In Silico Drug Designing Approach for Drimioidica of Human TSLP in Allergy and Asthma

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Abstract: Drimioidica are stomachic, emmenagogue, anthelmintic, purgative, and alexiteric. They are useful for paralysis, bronchitis, asthma, dropsy, rheumatism, renal calculi, leprosy, skin diseases, headache, diseases of the nose, internal pains, and scabies in indian traditional medicine. This evaluation also suggests that bufadienolides, flavonoids and steroids might be responsible for its bioactive potential. The pro-inflammatory cytokine Thymic Stromal Lymphopoietin (TSLP) is pivotal to the pathophysiology of widespread allergic diseases mediated by type 2 helper T cell (Th2) responses, including asthma and atopic dermatitis. The emergence of human TSLP as a clinical target against asthma calls for maximally harnessing its therapeutic potential via structural and mechanistic considerations. The phenol-2-carboxylic acid, (M8) showed interaction with THE-72, LEU-85, ASP-87. However, it was noted that there is a hydrogen bond between the derivatives of phenol-2-carboxylic acid was potent inhibitor for TSLP. Here we report the development of a new drimioidicaplantbasedisolated compounds, showing the silico discovery of and efficacy towards asthma activity.

Keywords: Drimioidica, Asthma activity, Schrodinger Maestro 11.9, Molecular docking, Glide score.

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1. INTRODUCTION

Drimiaindica is a reputed ayurvedic medicine for a number of therapeutic benefits, including for cardiac diseases, indigestion, asthma, dropsy, rheumatism, leprosy, and skin ailments¹. Phytochemical studies on the plant have revealed that alkaloids, flavonoids, phenols, and tannins are common in all parts, while steroids are only present in bulbs². A bronchodilator is helpful for breathing problems caused by narrowed or inflamed airways because it relaxes the lung muscles and dilates the airways. This medication is commonly used for the treatment of asthma and chronic obstructive pulmonary disease³. The *D. indica* bulb is used to treat chronic bronchitis and asthma in traditional medicine. To validate this claim scientifically, Bashir et al. studied an aqueous ethanol extract of the bulb in rabbit tracheal and guinea pig atrial preparations⁴. The extract inhibited contractions induced by carbachol (1 M) and K⁺ (80 mM) in rabbit tracheae, similar to dicyclomine. The results suggested the presence of Ca²⁺-channel blocking and anticholinergic mechanisms of the extract. The extract (0.01–1 mg/mL) increased the force of guinea pig atrial contractions without affecting their rate. This effect was perhaps mediated through the combined mechanism of an anticholinergic and Ca²⁺ antagonist accompanied by an inotropic effect. This in vitro report gave an idea about the possible role of *D. Indica* bulbs in bronchial diseases such as asthma and bronchitis. However, further studies with in vivo/clinical models are warranted before its use as a bronchodilator. Its purified fraction(s) or constituent(s) should be used to improve its efficacy and also to reduce dose sizes. The downside of aberrant signalling by TSLP has grave consequences for human health and imprints a massive healthcare and socioeconomic footprint. This is because type 2 helper T cell (Th2)-mediated inflammatory responses primed by activated DCs, are pivotal for the onset of widespread allergic diseases of the airways, skin and gut⁵. In fact, TSLP is now widely considered to underlie some of the most prevalent inflammatory allergic disorders, such as the atopic diseases (asthma, atopic dermatitis and atopic rhinitis), chronic obstructive pulmonary disease (COPD) and eosinophilic esophagitis^{6–9}, and has been annotated as a genetic risk factor for the development of asthma^{10–12}. Thymic stromal lymphopoietin (TSLP), is an interleukin-2 (IL-2) family cytokine produced in response to pathogenic stimuli by skin keratinocytes and epithelial cells in the lung and gut¹³. This study was aimed to provide pharmacological basis for the medicinal use of *U. indicain* broncho-spastic disorders like asthma and as cardiac stimulant¹⁴. In human asthma, there are lowered SNO concentrations in the lungs, likely attributable to up-regulated GSNOR activity¹⁵. The growing portfolio of computational drug design methods, medicinal chemists are confronted with large data amounts in a short time¹⁶. In many pastoral areas traditional medicine drimaindica used in primary source¹⁷. Fumariaindica is easily an available source for discovering and developing phyto-pharmaceuticals or drugs potentially useful for treatments of mental health problems commonly associated with numerous physical disorders and chronic diseases¹⁸. Here, we describe a selective and highly potent asthma drug development in used in silico method. The aim of use molecular docking with minimized number of steps is one of the purpose of modern synthesis new drug. Due to its high efficiency and selectivity, asthma agents consisting of combined molecules have gained great interests.

