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Identification of novel lead compounds and mutational analysis of intercellular adhesion molecule 1 in combination with lymphocyte function-associated antigen 1 protein involved in Rheumatoid Arthritis using *in silico* approach

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ABSTRACT

The objective of the study is to identify novel lead compounds and analyze the effect of mutations that result in the disruption of the salt bridge between Lys39 on ICAM1 (Intercellular Adhesion Molecule 1) and Glu241 on LFA1 (Lymphocyte function Associated Antigen 1), which could reduce the effect of Rheumatoid Arthritis. Work is done on the ICAM1-LFA1 (PDB ID: 1MQ8) protein. Mutations were induced into ICAM1 and LFA1 using SIFT and PredictSNP. Homology modeling was done using Discovery Studio. Protein-Protein docking was done using ZDOCK to get ICAM1^{M}-LFA1 and ICAM1^{M}-LFA1^{M} structures. Secondary structure analysis and non-bonded interaction studies were done. Then active site prediction was carried out on ICAM1-LFA1, ICAM1^{M}-LFA1 and ICAM1^{M}-LFA1^{M} structures. Compounds from plant and animal sources having immunosuppressant, anti-TNF and anti-inflammatory properties as well as standard drugs active against Rheumatoid Arthritis were identified. ADMET studies were done. Molecular docking was done using Lead IT. The best results were chosen based on their e-values. The *In silico* analysis of the current work proves that mutations in ICAM1 lead to disruption of the salt bridge between Lys39 and Glu241, which could reduce the effect of Rheumatoid Arthritis. Probable drugs effective against Rheumatoid Arthritis were identified from various plant and animal sources based on lowest e-value. The standard mutations in ICAM1 and use of various natural compounds as probable drugs could reduce the effects of Rheumatoid Arthritis. QSAR and molecular dynamics can be done on the best compounds chosen as probably drugs and further experimental analysis can be carried out.

Keywords: Rheumatoid Arthritis; ICAM1; LFA1; Lys39; Glu241; docking.

Abbreviations:
ICAM1: Intercellular adhesion molecule 1 protein; LFA1: Lymphocyte function-associated antigen 1 protein; M (^{M}): Proteins where mutations have been induced

INTRODUCTION

Rheumatoid Arthritis is a progressive inflammatory autoimmune disease with articular and systemic effects [1]. Modern advances in the medical treatment of Rheumatoid Arthritis have greatly alleviated patients' symptoms. Development of even more effective remedies could be spurred by discovery of the disease's etiology, but the cause of Rheumatoid Arthritis remains poorly understood and may involve a combination of genetic, environmental and stochastic factors [1]. It is of unknown etiology affecting approximately 1% of the world [2].

Due to the key role in the interaction between LFA1 (Lymphocyte function-associated antigen 1) and ICAM1 (Intercellular Adhesion Molecule 1) in immune responses, defining its structural basis is of great

interest. Furthermore, development of pharmaceutical antagonists of this interaction is of great importance for the treatment of autoimmune diseases.

The structure of the I domain of integrin αLβ2 bound to the Ig superfamily ligand ICAM1 reveals the open ligand binding conformation and the first example of an integrin-IgSF interface. The I domain Mg^{2+} directly coordinated Glu-34 of ICAM1 and a dramatic swing of I domain residue Glu-241 enables critical salt bridges at residues Lys-39 in ICAM-1 and Glu-241 in the I domain and Glu-34 in ICAM-1 and the Mg^{2+} ion in the I domain [4].

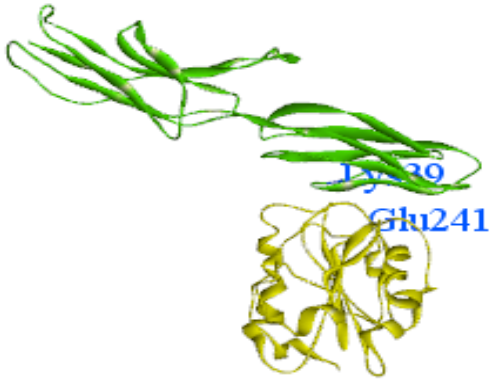

Figure 1. The green chains represent ICAM1 and the yellow chains represent LFA1.

