MOLECULAR DOCKING STUDIES OF PHYTOCOMPOUNDS FROM "WITHANIA SOMNIFERA" AGAINST IL-6 AND JAK3 TARGETS IN RHEUMATOID ARTHRITIS

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE AWARD OF THE DEGREE
OF

MASTER OF SCIENCE
IN
BIOTECHNOLOGY

Submitted by:

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CANDIDATE'S DECLARATION

I hereby certify that the work which I presented in the Major Project-II entitles "Molecular docking studies of phytocompounds from "Withania somnifera" against IL-6 and JAK3 targets in Rheumatoid Arthritis" in fulfilment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own, carried out during a period from Gagan Vishal Saini, under the supervision of Dr. Navneeta Bharadvaja.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other University. The work has been communicated in Scopus journal with the following details:

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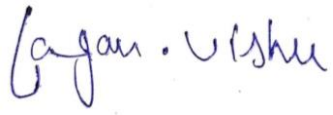

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CERTIFICATE

I hereby certify that the Project dissertation **titled "Molecular docking studies of phytocompounds from "*Withania somnifera*" against IL-6 and JAK3 targets in Rheumatoid Arthritis"** which is submitted by **Gagan Vishal Saini, 2K19/MSCBIO/21**, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science, is a record for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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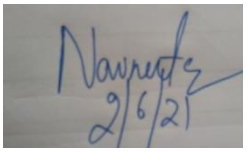

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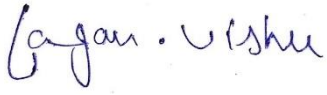

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ABSTRACT

Withania somnifera is the high valued plant known for its surprising therapeutic potentials. Withania somnifera is a significant shrub known for its versatility in ayurvedic system used for treatment of many disorders, from neurogenerative disorder to inflammatory illness. Rheumatoid arthritis (RA) is an autoimmune disease that is persistent in nature and with-long lasting effects, that is associated with joint pain, chronic inflammation, cartilage damage and bone erosion. Globally, 1-3 % of the population is afftected by it. The Rheumatoid arthritis is characterized by chronic inflammation, that is coordinated by Cytokine signaling and Signaling Pathways. And as we know Withania somnifera has anti-inflammatory properties that could use against Rheumatoid arthritis. IL-6 and JAK3 are connected with pathogenesis of rheumatoid arthritis (RA). Targeting these cytokines and signaling may open new approaches to treat Rheumatoid Arthritis. Docking studies concluded phyto constituents of Withania somnifera may have immense therapeutic potential against both anti-rheumatoid arthritis targets

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1. CHAPTER 1 INTRODUCTION

1.1.Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that is persistent in nature and with-long lasting effects, that is associated with joint pain, chronic inflammation, cartilage damage and bone erosion. Globally, 1-3 % of the population is suffering from this illness. Females are 2-3 times more susceptable [1] to the Rheumatoid Arthritis disorder than males especially those women who are having an age of 50-55 years. RA is characterized by Swelling around the synovial joints, chronic pain, stiffed muscles or joints, Tenderness and excaherbation in synovial joints including Knee joint, Elbows, Wrist, Shoulder joints knuckles and feet in the human body. Synovia or Synovial fluid, a viscous and thick fluidy substance (because hyaluronic acid is present in large amount; consisting of high protein content) is present in the synovial cavity, that helps in lubrication of synovial joints during friction between two bones[2]. Synovial joints and synovial cavity are lined by a 1-3 cells thick layer of membrane called the Synovial lining. Synovial cells that are present there provide nutrition to the cartilage and bone.

Synovial hypertrophied is the characterization of RA, in which normal synovial lining transforms from (1-3 cells) thick layer to 8-10 cells thick layer in result, joint space reduces. Joint space reduces, when synovial cavity is heavily targeted by own body's immune mechanism. Cavity is heavily accumulated with immune cells lymphocytes (T and B cells), inflammatory cells-neutrophils, mast cells, eosinophils, and macrophages. Angiogenesis occurs because of this auto-immune operation where new blood vessels are found near the inflamed area. Due to this, end result gets seriously affected by bones deformation, cartilage breakage, bones erosion and dysfunction of joints. Rheumatoid Arthritis escalates in a series of processes, several of phases occur before the clinical happening of Inflammatory Arthritis[3]. These pre-rheumatoid arthritis phases can be further studied to understand the mechanism pathophysiology of Rheumatoid Arthritis development/pathogenesis, so it can be used to target the Rheumatoid Arthritis.

No long-lasting and sustained treatment is available till now, but various Disease Modifying Anti-Rheumatic Drugs (DMARDs), steroidal drugs, and non-steroidal anti-inflammatory drugs (NSADs) are discovered[4] during the studying about Rheumatoid Disease since 1990s. Since no permanent treatment is there, people afftected with Rheumatoid Arthritis prefer these kinds of anti-inflammatory and steroidal drugs to get relief from pain and symptoms, although these drugs are costly with severe to low side-effects. This is the exact reason we have to find a way to deal with this chronic inflammatory illness by developing a treatment with maximum benefits,low cost, and less side-effects and by taking this anti-rheumatoid research to a next level to help scientific community. For many years a lot of studies has been done to find the exact specific trigger for Rheumatoid Arthritis. Several studies have failed to explain the exact causing agent related to the RA. However, Genetic and molecular studies have provided the information about molecular basis of RA, that is how cell signaling and signaling pathways play a role in Rheumatoid arthritis pathogenesis. In this major project, we selected the two major protein pro-inflammatory mediators involved in signaling pathways of Rheumatoid Arthritis that is Interleukin-6 and JAK3 as anti-rheumatoid arthritis targets. And also chosen the 18 phytocompounds (given in table 3.1) of Withania somnifera as 18 ligands that were going to interact with our protein targets (IL6 and JAK3). Our main objective was to predict the best oriented ligand-receptor complex structure with highest binding and stablity through molecular docking using computation methods such as SwissDock, Chimera, Molegro Molecular Viewer, and Open Babel softwares.

1.2.Interleukin-6

Interleukin 6 is basically a 26 kilo Dalton glycol-peptide belong to gene located at chromosome 7[5]. Various types of cells including B cells, T cells and other kind of immune cells that produce IL-6. IL-6 belongs to the member of the Interleukin cytokine family. In case of Rheumatoid arthritis; IL-6 plays a vital role in its pathogenesis[6]. Synovial fluid is fully abundant of IL-6, that helps in coordinating the damage of cartilage and bones. That’s why IL-6 is the perfect for anti-rheumatoid arthritis target.

1.3.JAK3

Jak3 belong to a tyrosine kinases family known as Janus Kinases. They play an important role as switching system that deactivate or activates the type cytokine I, Cytokine II, certain growth factors and their interaction with their receptors in signalling processes[7]. Jak3 is one of four members of the Janus Kinases. Janus kinases is also known as signal transducers and activators of JAK STAT pathways[8] that have shown immense promise in the treatment of Rheumatoid Arthritis. Both IL-6 and JAK3 are connected with pathogenesis of rheumatoid arthritis (RA). Targeting these cytokines and signaling may open new approaches to treat Rheumatoid Arthritis.

1.4.*Withania somnifera*: A medicinal Plant

Withania somnifera is the high valued plant known for its surprising therapeutic potentials. Withania somnifera is a significant shrub known for its versatility in ayurvedic system[9] used for treatment of many disorder, from neurogenerative disorder to inflammatory illness. It is a xerophytic plant, found in dried and hotter regions. It belongs to the Solanaceae family. Since ancient times, this medicinal shrub has been used by people over the generation for medicinal purposes. This plant is also famous in countries like China, Bangladesh, Nepal and sri Lanka just because phytochemical's therapeutic effects[10]. We Indians are also have been familiar with its medicina uses. Withania somnifera is the Indian Ginseng and called as Ashwagandha in Hindi[11]. It is known for medicinal properties including Anti-inflammatory[12], Anti-bacterial, Aphrodisiac, Anti-cancer[11], Adaptogenic, Anti-depression, and Anti-stress properties. Dried roots are rich in phytochemical that could be used for therapeutic use, studies show that leaves also have medicinal compounds. This plant has many phyto-compounds[13] including Phenolics, Alkaloids, Steroidal and other compounds[14].

The Rheumatoid arthritis is characterized by chronic inflammation, that is coordinated by Cytokine signaling and Signaling Pathways. And as we know Withania somnifera has anti-inflammatory properties that could use against Rheumatoid arthritis; which is an inflammatory disease. In this project, 18 phytocompounds were selected that may have an approach against Anti-rheumatoid arthritis target (IL6 and JAK3). We approached target-

ligand binding method to know the best complex between the targets (IL-6 and JAK3) and 18 phyto-compounds of Withania somnifera via molecular docking method (this is a blind docking).

2. CHAPTER 2 LITERATURE REVIEW

Withania somnifera is used in Ayurveda for Anti-inflammatory, Anti-bacterial, Anti-cancer, Anti-stress, Anti-depression, and other medicinal properties[15] and it has the potential to reduce inflammation[16] and Reactive Oxygen Species(ROS), apoptosis regulation, to improve mitochondrial function. Withania somnifera extract possesses anti-angiogenic activity[17] and has shown great potent activity for treatment of Rheumatoid arthritis. IL-6[18] and Jak3 are potent targets for Rheumatoid Arthritis[19]. Systematic studies have shown that Environmental factors such as diet and smoking cigarette[20] plays a role in developing chronic diseases such as Rheumatoid arthritis by interfering signaling and inflammatory pathways, due to that susceptibility to auto immune diseases increase. Pre-clinical studies have shown that Withania somnifera possesses protective effects against the radiation-induced weight loss[21], and due to regular consumption of W.somnifera, body weight increased along with the RBCs count, WBCs, blood platelets and hemoglobin content was restored. Quercetin was reported as a pro-longed anti-inflammatory phyto-compound that exhibits immense anti-inflammatory properties[22] and hence could be used againt RA as it is a chronic inflammatory disease. Quercetin is one of the 18 phyto-compounds from Withania somnifera belong to a family of flavonoids[23] and have great anti-oxidant and anti-inflammatory properties. Withaferin A has many potent therapeutic and pharmaceutical uses due to its anti-inflammatory properties along with anti-cancer[24]. A study was done on Phyto-compounds concluded that the flavonoids and phenolics have anti-rheumatoid arthritis effects[25]. Rheumatoid Arthritis has approached by many improved and modified therapeutics strategies since the last 3 decades but with the help of a strategy called (T2T) Treat to Target[26] had given an option to choose various mode of action so it can prevent from joint destruction in RA. The first step is to analyze and diagnose the disease so the specific drugs can be chosen in time, to start the T2T therapy in the duration of 6-12 weeks since the disease has diagnosed. Rheumatoid Arthritis could be better predicted by this T2T method. Currently, RA is being treated by medications such as **(DMARDs)** Disease-Modifying Anti-Rheumatic Drugs(Methotrexate, Sulfasalazine, Leflunomide, and Hydroxychloroquine (currently being used against covid-19), taken as the first-line dosage for newly diagnosed Rheumatoid Arthritis patients, Non-Steroidal Anti-Inflammatory Drugs **(NSAIDs)** (for pain

and inflammation), and the Glucocorticoids **(GCs)** used to suppress the stiffness, tenderness, pain, and inflammation caused by RA.

The molecularcal targeting therapies, on the other hand, are Jak3 inhibitors, TNF-α inhibitors, anti-CD20 monoclonal antibody, IL-1 inhibitor, blocker. Moreover, there are few new ongoing research about biological therapies including new TNF-α inhibitors, JAK/STAT inhibitors, Anti-Interleukin-6-receptor (mABs)[27].

3. CHAPTER 3 MATERIALS AND METHODS

3.1.Protein Structure Selection and Collection

In 1971, PDB (Protein Data Bank) was inaugurated by Brookhaven National Laboratories for the storage of records of biological macromolecular crystal structures[28] and later in October 1998, RCSB (Research Collaboratory for Structural Bioinformatics) had taken the hold of management of Protein Data Bank (PDB). Interleukin-6 (IL-6) and JAK3 both protein's 3D crystallographic structures were extracted from (Research Collaboratory for Structural Bioinformatics Protein Data BAnk) RCSB PDB (https://www.rcsb.org/). IL-6 was downloaded from pdb website by using PDB ID (1 ALU) [29] and JAK3 was downloaded and extracted by using PDB ID (3LXK) [30]. IL-6 was of 186 sequence long and JAK3 was of 327 sequence length.

3.2.Protein Editing

Both IL-6 and Jak3 were trimmed by using Molegro Molecular Viewer. We removed the water molecules and ligands. And then saved the pure form protein in pdb format as shown in (Fig.3.1 and Fig.3.2). Molegro Molecular Viewer (MMV) is an application for editing, trimming, studying and analyzing the interaction between ligands and macromolecules [27].

