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Towards the development of natural product based anti-inflammatory therapy: Computational investigations to identify selective inhibitors

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***Abstract*---**Background: Jasminum grandiflorum is a medical plant widely used in Ayurvedic herbal medicines in India. This plant is host to very novel medicinal potential molecules such as iridoids. Flavonoids and other small molecules are also elaborated by this plant. The present study was aimed to understand the computational inhibition of phytochemicals of Jasminum grandiflorum against anti-inflammatory molecular targets. Methods: The iridoids, flavonoids and all small molecules of Jasminum grandiflorum were categorized and subjected to molecular docking using Glide (Schrödinger Software suite) to assess the in silico anti-inflammatory potential of the compounds with molecular targets like COX1, COX2 and Prostaglandin E synthase (mPGES-1). Results: Among the tested compounds, the iridoids namely 10-hydroxy- ligstroside and 8-dehydroxy shanzhiside, the flavonoid butin-7-O-β-D-glucopyranoside and small molecules oleacein and 2-(3,4-dihydroxyphenyl)ethanol are predicted to exhibit high anti-inflammatory properties due to their low binding energy and high docking score. The bioactive compounds of Jasminum grandiflorum have good binding interaction with targeted protein. Conclusion: The overall revelation is that the targets 5WBE, 3NTG are inhibited by most of the compounds but more effectively by those with the 3', 4' dihydroxy phenyl group in the flavonoidal compounds and 3,4 dihydroxy phenyl ethyloxy group

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conjoint with secoiridoid moiety and an iridoid moiety. This study validates the involvement of iridoid and secoiridoid moieties and the dihydroxyl phenyl system in the interaction with anti-inflammatory target proteins.

Keywords---jasminum grandiflorum, iridoids, flavonoids, small molecules, anti-inflammatory, in silico, docking score.

Introduction

Inflammation is a complex biological response of our immune system occurring as a result of microbial infection, tissue necrosis and exposure to irritants (Sherwood and Toliver-Kinsky 2004) During inflammation, our immune cells produce certain inflammatory modulators (interleukins, NO, ROS, prostaglandin E2 and cytokines) to recover the damaged cells (Wang et al. 2019). However, the process of inflammation under certain circumstances can become more harmful and lead to the development of severe pathological conditions. Consistent inflammatory conditions lead to chronic inflammatory disorders, autoimmune diseases, diabetes, cancer, asthma, cardiovascular and neurodegenerative diseases (Furman et al. 2019) The suppression of immune modulators is an attractive therapeutic strategy to overcome inflammatory diseases (Kanterman et al. 2012). Traditionally nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat mild to moderate inflammatory conditions (Robb et al. 2020; Jordan et al. 2020; Sylvester 2019). It was witnessed that there are a variety of NSAID's approved by US-FDA in recent years that directly target the function of cyclooxygenase enzymes (COX-1 and COX-2). COX-1 and COX-2 are the enzymes involved in the production of prostaglandin (Abdelall et al. 2019). Prostaglandin endoperoxide H synthase-1 and -2 are the cyclooxygenases involved in the conversion of free arachidonic acid into prostaglandin H2. NSAIDs get directly bound to the active site of these enzymes to prevent the formation of prostaglandin H2 (Cingolani et al. 2017). However, the administration of NSAIDs is associated with several unpredictable effects and post therapeutic effects. This seems to be very common when considering the allopathic practices, and it required further efforts towards the development of successive anti-inflammatory drug candidates. To avoid these issues, biological resources, especially medicinal plants are being explored for their anti-inflammatory potential since long.

Jasminum is a common genus of flowering plants belonging to the *Oleaceae*, family and a widely used source of aromatic flowers (Joy and Raja 2008). There are more than 197 species recognized world-wide. Since ancient times the crude extracts or preparations of *Jasminum* are used to treat wide array of diseases (Balkrishna et al. 2021). *Jasminum grandiflorum* displays wider chemical diversity and is rich in iridoids, alkaloids, triterpenes and flavonoids (Chaturvedi et al. 2013). The phenolic compounds of *J. grandiflorum* are found effective against central nervous system (CNS) related enzymes (Ferreres et al. 2014) and act as a good antibacterial agent (Joy and Raja 2008). Over 72 bioactive metabolites were reported from the dichloromethane and n-butanol fractions of *J. grandiflorum* with the dominance of secoiridoids (El-Shiekh *et al.* 2021). The ethanolic extract of *J. grandiflorum* is proved to enhance wound healing by *in vivo* studies (Nayak

and Mohan 2007). The aerial parts of *J. grandiflorum* express anti-inflammatory activity (El-Shiekh et al. 2021). The present study was aimed to understand the computational inhibition of phytochemicals of *Jasminum grandiflorum* against anti-inflammatory molecular targets like COX1, COX2 and Prostaglandin E synthase (mPGES-1). Selective inhibition of COX1, COX2 and mPGES-1 is expected to provide a positive impact in controlling inflammatory response molecules.