2. MATERIALS AND METHODS

2.1 Preparation of Ligands

Structures of ligands sketched and saved in SDF format were imported via selecting file. The imported ligands (M1-M8) were set to minimize under force field OPLS 3e. Minimization calculations can be performed on all structures of Drimiaindia derivatives.

2.2 Preparation of Protein

X-ray crystalline structure of human TSLP in complex with TSLPR and IL-7Ralphaprotein PDB 5J11 was imported from Protein Data Bank (PDB) to workspace, which further set to preprocess followed by review and modification to remove unwanted chains and residues, further refined under force field of OPLS3e. The results were monitored in the job monitor.

2.3 Molecular Docking

The compounds M1-M8 selected for molecular docking have some collective structural features. All the lead compounds showed good binding energy and exhibited interactions and better lower free energy values, indicating more thermodynamically favoured interaction. As for Glide docking, crystal structures of 5J11 have been prepared by the protein preparation wizard in Schrodinger suite. Afterwards, receptor grids were generated before docking with the active site determined by the position of co crystal ligand. Crystal structures of 5J11 were imported into Glide, defined as the receptor structure and the location of active site with a box. The OPLS 3e force field was used for grid generation. The standard precision (SP) and the extra precision (XP) protocols were set for docking studies with crucial residues, in constrained binding to get accurate results. Binding affinity was retrieved running Prime MM-GBSA. All other parameters were maintained as default.

3. RESULTS AND DISCUSSION

3.1 Molecular Docking

The emergence of human TSLP as a clinical target against asthma calls for maximally harnessing its therapeutic potential via structural and mechanistic considerations¹⁹. The emergence of TSLP as a central orchestrator of Th2 responses that initiate allergy and inflammation has placed therapeutic targeting of TSLP-mediated signalling against major chronic diseases such as allergic asthma and atopic dermatitis at center stage²⁰. To dock, M1–8 structures of ligands have been determined. Meanwhile, these ligands were used to conduct native docking to measure the docking conformations. Three different docking programs SP Glide, and XP Glide, Prime MM-GBSA were used for improving the accuracy of prediction. Then, Xscore followed by molecular docking was reliable and accurate for forecasting protein-ligand binding free energies (Table I). The docking results were evaluated by comparing values of score energy, SP Glide, XP Glide, and Binding energy. Through analysis of these results of docking simulations, most binding energy scores could accurately forecast the ligand activities. The lowest binding energy and the highest docking score demonstrated that these compounds (ligands) presented well favorable interactions. The docked ligands M8, M6, M5, drimiaindica, derivatives showed the best range of Docking score, XP Gscore and Binding energy (Table I). Structures of ligands sketched and saved in SDF format were

Table 1. Glide Docking and binding energy scores						
Title	Docking score	Glide gscore	Glide emodel	XP GScore	MM GBSA Bind	dG
M8	-5.82	-5.82	-72.687	-5.82	-21.548	
M6	-3.259	-3.259	-59.841	-3.259	-29.785	
M5	-2.72	-2.72	-63.794	-2.72	-49.84	
M4	-2.394	-2.394	-72.705	-2.394	-57.21	
M1	-2.223	-2.223	-59.841	-2.223	-40.16	
M2	-2.08	-2.08	-72.687	-2.08	-48.3	
M7	-2.05	-2.05	-53.779	-2.05	-33.6	

3.2 Inhibitor Binding Analysis

The least binding energy and the most rational binding pattern between the inhibitors and 5J11 were selected by the three docking protocols. As expected, Drimia india derivatives (compounds M1-M8) bound in the active site validating the prediction by molecular docking with 5J11.

