelial cells [5]. The activation of IL-6-type cytokines occurs via the gp130 signalling probe, which is a transmembrane protein present in the majority of cytokine receptor systems. This activation triggers the Janus family of tyrosine kinases (JAKs), which include JAK2, Tyk2, and JAK2. The association between interleukin-6 (IL-6) and gp130 is established via an IL-6-specific receptor known as IL-6R. The IL-6R and gp130 extracellular domains form a functional hexameric signalling complex with IL-

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6 on target cells. This complex then binds to JAK proteins, therefore initiating downstream signalling pathways. IL-6 has two distinct mechanisms of action: cis and trans. The phenomenon of classical (cis)-signalling is limited to cells that express the membrane-bound IL-6 receptor (mIL-6R), which is known to possess homeostatic and anti-inflammatory properties. Conversely, in the process of IL6 trans-signalling, IL6 interacts with a soluble IL6 receptor (sIL6R) and exhibits deleterious pro-inflammatory properties [6], [7], [8].

The development of several diseases, including psoriasis, diabetes, spondylitis, and multiple sclerosis, is linked to the disruption of IL-6 signalling [9], [10]. Elevated levels of IL-6 have been seen in individuals who have rheumatoid arthritis (RA) [11], [12]. There have been reports indicating that individuals experiencing depression have elevated levels of IL-6 [13].

Currently, IL-6 inhibitors, including siltuximab, tocilizumab, and sarilumab, have been discovered and are employed for the treatment of a number of chronic inflammatory conditions. Furthermore, the inhibition of IL-6 signaling by the direct inhibition of the association between IL-6R and IL-6 has been found to mitigate the advancement of cytokine storm in COVID 19 effectively. Despite the documented benefits associated with monoclonal antibody therapy, it is essential to acknowledge that these biological agents also possess significant drawbacks. These include the high cost, requirement of IV administration, and the potential for eliciting robust immune responses [6]. In contrast, utilizing natural products for therapy has many notable benefits, such as easier oral delivery, potential enhancement of pharmacokinetic characteristics, reduced treatment expenses, increased control, and decreased toxicity [14], [15], [16]. The use of oral bioavailability has notable advantages in relation to accessibility, adherence, and extensive usage, making this therapeutic approach more appropriate for prolonged periods of treatment. In recent times, several researchers have found a range of natural substances that serve as direct inhibitors of IL-6 [17]. This cheminformatics research was thus undertaken to investigate a range of potential natural compounds that might serve as safe and novel antagonists of IL-6.

2. Methods

2.1. Functional Protein Association Network

The functional protein association network was evaluated utilizing the STRING database, which gathers, assesses, and aggregates all publicly accessible databases of protein-protein interaction data, supplemented by computational projections [18], [19].

2.2. Molecular Docking Studies

2.2.1. Protein Preparation

The crystal structure of the extra-cellular domains of human interleukin-6 receptor alpha chain (PDBID 1N26) was retrieved from the protein databank (https://www.rcsb.org/) [17]. The protein preparation wizard within the Glide program (Schrödinger Release 2021-1: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY, 2021) was used to rectify certain deficiencies in the downloaded protein [20].

2.2.2. Ligand Preparation

The Enzo Lifesciences library (https://www.enzolifesciences.com), which contains over 500 compounds (BML-2865), was downloaded. The ligands in the library were then processed using the LigPrep module in the Schrödinger suite (Schrödinger Release 2021-1: LigPrep, Schrödinger, LLC, New York, NY, 2021). [21], [22].

2.2.3. Active Site Prediction

The binding site of the protein (PDB ID 1N26) was determined using the SiteMap program from the Schrodinger suite (Schrodinger Release 2021-1: SiteMap, Schrodinger, LLC, New York, NY, 2021) using the default settings [23], [24].

2.2.4. Virtual Screening

The docking of prepared ligands on the most optimal active site, as predicted by SiteMap, was conducted using the Glide module at XP setting. The resulting output was configured as a pose viewer (PV) file and subsequently visualized using the pose viewer tool.[25].

2.3. Screening of Absorption, Distribution, Metabolism, Elimination, Toxicity (ADMET) Indices

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The ADMET properties of the most prominently docked compounds were assessed via the pkCSM (http://biosig.unimelb.edu.au/pkcsm/). [26].