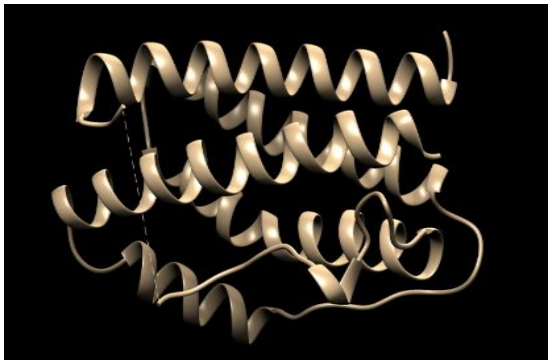

Fig 3. 1 Interleukin-6 protein after editng

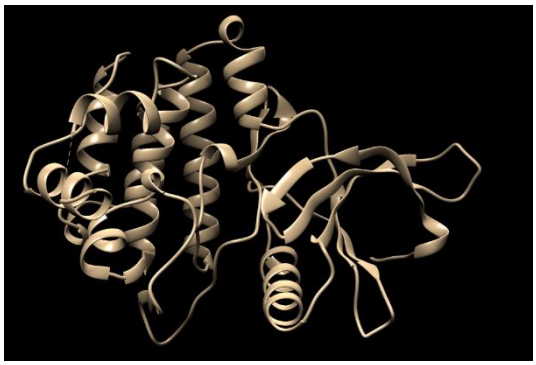

Fig 3. 2 JAK3 protein after editing

3.3.Ligand Selection

The 18 phyto-compounds we used in this docking process is retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) by using their pubchem ID given in Table.3.1. PubChem allows a set of web servers[31] for acquiring, retrieving and examining biological end results stored in PubChem databases.

Sr. no.	*Withania somnifera* 18 Compounds	PubChem ID
1.	Tannic Acid	161297
2.	Rutin	5280805
3.	Somniferine	14106343
4.	Withasomniferol C	101710597
5.	Withaferin A	265237
6.	Chlorogenic Acid	1794427
7.	Quercetin	528034
8.	Withanolide A	11294368
9.	Kaempferol	528034
10.	Gallic Acid	370
11.	Choline	305
12.	Dulcitol	11850
13.	Withasomniferol B	101710596
14.	Withasomniferol A	101710595
15.	Cuscohygrine	120154
16.	Anaferine	443143
17.	Anahygrine	12306778
18.	Isopelletierine	92987

Table 3. 1 Eighteen phyto-compounds (with their PubChem Id) used as ligands against anti-rheumatoid arthritis targets.

3.4.Interconversion of ligand's format

We used Open Babel software (http://openbabel.org) for interconversion of ligands from sdf format to mol2 format due to the SwissDock restrictions; online docking software that we used only access to attach files in pdb or mol2 format. Open Babel is a chemical toolbox application that interconverts approximately 110 formats[32].

3.5.Molecular Docking

To execute the molecular docking between protein targets of Rheumatoid Arthritis (Interleukin-6 and JAK3) and 18 ligands of Withania somnifera (given in Table.3.1), the software we used is SwissDock (http://www.swissdock.ch) a web server for protein/small molecule docking.

The first step was to upload the first target Interleukin-6 in pdb format with uploading one of the 18 phyto-compounds selected as ligands in mol2 format and ran the docking program by submitting the target-ligand data. And performed the same method with other 17 phytocompounds one by one with IL-6. Then after the submission of all the data of target IL6 all all the 18 compounds. We repeated the method again but replaced the target; instead of IL-6 we used JAK3 as target, submitted the docking data of 18 Withania somnifera ligands one by one with JAK3 target. After submitting the data we got 36 target-ligand complex based results, 18 complexes from the IL-6 target with 18 different ligands from Withania somnifera, and 18 complexes from JAK3 target with 18 different ligands of Withania somnifera.

3.6.Visualization

For analyzing, understanding and processing the data for viewing those 36 target-complex structures we got as results, we used UCSF Chimera software. UCSF Chimera allows 3D visualization of molecular structures and related data, including supramolecular structures, and multiple sequence alignments[33].

4. CHAPTER 4 RESULTS AND DISCUSSIONS

Medicinal plants possess diverse phytochemicals including Flavonoids, Alkaloids, Phenolics, Steroidal, and other compounds, which can be significant for the synthesis of many therapeutic agents. Docking studies produced pivotal information regarding the orientation of the ligands in the binding pocket of the target protein. Two potential anti-rheumatoid arthritis targets (INTERLEUKIN-6 and JAK3) was docked with all the 18 phyto-compounds, by using SWISSDOCK tool. The active site residues of the target protein were predicted using SwissDock and were analyzed as ASN 61, GLU106, ASP 140, SER107, LEU 64, LEU 62, ASN 832, LYS 830, PHE 833, LEU 905, GLY 831, ARG 916, SER 1031, and ARG 953.

According to the binding affinity and energy obtained from 36 complexes in the form of delta G (Kcal/mol), Interleukin 6-Tannic Acid complex and JAK3-Tannic Acid complex showed the highest affinity with a binding energy (delta G) of -9.166905 Kcal/mol and -12.074078 Kcal/mol respectively. And they both showed the best 3D orientation, configuration, and interaction of all the 36 target-ligand based complexes. The results were analyzed through UCSF Chimera software. Two hydrogen bonds were present in interleukin 6-Tannic Acid, and Three hydrogen bonds were in JAK3-Tannic Acid complex (as shown in Table.4.1 and Table.4.2 respectively).

The binding pockets of IL6 target where tannic acid formed hydrogen bonds are ASN 61 and ASP 140 at a distance of 2.005 Å and 2.397 Å (given in Table.4.1). The binding pockets of JAK3 where tannic acid formed hydrogen bonds are ASN 832, LYS 830, and ILE 991 at a distance of 2.448 Å, 2.373 Å, and 1.930 Å (given in Table.4.2). Although, other 34 compounds also showed good binding energy high range of -8.7 to lowest range of 5.4 with Interleukin-6 target. Exceeding from 20 different poses were oriented for every single complex structure out of which best oriented with highest energy level complex are chosen due to high binding affinity along with more hydrogen bonds.

Sr. no.	Complex (Target-Ligand)	Estimated ΔG (kcal/mol)	No of H bonds	Intra-residue H-bonds Distance
1.	Interleukin 6-Tannic Acid	-9.166905	2	2.005 Å/2.397 Å
2.	Interleukin 6-Rutin	-8.7580595	1	2.559 Å
3.	Interleukin 6-Somniferine	-7.834656	1	2.496 Å
4.	Interleukin 6-Withasomniferol C	-7.775645	1	2.176 Å
5.	Interleukin 6-Withaferin A	-7.574546	1	2.492 Å
6.	Interleukin 6-Chlorogenic Acid	-7.3979516	1	2.271 Å
7.	Interleukin 6-Quercetin	-7.35233	3	2.426Å/2.607 Å
8.	Interleukin 6-Withanolide A	-7.11187177	1	2.39 Å
9.	Interleukin 6-Kaempferol	-7.0464	2	2.460 Å
10.	Interleukin 6-Gallic Acid	-6.9476986	2	2.347 Å
11.	Interleukin 6-Choline	-6.9455814	1	2.269 Å
12.	Interleukin 6-Dolcitol	-6.887075	2	2.435Å/2.498 Å
13.	Interleukin 6-Withasomniferol B	-6.7357774	1	2.492Å
14.	Interleukin 6-Withasomniferol A	-6.5323944	1	2.366Å
15.	Interleukin 6-Cuscohygrine	-6.51368	1	2.006Å
16.	Interleukin 6-Anaferine	-6.438672	1	2.075Å
17.	Interleukin 6-Anahygrine	-6.3276896	1	2.240Å
18.	Interleukin 6-Isopelletierine	-5.85198	2	2.432 Å

Table 4. 1 Analysis of resulted Target-ligand (Interleukin6-18phytocompounds) with estimated energy, number of hydrogen bonds and their Intra-residue H-bonds Distance between target and ligand.

Sr. no.	Complex (Target-Ligand)	Estimated ΔG (kcal/mol)	No of H bonds	Intra-residue H-bonds Distance
1.	JAK3-Tannic Acid	-12.074078	3	2.448 Å/2.373 Å/1.930 Å
2.	JAK3-Chlorogenic Acid	-8.157185	2	2.218Å/2.059 Å
3.	JAK3-Quercetin	-7.9316998	1	2.513 Å
4.	JAK3-Kaempferol	-7.8692446	1	2.513 Å
5.	JAK3-Somniferine	-7.738031	1	3.102 Å
6.	JAK3-Withasomniferol B	-7.577868	1	2.177 Å
7.	JAK3-Rutin	-7.522298	2	2.602Å/2.166 Å3c
8.	JAK3-Withasomniferol C	-7.517595	1	2.293 Å
9.	JAK3-Anahygrine	-7.1745462	1	3.103 Å
10.	JAK3-Withasomniferol A	-7.158677	1	2.529 Å
11.	JAK3-Cuscohygrine	-7.1364365	1	3.075 Å
12.	JAK3-Gallic Acid	-6.8791966	1	2.391 Å
13.	JAK3-Withanolide A	-6.8321	2	2.369 Å/2.513Å
14.	JAK3-Dolcitol	-6.8012233	1	2.480Å
15.	JAK3-Anaferine	-6.67199447	1	2.352 Å
16.	JAK3-Isopelletierine	-6.5186887	1	2.437 Å
17.	JAK3-Withaferin A	-6.445368	2	2.010 Å/ 2.396 Å
18.	JAK3-Choline	-5.414158	1	2.330 Å

Table 4. 2 Analysis of resulted Target-ligand (JAK3-18phytocompounds) with estimated energy, number of hydrogen bonds and their Intra-residue H-bonds Distance between target and ligand.