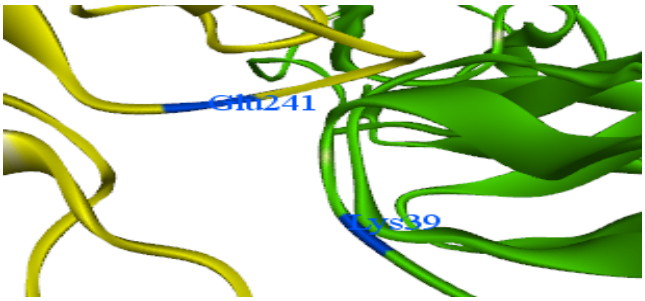

Figure 2. In the ICAM1-LFA1 structure, the salt bridge between Lys39 on ICAM1 and Glu241 on LFA1 is labeled (in blue)

The pathobiology of Rheumatoid Arthritis is multifaceted and involves T cells, B cells and the complex interaction of many pro-inflammatory cytokines, including TNF-α and IL-6. These cytokines are messengers that activate and differentiate effector cells that cause local and systemic symptoms associated with this disease [1]. Due to the association between ICAM1 on the synovial macrophage and LFA1 on the self-reactive Th 1 cell, cytokines such as IL-1, IL-6, IL-11, IL-18, TNF-α (Tumor necrosis factor alpha) are released. TGF-β, IL-6, IL-21, IL-1b and IL-23 appear to be involved in Th cell differentiation, thereby are involved in the release of IL-17. The action of all these pro-inflammatory cytokines results in the conversion of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) present on the Osteoblasts, mononuclear cells that synthesize the bone, to RANK (Receptor Activator of Nuclear Factor Kappa-B) on the Osteoclast. Osteoclasts are multinucleated cells formed by the fusion of mononuclear progenitors of the monocyte/macrophage family. The primary mediators of bone resorption, these cells populate the synovial membranes of patients with Rheumatoid Arthritis and are polarized on bone. Macrophage-driven osteoclastogenesis requires the presence of macrophage colony-stimulating factor (MCSF) and results from the interaction of the RANK and the RANK ligand (RANKL). RANKL expression is regulated by pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-17. MCSF, IL-6 and IL-11 can also support human osteoclast formation from peripheral blood mononuclear cells by a RANKL-independent mechanism [1].

After extensive literature survey, it was established that inducing mutations in ICAM1 sought to reduce inflammation in Rheumatoid Arthritis. In the case of Multiple Sclerosis, which is quite similar to Rheumatoid Arthritis, K allele of the ICAM1 codon 469 mutation was thought to contribute to the pathogenesis of MS through increasing levels of sICAM1 and establish inflammation [3]. ICAM1 expression was seen to decline in patients who had a significant clinical response to drug treatment or due to other alterations [5]. Non synonymous mutations were thus obtained for ICAM1. For LFA1, the mutations were generated from PDB. The mutations were then manually induced in both individual sequences to check for a distortion of structure, thereby leading to a variation in function.

In response to the prevalence of Rheumatoid Arthritis among people and the dire need of a cure, this study aims to highlight a pathway implicated in Rheumatoid Arthritis. The study aims to analyze the folding mechanism of $ICAM1^{M}$ with LFA1 and $ICAM1^{M}$ with $LFA1^{M}$ with special focus on the salt bridge and to analyze effect of mutation on structure-function relationship. The binding pattern of ICAM1-LFA1, $ICAM1^{M}$-LFA1 and $ICAM1^{M}$-$LFA1^{M}$ proteins with ligand library will also be studied.

This study aims to generate natural compounds that might have the potential to be candidate drugs thereby relieving the symptoms of Rheumatoid Arthritis. The toxicity of the selected best compounds will also be studied, to check if the candidate drugs are viable. Mutational analysis is to be performed as a way to block or distort ICAM-LFA1 structure, thereby reducing inflammation.

MATERIALS AND METHODS

The databases and tools used for this study were Accelrys Discovery Studio, CASTp (http://sts.bioengr.uic.edu/castp/), Chou & Fasman Secondary Structure Prediction Server (http://www.biogem.org/tool/chou-fasman/), dbSNP (www.ncbi.nlm.nih.gov/SNP), FlexX (BioSolve IT), GenBank (www.ncbi.nlm.nih.gov/genbank), KEGG Database (www.genome.jp/kegg/), PoPMuSiC (http://babylone.ulb.ac.be/popmusic), Porter (distill.ucd.ie/porter/), PubChem Project

(https://pubchem.ncbi.nlm.nih.gov/), PubMed (www.ncbi.nlm.nih.gov/pubmed), Predator (http://mobyle.pasteur.fr/cgi-bin/portal.py?#forms::predator), PredictSNP(http://loschmidt.chemi.muni.cz/predictsnp/), RCSB PDB (www.rcsb.org/), SAVes (nihserver.mbi.ucla.edu/SAVES/), SIFT (http://sift.jcvi.org/), UniProt (www.uniprot.org/), ZDOCK (zdock.umassmed.edu/) and Zinc DB (http://zinc.docking.org/).