Materials and Methods

Retrieval of Protein and Ligand Structures

The structure of all the compounds isolated and reported from *Jasminum grandiflorum* are represented in our earlier paper (Bharathi et al. 2020). From this array of compounds, a set of compounds flavonoids [F 1 to F 11], iridoids [I 1 to I 21] and small molecules [SM 1 to SM 8] were shortlisted as given in Table 1, Table 2 & Table 3 respectively. The 2D structures of the compounds were drawn in Chemdraw Profession 16.0 version to predict the molecular properties. The 3D structures of the compounds were drawn in Chem3D 16.0 version. The protein structures namely COX1 (5WBE), COX2 (3NTG) and mPGES-1 (4YL3) were retrieved from Protein Data Bank (PDB) (http://www.rcsb.org).

Table 1
Flavonoids Shortlisted for *in silico* Studies

Flavonoids	
Code	Ligand
F 1	Kaempferol-3,7-O-di-β-D-glucopyranoside
F 2	Kaempferol-3-O-(6"-O-acetyl)-β-D-glucopyranoside
F 3	Quercetin-3-O-sambubioside
F 4	Sulfurein
F 5	Butin-7-O-β-D-glucopyranoside
F 6	Acacetin-7-O(α-D-apiofuranosyl) (1→6)-β-D-glucopyranoside
F 7	Kaempferol-3-O-(2,6-di-rhamnosyl)glucoside
F 8	Quercetin-3-O-(2,6-di-rhamnosyl)glucoside
F 9	Quercetin-3-O-(6-rhamnosyl)glucoside
F 10	Kaempferol-3-O-α-L-rhamnopyranosyl(1→3)-[α-L-rhamnopyranosyl(1→6)]-β-D-galactopyranoside
F 11	Kaempferol-3-O-rutinoside

Table 2
Iridoids Shortlisted for *in silico* Studies

Iridoids	
Code	Ligand
I 1	Oleuropein

I 2	2"-Methoxy Oleuropein
I 3	(2"S)-2"-Methoxy oleuropein
I 4	Demethyl oleuropein
I 5	Ligstroside
I 6	Oleoside di-methyl ester
I 7	6-O-methy-Catalpol
I 8	Deacetyl asperulosidic acid
I 9	Aucubin
I 10	8-dehydroxy shanzhiside
I 11	Loganin
I 12	2''-epifraxamoside
I 13	Demethyl-2''-epifraxamoside
I 14	Jasminanhydride
I 15	7-ketologanin
I 16	Oleoside-11-methyl ester
I 17	7-glucosyl-11-methyl oleoside
I 18	8-epi-kingiside
I 19	10-hydroxy-oleuropein
I 20	10-hydroxy- ligstroside
I 21	Oleoside-7, 11-dimethyl ester

Table 3
Small Molecules Shortlisted for *in silico* Studies

Small Molecules	
Code	Ligand
SM 1	Olivil
SM 2	Oleacein
SM 3	2-(3,4-dihydroxyphenyl)ethanol
SM 4	3,5-dihydroxy-2,4-dimethyl-hexanoic acid 4-hydroxy phenyl ester
SM 5	2-hydroxymethyl-3-methyl-butyric acid phenyl ester
SM 6	cis-5-(2-Pentenyl) Pentanolide
SM 7	(Z)-Jasmone
SM 8	(Z)-methyl jasmonoate

Preparation of the Ligand

The ligand was prepared by LigPrep 6.4 module on Maestro 11.8 window. The retrieved structure of the selected compounds was used for the ligand preparation. Different structures of each input structure with different parameters were produced using the LigPrep (ionization states, tautomers stereochemistry and ring conformations). The process of addition and removal of atom, molecules and neutralizing charged groups was done in LigPrep. The bond

angle and bond orders were optimized using OPLS_2005 force field.

Preparation of the Protein

In Schrödinger suite, Maestro is the Graphical User Interface (GUI) that accepts a raw state protein *i.e.* incorrect bond order assignments, missing hydrogen atoms, orientations or charge states of different groups and alters the raw state protein to suitable structure for the calculations. The 3D structures of the proteins so obtained were used to prepare the protein using the protein preparation wizard. The prepared proteins were used further for the docking studies.