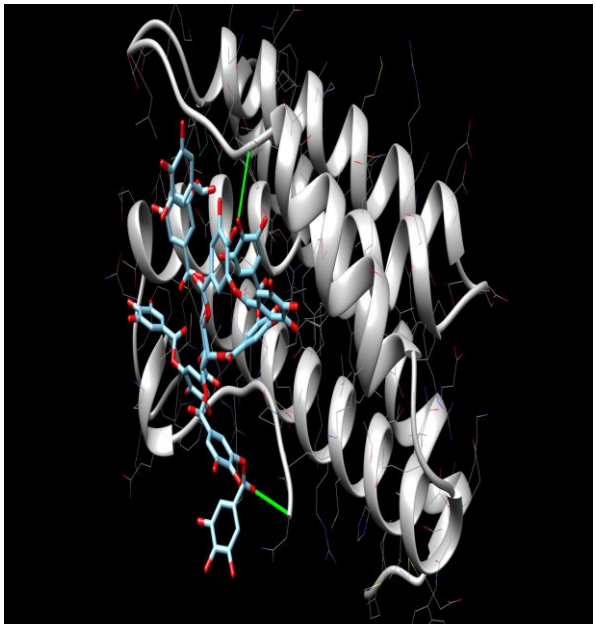

Fig 4. 1IL6-Tannic Acid

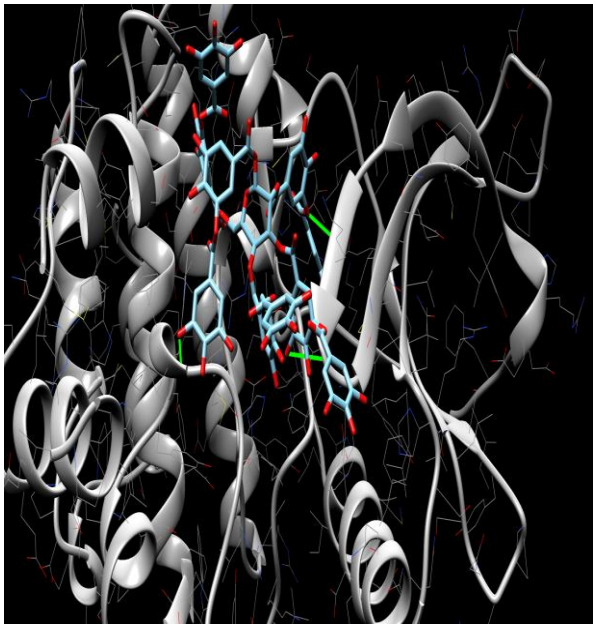

Fig 4. 2JAK3-Tannic Acid

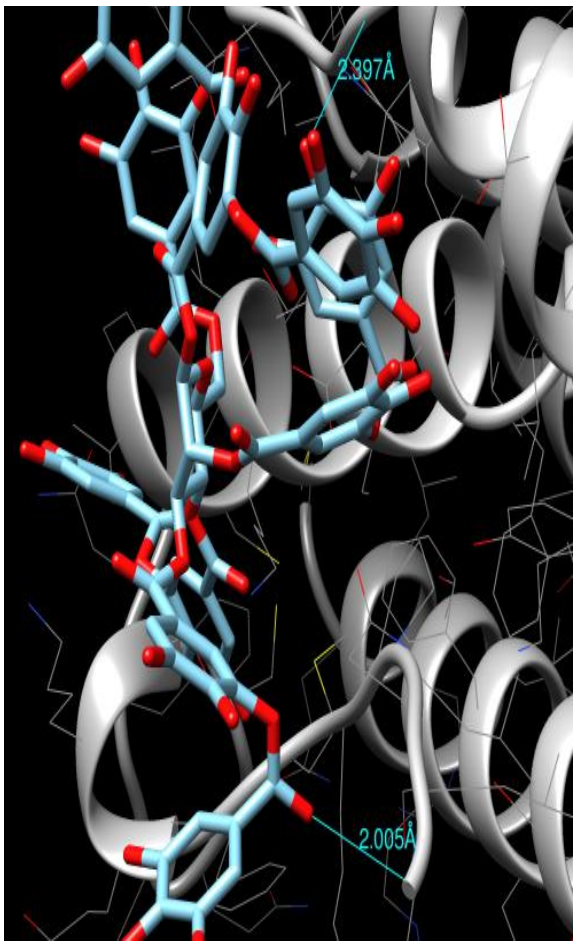

Fig 4. 3IL6-Tannic Acid with H dis

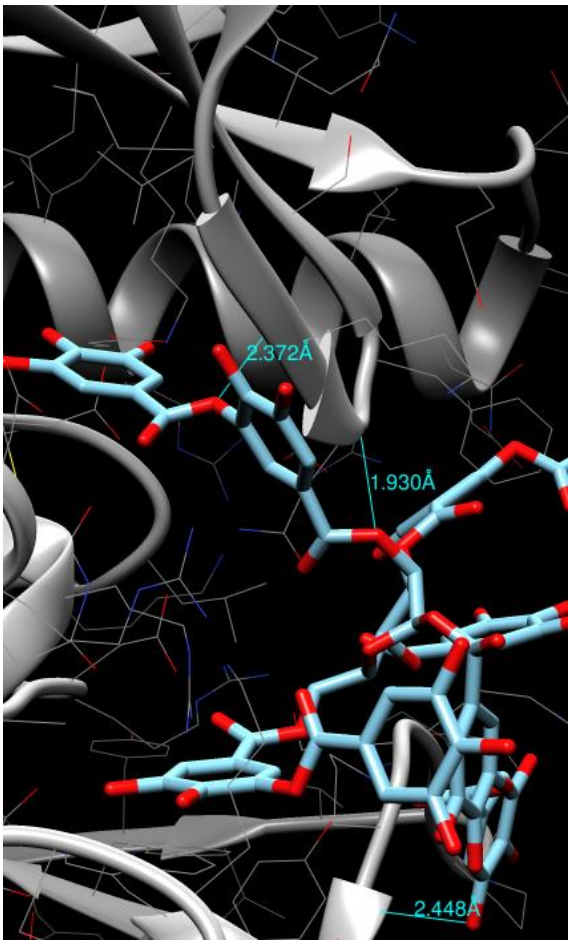

Fig 4. 4JAK3-Tannic Acid with H dis

Comparison between IL6-Tannic Acid and JAK3-Tannic Acid

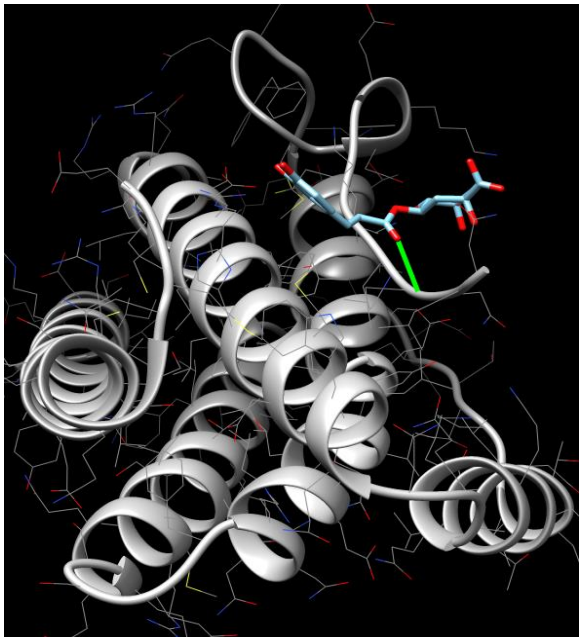

Fig 4. 5IL6-Chlorogenic Acid

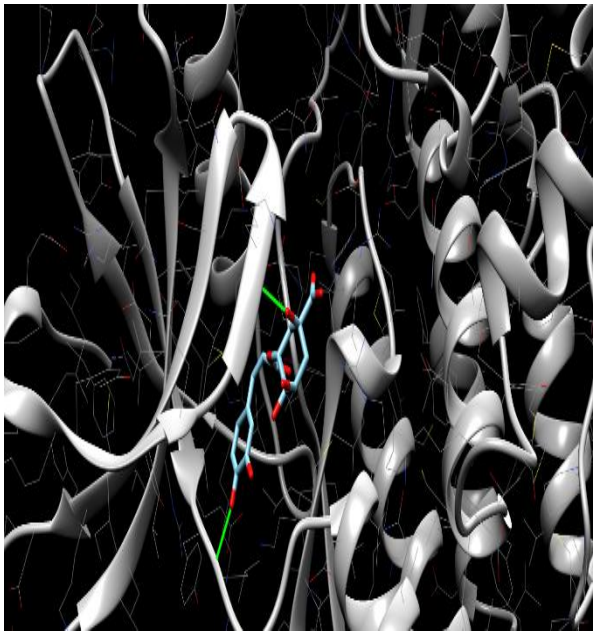

Fig 4. 6JAK3-Chlorogenic Acid

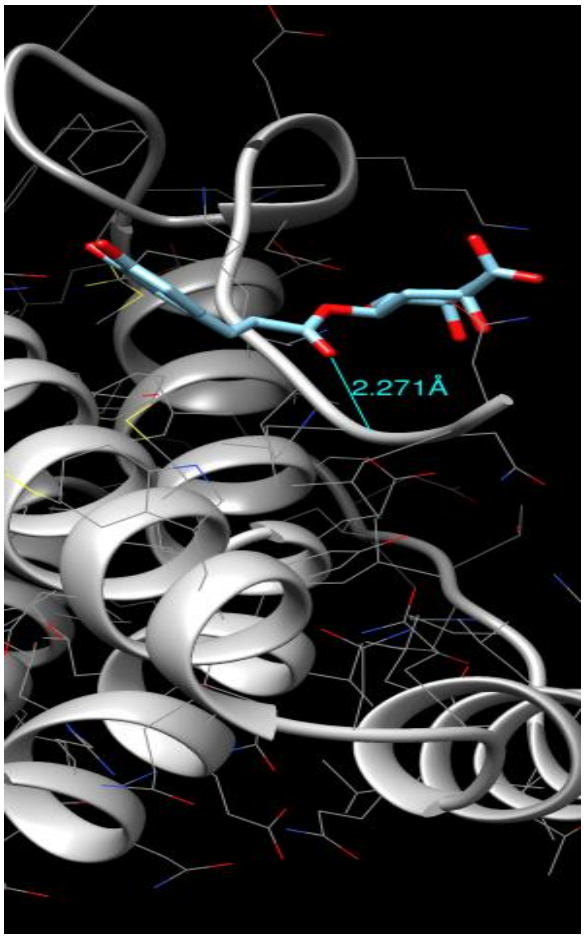

Fig 4. 7 IL6-Chlorogenic Acid with H dis

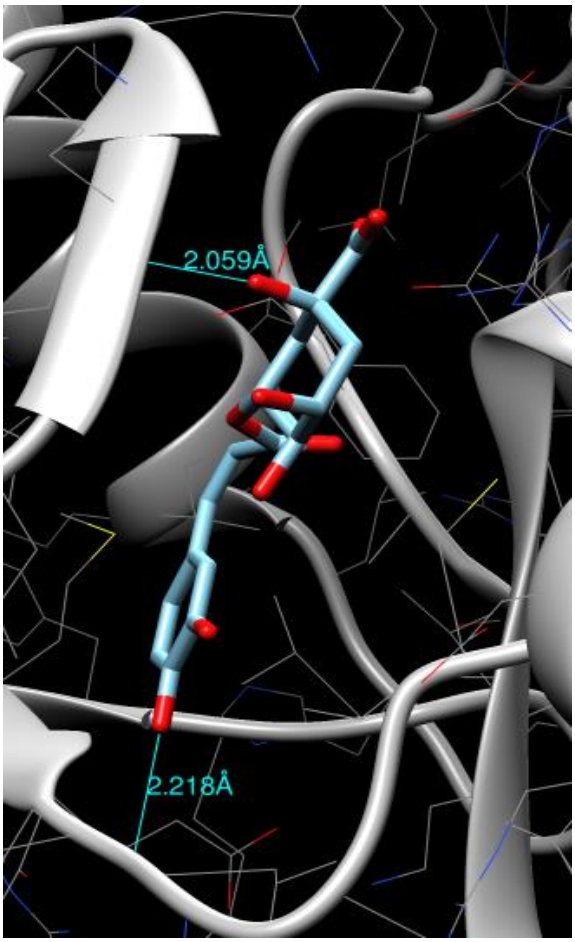

Fig 4. 8JAK3-Chlorogenic Acid with H dis

Comparison between IL6-Chlorogenic Acid and JAK3-Chlorogenic Acid

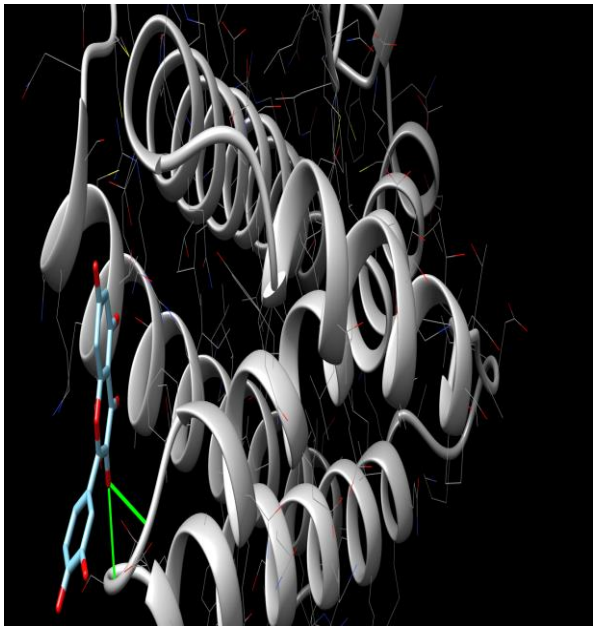