The entire work can be divided into three parts (Part A, Part B and Part C).

Part A

Part A dealt with identifying the target protein, active site prediction and minimization. After literature survey, the target was identified as the ICAM1-LFA1 protein and the protein structure was downloaded from RCSB PDB having accession number IMQ8. Mutations were then induced to ICAM1 using dbSNP, SIFT and validated using PredictSNP and induced to LFA1 through literature survey and SIFT, and validated using PredictSNP (LFA1 mutations were mentioned on RCSB PDB Accession number: 1MQ8).

Homology modeling was done using Discovery Studio to model the structure of ICAM1, mutated ICAM1 ($ICAM1^M$), LFA1 and mutated LFA1 ($LFA1^M$).

Table 1. Homology Modeling Results

Model Structure Molecule	DOPE scores	RMSD scores
ICAM1	-15428.435547	0.304
MutatedICAM1	-15461.609375	0.286
LFA1	-20487.187500	0.276
MutatedLFA1	-20334.146484	0.277

The above table shows the results of homology modeling, done using Discovery Studio in terms of DOPE scores and RMSD scores. DOPE refers to discrete optimized protein energy and RMSD refers to root-mean-square deviation. The above results displayed are the best models obtained for each sequence (ICAM1, Mutated ICAM1, LFA1, and Mutated LFA1) after homology modeling. Models having lower RMSD scores were chosen and displayed in the above table. Protein-protein docking was then done using ZDOCK to obtain the structures of $ICAM1^M$-LFA1 and $ICAM1^M$-$LFA1^M$. Protein minimization for the template protein and the two mutated proteins was done using Discovery Studio. The active site pockets were identified using CASTp and minimization was done using Discovery Studio. The mutated proteins $ICAM1^M$-LFA1 and $ICAM1^M$-$LFA1^M$ were analyzed and compared to the template ICAM1-LFA1 protein using secondary structure prediction tools such as Chou Fasman, Predator and Porter as well as non-bonded interaction studies using Discovery Studio.

Part B

Part B dealt with identifying the lead compounds and lead minimization. Through literature survey, compounds from natural sources were identified and their structures were downloaded from PubChem Project and Zinc DB. The same was done for standard drug compounds taken for comparison studies. Three separate ligand libraries were prepared using Discovery Studio for plant sources, animal sources and standard drugs. Ligand minimization was done followed by filtering using Lipinski's Rule of Five. ADMET properties were studied for plant compounds only. All animal compounds and standard drugs were considered for further studies irrespective of the filtering process because the animal compounds which were basically essential fish oils had high molecular weight, but were known to have medicinal properties. The standard drugs were already in use.

Part C

The third part involved molecular docking using FlexX (BioSolve IT) where the template protein and the two mutated protein active sites were docked against the three ligand libraries of plant compounds, animal compounds and standard drugs. Best results were chosen based on e-value.

RESULTS AND DISCUSSION

Secondary Structure Analysis

The sheet and helix ranges where distortions (point mutations, etc.) occur in $ICAM1^M$-LFA1 and $ICAM1^M$-$LFA1^M$ when compared to ICAM1-LFA1 are displayed in Table 2. Secondary structure analysis shows that the mutations induced in ICAM1 bring about structural changes which could affect the function. This change in function could result in lowering the effects of Rheumatoid Arthritis, and hence help in the management of the disease.

Non Bonded Interaction Analysis

Comparisons were done with special emphasis on the salt bridge between Lys39 on ICAM1 and Glu241 on LFA1 in the ICAM1-LFA1 structure. Due to the effect of the various mutations, the salt bridge interaction of interest is no longer present (displayed in Table 3). Also, the number of non-bonded interactions is less in the mutated structures (8 interactions each) when compared to the wild structure (12 interactions). This indicates possible weaker interactions and less stable complexes.

