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Insilico Assessment of Phytoconstituents in *Myxopyrum Smilacifolium* Blume against Arthritis

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Myxopyrum smilacifolium **Blume geographical occurrence is southern part of India and its usage for the treatment of various diseases has been marked in Traditional Medicine. The present study was aimed to examine the phytoconstituents in Myxopyrum smilacifolium Blume for antiarthritic activity by insilico approach. Antiarthritic activity of phytoconstituents in Myxopyrum smilacifolium Blume was performed by using software Autodock 4.0. For each phytoconstituents the pharmacokinetic parameters are also assessed by online tools. The study revealed that phytocompounds, Arenarioside, Verbascoside and Myxopyroside showed docking score of about -16.4 kcal/mol, -10.6kcal/mol and -6.5 kcal/mol comparatively high when compared with the docking score of standard Ibuprofen of about -6.2 kcal/mol. It had proven to posses the inhibition activity against inflammatory mediator as it shown a good binding affinity between ligand and the receptor site COX-2. The evaluated pharmacokinetic parameters of the only 3 phytoconstituents obeyed Lipinski's rule of 5. Arenarioside, Verbascoside and Myxopyroside are the phytoconstituents of Myxopyrum smilacifolium Blume shown high docking score and it can be explored further for SAR and simulation studies are needed to ensure the antiarthritic activity.**

Keywords: Arenarioside; Docking; In silico; Lipinski's; Myxopyrum.

A musculoskeletal condition results in excruciating long-term joint pain, edema, and movement restriction. A sizable portion of the population is affected by these diseases and their mortality rate has increased.[1] The most prevalent musculoskeletal disorder worldwide and a condition as old as mankind is arthritis. More than 100 different types of arthritis exist. Among these are autoimmune disorders such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, and others. The arthritis foundation estimates that two-thirds of people had arthritis in 2007, and the census indicates that by 2030, that number will rise to 40% of the population.[2-3] Although there are several therapies for different types of arthritis, each has its own disadvantages. Natural treatments of plant

origin were evaluated for their safety, effectiveness, and lack of side effects, which presents a fresh option, to overcome these shortcomings.

The Oleaceae family includes the huge woody twining shrub known as Myxopyrum smilacifolium Blume.[4] It is also known as chaturdharalata in Telugu. In earlier research on the Myxopyrum genus, irridoid glycosides were found. Although they have a long history in the Indian traditional medical system, there hasn't been a thorough scientific investigation into the plant's anti-arthritic properties. Therefore, the current study reveals the evaluation of Myxopyrum smilacifolium Blume antiarthritic activity.

MATERIALS AND METHODS

Molecular docking

Receptor and Ligand Preparation

Iridoid glycosides were discovered in an earlier studies by phytochemical analysis of *Myxopyrum smilacifolium Blume* leaf tissue using GC and GC-MS.[5] *Myxopyrum smilacifolium Blume* phytoconstituent structures were obtained using PubChem and information on COX-2 was obtained via Protein Data Bank (PDB ID: 5IKR) at www.rcsb.org/pdb (Figure 1). Polar hydrogen bonds were added and the water atoms were removed from the pdb file. Docking tests using AutoDock/vina were carried out to determine the coupling mode and cooperative behavior of the chosen drugs and target. Using Auto Dock, the pdbqt files of the receptor protein and phytocompounds from *Myxopyrum smilacifolium Blume* were able to access the dynamic location of the receptor for compound interaction. The framework size restrictions were scaled within X, Y, and Z coordinates to provide a proper binding adjustability at the docked site. An amalgamation of the pdbqt papers was made into a design (conf) file. Discovery Studio carried out the tying investigations (BIOVIA). Openly available online SwissADME programming predicted the physiochemical characteristics and pharmacokinetics of the chosen substances.

RESULTS AND DISCUSSION

In-silico Study of Phytoconstituents in *Myxopyrum smilacifolium Blume*

In order to assess the possibility of phytocompound being reasonable for antiarthritic property, the docking score was investigated by checking out the binding affinity towards the protein. Phytoconstituents are also assessed to predict their absorption, distribution, metabolism, excretion and toxicity by using online tools. 2 out of 5 phytocompounds obeyed Lipinski's Rule of 5. The phytocompounds are along with their structures, PubChem ID and the canonical smiles were represented. (Figure 2, Table 1 & 2)

Docking studies revealed that phytoconstituents Arenarioside, Verbascoside, Myxopyroside had docking score of -16.4, -10.6 and -6.5 kcal/mole which showed hydrogen bonding interactions. No phytocompounds formed hydrophobic interactions. The docking score outcomes were predicted and their interactions between protein and ligand were explored. (Table 4 & Figure 3).