Among the set, three compounds were selected, which represented good interactions with the target protein, including compounds M6, M5. From the docking results, the Phenol-2-carboxylic acid, (M8) showed interaction with THE-72, LEU-85, ASP-87. However, it was noted that there is a hydrogen bond between the Phenol-2-carboxylic acid derivatives of M8 as potent inhibitor.

Fig 1-A,B

Fig 1.A,B 3D representation of M8(2-Hydroxybenzoic acid) in the binding pocket inhibition of TSLP

The molecular docking results are recommended enhancement of the polar interactions with the THE-72, LEU-85, ASP-87 side chain of the binding site in fig1A,B

Fig 2. Schematic 2D representation of M6(5,7-Dihydroxy-2-(3,4-dihydroxyphenyl)-4H-chrome-4-one) in the binding pocket inhibition of TSLP 5J11

The ligand (M6) docking with protein TSLP 5J11 H-bond with GLU-40 amino acid and ASP-87 with two H-bond shows (fig 2).

Fig 3. Schematic 2D representation of M5(3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) in the binding pocket of inhibition of TSLP 5J1I

The molecular docking results are recommended enhancement of the polar interactions with the ligand (M5) docking with protein TSLP 5J1I H-bond with GLU-40 amino acid shows in (fig 3).

Fig 4. Schematic 2D representation of M4 (S)-5,6-Dihydro-5-((10S,13R,14S,17S)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-10,14-dihydroxy-13-methyl-1H-cyclopenta(a)phenanthren-17-yl)pyran-2-one in the binding pocket of inhibition of TSLP 5J1I

The molecular docking results recommends enhancement of the polar interactions with the ligand (M4) two h-bonding between hydroxyl group and amino acid GLU-40,THR-41,ASN-73 it shows (fig 4).

Fig 5. Schematic 2D representation of M1 (5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chrome-4-one) in the binding pocket of inhibition of TSLP 5J1I. The ligand (M1) shows the interaction with binding of hydroxyl group and amino acid GLU-40 shows (fig 5).

Fig 6. Schematic 2D representation of M3 ((R)-5,6-Dihydro-5-((10 S ,13R,14R,17S)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-10,14,-dihydroxy-13-methyl-1H-cyclopenta (a)phenanthren-17-yl)pyran-2-one in the binding pocket of inhibition of TSLP in the binding pocket of 5J11

The docked ligand, M3 was selected to unveil its binding pose and binding interactions in the protein binding pocket. The binding amino acid and ligand interaction is ASN-72 and ASP-87 (fig 6). Although the high potency of our compound M8 was surprisingly pleasant to us, it was important to study binding features of this compound using computational tools. Molecular docking (M8) showed interaction with THR-72, LEU-85, ASP-87. The ligand (M3) with the most important H-bond between ASN7-73, ASP87 of the amino acid (fig6). From the docking results, the best binding compound to be M8) Drimia Indica is the most common plant used in traditional medicine for various ailments. The chemical constituents of this plant were analyzed for its asthma action through docking studies. They are useful for asthma, diseases of the nose, internal pains, and scabies in Indian traditional medicine. The study is focused to examine the comparative molecular docking studies on the target M1-M8 to identify docking energy and Hydrogen bond interaction of ligand. Hence further analysis through in vitro and in vivo studies will prove the action of this compound. From the docking results, the Phenol-2-carboxylic acid, (M8) showed interaction with THR-72, LEU-85, ASP-87.

4. CONCLUSION

However, in order to maximally harness the therapeutic

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potential of TSLP-mediated signalling, it will be essential to dissect the structural and mechanistic basis for its bioactivity. Here we concluded that compound drimia indica from this plant render asthma action against asthma, and it may be used as drug through future studies.

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6. AUTHORS CONTRIBUTION STATEMENT

Ms.Saamanthi performed computational Molecular docking and wrote the paper. Dr.S.Aruna and Dr.R.Girija are designed the project supervised and wrote the paper. The manuscript was written through contributions of all authors.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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