Thus, by the secondary structure analysis and the study of non- bonded interactions, we may conclude that mutations in ICAM1 can be potentially effective in controlling Rheumatoid Arthritis.

Table 2. Secondary Structure Prediction

Tools	Helices			Sheets		
	ICAM1-LFA1	ICAM1^{M}-LFA1	ICAM1^{M}-LFA1^{M}	ICAM1-LFA1	ICAM1^{M}-LFA1	ICAM1^{M}-LFA1^{M}
Chou Fasman	106-114	106-*115*	106-114	119-123	-	119-123
	197-214	197-*215*	197-214			
	222-259	222-*239*	222-240			
				340-358	340-358	340-*360*
	-	*244-259*	*244-259*			
Predator	158-164	158-*173*	158-*173*	113-120	-	-
				-	*120-125*	*120-125*
	201-215	201-*217*	201-215			
				-	*141-150*	*141-150*
	220-227	*222*-227	220-227			
				-	*183-190*	*183-190*
Porter	199-215	199-*214*	-	-	*172-176*	*172-176*
				-	*232-236*	*232-236*
				-	*286-293*	*286-293*
				-	*310-316*	*310-316*

The *italics* and underlined region define the distortions in comparison to the ICAM1-LFA1 sequence. The numbers in each column represent the range of either helices or sheets in the secondary structure of the protein. Secondary structure prediction was carried out using tools such as Chou Fasman, Predator and Porter.

Table 3. Non Bonded Interaction Analysis

ICAM1-LFA1			ICAM1^{M}-LFA1			ICAM1^{M}-LFA1^{M}		
Interaction	**Donor (From)**	**Acceptor (To)**	**Interaction**	**Donor (From)**	**Acceptor (To)**	**Interaction**	**Donor (From)**	**Acceptor (To)**
Hydrogen Bond;Electrostatic	A:LYS39	B:GLU241	Electrostatic	:LYS67	:GLU243	Hydrogen Bond;Electrostatic	:LYS67	:GLU243
Electrostatic	B:MG901	A:GLU34	Hydrogen Bond	:TYR110	:HIS226	Hydrophobic	:LEU157	:PHE159
Hydrogen Bond	B:HOH1	A:GLU34	Hydrogen Bond	:THR200	:LEU45	Hydrophobic	:HIS226	:PHE200
Hydrogen Bond	A:ASN68	B:THR243	Hydrophobic	:LEU157	:PHE159	Hydrophobic	:VAL36	:LEU229
Hydrogen Bond	A:GLN73	B:THR243	Hydrophobic	:LEU45	:TYR202	Hydrophobic	:ILE37	:LEU229
Hydrogen Bond	B:THR206	A:GLU34	Hydrophobic	:LEU229	:LEU38	Hydrophobic	:PRO39	:MET227
Hydrogen Bond	A:PRO36	B:SER141	Hydrophobic	:PRO39	:MET227	Hydrophobic	:PHE200	:LYS225
Hydrophobic	A:PRO36	B:MET140	Hydrophobic	:VAL44	:LEU229	Hydrophobic	:TYR202	:LEU45
Hydrophobic	A:MET64	B:MET140	NS	NS	NS	NS	NS	NS
Hydrophobic	A:MET64	B:LEU205	NS	NS	NS	NS	NS	NS
Hydrophobic	A:TYR66	B:LEU205	NS	NS	NS	NS	NS	NS
Hydrophobic	B:HIS264	A:LYS39	NS	NS	NS	NS	NS	NS

The above table shows the non bonded interaction analysis, where data is obtained using Discovery Studio. The amino acid interaction between donor and acceptor atom positions is also displayed.

Protein-Ligand Docking

Protein-Ligand Docking was done using Lead IT (FlexX). Lower docking scores indicate a stable system and thus a likely binding interaction.

The standard drugs considered for analysis are Methotrexate, Azathioprine, Celecoxib, Glucosamine and Sulfasalazine respectively. Each ligand was docked with native and mutated forms of ICAM1-LFA1 complex using default parameters of FlexX. From the outcome of analysis, it was observed that Sulfasalazine displayed better affinity of binding with ICAM1-LFA1 (-30.9510 kcal/mol) whereas Methotrexate was found to be the drug of choice against ICAM1^{M}-LFA1 and ICAM1^{M}-LFA1^{M}, respectively, and hence considered as standard drug against these mutated forms (refer to Table 4).