Generation of Glide receptor Grid

In the SiteMap module of the Schrödinger suite, the optimized and refined structure of the proteins was processed to specify the receptor site location. In the grid, the receptor shape and properties are represented by numerous sets of fields, which progressively give the ligand poses scoring more accurate scoring. SiteMap module produces the possible potential receptor binding sites with quantitative site-score values in the receptors for each site through optimizing the hydrophobicity, size, exposure, contacts, hydrophilicity, enclosure, and H-bond donor-acceptor balance. The generated grid files were used to dock the ligands.

Molecular Docking using Glide

Glide XP docking (Schrödinger, LLC, and New York-3) was carried out after constructing grid by selecting centroid of active site residues at the radius of 3Å that resulted from the sitemap. The default parameters were selected by keeping ligand flexible with docking calculations set as XP extra-precision. The formation of hydrogen bond between the ligand and the residues of the active site and its length along with Glide XP score were recorded. After docking, the protein and ligand were viewed in Glide posse viewer. Finally, the best docked poses images along with the docking scores were saved.

Results and Discussion

To identify the different interactions of phytochemical-based inhibitors of COX1, COX2 and mPGES-1, molecular docking studies were carried out using Schrödinger molecular docking tools. Post docking analysis revealed that most of the tested compounds fall within the binding pockets whereas the native ligands were found in the crystalline structure.

Molecular Interactions of Flavonoids

The results of interaction between the amino acid residues of COX1, COX2, mPGES-1 and chosen flavonoids are summarized in Table 4. A total of 11 flavonoids were docked against the molecular target of anti-inflammatory responders. Among the 11 flavonoids, only top hits with the least binding energy are presented in Fig. 1. The hydroxyl group present in the aromatic ring of butin-7-O-β-D-glucopyranoside (F 5) was found interacted with MET 508 of 3NTG by a single H-bond with the energy of -8.32 kcal/mol. Similarly, strong interactions of butin-7-O-β-D-glucopyranoside were observed for 5WBE with the amino acid

residues TYR 355, LEU 352, SER 530 with docking score of -9.96 kcal/mol. Exclusively, TYR 385 of 5WBE formed a salt bridge with aromatic carbon of butin-7-O-β-D-glucopyranoside. TYR 355 was present in the active site of COX1, which allowed to bind arachidonic acid to encourage the prostaglandin H2 production. A similar kind of interaction was observed for the mofezolac-COX1 complex with a single H-bond. Mofezolac is the well-known selective inhibitor of COX1. Similarly, hydrophophic interaction was observed for L352/TYR 385-mofezolac-COX1 complex (Cingolani et al. 2017).

In the present study, the observed interaction of butin-7-O-β-D-glucopyranoside was as similar as the interaction formed by the mofezolac-COX1 complex. This shows that butin-7-O-β-D-glucopyranoside might be acting as a selective inhibitor of COX1 function. There are four different H-bonds (THR 131, SER 127, ARG 126 and GSH 202) and salt bridge (TYR 130) that were formed between the quercetin-3-O-sambubioside (F 3) and active site of 4YL3 with the docking score of -4.39 kcal/mol. THR 131, SER 127, ARG 126 are the well-known amino acid residues found in the catalytic site of 4YL3, crystalline structure of 4YL3 clearly demonstrated that most of the interacted resides are found within the catalytic region of mPGES-1. Especially imidazole containing mPGES-1 inhibitors formed strong interaction only with these residues (Luz et al. 2015). From this result, we conclude that the molecular interaction of the flavonoids F 3, F 4, F 5, F 8, F 9 is most effective with the target protein 5WBE followed by that with 3NTG.

Table 4
Molecular interaction and docking score of selected flavonoids with anti-inflammatory molecular target

5WBE			3NTG			4YL3		
Ligand	Docking Score	Glide Energy	Ligand	Docking Score	Glide Energy	Ligand	Docking Score	Glide Energy
F 5	-9.966	-45.425	F 5	-8.323	-37.822	F 3	-4.398	-23.111
F 8	-8.799	-42.9	F 5	-8.017	-37.978	F 5	-4.213	-36.431
F 9	-8.628	-44.25	F 8	-7.486	-37.004	F 4	-3.68	-29.89
F 4	-6.797	-39.063	F 4	-6.922	-33.683	F 3	-3.192	-31.79
F 3	-6.719	-52.844	F 9	-5.223	-33.846	-	-	-