Fig 4. 9IL6-Quercetin

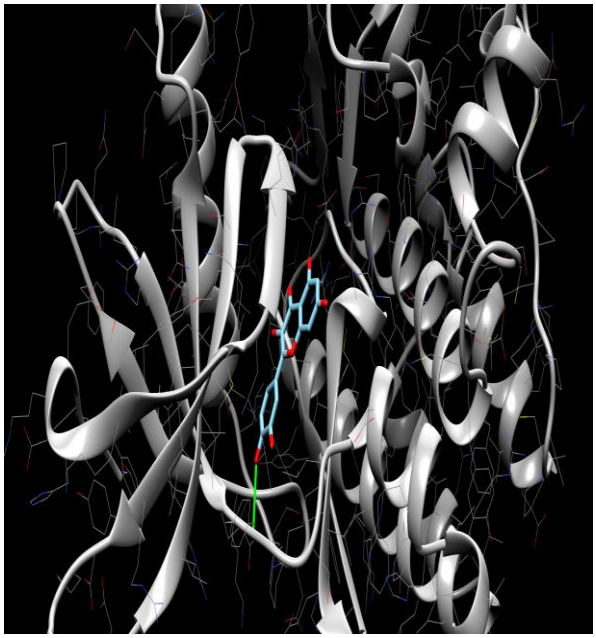

Fig 4. 10 JAK3-Quercetin

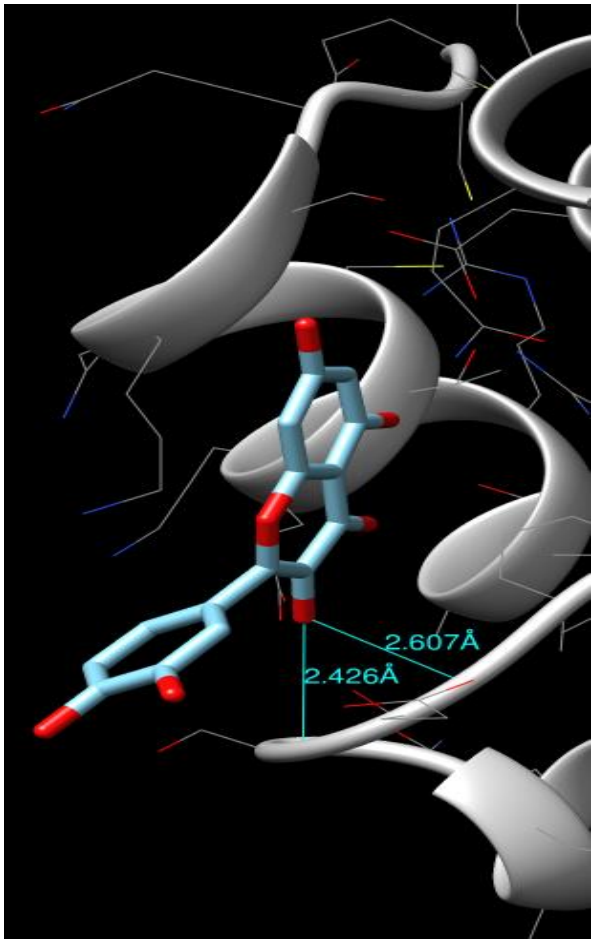

Fig 4. 11 IL6-Quercetin with H dis

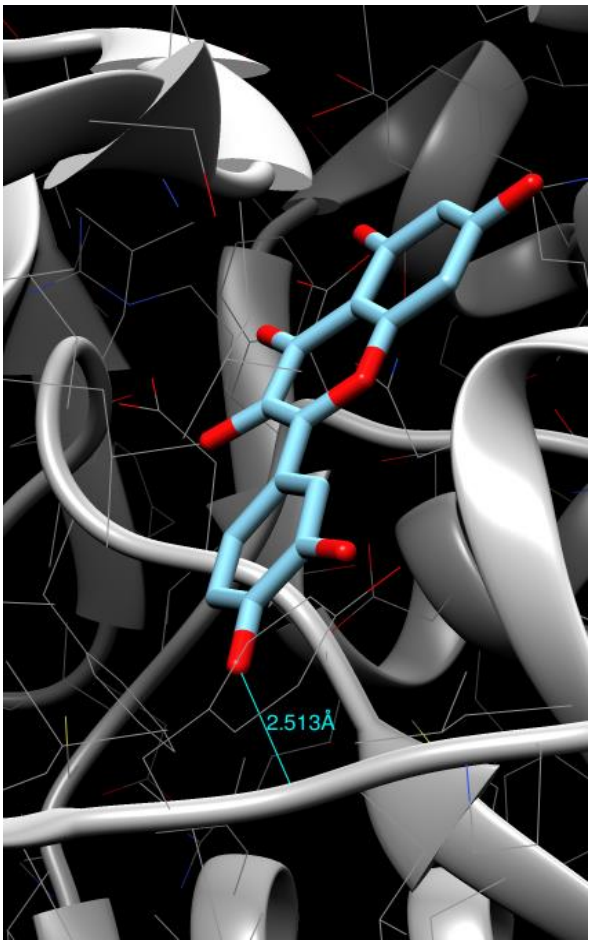

Fig 4. 12JAK3-Quercetin with H dis

Comparison between IL6-Tannic Acid and JAK3-Tannic Acid

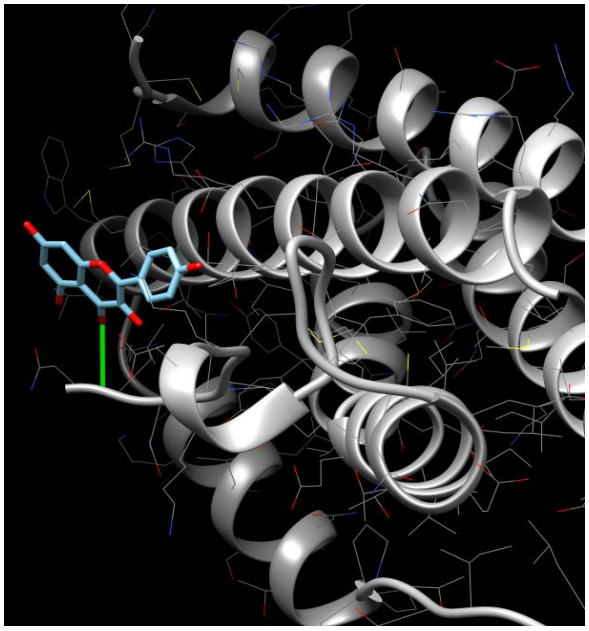

Fig 4. 13 IL6-Kaempferol

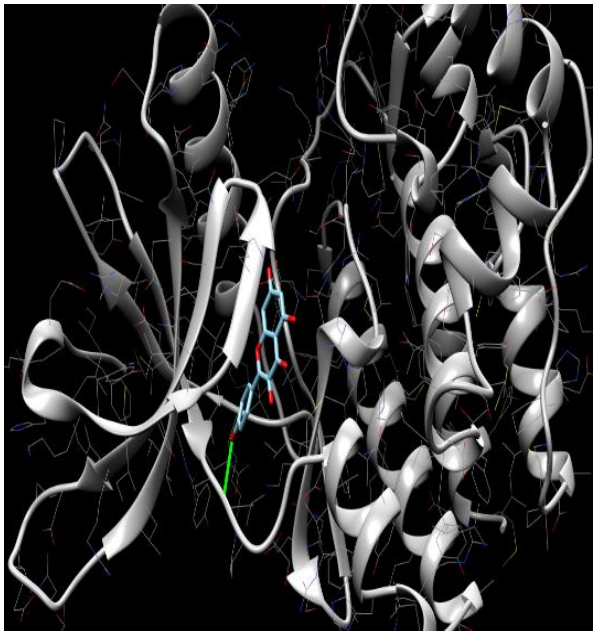

Fig 4. 14. JAK3-Kaempferol

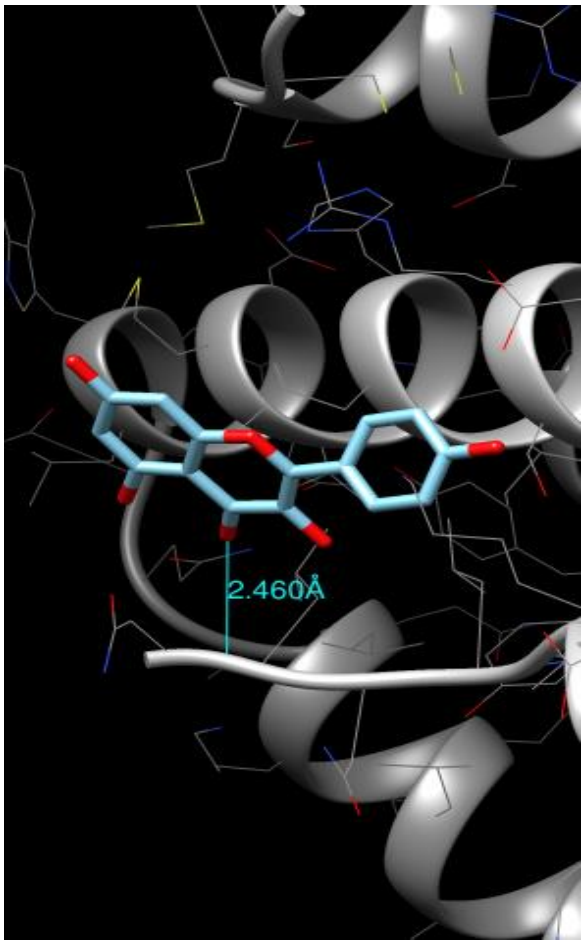

Fig 4. 15 IL6-Kaempferol with H dis

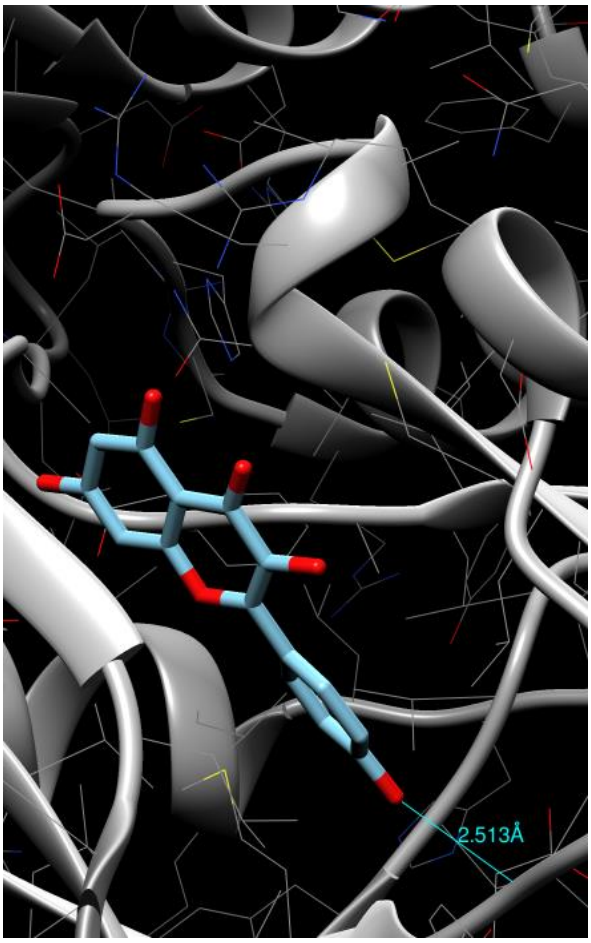

Fig 4. 16 JAK3-Kaempferol with H dis

Comparison between IL6-Kaempferol and JAK3-Kaempferol

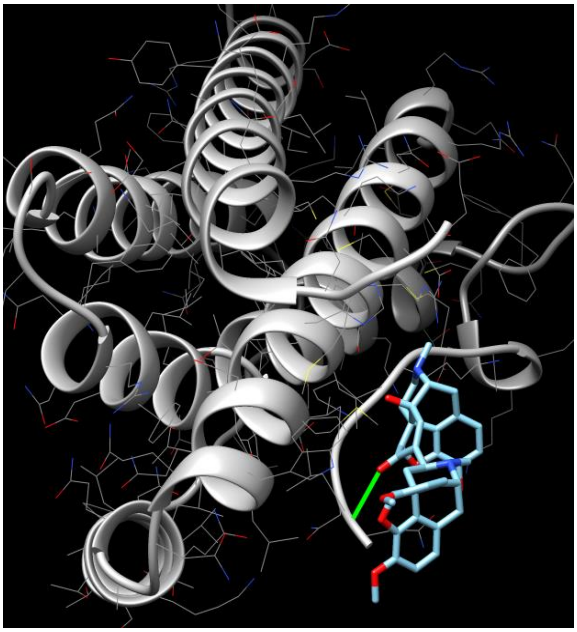

Fig 4. 17 IL6-Somniferine