ICAM1-LFA1

While Sulfasalazine has lower docking score than malic acid, malic acid has more number of interactions than Sulfasalazine (displayed in Table 5). Sulfasalazine also causes severe side effects when administered. Side effects include stomach upset, nausea, vomiting, loss of appetite, headache, dizziness, or unusual tiredness. Sulfasalazine may also cause temporary male infertility which is reversible when the medication is stopped. This medication may rarely cause very serious allergic reactions (e.g., Stevens-Johnson syndrome), blood disorders (e.g., agranulocytosis, aplastic anemia), liver damage, nerve/muscle problems and infections [7].

Table 4. Comparison of dock scores of standard drugs vs native and mutated forms of ICAM1-LFA1 complex

Protein Complex	Docking Score (kcal/mol)				
	Methotrexate	Azathioprine	Celecoxib	Glucosamine	Sulfasalazine
ICAM1-LFA1	-30.5668	-26.7913	-24.5477	-24.2894	-30.9510
ICAM1^{M}-LFA1	-31.0782	-22.4541	-18.7684	-26.1496	-22.7127
ICAM1^{M}-LFA1^{M}	-23.9502	-18.7837	-19.6903	-23.6060	-21.3368

Table 5. ICAM1-LFA1 Protein-Ligand Docking Results

Compound Name	Docking Score (kcal/mol)	No. of Interactions	Amino Acid	Amino Acid Atom	Ligand Atom	Length (A°)
Malic acid (Plant Source)	-25.1720	9	SER139	HN	O5	1.7973
			SER139	HG	O1	2.4688
			SER139	HG	O5	1.5485
			THR206	HG1	O1	1.9439
			ASP239	HN	O4	2.4445
			GLY240	HN	O2	2.4560
			GLY240	HN	O4	1.9084
			GLU241	HN	O4	1.9034
			THR206	OG1	H13	1.8799
Retinol (Animal Source)	-10.4184	2	THR206	HG1	O1	1.9531
			THR206	OG1	H51	1.8032
Sulfasalazine (Standard Drug)	-30.9510	8	SER139	HG	O5	2.4436
			SER141	HG	O5	2.3948
			THR206	HG1	O5	1.8897
			ASP239	HN	O6	1.7767
			GLY240	HN	O4	1.6210
			GLU241	HN	O4	1.8984

The above table shows the docking scores in kcal/mol, the amino acid, and the interaction with the amino acid and ligand atom, as well as the bond length in angstrom units. The compounds being compared are Malic acid (plant source), Retinol (animal source) and Sulfasalazine (standard drug).

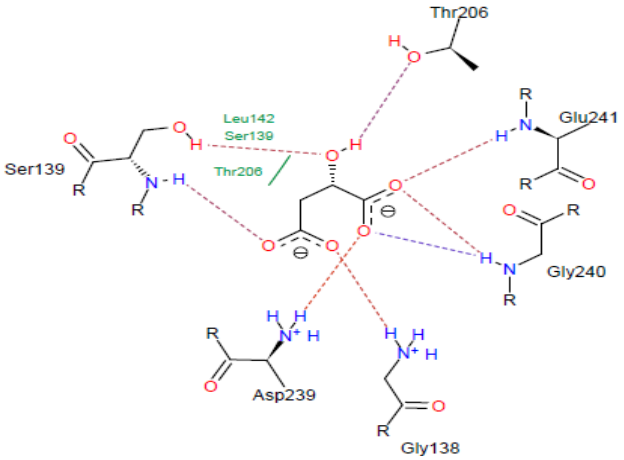

Figure 3. Malic acid has lowest docking score (-25.1720) amongst lead compounds from plant sources and hence shows highest binding affinity to ICAM1-LFA1 active site.

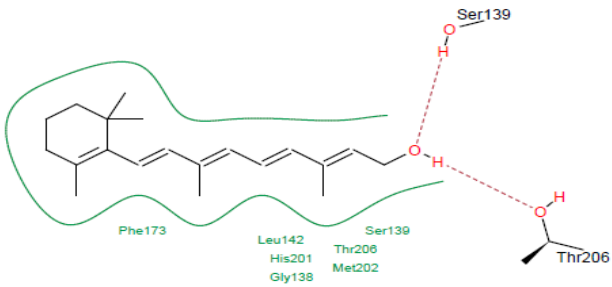

Figure 4. Retinol has lowest docking score (-10.4184) amongst lead compounds from animal sources and hence shows highest binding affinity to ICAM1-LFA1 active site.