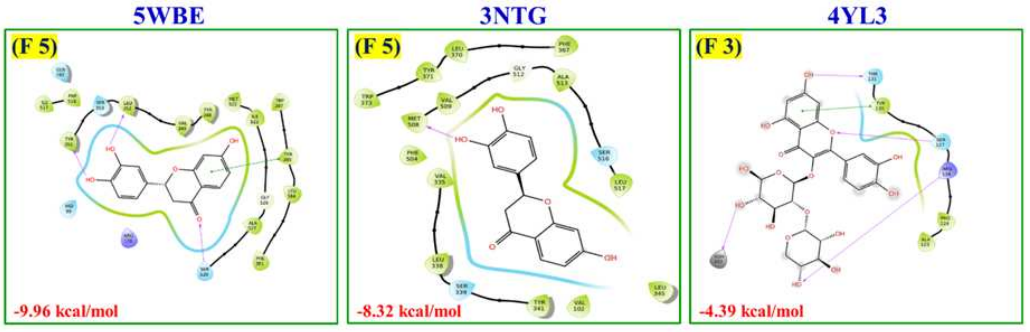


Fig. 1. Two-dimensional representation of selected flavonoids with the amino acids present in the catalytic site of anti-inflammatory molecular target

Molecular Interactions of Iridoids

Interaction of Iridoid phytochemicals derived from *J. grandiflorum* with 3NTG, 5WBE, 4YLE is represented by Fig. 2, and corresponding 2D images of protein ligand complex were presented in Fig. 2. The compounds giving high docking score were listed in Table 5. The iridoid compounds I 4, I 6, I 8, I 9, I 10, I 11, I 15, I 16, I 19, I 20 and I 21 express good docking score. The molecular interaction of the same iridoids with 4YL3 target is found to be less compared to that with 3NTG and 5WBE. Most of the tested compounds anchored in the catalytic sites of 5WBE and produced differential binding energy and docking score. The highest docking score was observed for 8-dehydroxy shanzhiside (I 10) with the active site of 5WBE. It produced a docking score of -9.02 kcal/mol. This compound interacted with HIS 90 and SER 530 by forming hydrogen bonds through oxygen and hydroxyl functional groups (Fig. 2). HIS 90 was one among the polar residues found in the active site of 5WBE, it forms vander Waals interactions with methoxyphenyl group of mofezolac (Cingolani et al. 2017). Similarly, deacetyl asperulosidic acid (I 8) interacted with amino acid residues SER 127 and THR 131 at the catalytic site of 4YL3 with the docking score of -3.77 kcal/mol. There are three hydrogen bonds formed between the amino acid residues of 4YL3 with differential bond length. Previously, 8-dehydroxy shanzhiside was reported to be isolated from an aqueous extract of *Lamiophlomis rotate* with hemostatic effect (Li et al. 2009). Later it was isolated from the buds of *Jasminum officinale* L. var. with anti-HBV properties (Zhao et al. 2011). Considering 3NTG, 10-hydroxy- ligstroside (I 20) was the most promissing active ligand found in the catalytic site with the binding affinity of -8.23 kcal/mol (Fig. 2). The hydroxy functions found in the processed structure of 10-hydroxy- ligstroside formed strong interaction with amino acid residues like GLU 510, SER 339, TRP 373 and TYR 371. This binding affinity provides evidence of the active inhibition of function of the inflammatory target 3NTG.

Table 5
Molecular interaction and docking score of selected iridoids with anti-inflammatory molecular target

5WBE			3NTG			4YL3		
Ligand	Docking Score	Glide Energy	Ligands	Docking Score	Glide Energy	Ligand	Docking Score	Glide Energy
I 10	-9.023	-40.606	I 20	-8.235	-8.695	I 6	-3.772	-27.989
I 11	-8.949	-47.595	I 9	-8.057	-35.857	I 8	-3.732	-24.982
I 16	-8.922	-47.385	I 16	-7.711	-30.667	I 9	-3.464	-21.723
I 15	-8.866	-46.047	I 10	-6.941	-31.933	I 19	-3.271	-31.519
I 21	-7.889	-42.303	I 4	-6.892	-30.688	I 6	-3.263	-24.737
I 6	-7.312	-34.011	I 21	-6.584	-30.53	I 20	-3.163	-32.8
I 4	-7.177	-38.773	I 19	-6.411	-12.538	I 10	-3.13	-22.756
I 9	-7.173	-26.869	I 6	-6.122	-20.032	I 4	-3.107	-34.29