2.4. Molecular mechanics-generalised born surface area (MM-GBSA) Assessment

The ligand-receptor complexes' binding free energy was calculated using Prime's MM-GBSA component. The XP dock PV file serves as the data source for this calculation. The relative energies of the complex were evaluated using the VSGB solvation method and the OPLS3 force field. The binding free energy may be calculated using Equation (1). [27].

$$\Delta G_{(bind)} = G_{complex} - G_{protein} - G_{ligand} \quad (1)$$

where

$G_{complex}$= protein–ligand complex energy

$G_{protein}$= protein energy

G_{ligand}= ligand energy

3. Result and Discussion

3.1. Functional Protein Association Network Analysis

IL-6 performs a crucial function in the immune response, exerting its impact via sophisticated signalling pathways. When IL-6 binds to its receptor, it triggers a series of processes that include the Interleukin-6 Receptor (IL6R) and Cytokine Family Signal Transducer (IL6ST), which is also referred to as gp130. As a result of this association, the tyrosine-protein kinases JAK1 and JAK2 are activated. Following this, the activation of downstream signalling pathways occurs, resulting in the control of diverse immunological responses. IL-6 exhibits unique functionalities in comparison to other interleukins such as IL-2, IL-3, IL-10, and IL-1β. However, it can engage in complex interactions with these interleukins, hence exerting an influence on immune cell proliferation, differentiation, and cytokine production [3], [4], [8]. The relevance of IL-6 in regulating immunological responses and maintaining immune homeostasis is underscored by the complicated network of interactions it involves. The co-expression assessment was performed using the STRING web server, which yielded co-expression scores derived from the RNA expression patterns and protein coregulation recorded by Proteome HD (Fig.1). The functional partners of the IL-6 protein were predicted with a high level of confidence (score ≈ 1) including IL2, IL-6, L6ST, Interleukin-6 Receptor (IL6R), IL-3, IL-10, IL-1β, JAK1 and JAK2 (Fig.1). Regardless of the extensive studies demonstrating the role of IL-6 in immunity and inflammation via its interactions with other proteins, there is a scarcity of safe and cheap IL-6 inhibitors. Hence, the objective of this work was to ascertain the potential of natural derivatives as inhibitors of IL-6.

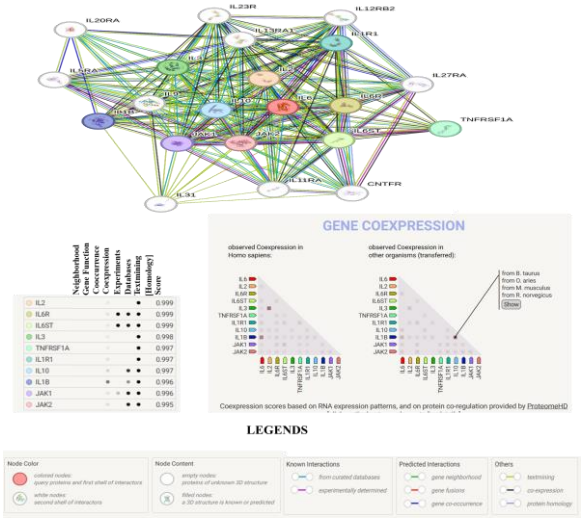

Fig. 1. Analysis of co-expression and protein-protein networks.

The protein-protein network and co-expression study of IL-6 was performed using STRING. The highlighted edges depict several kinds of evidence used to predict the correlations.

3.2. Virtual Screening of natural compounds

The crystal structure of IL-6 (PDBID: 1N26), which was obtained from the Protein Data Bank, was first visualized using the Schrödinger suite's Maestro module (Fig. 2A). The obtained protein was subsequently processed using the protein preparation wizard (Fig. 2B). The active site of the processed protein was found using the SiteMap module of the Schrodinger suite. Using SiteMap, four potential active sites were identified, and site 1 was used for screening (Fig. 3). Following a successful docking, several metrics were obtained, including the docking score, glide evdw (Van Der Waals energy), glide ecol (Coulomb energy), glide energy (Van Der Waals energy + Coulomb energy) and hydrogen bonds against IL-6.

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Docking scores were used to investigate and evaluate the ligands' binding affinities with IL-6. The docking scores of numerous compounds were less than -5, but only the 33 compounds with the highest scores were chosen for additional analysis (Table 1).