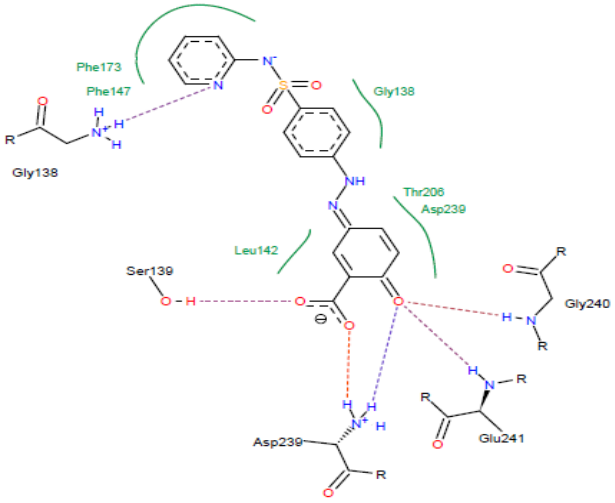

Figure 5. Sulfasalazine has lowest docking score (-30.9510) amongst standard drugs and hence shows highest binding affinity to ICAM1-LFA1 active site.

ICAM1^{M}-LFA1

While Methotrexate has more number of interactions and lower docking score than succinic acid and retinol (displayed in Table 6), it also causes various severe side effects when administered. Methotrexate can cause side effects such as abdominal pain, chills or fever, dizziness, hair loss, headache, light sensitivity, itching, liver problems, low blood counts [8]. Women must avoid becoming pregnant while taking this medication. Pregnant women who have psoriasis or rheumatoid arthritis must not use Methotrexate [6]. The below table shows the docking scores in kcal/mol, the amino acid, and the interaction with the amino acid and ligand atom, as well as the bond length in angstrom units. The compounds being compared are Succinic acid (plant source), Retinol (animal source) and Methotrexate (standard drug).

Table 6. ICAM1^{M}-LFA1 Protein-Ligand Docking Results

Compound Name	Docking Score (kcal/mol)	No. of Interactions	Amino Acid	Amino Acid Atom	Ligand Atom	Length (A°)
Succinic acid (Plant Source)	-22.1889	4	LYS203	HZ2	O4	2.2864
			LYS222	HZ3	O3	2.3163
			HIS223	HN	O1	1.7183
			VAL224	HN	O1	2.0854
Retinol (Animal Source)	-10.5817	3	MET227	HN	O1	2.3853
			LEU228	HN	O1	2.0383
			PHE198	O	H51	2.2283
Methotrexate (Standard Drug)	-31.0782	7	SER164	HN	N11	2.3393
			GLN197	HN	O2	1.7487
			PHE198	HN	N9	2.0524
			PHE198	HN	N10	2.2691
			LYS222	HN	O4	2.4766
			LYS222	HZ3	O4	1.9567
			HIS223	HN	O5	1.9902

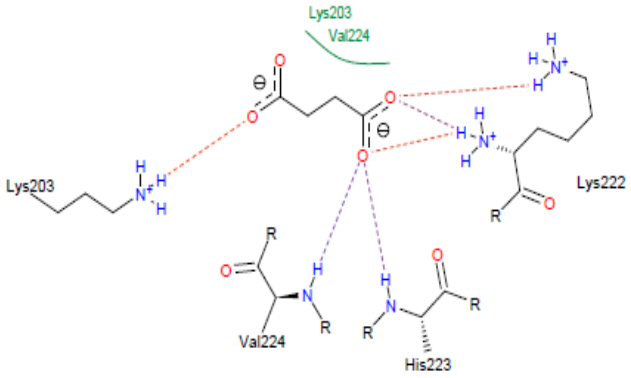

Figure 6. Succinic acid has lowest docking score (-22.1889) amongst lead compounds from plant sources and hence shows highest binding affinity to ICAM1^{M}-LFA1 active site.