Investigations on single leaf of *Myxopyrum* and isolation of an irridoid glucoside called myxopyroside representing that the compound is related to the genus Nyctanthes. Chromatography of Merck Lobar Lichoprep RP-18 of size B of column elution with solvent system of water and methanol in the ratio of 7:2 were used which yielded of about 5 mg of Myxopyroside. It displayed 18 signals in ^{13}C NMR spectrum evidenced the presence of aglycone moiety dihydroxy substituted for Sythide Dimethyl Ester. NMR spectral study also revealed the presence ester derivatives of Myxopyroside. NSAIDs pharmacological effect is due to inhibiting cyclooxygenase (COX), involved in the synthesis of prostaglandin PGs. The extensive use of NSAIDS resulted in various adverse effects for instances myocardial infarction.[5-7] The phytochemical principles like polyphenols, had marked for the inhibition of inflammatory mediators TNF-á, NO, IL-1â and MCP-1. The other phytocompounds

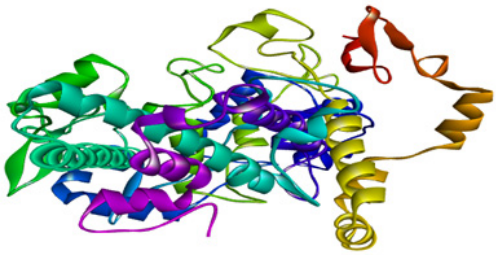

Fig. 1. COX-2 (Protein ID: 5IKR)

like polyphenols, quercetin and kaempferol also marked to inhibit NOs and COX-2.[8-11] Plants have been used due to various phytochemicals synthesized as secondary metabolites plant extracts and phytochemicals can be of great significance in therapeutic treatments. The compounds are known by their active substances such as phenols, alkaloids, and tannins.[12] No clinical trials compared the efficiency of various agents for the treatment of rheumatoid arthritis. The studies had shown COX-2 selective inhibitor provides effective relief of pain in rheumatoid arthritis.[13]

The docking research disclosed an engrossing perspective of stated ligands towards receptor COX-2. Protein Ligand interaction shown Arenarioside, Verbascoside, Myxopyroside, 3-Formylindole and 5-Hydroxy Methyl Furfural shown hydrogen bonds to ARG 216, ASN 144, HIS 226, GLY 225, VAL 220, VAL 228 illustrated in Table 3. The docking score of Arenarioside,