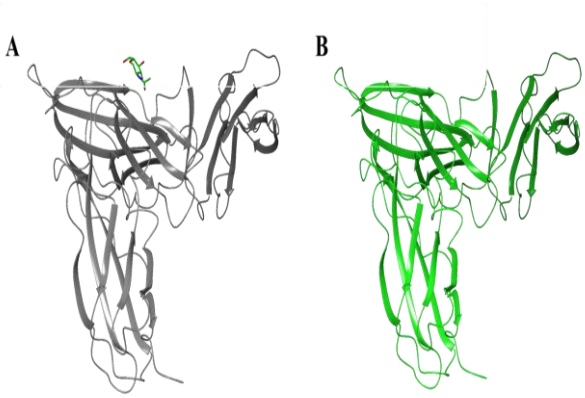


Fig. 2. **Human IL-6**. (A) Structure of IL-6 (PDBID: 1N26) downloaded via Protein Data Bank (B) Preprocessed IL-6 structure.

All the chosen natural compounds i.e. (-)-Epigallocatechin gallate, Kanamycin sulfate, Amygdalin, Marein, Isorhamnetine-3-glucoside, Myricitrin, Vitexin, Streptozocin, Naringenin-7-O-glucoside, Rosmarinic acid, Maritimein, Quercitrin, Shikimic acid, Piceatannol, Eriodictyol, Butein, trans-3-Indoleacrylic acid, Lavendustin A, Myricetin, (+)-Taxifolin, Rhamnetine, Fisetin, Luteolin, Phlorizin, Homoorientin, Indole-3-butyric acid, Dihydrorobinetine, Aucubin, Carminic acid, Eriodictyol-7-O-glucoside, Chlorogenic acid, Tubericidin and Caffeic acid possess docking score in between -7.4 to-5.4. Covalent energy, Van Der Waals energy and hydrogen bonds are essential components in the optimal binding affinity of the chosen natural derivatives, according to docking studies. The 3D and 2D docking poses revealed that PRO121 and LYS 126 play a substantial role in ligand binding to IL-6 (Fig. 4-5).

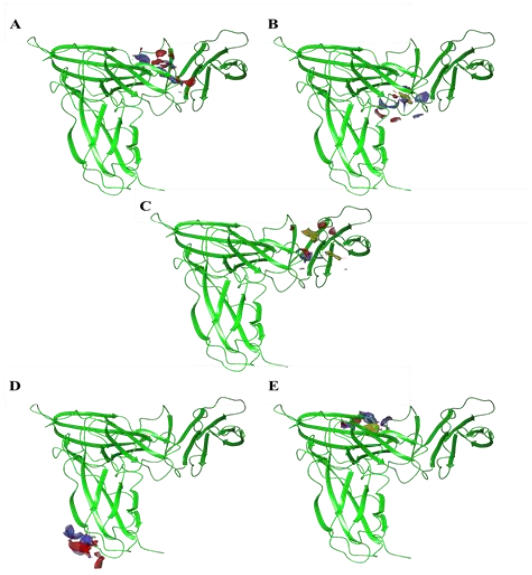
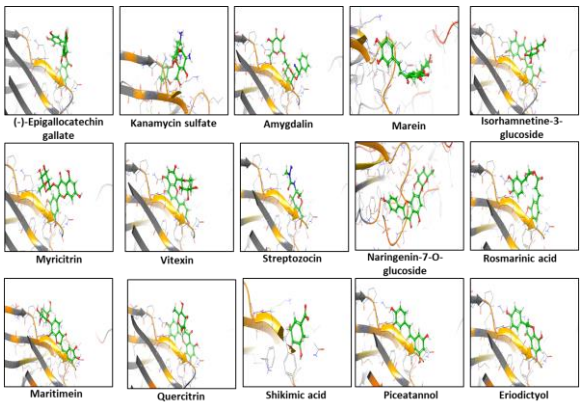


Fig 3. Binding Sites obtained through SiteMap. 5 potential active sites obtained via SiteMap

3.3. MM-GBSA calculations

The best docked natural derivatives were subjected to MM-GBSA calculations in order to get further confirmation. The congeneric series of ligands is ranked by MM-GBSA according to their free energies [28]. Table 3 displays the comparative binding free energy (G_{bind}) of the selected natural derivatives, as computed using the prime module. The best docked molecules have a binding free energy within the range of -30.4 to -65.4 kcal/mol, suggesting an optimal affinity of best docked molecules against IL-6.



