INSILICO MOLECULAR DOCKING STUDY ON GLYCOSIDES OF INDANE AGAINST ASTHMA

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ABSTRACT: The genera of *indigofera* (Family Fabaceae) are distributed throughout India and are medicinally useful. *Indigofera tinctoria Linn* (Fabaceae) has been extensively used in various folklore and traditional medicines, Studies on the plant reveal low toxicity. The plant possesses antitoxic, hemostatic, sedative properties and is useful in the treatment of piles, healing of ulcers, dropsy. The roots stems and leaves are useful for promoting growth of hair, in gastropathy, splenomeghaly, cepholagia, cardiopathy, chronic bronchitis, asthma and ulcers. Extracts of *I tincoria* (whole plant) contains "indicant", about 2.5% alkaloids, about 0.5% stimulant deobstruent, antiseptic and astringent . The 3D crystal structure of the protein 11-beta hydroxysteroid dehydrogenase (11-bHSD) was retrieved from protein Data Bank (PDB) and protein binding sites of the compounds were identified. The 2D structure of *Indican* compounds of glycosides of indane were obtained from the Pubchem database. The present study analysed the molecular docking studies on protein which is responsible for *Asthma* with the compounds evolved from *Indigofera tinactoria Linn.* The Docking was done by schrodinger Maestero 11.9 software tool, *Indican* compounds of glycosides of indane having best binding score than the other compounds. Hence it has been concluded Glycosides *of indane* can be used as a Anti asthmatic drug.

KEYWORDS: *Indigofera tinctoria* linn, Indican, 11-beta hydroxysteroid dehydrogenase, Anti asthmatic drug, Maestero 11.9, Glide.

INTRODUCTION:

Asthma is a chronic respiratory syndrome. Chronic cough, as the presenting symptom, is the fifth most common problem seen by office-based physicians [(6)]. Of those patients whose chronic cough goes undiagnosed, as many as a third to half of these patients have unrecognized asthma [(7,8)] In many of these undiagnosed cases, the only symptom or sign is the cough. When cough is the sole manifestation of reactive airway disease, it is termed cough variant Asthma [(9)] Studies of *Indigofera tinctoria Linn* has shows that it possesses low toxicity. Phytochemical evaluation of leaf extract of *Indigofera tinctoria Linn* has been carried out to characterize some constituents present therein. Qualitative analysis of the extracts showed the presence of flavonoids, alkaloids, glycosides, terpenoids.[(1)] An Insilco study to identify possible drug target for blocking the 11-beta hydroxysteroid dehydrogenase (11-bHSD) enzyme that catalyses the conversion of hydrocortisone to cortisone in the cholesterol metabolism the level of hydrocortisone, which plays a vital role in the control of asthma has been attempted [(5)] The inhibition of 11-bHSD by Phytochemical compounds of leaf extract in *Indigoferra tinctoria* resulted ultimately controlling the Asthma. Medicinal herbs have a long history in improving human health and curing various diseases. A wide interest has been made for researchers using herbal material in identification of the active components and verification of their efficiency. All modern clinical drugs over 50% are of natural product origin India has an extensive rich heritage of herbal medicine since from the time of Ayurveda with medicinal properties[(11,12)] *Indigofera tinctoria Linn* is distributed in south and south East Asia and Tropical Africa, In India it is found almost throughout and cultivated in many parts. The plant *Indigofera tinctoria Linn* is popularly known as true indigo and used in treatment of various ailments. Nili is the reputed drug produced from this plant which is used in Ayurveda for promotion of hair growth. In wondering this info lead to carry out a docking studies of the Asthmatic protein 11-bHSD and Phytocompounds namely Indican (Glycosides of indane), Louisfieserone, Rotenoid, Rutin which were downloaded from PubChem website, PubChem is an open archive consisting of a set of three primary public

databases (BioAssay, Compound, and Substance). It contains information on a broad range of chemical entities, including small molecules, lipids, carbohydrates, and (chemically modified) amino acid and nucleic acid sequences (including siRNA and miRNA). PubChem contains more than 150 million depositor-provided chemical substance descriptions, 60 million unique chemical structures, and 225 million biological activity test results provided from over 1 million biological assay records[(12)] Indican reveals a better binding of the ligand to the protein. The study was done based on three Docking programs of Schrodinger Glide software which is run on Maestro 11.9. i.e., standard precision (SP) Glide, Extra precision (XP) Glide, Prime MM-GBSA to reveal the binding. The docking programs successfully works by binding the protein and the ligand gives very useful data about the Binding energy, Docking score, hydrogen bonds between them, hydrophobic bonds, inter atomic contents between them, and the neighbouring amino acids to which the ligand has contact. All these studies will give perception in determining the property of the targeted phytocompounds against Asthma protein.