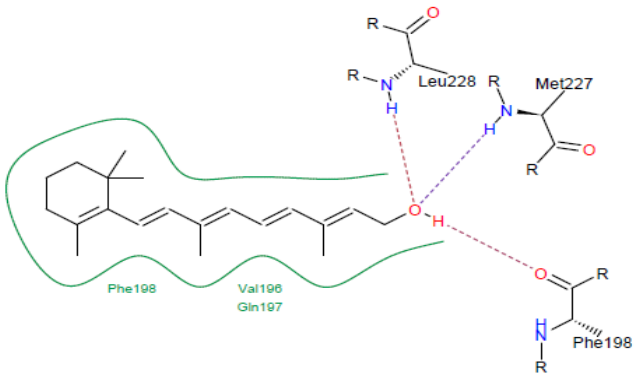

Figure 7. Retinol has lowest docking score (-10.5817) amongst lead compounds from animal sources and hence shows highest binding affinity to ICAM1^{M}-LFA1 active site.

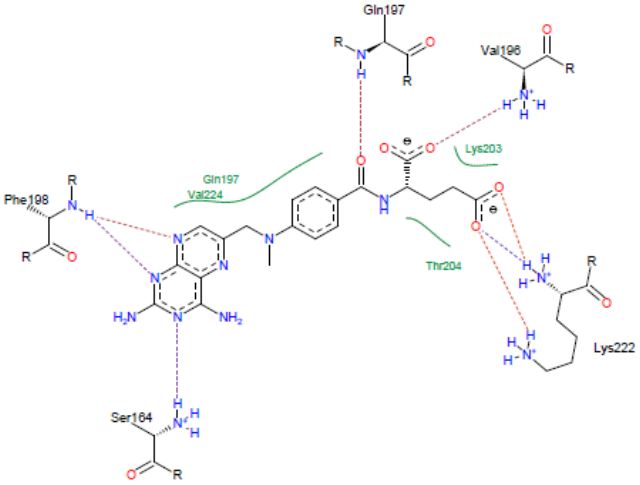

Figure 8. Methotrexate has lowest docking score (-31.0782) amongst standard drugs and hence shows highest binding affinity to ICAM1^{M}-LFA1 active site.

ICAM1^{M}-LFA1^{M}

2-hydroxycinnamic acid has lower docking score and equal number of interactions compared to methotrexate (displayed in Table 7) [6]. Hence 2-hydroxycinnamic acid can be an effective probable drug. The below table shows the docking scores in kcal/mol, the amino acid, and the interaction with the amino acid and ligand atom, as well as the bond length in angstrom units. The compounds being compared are 2-hydroxy cinnamic acid (plant source), Retinol (animal source) and Methotrexate (standard drug).

Table 7. ICAM1^{M}-LFA1^{M} Protein-Ligand Docking Results

Compound Name	Docking Score (kcal/mol)	No. of Interactions	Amino Acid	Amino Acid Atom	Ligand Atom	Length (A°)
2-hydroxy cinnamic acid (Plant Source)	-24.5677	5	LYS203	HZ1	O1	2.3774
			LYS203	HZ3	O1	2.4356
			LYS222	HN	O2	1.5395
			LYS222	HZ2	O3	1.8523
			HIS223	HN	O2	2.0832
Retinol (Animal Source)	-12.6892	3	GLU205	HN	O1	2.3865
			PHE206	HN	O1	1.6000
			PHE206	O	H51	1.5239
Methotrexate (Standard Drug)	-23.9502	5	ARG76	HH12	O4	2.3270
			ARG76	HH12	O5	1.4946
			ARG76	HH22	O4	1.6891
			MET165	SD	H52	2.3252
			MET165	O	H55	2.4043

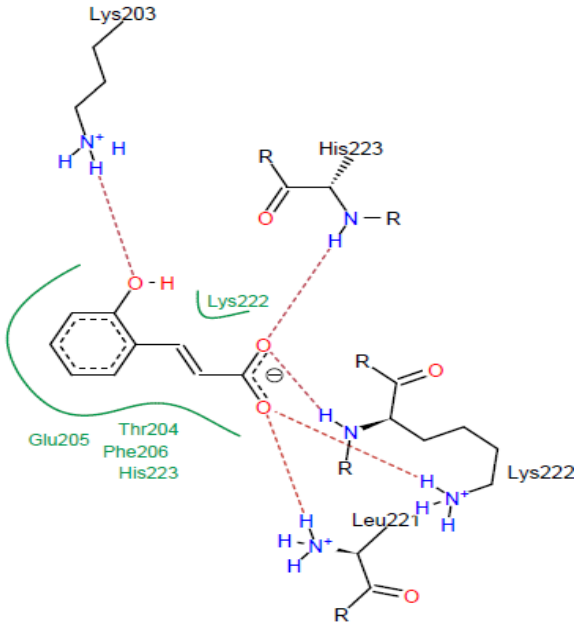

Figure 9. 2-hydroxycinnamic acid has lowest docking score (-24.5677) amongst lead compounds from plant sources and hence shows highest binding affinity to ICAM1^{M}-LFA1^{M} active site.