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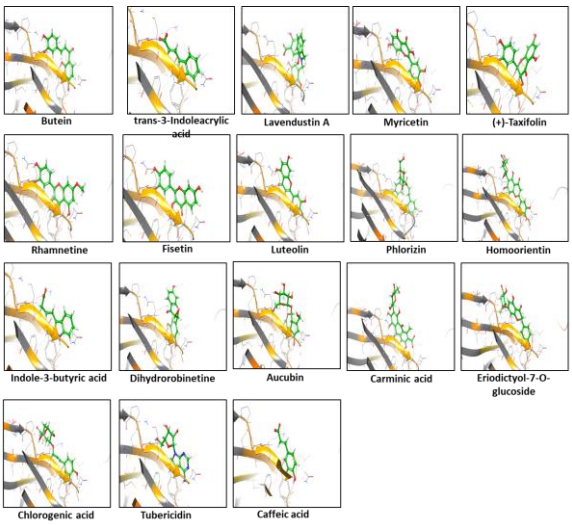

Fig. 4. 3D docking poses of top docked natural derivatives with IL-6.

3.4. ADMET Assessment

ADMET studies play a critical role in drug discovery and development. These studies assist in identifying a drug's drug-like characteristics. Up to 50% of pharmaceutical candidates are estimated to fail due to inadequate effectiveness, with up to 40% failing due to previous toxicity. Phenylpropanolamine hydrochloride and mibefradil have been withdrawn from the marketplace due to toxicity or drug-drug interactions. Regulators and pharmaceutical companies have recognized that ADME/Tox studies are expected to influence drug candidates' overall quality and likelihood of success in the following phases, as well as their pharmacological attributes. Because the result is so critical, these trials are being conducted early in the drug development process. Because extensive and expensive ADMET experimental techniques cannot be performed for every chemical, in silico ADMET prediction is currently the preferred strategy for early drug development. High-quality in-silico ADMET model development has enabled the simultaneous analysis and optimization of chemical efficacy and druggability properties. pkCSM is one of the open-source web servers used for ADMET profiling.

The molecular weight of a drug has a substantial influence on its oral bioavailability (preferably 500 or less) [29].. With the exception of Kanamycin sulphate, all of the chosen natural derivatives possessed molecular weights below 500. With the exception of Streptozocin, Amygdalin, Chlorogenic acid, Carminic acid and Kanamycin sulphate, all natural derivatives exhibit intestinal absorption rates exceeding 30%, indicating favorable oral bioavailability. Additionally, knowledge of the manner in which

compounds interact with cytochromes P450 (CYP) is vital. Drug clearance occurs through the metabolic biotransformation facilitated by CYP isoenzymes. (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). These isoforms are involved in the metabolism of approximately fifty to ninety percent of modern pharmaceuticals. Without a doubt, the inactivation of these isoenzymes is a significant factor in pharmacokinetics-related drug interactions; diminished clearance may result in toxic or other undesirable side effects [30].

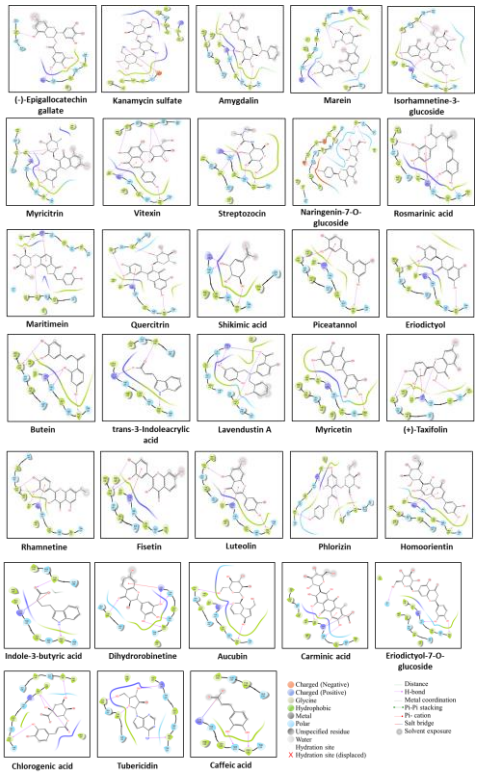

Fig. 5. 2D docking poses of top docked natural derivatives with IL-6.