I 8	-6.482	-26.772	I 8	-6.049	-21.936	I 16	-3.089	-26.197

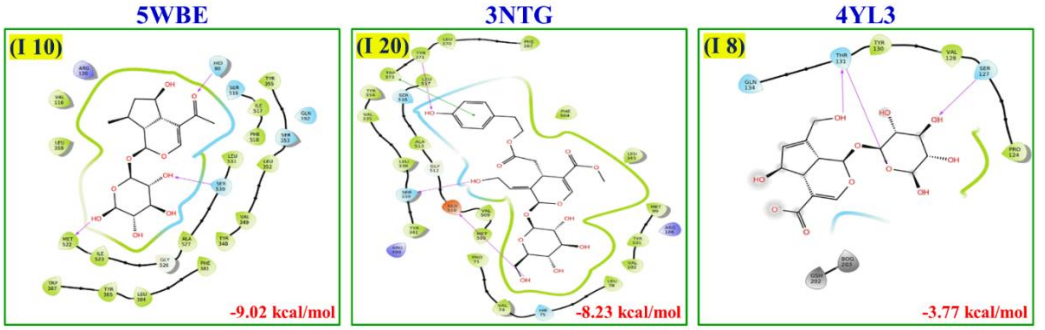


Fig. 2. Two-dimensional representation of selected iridoids with the amino acids present in the catalytic site of anti-inflammatory molecular target

Molecular Interactions of Small molecules of *J. grandiflorum*

Among the ten selected small molecules, the SM 1, SM 2, SM 3, SM 5, SM 8 express effective molecular interaction. The top two small molecules that exhibited a good docking score with 3NTG, 5WBE and 4YL3 were oleacein (SM 2) and 2-(3,4-dihydroxyphenyl) ethanol (SM 3). Among these top two molecules, oleacein was found to show the best docking conformation with a binding affinity of -7.95 kcal/mol towards 3NTG and -7.57 kcal/mol towards 5WBE (Table 6 and Fig. 3). Phytocompounds of *C. adansonii* showed strong interaction with the inflammatory molecular targets which is proven by both *in vitro* and *in silico* analysis. Molecular docking studies have proven the interaction of coumarin derivatives with the active sites of the target protein by means of the highest docking score and lowest binding energy. It produced -2.72 kcal/mol binding energy when interacted with the COX-2 (Thirumalaisamy et al. 2018). Oleacein is a decarboxymethyl elenolic acid found in some of the plant resources, has proven antioxidant, anticancer and anti-inflammatory activity (Cirmi et al. 2020; Karkovic Markovic et al. 2019). In particular, oleacein synergistically enhances the anti-inflammatory activity of haptoglobin 1-1 and 2-2 is related to atherosclerosis by reduce the release of elastase, MMP-9 and interleukin IL-8 from human macrophages (Filipek et al. 2015). Oleacein showed anti-cancer effects against neuroblastoma cells (Cirmi et al. 2020). Followed by Olivil, 2-hydroxymethyl-3-methyl-butyric acid phenyl ester was found to be the best hit. 2-(3,4-dihydroxyphenyl) ethanol is significantly bound to the active site of 4YL3 with the docking score of -4.09 kcal/mol. This binding affinity produced two distinguished H-bonds with the amino acid residues of GLN134 and THR131 (Table. 4 and Fig. 3).

Table 6
Molecular interaction and docking score of selected small molecules with anti-inflammatory molecular target

5WBE			3NTG			4YL3		
Ligand	Docking	Glide	Ligand	Docking	Glide	Ligand	Docking	Glide

	Score	Energy		Score	Energy		Score	Energy
SM 2	-7.579	-37.712	SM 2	-7.955	-44.472	SM 3	-4.094	-17.383
SM 1	-6.794	-27.462	SM 1	-7.913	-33.995	SM 5	-3.498	-14.343
SM 5	-6.782	-33.112	SM 5	-6.709	-31.321	SM 6	-3.491	-18.076
SM 8	-6.11	-30.887	SM 8	-6.448	-28.9	SM 8	-3.428	-18.431
SM 6	-5.725	-24.81	SM 6	-6.284	-25.212	-	-	-
SM 7	-5.067	-23.449	SM 7	-5.595	-24.128	-	-	-
-	-	-	SM 3	-5.527	-27.241	-	-	-
-	-	-	SM 4	-5.245	-38.935	-	-	-