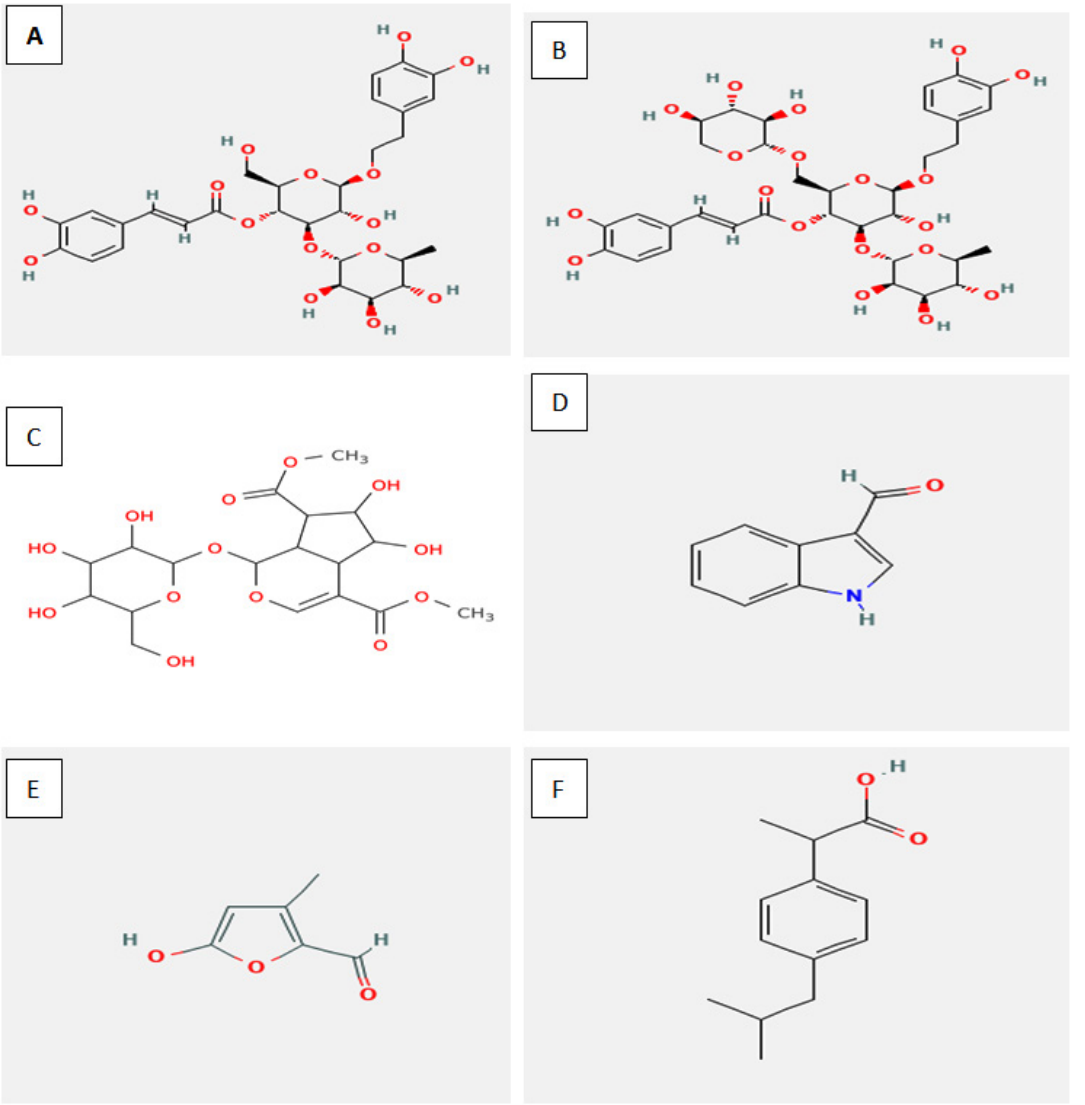

Fig. 2. Structures of Phytoconstituents A) Verbascoside B) Arenarioside C) Myxopyroside D) 3-Formylindole E) 5- Hydroxy methyl furfural F) Ibuprofen

Verbascoside, Myxopyroside, 3-Formylindole, 5-Hydroxy Methyl Furfural is around "16.4, -10.6, -6.5, -4.5, -4.7, 5.8 kcal/mol respectively. In the present study, five ligands of *Myxopyrum smilacifolium Blume* at the receptor COX-2 energetic site and the docking score was analyzed by the use of software Autodock 4.0. It shown good docking score of about -16.4 kcal/mol, -10.6 kcal/mol and -6.5 kcal/mol between Arenarioside, Verbascoside, Myxopyroside with receptor COX-2 which proved that it strongly inhibits the inflammatory mediators, as it shows strong binding affinity with receptor. The pharmacokinetic study was explored by SwisADME tool shown that Arenarioside, Verbascoside, Myxopyroside GI absorption is low where as 3-Formylindole,

Table 1. Phytoconstituents of *Myxopyrum smilacifolium Blume* representing Canonical Smiles

No.	Ligand	Pubchem ID	Canonical Smiles	Molecular Formula	Molecular Weight
1.	Verbascoside	5281800	CC1C(C(C(C(O1)OC2C(C(OC(C2OC(=O)C=CC3=CC(=C(C=C3)O)O)CO)OCCC4=CC(=C(C=C4)O)O)O)O)O)O	$C_{29}H_{36}O_{15}$	624.6
2.	Arenarioside	6442994	CC1C(C(C(C(O1)OC2C(C(OC(C2OC(=O)C=CC3=CC(=C(C=C3)O)O)COC4C(C(C(CO4)O)O)O)OCCC5=CC(=C(C=C5)O)O)O)O)O)O	$C_{34}H_{44}O_{19}$	756.7
3.	Myxopyroside	–	COC(=O)C1C(O)C(O)C2C1C(OC1OC(CO)C(O)C(O)C1O)OC=C2C(=O)OC	$C_{18}H_{26}O_{13}$	450.391
4.	3-Formylindole	10256	C1=CC=C2C(=C1)C(=CN2)C=O	C_9H_7NO	145.16
5.	5- Hydroxy methyl furfural	237332	C1=C(OC(=C1)C=O)CO	$C_6H_6O_3$	126.11
6.	Ibuprofen	3672	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O	$C_{13}H_{18}O_2$	206.28