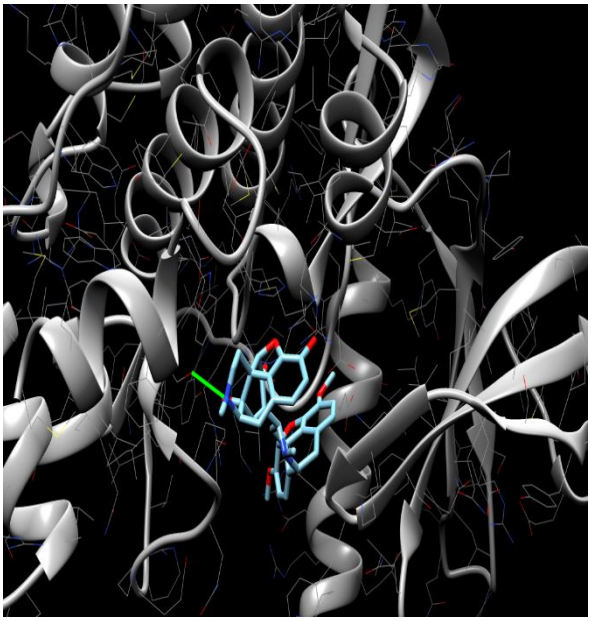

Fig 4. 18JAK3-Somniferine

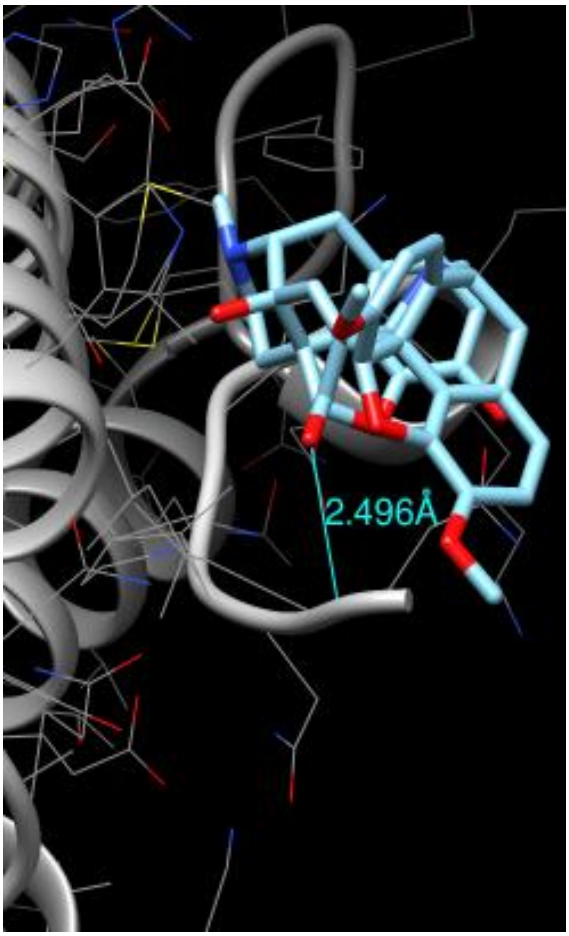

Fig 4. 19 IL6-Somniferine with H dis

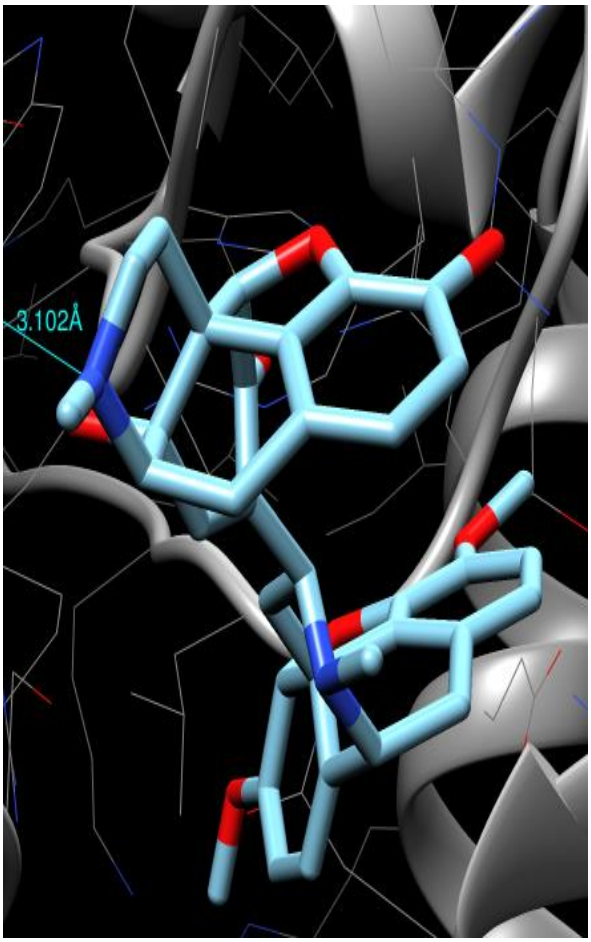

Fig 4. 20 JAK3-Somniferine with H dis

Comparison between IL6-Somniferine and JAK3-Somniferine

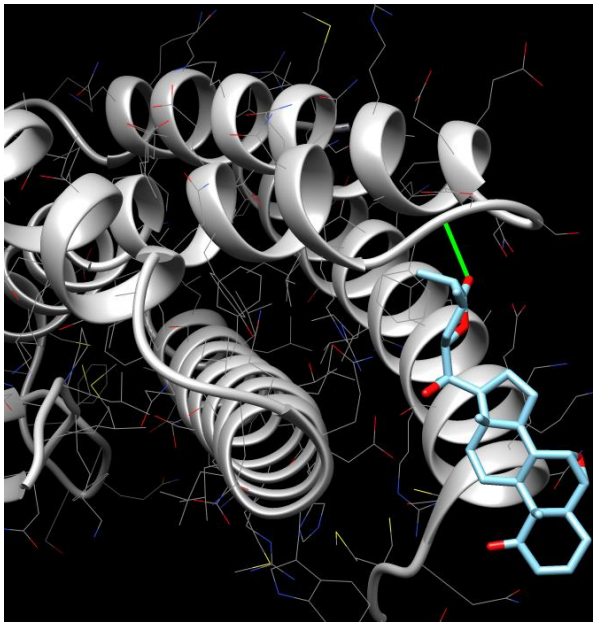

Fig 4. 21 IL6-Withasomniferol B

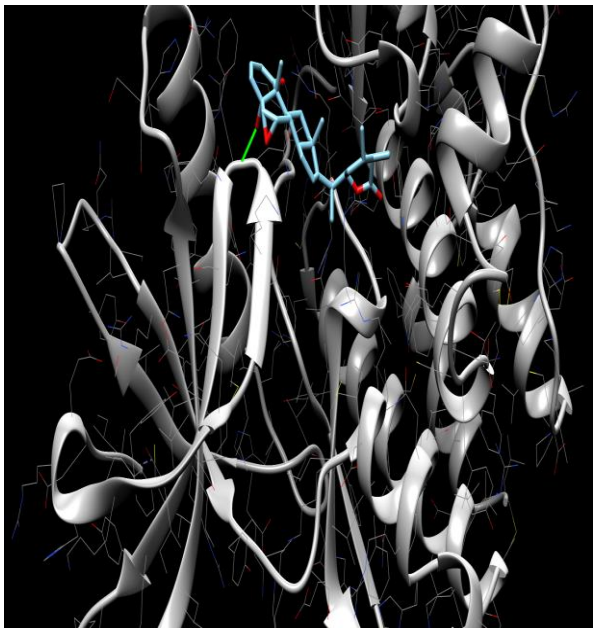

Fig 4. 22JAK3-Withasomniferol B

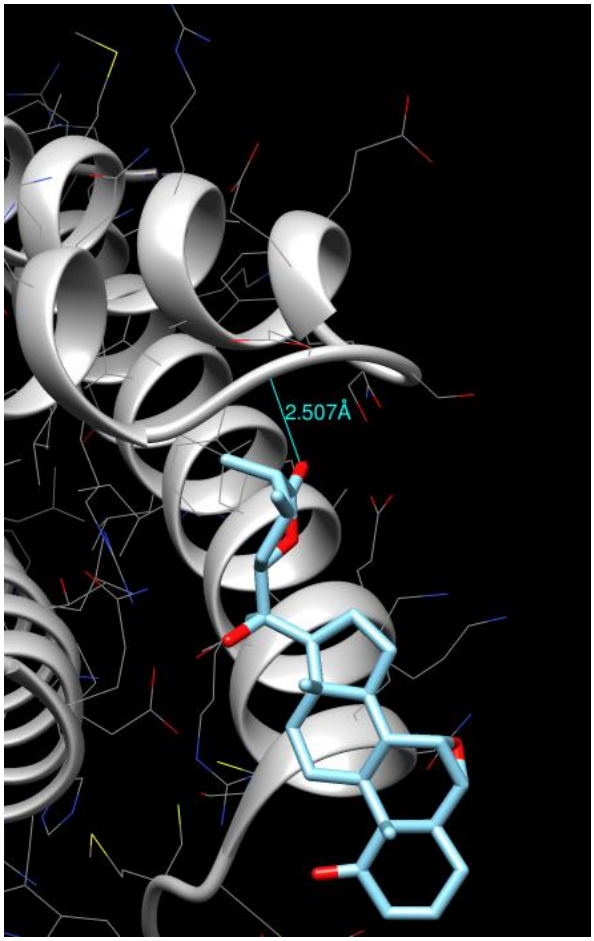

Fig 4. 23IL6-Withasomniferol B with H dis

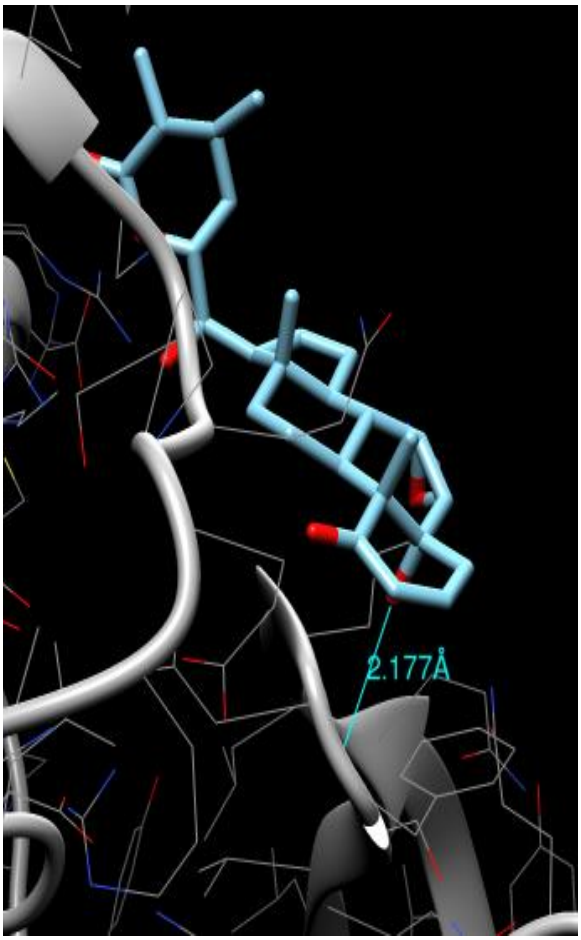

Fig 4. 24JAK3-Withasomniferol B with H dis

Comparison between IL6-Withasoniferol B and JAK3-Withasomniferol B

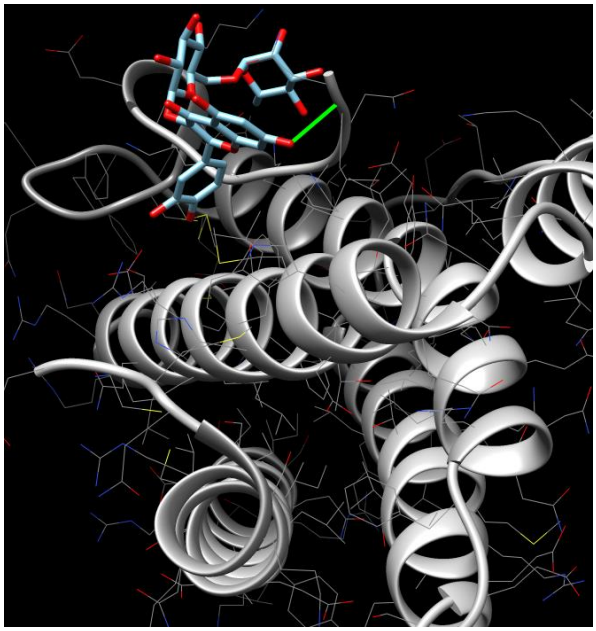

Fig 4. 25IL6-Rutin

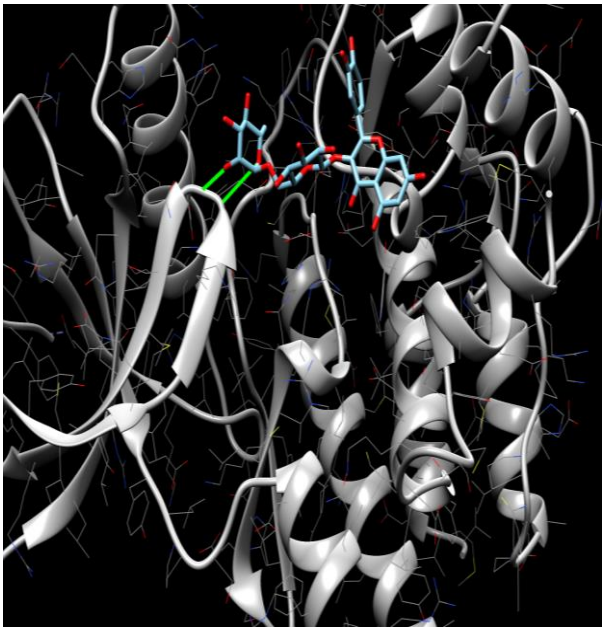