The absence of inhibitory activity against CYP2D6, CYP2C9, or CYP3A4 in the selected compounds indicates a favourable safety profile. With the exception

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of (-)-Epigallocatechin gallate, Piceatannol, Eriodictyol, Butein, Lavendustin A, Myricetin, Rhamnetine, Fisetin, Luteolin and Dihydrorobinetine, all of the selected natural derivatives does not exhibit CYP inhibitory property. The renal uptake transporter known as Organic Cation Transporter 2 (OCT-2) is responsible for managing the renal clearance and elimination of drugs and endogenous substances [31]. The concomitant administration of OCT-2 inhibitor and substrate could end in adverse pharmacological interactions. The ADMET profile showed that none of the selected substances could be carried by OCT-2, suggesting a reduced possibility of adverse reactions. The Ames toxicity test is a computer-based technique that evaluates a chemical compound's potential for mutagenicity by using prediction models [32]s. The pkCSM investigation indicates that most of the selected natural derivatives are negative for AMES. Moreover, one of the primary reasons for drug development prescription withdrawals is heart toxicity. One typical mechanism of cardiotoxicity is drug binding to the cardiac potassium channel encoded by the human ether-a-go-go gene (hERG), which leads to long QT syndrome and, eventually, sudden death [33].. Based on pkCSM analysis of the molecules, most of the selected compounds does not have hERG I/II inhibitory properties with the exception of (-)-Epigallocatechin gallate, Isorhamnetine-3-glucoside, Myricitrin, Vitexin, Quercitrin, Lavendustin A, Fisetin, Luteolin and Homoorientin suggesting a lower risk of cardiac toxicity. A p-glycoprotein (pgp) substrate is a compound that facilitates drug absorption, drug excretion, and other vital processes facilitated by the P-glycoprotein transporter. Such activities may result in physiological alterations or modifications in the physiological responses to different drugs. P-glycoprotein is a transporter that has been the subject of extensive research due to its role in drug resistance and drug-drug interactions. Most of the selected natural derivatives have the potential to act as pgp substrates, with the exception of Streptozocin, Shikimic acid, Indole-3-butyric acid and Tubericidin (Table 3). pkCSM analysis demonstrated that Shikimic acid, Indole-3-butyric acid Tubericidin had good drug-like attributes and could act as a safe and effective IL-6 inhibitors.

4. Conclusion

IL-6 is closely linked with immunity and inflammation. To gain preliminary insights into the functions of IL-6, we investigated interactions between IL-6 and various proteins, including JAK, as well as other cytokines, including IL-3, IL-10, and IL-1β, in the current study using STRING. Further, docking and MM-GBSA were utilized to a library of natural derivatives; 33 compounds with the highest docking scores (<-5.2) and good MM-GBSA binding energies (-30 kcal/mol) were chosen. Furthermore, ADMET profiling via pkCSM demonstrated that out of the 33 derivatives, only 3, namely Tubericidin, Shikimic acid, and Indole-3-butyric acid, demonstrated excellent drug-like properties and have the potential to function as a potent and safe inhibitor of IL-6. Nevertheless, further in vivo and in vitro investigations are necessary to validate these findings.

Data Availability Statement: Data will be available on request.

Conflicts of Interest: The authors declare no conflict of interest.

Funding Authors states that no funding is involved.

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35. Tables

Table 1 Docking indices assessment of natural derivatives using Glide

S.No	Compounds	Docking Score	glide evdw	glide ecoul	glide energy	XP HBond
1	(-)-Epigallocatechin gallate	-7.369	-24.177	-21.039	-45.216	-4.504
2	Kanamycin sulfate	-7.341	-22.342	-15.378	-37.719	-6.339
3	Amygdalin	-7.275	-24.714	-17.712	-42.426	-5.234
4	Marein	-7.235	-28.926	-15.818	-44.744	-4.113
5	Isorhamnetine-3-glucoside	-7.21	-23.812	-22.709	-46.521	-3.847
6	Myricitrin	-6.815	-29.089	-16.424	-45.513	-4.16
7	Vitexin	-6.666	-31.059	-12.799	-43.858	-3.342
8	Streptozocin	-6.647	-17.117	-14.694	-31.812	-4.283
9	Naringenin-7-O-glucoside	-6.636	-23.613	-8.149	-31.761	-3.162
10	Rosmarinic acid	-6.606	-26.049	-14.188	-40.237	-3.686
11	Maritimein	-6.414	-29.776	-11.332	-41.109	-3.59
12	Quercitrin	-6.296	-27.992	-15.678	-43.67	-3.659
13	Shikimic acid	-6.047	-14.867	-13.49	-28.357	-3.281
14	Piceatannol	-5.908	-18.415	-15.856	-34.272	-3.025
15	Eriodictyol	-5.762	-21.428	-11.172	-32.601	-3.178
16	Butein	-5.761	-22.102	-16.795	-38.897	-3.249
17	trans-3-Indoleacrylic acid	-5.731	-17.329	-7.063	-24.391	-0.844
18	Lavendustin A	-5.718	-22.444	-19.024	-41.468	-2.879
19	Myricetin	-5.67	-28.592	-9.467	-38.06	-2.585
20	(+)-Taxifolin	-5.668	-25.917	-11.336	-37.254	-2.957