Table 2. ADMET Analysis of phytoconstituents in *Myxopyrum smilacifolium Blume*

Ligands	Drug Likeness	Molar Refractivity	Consensus Log Po/W	H bond Acceptor	H Bond donors	GI Absorption
Verbascoside	3	148.42	-0.43	15	9	Low
Arenarioside	3	174.84	-1.95	19	11	Low
Myxopyroside	2	94.62	-2.53	13	6	Low
3-Formylindole	0	43.69	1.72	1	1	High
5- Hydroxy methyl furfural	0	30.22	0.19	3	1	High
Ibuprofen	0	62.18	3.00	2	1	High

[a]Acceptable Molecular weight range <500
[b]Acceptable range of Hydrogen bond donor ≤ 5
[c b]Acceptable range of Hydrogen bond acceptor ≥ 10
[d]High Lipophilicity (expressed as LogP, acceptable range < 5
[e]MR between 40 & 130

5-Hydroxy Methyl Furfural, 3-Formylindole GI absorption is high depicted in Table 3. Arenarioside, Verbascoside and Myxopyroside had shown high docking score around -16.4, -10.6 and -6.5 kcal/mol when compared with standard drug Ibuprofen -6.2 kcal/mol. Hence the research on phytoconstituents against inflammatory mediators is in need which replaces the NSAIDS so that their adverse effect can combat.