Fig 4. 26 JAK3-Rutin

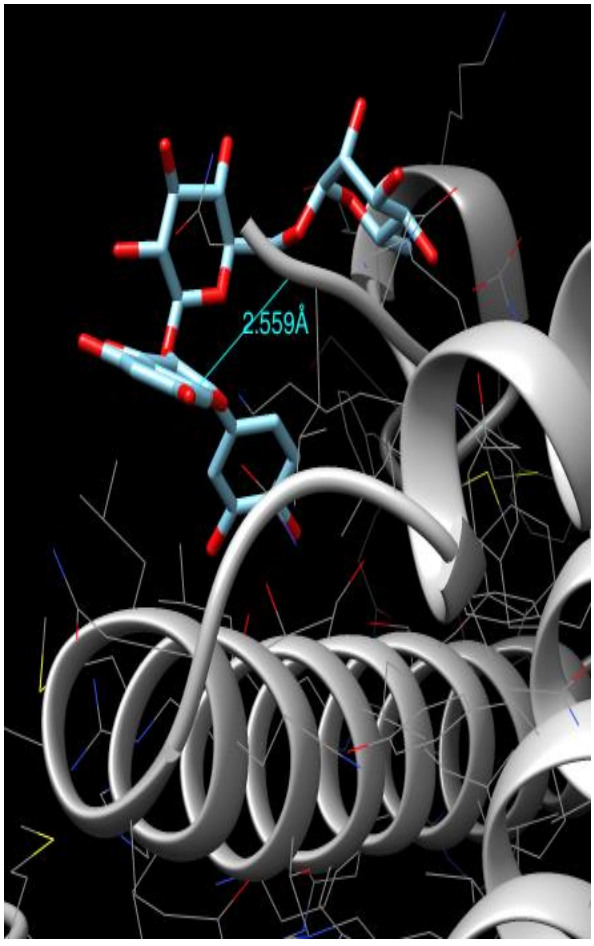

Fig 4. 27 IL6-Rutin with H dis

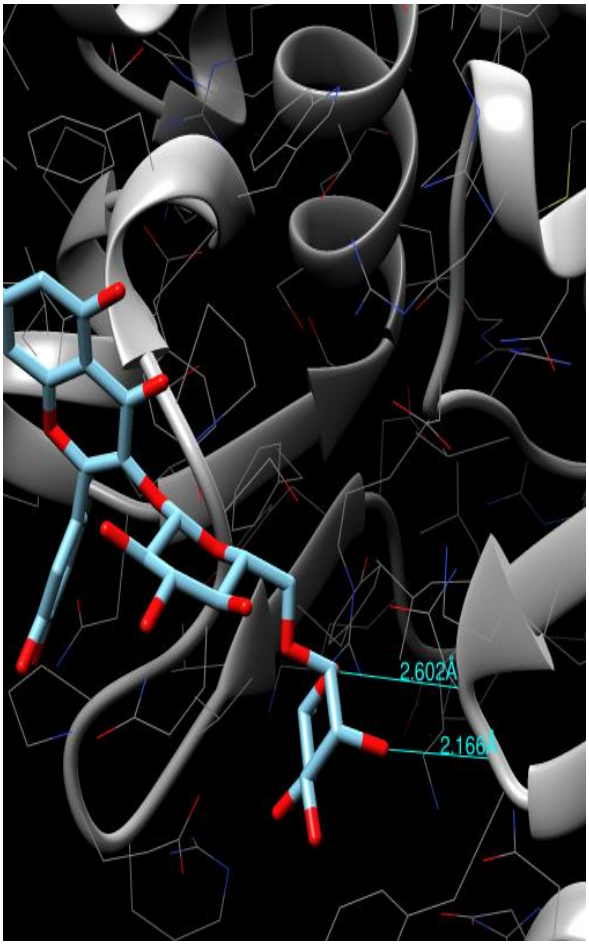

Fig 4. 28JAK3-Rutin with H dis

Comparison between IL6-Rutin and JAK3-Rutin

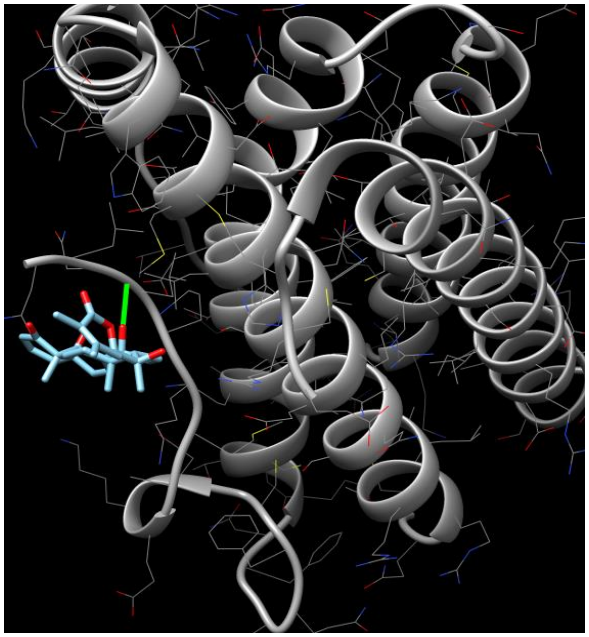

Fig 4. 29IL6-Withasomniferol C

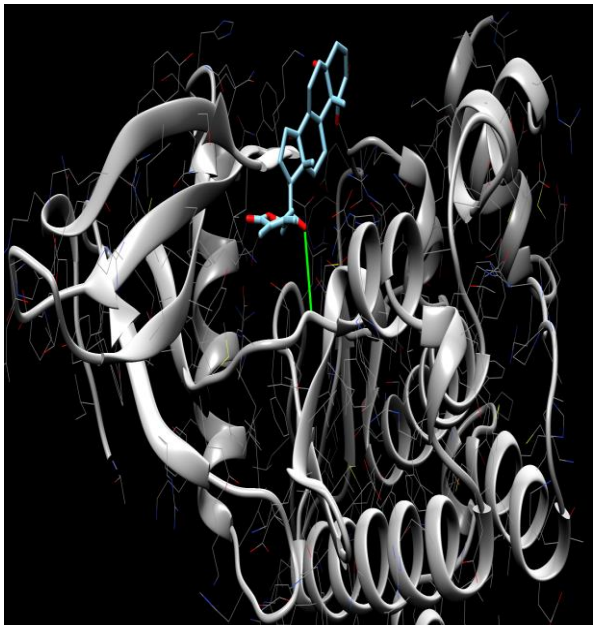

Fig 4. 30 JAK3-Withasomniferol C

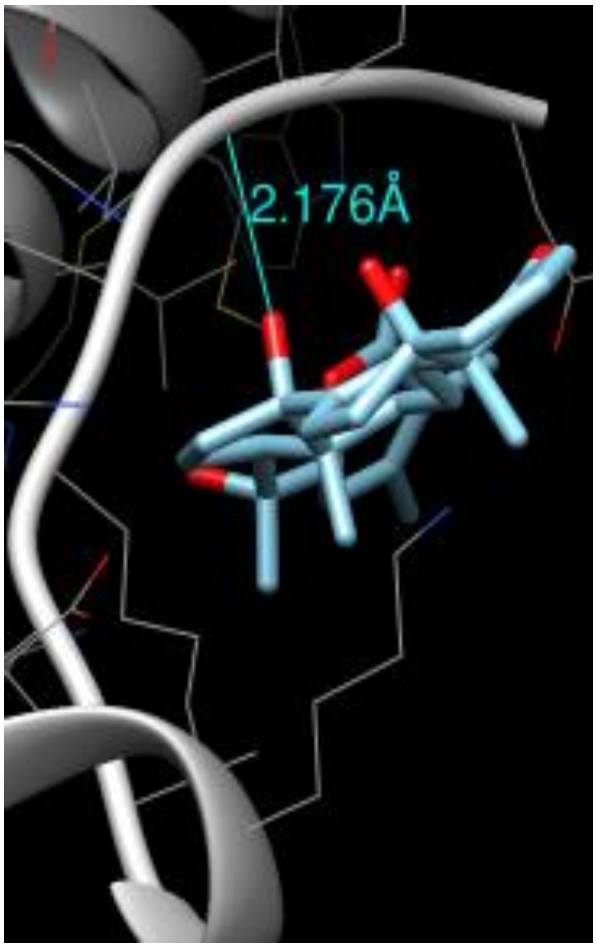

Fig 4. 31IL6-Withasomniferol C with H dis dis

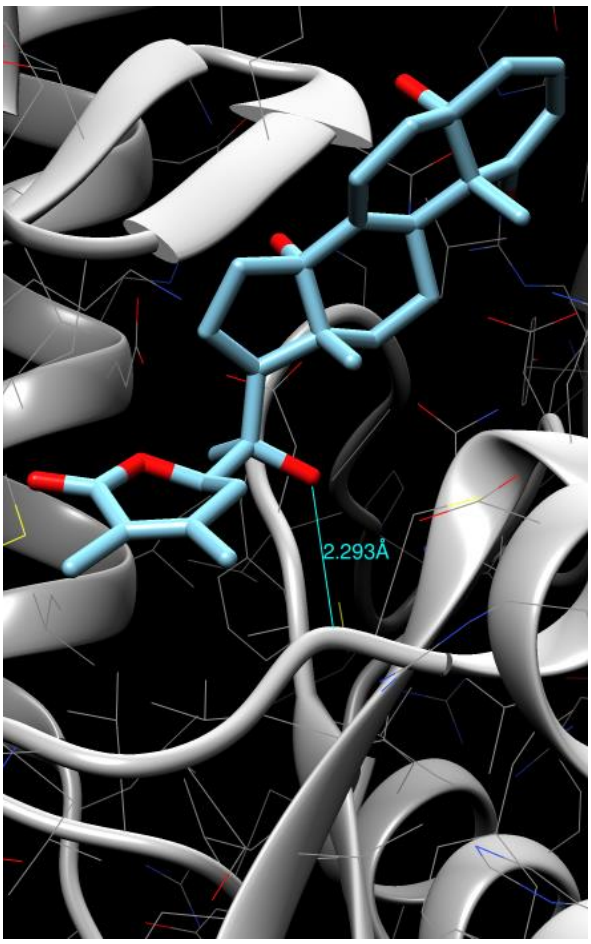

Fig 4. 32 JAK3-Withasomniferol C with H

Comparison between IL6-Withasomniferol C and JAK3-Withasomniferol C

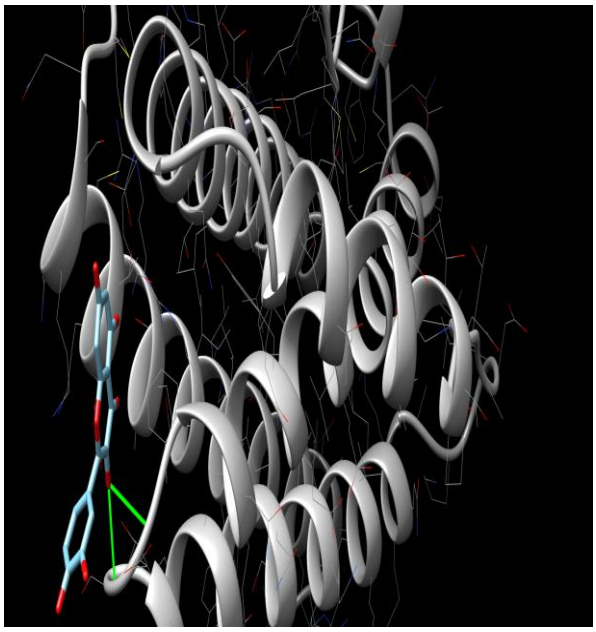

Fig 4. 33IL6-Anahygrine

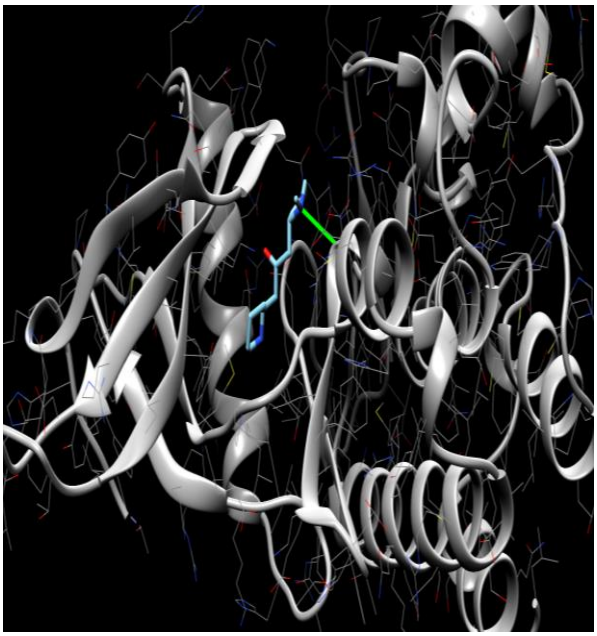

Fig 4. 34 JAK3-Anahygrine