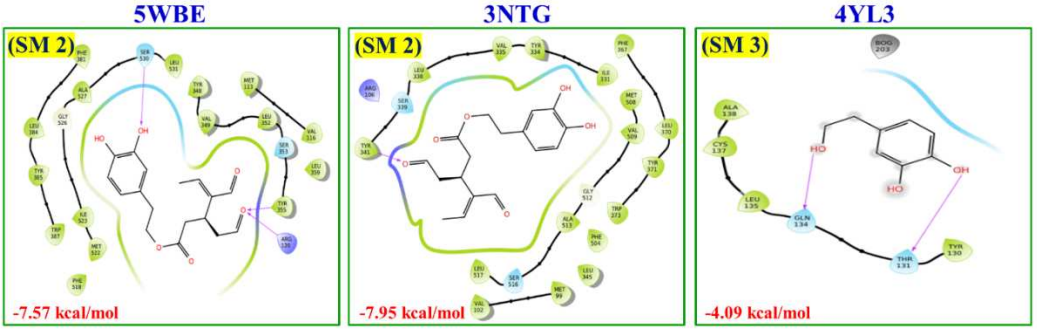
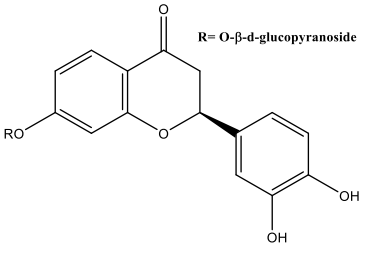


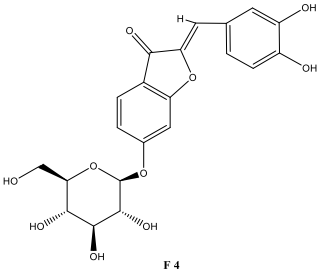
Fig. 3. Two-dimensional representation of selected small molecules with the amino acids present in the catalytic site of anti-inflammatory molecular target

Chart 1, 2, 3 represent the structures of the compounds of *Jasminum grandiflorum* that gave effective molecular interaction with the anti-inflammatory targets 3NTG and 5WBE.

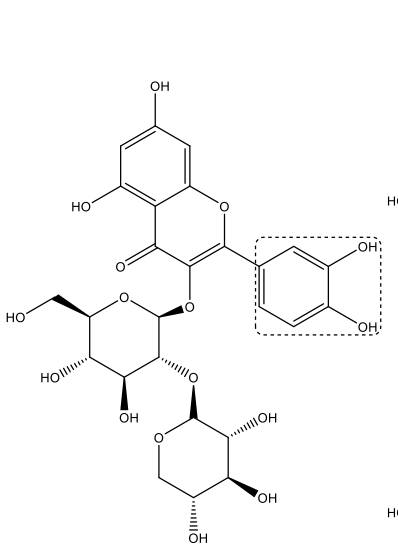
Chart 1 - Flavonoids



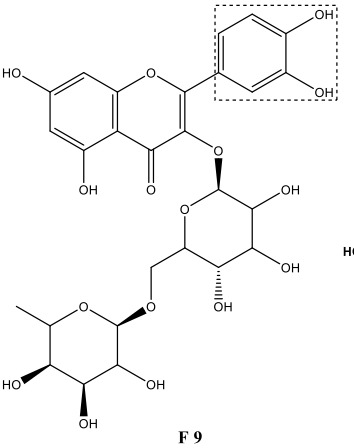
F 5



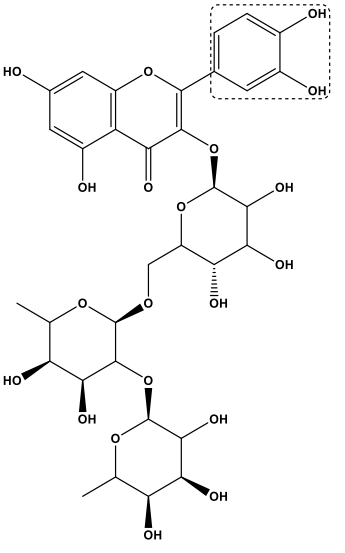
F 4



F 3

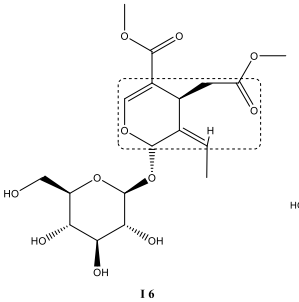


F 9

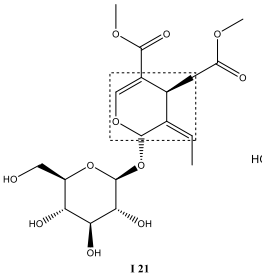


F 8

Chart 2 – Iridoids



I 6



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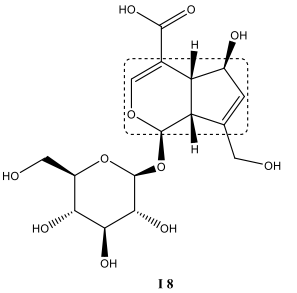