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21	**Rhamnetine**	**-5.654**	**-27.941**	**-9.761**	**-37.702**	**-2.88**
22	**Fisetin**	**-5.628**	**-25.968**	**-8.628**	**-34.596**	**-3.282**
23	**Luteolin**	**-5.618**	**-23.737**	**-9.895**	**-33.632**	**-2.315**
24	**Phlorizin**	**-5.616**	**-18.487**	**-20.206**	**-38.692**	**-3.378**
25	**Homoorientin**	**-5.611**	**-29.403**	**-10.818**	**-40.221**	**-2.94**
26	**Indole-3-butyric acid**	**-5.575**	**-16.234**	**-8.744**	**-24.978**	**-1.602**
27	**Dihydrorobinetine**	**-5.533**	**-20.619**	**-14.891**	**-35.509**	**-3.075**
28	**Aucubin**	**-5.529**	**-22.909**	**-11.863**	**-34.772**	**-2.438**
29	**Carminic acid**	**-5.481**	**-31.651**	**-8.84**	**-40.491**	**-3.237**
30	**Eriodictyol-7-O-glucoside**	**-5.457**	**-33.258**	**-8.932**	**-42.19**	**-2.4**
31	**Chlorogenic acid**	**-5.452**	**-28.277**	**-7.587**	**-35.864**	**-2.2**
32	**Tubericidin**	**-5.42**	**-17.879**	**-12.945**	**-30.824**	**-2.218**
33	**Caffeic acid**	**-5.409**	**-14.673**	**-13.864**	**-28.536**	**-2.784**

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Table 2 MMGBSA assessment of top docked natural derivatives using Prime

S.No	Compounds	MMGBSA ΔG_{Bind}	MMGBSA ΔG_{Bind} Coulomb	MMGBSA ΔG_{Bind} Covalent	MMGBSA ΔG_{Bind} H bond
1	**(-)-Epigallocatechin gallate**	-54.08	-39.24	6.72	-2.51
2	**Kanamycin sulfate**	-50.38	17.77	0.21	-2.08
3	**Amygdalin**	-50.34	-19.94	2.49	-2.58
4	**Marein**	-61.58	-19.57	9.21	-1.54
5	**Isorhamnetine-3-glucoside**	-57.34	-45.63	5.1	-1.89
6	**Myricitrin**	-59.07	-26.71	2.34	-1.95
7	**Vitexin**	-63.28	-29.01	3.81	-1.11
8	**Streptozocin**	-30.42	-5.58	4.17	-2.46
9	**Naringenin-7-O-glucoside**	-65.36	-8.48	7.07	-0.55
10	**Rosmarinic acid**	-53.25	-42.88	5.67	-3.98
11	**Maritimein**	-57.26	-23.24	3.37	-1.31
12	**Quercitrin**	-60.33	-33.43	4.3	-1.44
13	**Shikimic acid**	-34.29	-40.84	-0.84	-1.43
14	**Piceatannol**	-50.67	-31.49	4.89	-0.87
15	**Eriodictyol**	-35.54	-14.94	5.7	-1.33
16	**Butein**	-53.04	-36.31	5.21	-1.55
17	**trans-3-Indoleacrylic acid**	-31.45	-42.61	1.78	-1.25
18	**Lavendustin A**	-43.56	-46.05	9.78	-4.09
19	**Myricetin**	-38.83	-13.65	3.99	-1.07
20	**(+)-Taxifolin**	-44.7	-21.51	1.61	-1.54
21	**Rhamnetine**	-48.16	-21.92	2.48	-0.99
22	**Fisetin**	-43.56	-18.77	2	-1.31
23	**Luteolin**	-47.64	-17.86	3.07	-0.87