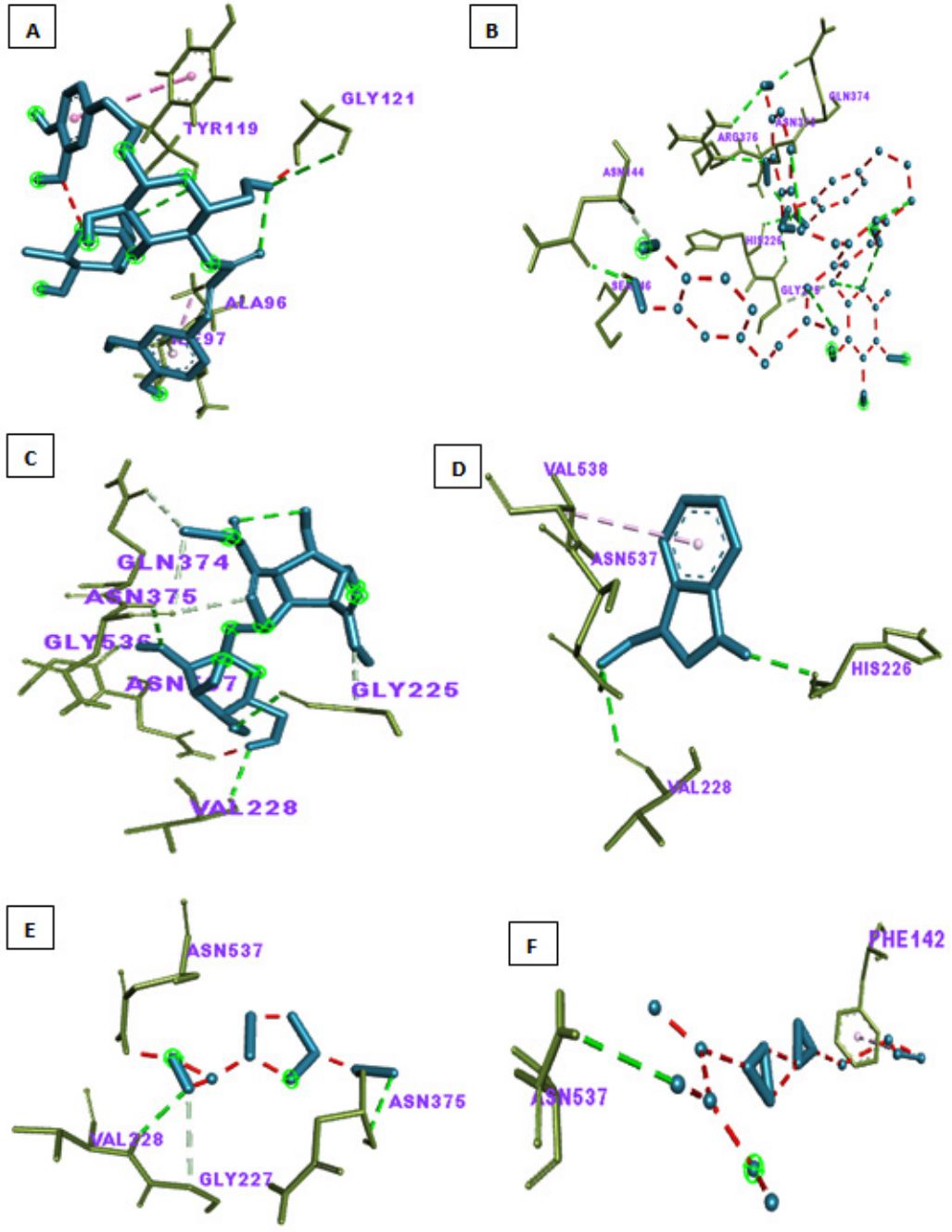

Fig. 3. 3D interactions of phytocompounds (Ligands) with receptor COX-2 A) Verbascoside B) Arenarioside C) Myxopyroside D) 3-Formylindole E) 5- Hydroxy methyl furfural F) Ibuprofen.

Table 3. Docking Simulation between COX-2 and Phytoconstituents in *Myxopyrum smilacifolium*

No.	Phytocompounds	Highest conformation Binding Energy (kcal/mole)	Hydrogen bonds
1.	Verbascoside	-10.6	TYR 119, ALA 96, HIS226, ILE 97
2.	Arenarioside	-16.4	ASN 144, ARG 376, ASN 375, GLN 374, HIS 226, SER 416, GLY 225
3.	Myxopyroside	-6.5	GLY 536, GLY 225, VAL 220, ASN 537, ASN 375, GLN 374
4.	3-Formylindole	-4.5	VAL 538, ASN 537, VAL 228, HIS 226
5.	5- Hydroxy methyl furfural	-4.7	ASN 537, VAL 228, GLY 227, ASN 375
6.	Ibuprofen	-6.2	PHE 142, ASN 537

Table 4. Docking score of Phytoconstituents at the active site of COX-2

Ligands	Mode of conformation RMS binding affinities in ΔG (Kcal/mol)								
	1	2	3	4	5	6	7	8	9
Verbascoside	-10.6	-10.1	-9.9	-8.5	-8.5	-8.4	-8.3	-8.1	-8.0
Arenarioside	-16.4	-16.1	-15.9	-15.3	-15.2	-14.9	-14.7	-14.6	-14.6
Myxopyroside	-6.5	-6.3	-6.2	-6.1	-6.0	-5.9	-5.9	-5.7	-5.6
3-Formylindole	-4.5	-4.5	-4.5	-4.4	-4.4	-4.2	-4.0	-4.0	-3.8
5- Hydroxy methyl furfural	-4.7	-4.6	-4.4	-4.3	-4.2	-4.1	-4.1	-4.0	-4.0
Ibuprofen	-6.2	-6.0	-5.7	-5.7	-5.7	-5.6	-5.6	-5.4	-5.4

CONCLUSION

An inflammatory mediator plays a vital role in arthritis. Limited Phytoconstituents were investigated for inhibition of inflammatory mediators in inflammatory conditions. The earlier studies on *Myxopyrum smilacifolium Blume* revealed the presence of irridoid glycosides. ADMET evaluation of phytoconstituents was carried on. The molecular docking results had shown the verdict that Arenarioside revealed the good docking score. SAR model is required prove its efficacy. The study outcome confirms the ethnomedicinal use of *Myxopyrum smilacifolium Blume* might be a good resource to suppress the inflammatory mediators in arthritis.

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Conflict of Interest

No conflict of Interest.

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