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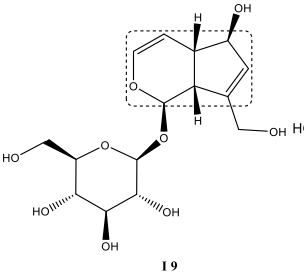

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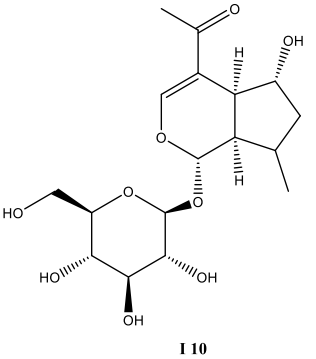

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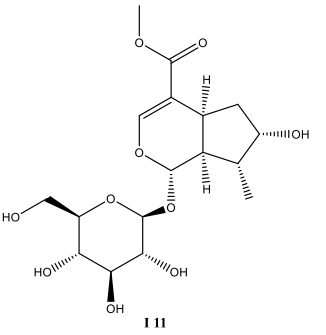

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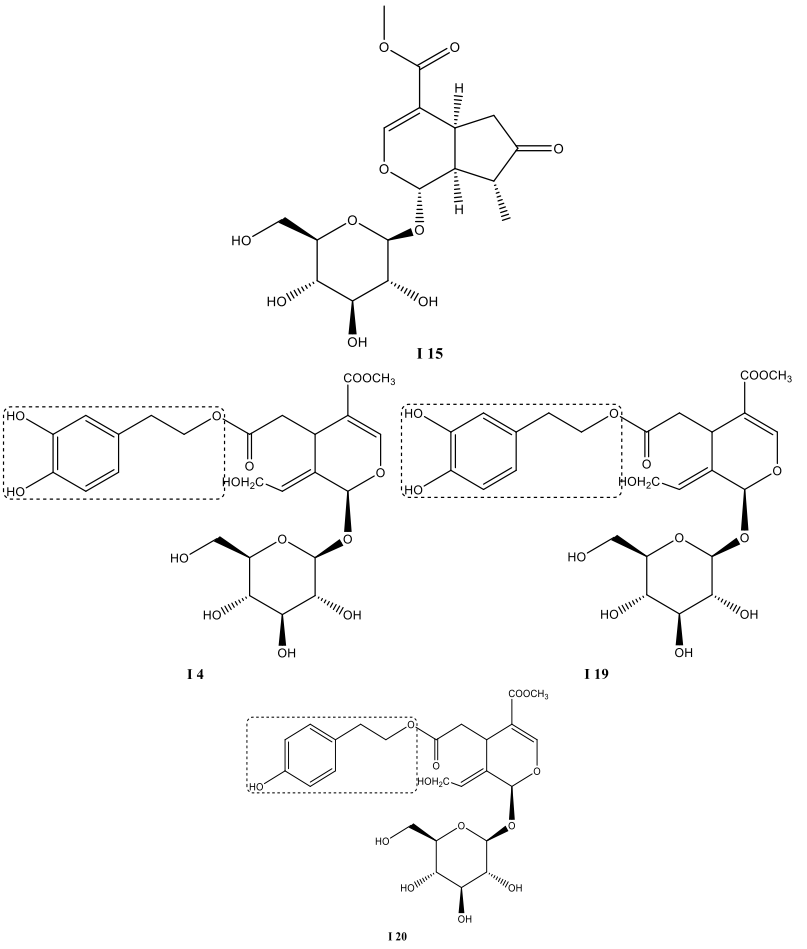
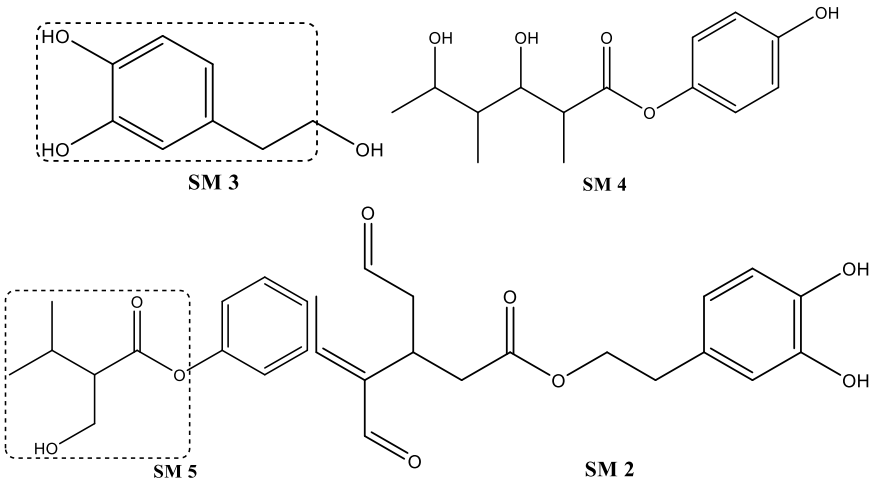
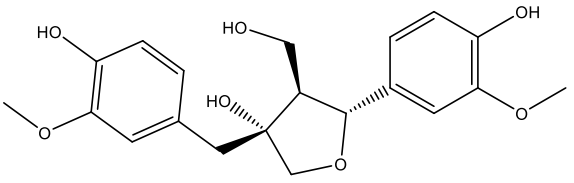
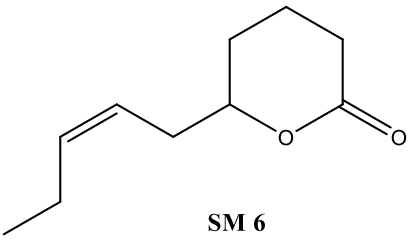