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24	**Phlorizin**	-55.97	-53	4.1	-3.35
25	**Homoorientin**	-48.76	-18.94	4.52	-1.42
26	**Indole-3-butyric acid**	-36.72	-37.67	4.66	-2.82
27	**Dihydrorobinetine**	-40.36	-23.93	3.5	-1.61
28	**Aucubin**	-54.34	-17.09	6.57	-1.43
29	**Carminic acid**	-45.51	-39.79	3.72	-1.39
30	**Eriodictyol-7-O-glucoside**	-49.05	-12.17	8.51	-0.85
31	**Chlorogenic acid**	-51.16	-23.54	6.47	-1.31
32	**Tubericidin**	-34.03	-19.92	4.35	-2.25

Table 3 ADMET attributes of top docked natural derivatives using pkCSM

S.No	**Compounds**	MW	**IA (%)**	**Pgp substrate**	**BBB Permeability**	**CYP1A2/ CYP2C19/ CYP2C9/ CYP2D6/ CYP3A4 Inhibition**	**Renal OCT2 Substrate**	**AMES Toxicity**	**hERG I/II Inhibition**
1	**(-)-Epigallocatechin gallate**	458.4	48.93	Yes	-2.078	Yes	No	Yes	Yes
2	**Kanamycin sulfate**	582.6	0	Yes	-2.316	No	No	No	No
3	**Amygdalin**	457.4	18.329	Yes	-1.122	No	No	No	No
4	**Marein**	450.4	35.273	Yes	-1.468	No	No	Yes	No
5	**Isorhamnetine-3-glucoside**	478.4	41.984	Yes	-1.797	No	No	Yes	Yes
6	**Myricitrin**	464.4	46.034	Yes	-2.064	No	No	Yes	Yes
7	**Vitexin**	432.4	56.53	Yes	-1.671	No	No	Yes	Yes
8	**Streptozocin**	265.2	17.794	No	-1.332	No	No	Yes	No

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9	**Naringenin-7-O-glucoside**	434.4	47.31	Yes	-1.237	No	No	Yes	No
10	**Rosmarinic acid**	360.3	51.68	Yes	-1.511	No	No	No	No
11	**Maritimein**	448.4	42.709	Yes	-1.339	No	No	Yes	No
12	**Quercitrin**	448.4	50.075	Yes	-1.777	No	No	Yes	Yes
13	**Shikimic acid**	174.2	33.015	No	-0.874	No	No	No	No
14	**Piceatannol**	244.2	88.674	Yes	-0.834	Yes	No	No	No
15	**Eriodictyol**	288.3	76.141	Yes	-0.939	Yes	No	Yes	No
16	**Butein**	272.3	79.842	Yes	-0.92	Yes	No	No	No
17	**trans-3-Indoleacrylic acid**	187.2	91.208	Yes	0.106	No	No	No	No
18	**Lavendustin A**	381.4	58.227	Yes	-1.237	Yes	No	No	Yes
19	**Myricetin**	318.2	65.877	Yes	-1.694	Yes	No	Yes	No
20	**(+)-Taxifolin**	304.3	59.995	Yes	-1.234	No	No	Yes	No
21	**Rhamnetine**	316.3	81.02	Yes	-1.367	Yes	No	No	No
22	**Fisetin**	286.2	85.456	Yes	-1.114	Yes	No	No	Yes
23	**Luteolin**	286.2	84.392	Yes	-1.151	Yes	No	No	Yes
24	**Phlorizin**	436.4	45.998	Yes	-1.304	No	No	Yes	No
25	**Homoorientin**	448.4	39.448	Yes	-2.045	No	No	Yes	Yes
26	**Indole-3-butyric acid**	203.2	91.047	No	0.001	No	No	No	No
27	**Dihydrorobinetine**	304.3	62.862	Yes	-1.251	Yes	No	Yes	No
28	**Aucubin**	346.3	33.458	Yes	-0.994	No	No	No	No
29	**Carminic acid**	492.4	1.933	Yes	-2.266	No	No	Yes	No
30	**Eriodictyol-7-O-glucoside**	450.4	40.066	Yes	-1.443	No	No	Yes	No

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31	**Chlorogenic acid**	354.3	17.157	Yes	-1.443	No	No	No	No
32	**Tubericidin**	266.3	60.093	No	-1.168	No	No	No	No
33	**Caffeic acid**	180.2	55.525	Yes	-0.836	No	No	No	No