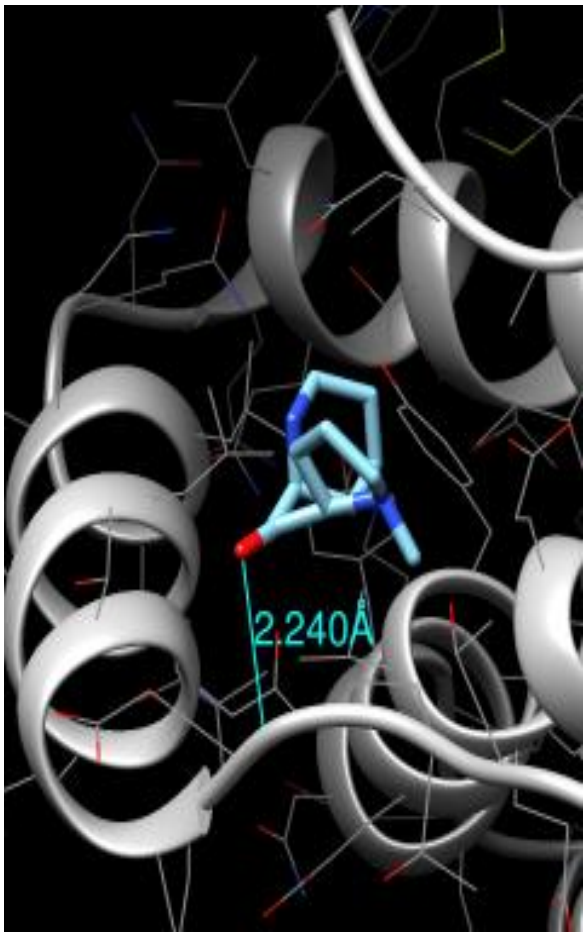

Fig 4. 35 IL6-Anahygrine with H dis

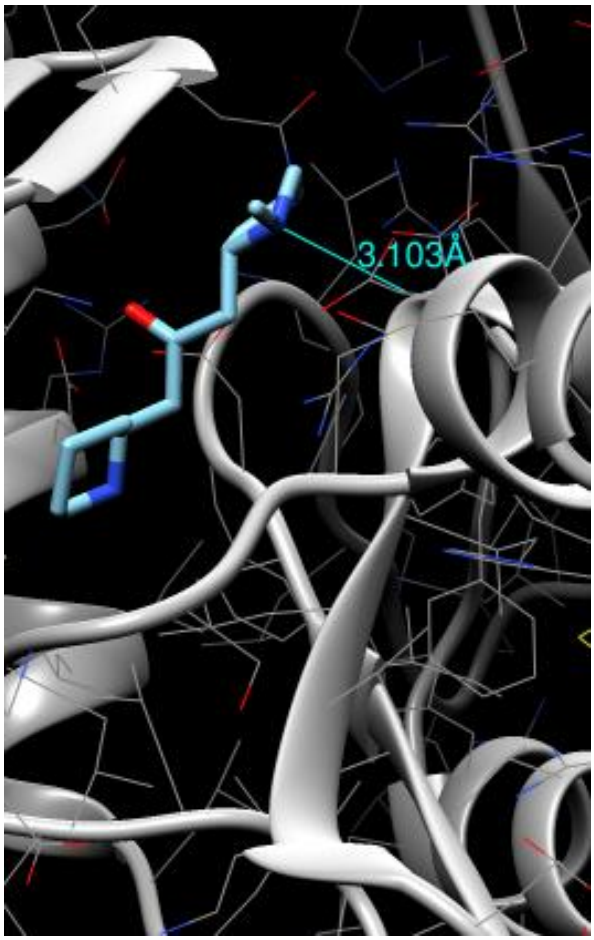

Fig 4. 36 JAK3-Anahygrine with H dis

Comparison between IL6-Anahygrine and JAK3-Anahygrine

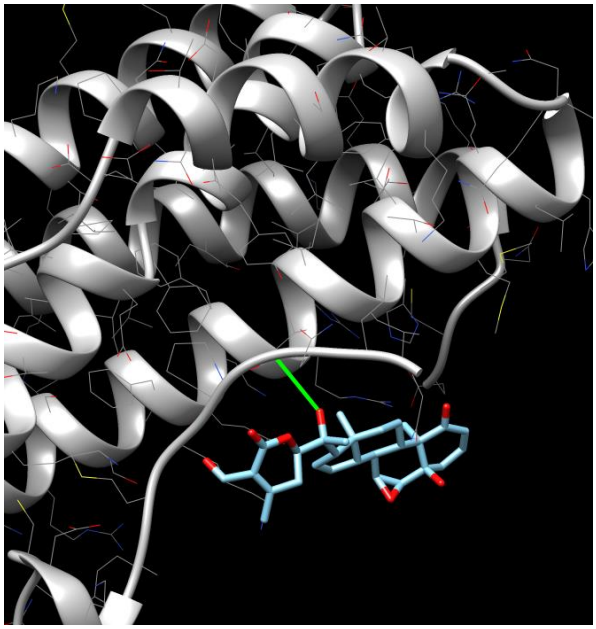

Fig 4. 37IL6-Withasomniferol A

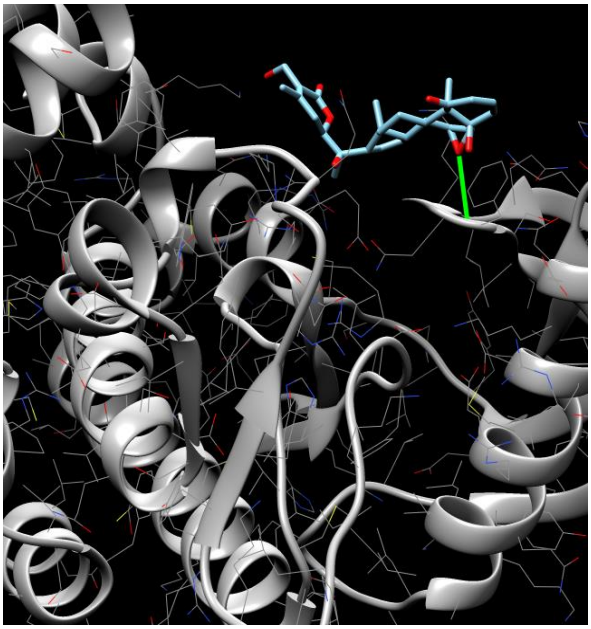

Fig 4. 38 JAK3-Withasomniferol A

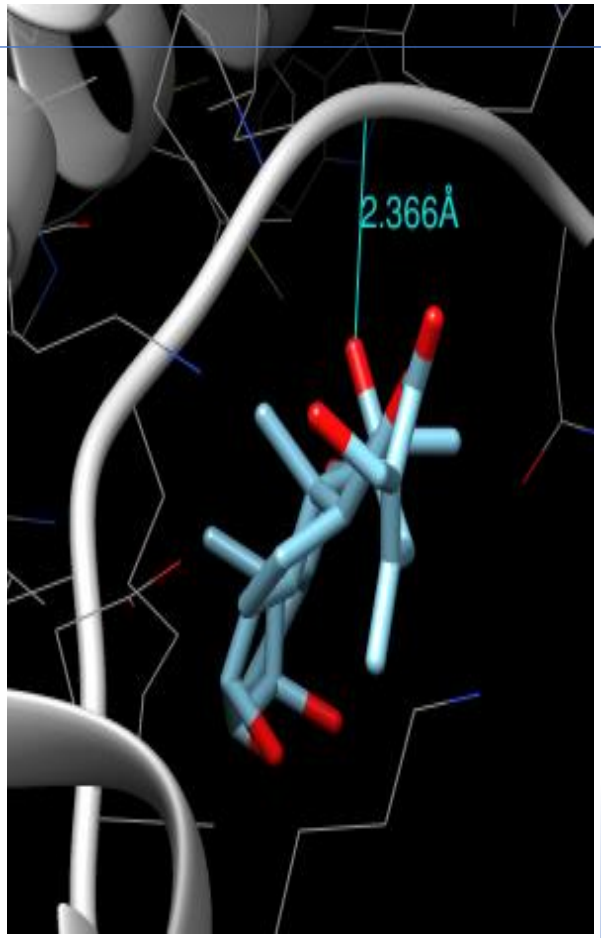

Fig 4. 39. IL6-Withasomniferol A with H dis

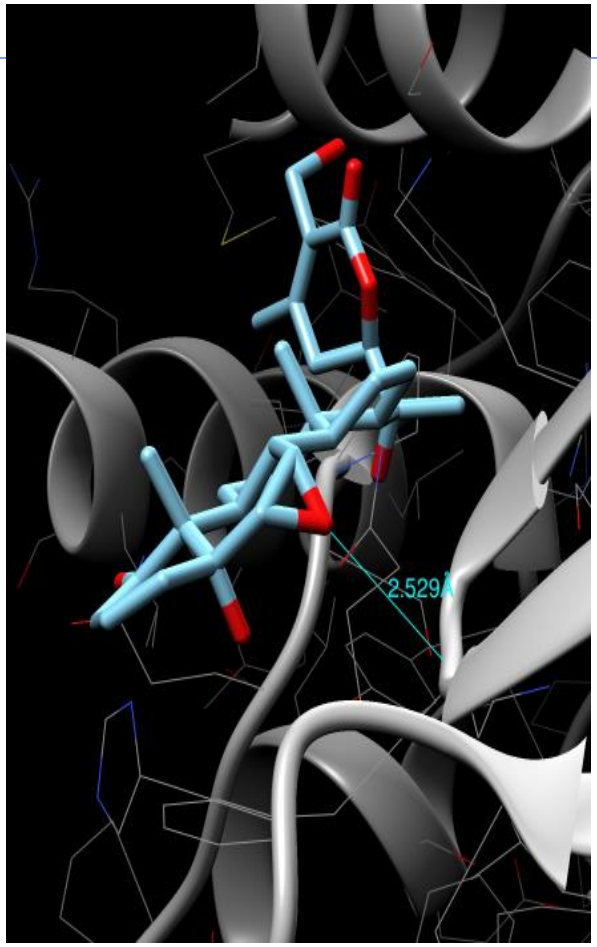

Fig 4. 40 JAK3-Withasomniferol A with H dis

Comparison between IL6-Withasomniferol A and JAK3-Withasomniferol A

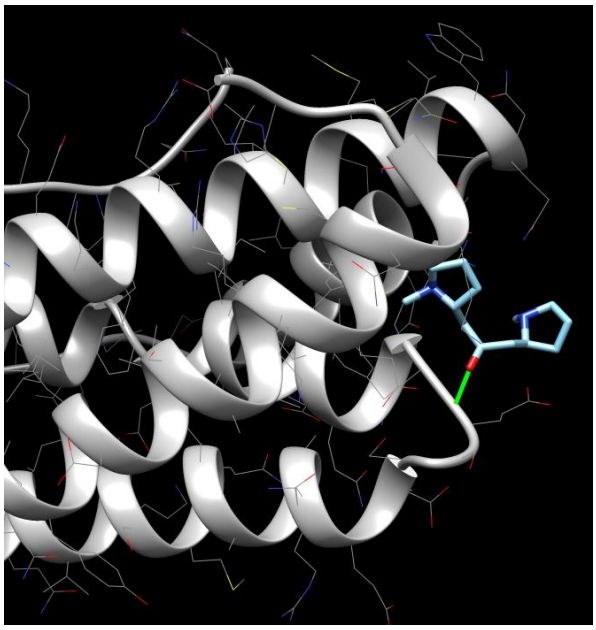

Fig 4. 41IL6-Cuscohygrine

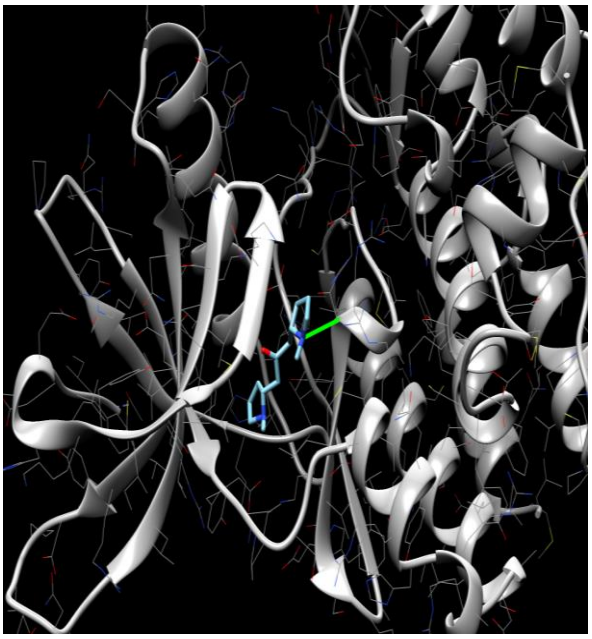

Fig 4. 42JAK3-Cuscohygrine

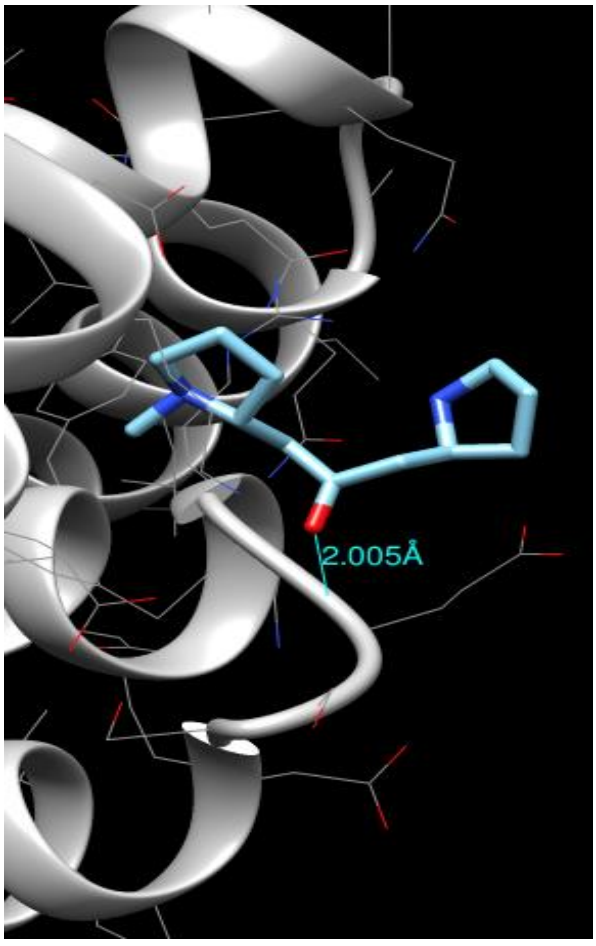