Chart 3 - Small Molecules

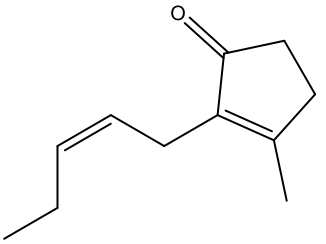




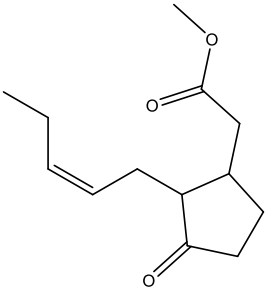
SM 1



SM 6



SM 7



SM 8

The dotted regions are the functionalities showing effective docking score. The most effective chemical moieties interacting with target are representatively indicated here.

Conclusion

In the present work, the protein-ligand interaction of the compounds elaborated by *Jasminum grandiflorum* was investigated. The present approach exposed that the selected compounds displayed significant anti-inflammatory properties. Out of the phytochemical ligands selected for this study 5 of 11 flavonoids, 19 of 21 iridoids and two small molecules were found to express satisfactory binding interaction as predicted by Maestro Schrodinger software. The compounds exactly bind into the catalytic region and selected compounds formed H-bond interactions more than or equal to the H-bond formed by the native ligand of the targets.

The computational investigation revealed that most of the compounds analyzed *in silico* showed good molecular interactions with two of the three anti-inflammatory targets chosen for the studies namely 5WBE and 3NTG. The docking score ranges from -6 to -9 kcal/mol for the interaction of the compounds with 5WBE and 3NTG. However, docking score is less for the interaction of the compounds with 4YL3. It was observed that among the flavonoid compounds, those compounds

which possessed a 3',4'-dihydroxy phenyl moiety as the C-ring of the flavone expressed high docking score. For the iridoidal compounds analysed, it was observed that the presence of secoiridoidal moiety with hydroxyl group at the C-10 position and 3,4 dihydroxy phenyl ethyloxy moiety imparted good molecular interaction as evidenced from the docking score. The presence of iridoid moiety provides an effective molecular interaction. The compounds containing a 10-hydroxy substituent on the iridoidal skeleton also show effective molecular interactions against the target proteins 5WBE and 3NTG**.** Among the small molecules analysed those with 3, 4, dihydroxy phenyl ethyloxy moiety in their structure interacted effectively with the proteins 5WBE and 3NTG. The overall revelation is that the targets 5WBE, 3NTG sourced from the COX1 and COX2 respectively are inhibited by most of the compounds but more effectively by those with the 3', 4' dihydroxy phenyl group in the flavonoidal compounds and 3,4 dihydroxy phenyl ethyloxy group conjoint with secoiridoid moiety and an iridoid moiety with or without 10 hydroxy group. It is also revealed that such compounds do not effectively inhibit 4YL3 sourced from mPGES-1.It can be concluded from docking results that 10-hydroxy- ligstroside, 8-dehydroxy shanzhiside, butin-7-O-β-D-glucopyranoside, oleacein and 2-(3,4-dihydroxyphenyl)ethanol are most prospective as potential COX1, COX2 and mPGES-1 inhibitors. However, additional biological study would help in specifying compounds against inflammatory responders of the biological system.

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

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Conflict of Interest

The authors declare no Conflict of Interest

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