MATERIALS AND METHODS:

All four Chemical structures namely Indican (Glycosides of indane), Louisfieserone, Rotenoid, Rutin (A1-A4) of *Indigofera tinctoria Linn* phytocompounds were retrieved from PubChem website in SDF format. The docking studies were performed with standard precision (SP) Glide, and extra precision (XP) Glide and MGBSA Prime in Schrodinger software.

Preperation of Protien:

X-ray crystalline Structure of protein 4P38 (11-beta hydroxysteroid dehydrogenase) was imported from Protein Data Bank (PDB) to workspace. Protein was prepared with the Protein Preparation Wizard in Maestro11.9 using default options, bond orders were assigned, hydrogens were added, metals were treated, and water molecules 5 A˚ beyond hetero groups were deleted, which further set to preprocess followed by review and modify to remove unwanted chains and residues, further refined under forcefield of OPLS3e. The results were monitored in job monitor.

Preperation of Ligands:

Structures of ligands sketched and saved in SDF format were imported via selecting file. The imported ligands (A1 - A4) were set to minimize under force field OPLS3e. Minimization calculations can be performed on all structures of Indican (Glycosides of indane), Louisfieserone, Rotenoid, Rutin .

Molecular Docking:

As for Glide docking, crystal structures of 4P38 should be 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 4P38 were imported into Glide, defined as the receptor structure and the location of active site with a box. The OPLS3e force field was used for grid generation [12-13]. 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. Docking programs have proven relatively successful in accurately reproducing known poses of drug-like molecules from co-crystal structures, with Glide consistently performing among the top of the programs[18]

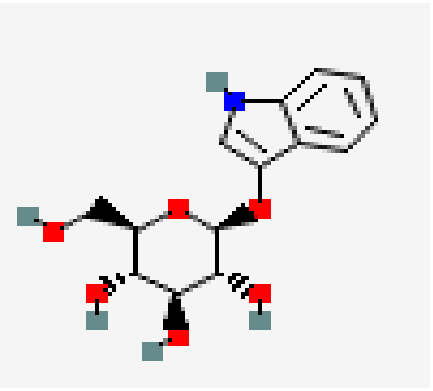
RESULT AND DISCUSSION:

Validating active group of ligands (A1-A4):

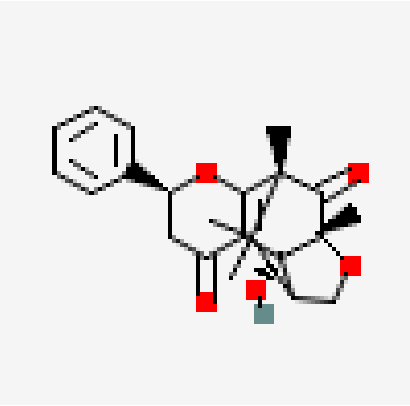
The 2D structures (A1-A4) of Indican (Glycosides of indane), Louisfieserone, Rotenoid, Rutin were run in Qikprop tool of Schrodinger Glide software to proceed for further elucidation.

Structure of Phytochemicals (A1-A2)

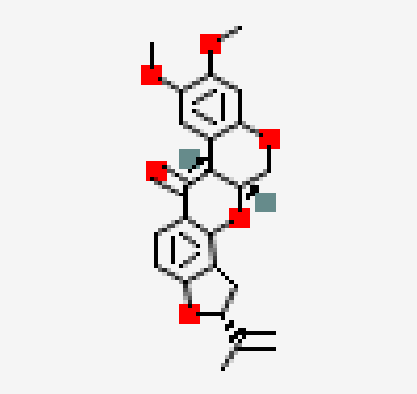
Figure 1



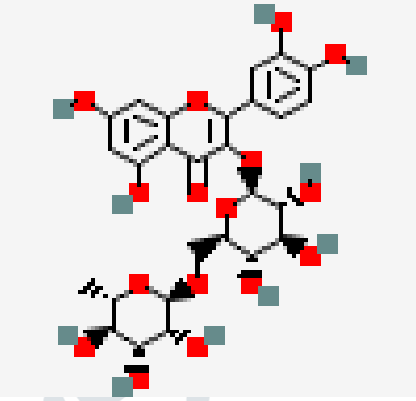
Indican



Louisfieserone



Rotenoid



Rutin

Molecular Docking.