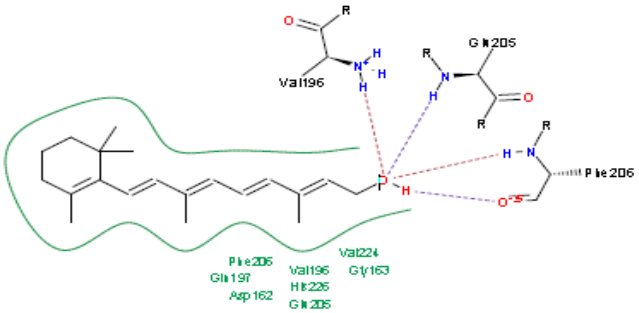

Figure 10. Retinol has lowest docking score (-12.6892) amongst lead compounds from animal sources and hence shows highest binding affinity to ICAM1^{M}-LFA1^{M} active site.

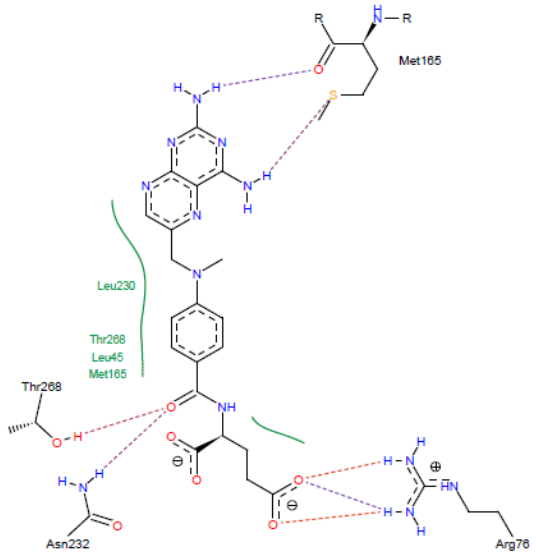

Figure 11. Methotrexate has lowest docking score (-23.9502) amongst standard drugs and hence shows highest binding affinity to ICAM1^{M}-LFA1^{M} active site.

CONCLUSION

Through literature survey, we learned that Rheumatoid Arthritis is one of the most prevalent autoimmune disorders that cause severe joint pain and inflammation in old and young alike.

The *in silico* analysis of the current study, proves that the eight non-synonymous deleterious mutations (G241R, P352L, R478W, K155N, V315M, R397Q, P194A, E283K) in ICAM1 protein lead to disruption of the salt bridge between Lys39 on ICAM1 (Chain A) and Glu241 on LFA1 (Chain B), which could reduce Rheumatoid Arthritis. Secondary structure analysis and non-bonded interactions validated our theory that mutations in ICAM1 could cause a structure-function relationship distortion.

Probable drugs effective against Rheumatoid Arthritis were identified from various plant sources such as *Andrographis paniculata, Artemisia vestita, Berberis vulgaris, Bupleurum falcatum, Camellia sinensis, Campylotropis hirtella, Clerodendron trichotomum, Curcuma longa, Dracocephalum kotschyi, Glycyrrhiza uralensis, Salvia mirzayanii, Tripterygium wilfordii, Urtica dioica* and animal sources such as fish oils. Since they are mainly derived from medicinal plants and essential fish oils, they are less likely to have side effects. While the standard drugs such as Methotrexate, Sulfasalazine, etc. showed better binding affinity, their toxic properties make them less viable as medications for chronic use. Toxicity prediction and analysis of the best natural compounds show low carcinogenicity and side effects compared to the FDA approved drugs in various animal models.

Future screening of the probable drug compounds using QSAR studies will identify the best lead compounds to initiate experimental analysis and clinical trials. Molecular dynamic studies can also be carried out to garner a proper understanding of drug simulations in the body. Site-Directed Mutagenesis can be carried out to study the effect of the mutations discussed. These mutations, which reduce the effects of rheumatoid arthritis, might open up a new path into the management and treatment of the disease.

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