To date, seven structures of ligands have been determined. Meanwhile, these ligands were used for 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 1).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 A1, A2, A3, A4 showed the best range of Docking score, XP Gscore and Binding energy.(Table 1).

Schematic representation of MolecularDocking

Figure 2

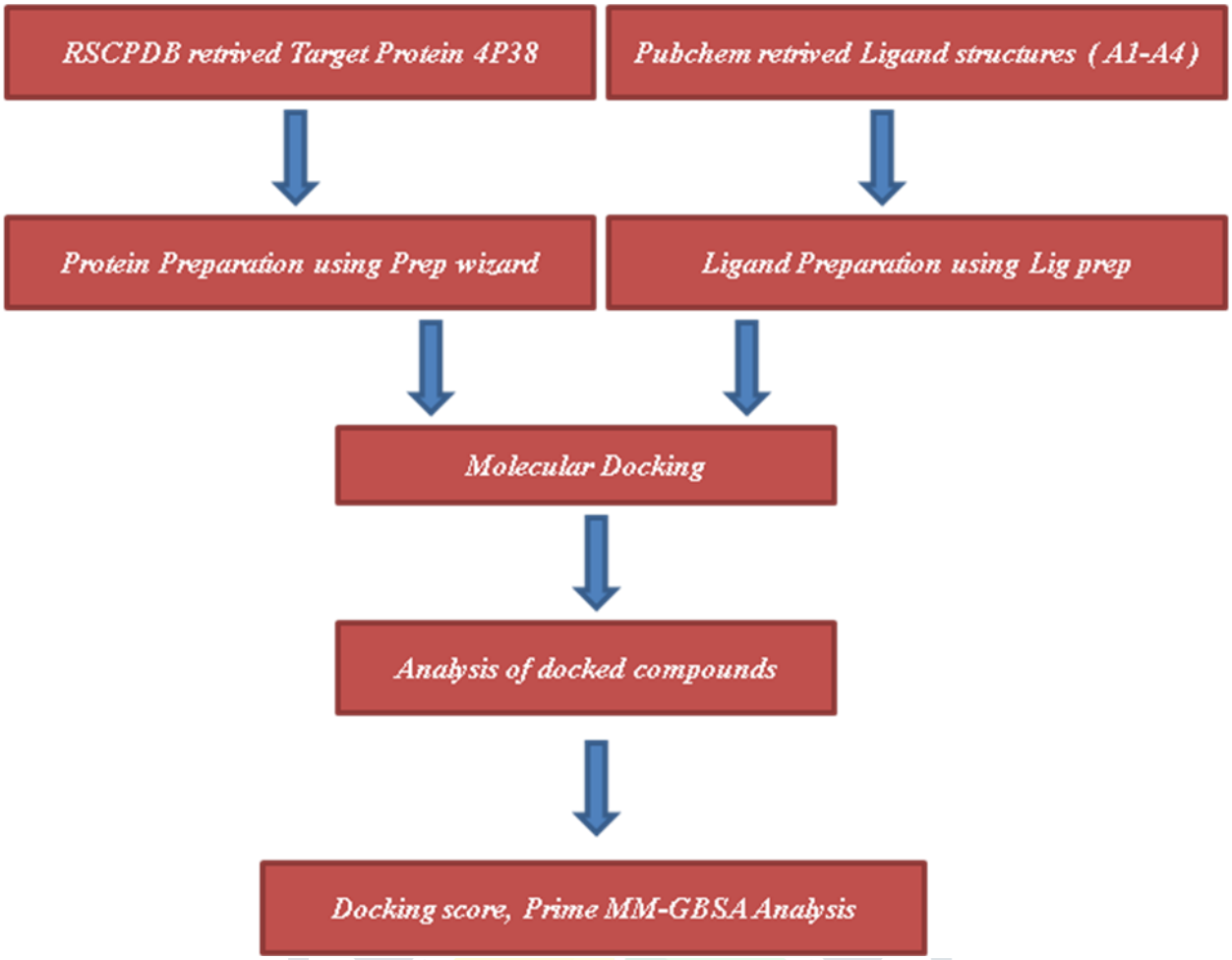
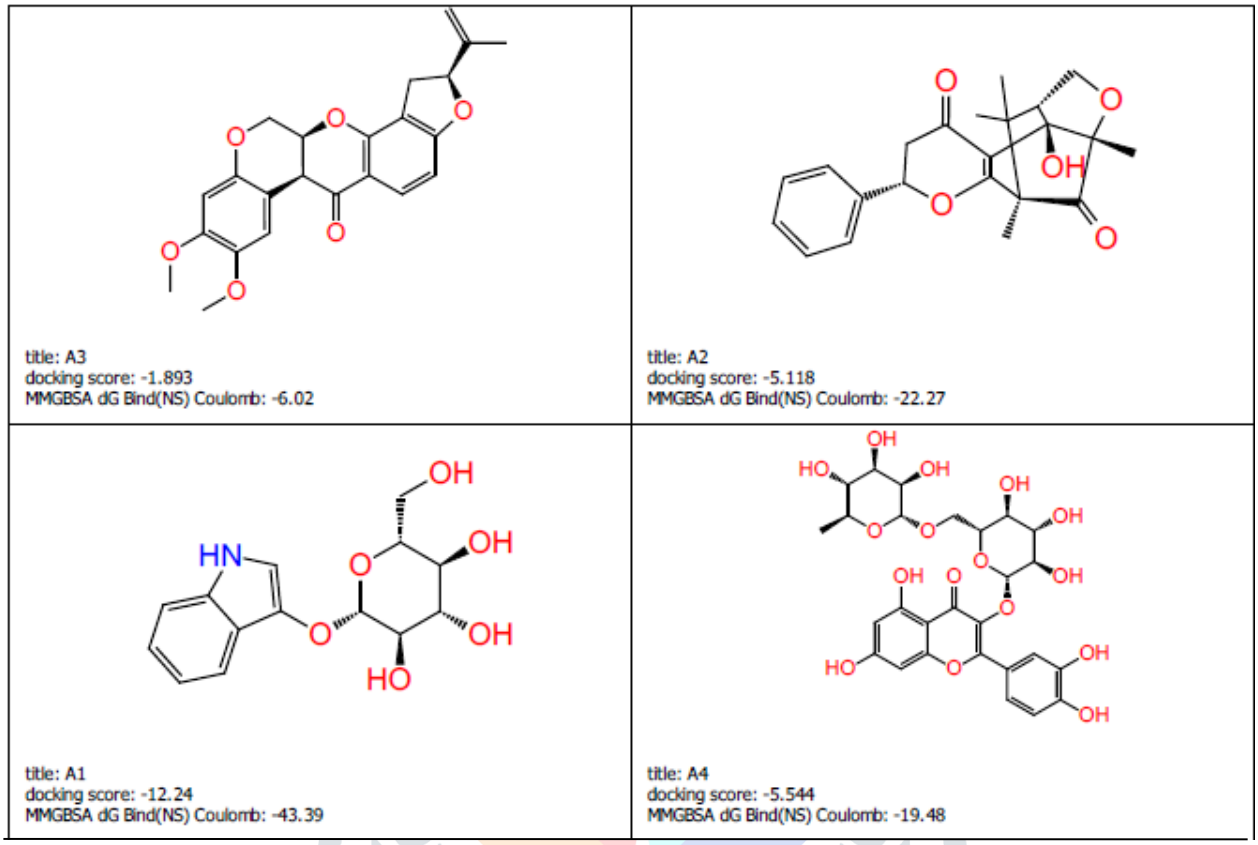


Table 1

Title	Compounds	Docking score	Glide gscore	XP GScore	MMGBSA dG Bind
A1	Indican	-12.24	-12.24	-12.24	-41.26
A4	Louisfieserone	-5.544	-5.544	-5.544	-17.44
A2	Rotenoid	-5.118	-5.118	-5.118	-16.78
A3	Rutin	-1.893	-1.893	-1.893	-42.34

Diagramatic representation of Binding energy and Docking score

Figure 2

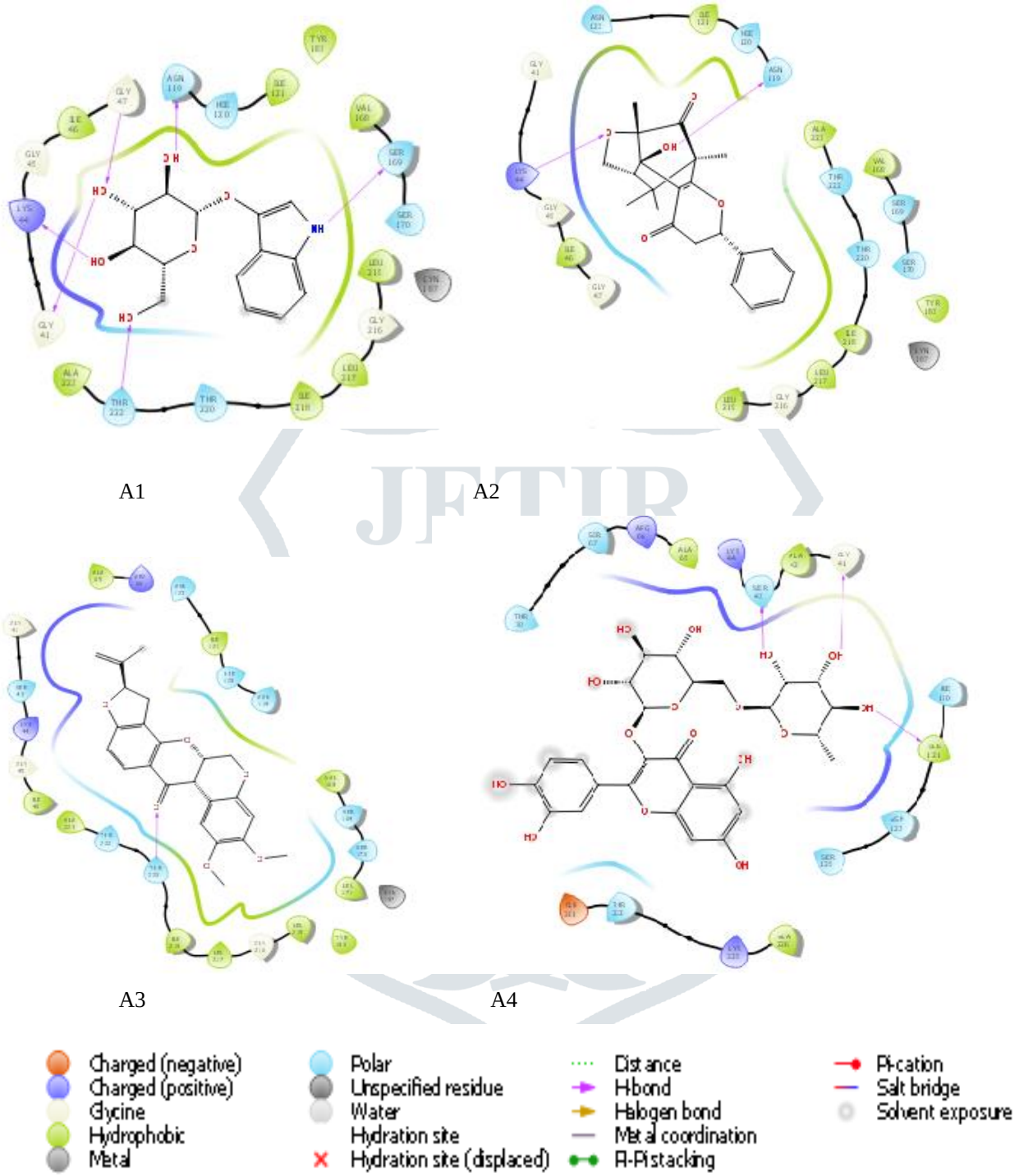


Inhibitor Binding Analysis:

The least binding energy and the most rational binding pattern between the inhibitors and 4P38 were selected by the three docking protocols. As expected, Indican (compound A1) bound in the active site validating the prediction by molecular docking with 4P38. Among the set, top compounds were selected, which represented good interactions with the target protein (Figure 2). From the docking results, Indican (A1) shown interaction with THR, ASP, GLY, LYS , SER which had Four Hydrogen bond interactions. *Viz* Louisfeiserone (A2) showed Two Hydrogen bonds, Rutenoid (A3) showed One Hydrogen bond, Rutin (A4) showed Three Hydrogen bonds.

2D representation of Docking Analysis

Figure 3



CONCLUSION:

As a result of this computational experimental study of Four competitive ligands of *Indigofera tinctoria linn* and 4P38. To identify the docking accuracy about this target, docking simulation were evaluated. Interestingly, these docking results showed good interactions for all four inhibitors. Docking results were merged, which allowed us to weigh different binding patterns in the active sites. In a word, we identified that Four hydrogen bond acceptors and heterocyclic rings, one with Oxygen and the other with Nitrogen, were essential anchoring points in Indican (A1) played a pivotal role in binding affinity. This provides lowest energy ligands, docked into the target pocket with best possible pose. The compound Indican (Glycosides of Indane) are quantified using the docking score to act against anti Asthmatic activity, The study is conducive for designing an accurate drug for treating Asthma.

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