Fig 4. 43 IL6-Cuscohygrine with H dis

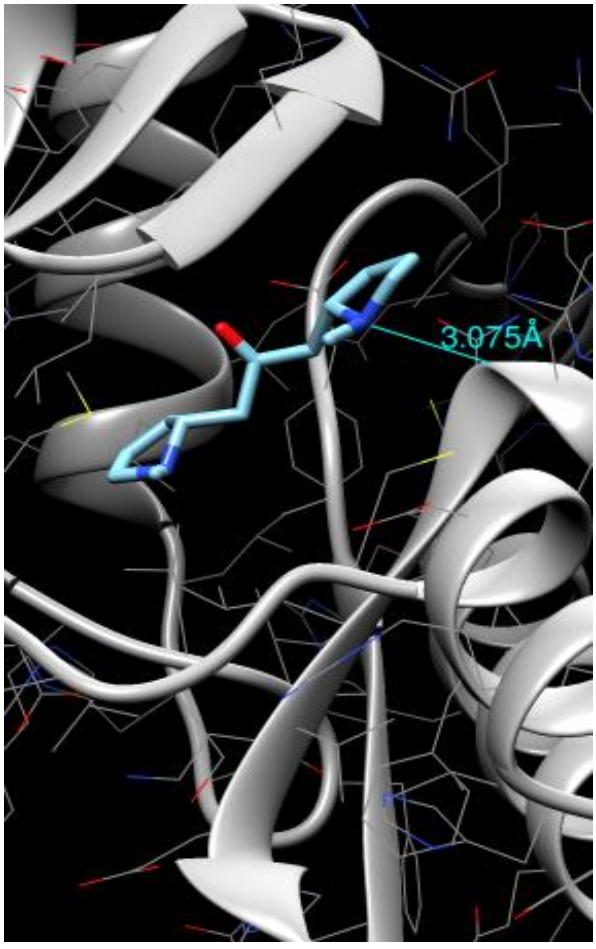

Fig 4. 44JAK3-Cuscohygrine with H dis

Comparison between IL6-Cuscohygine and JAK3-Cuscohygrine

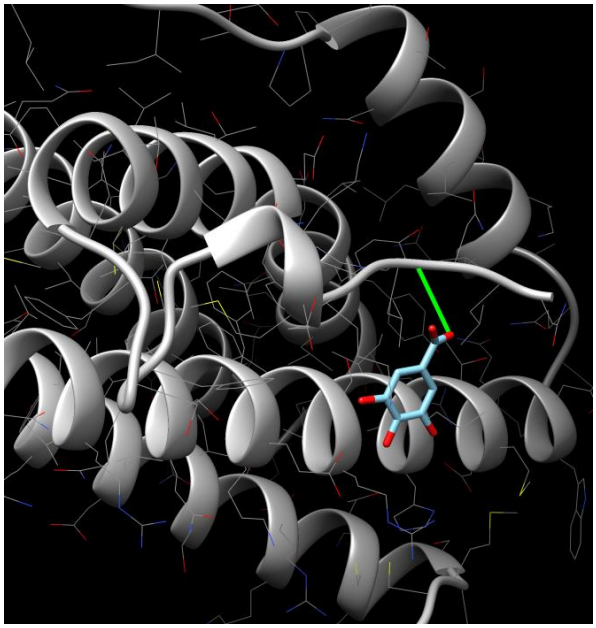

Fig 4. 45IL6-Gallic Acid

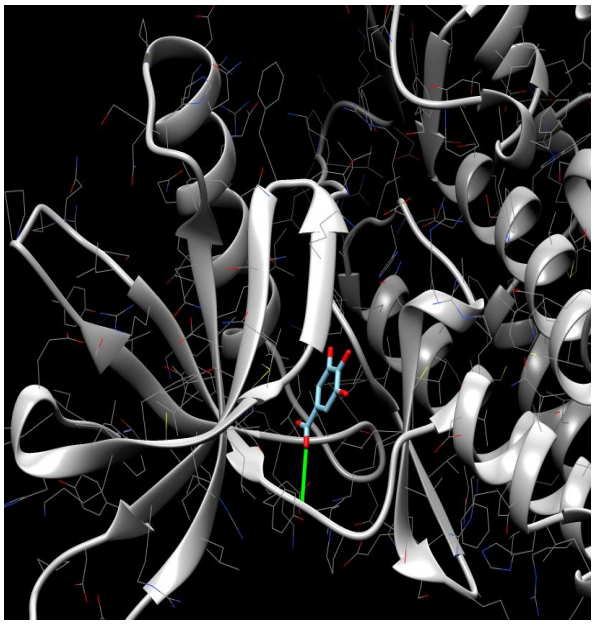

Fig 4. 46JAK3-Gallic Acid

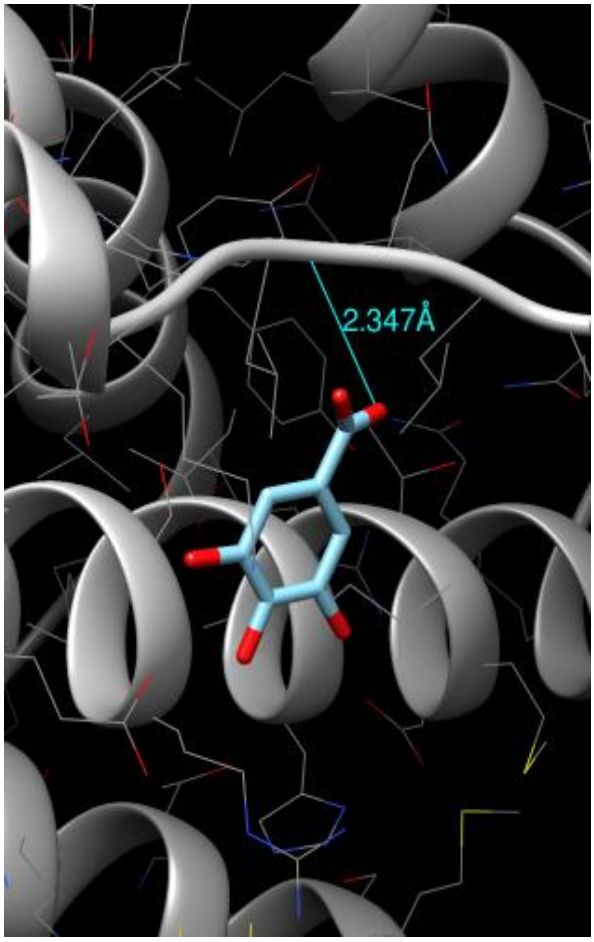

Fig 4. 47IL6-Gallic with H dis

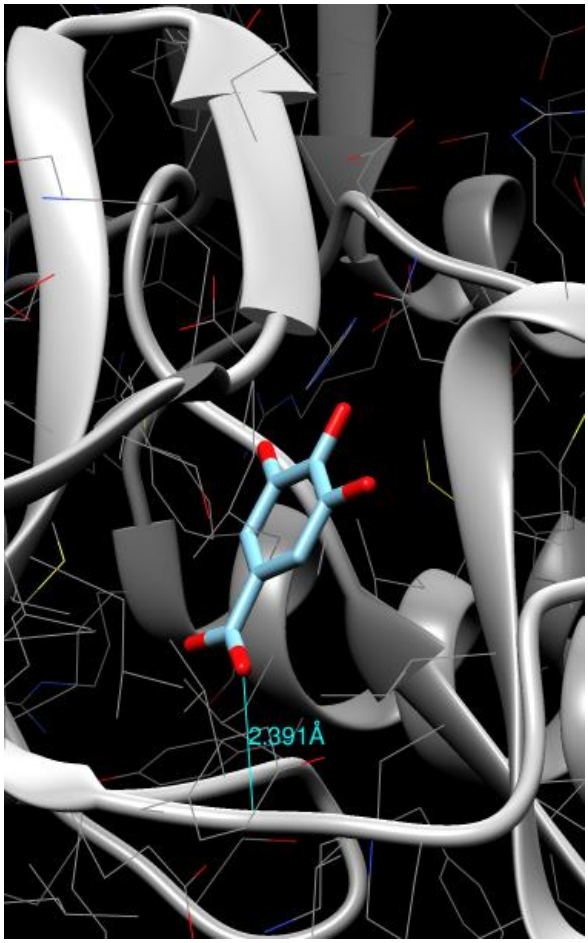

Fig 4. 48JAK3-Gallic with H dis

Comparison between IL6-Gallic Acid and JAK3-Gallic Acid

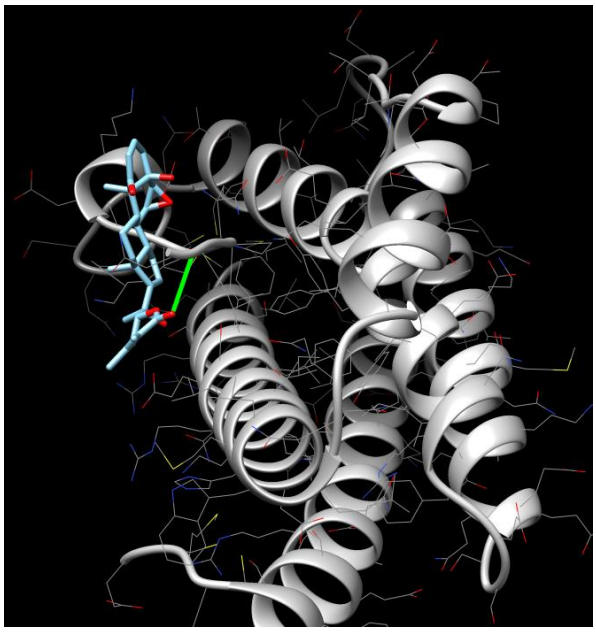

Fig 4. 49 IL6-Withanolide A

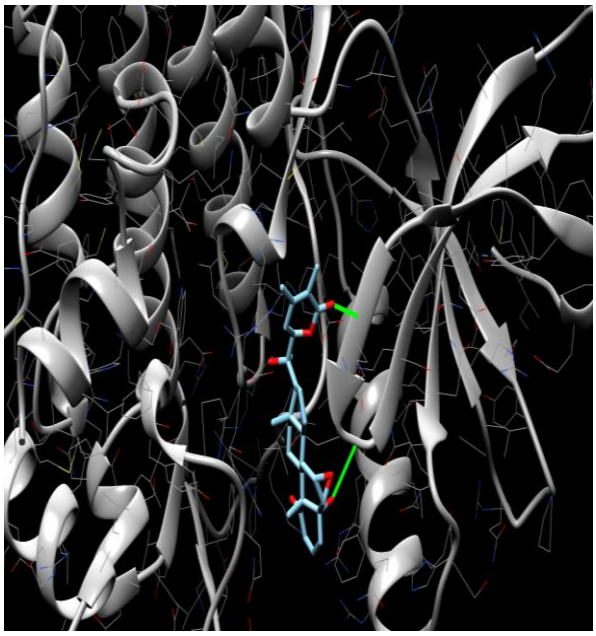

Fig 4. 50JAK3-Withanolide A

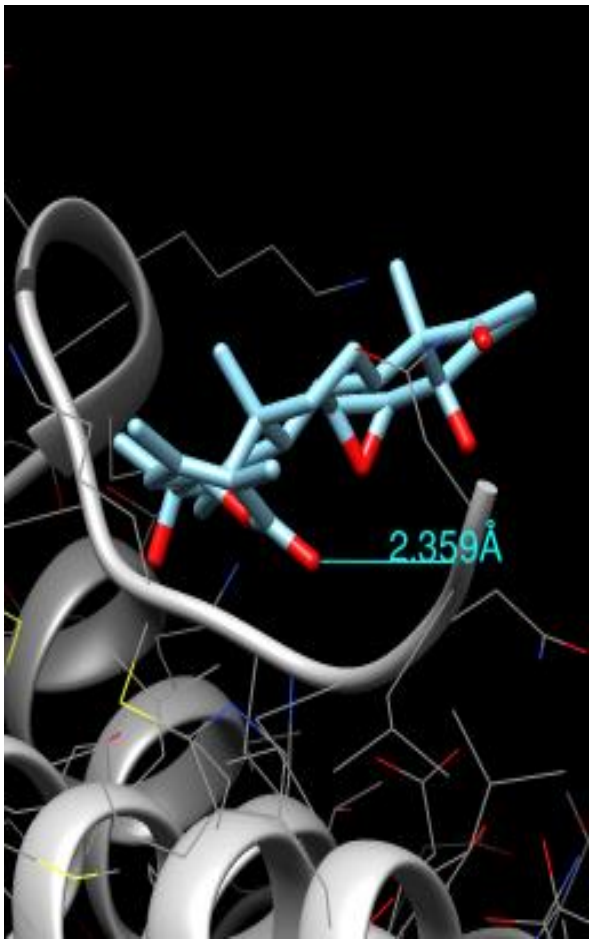

Fig 4. 51IL6-Withanolide A with H dis

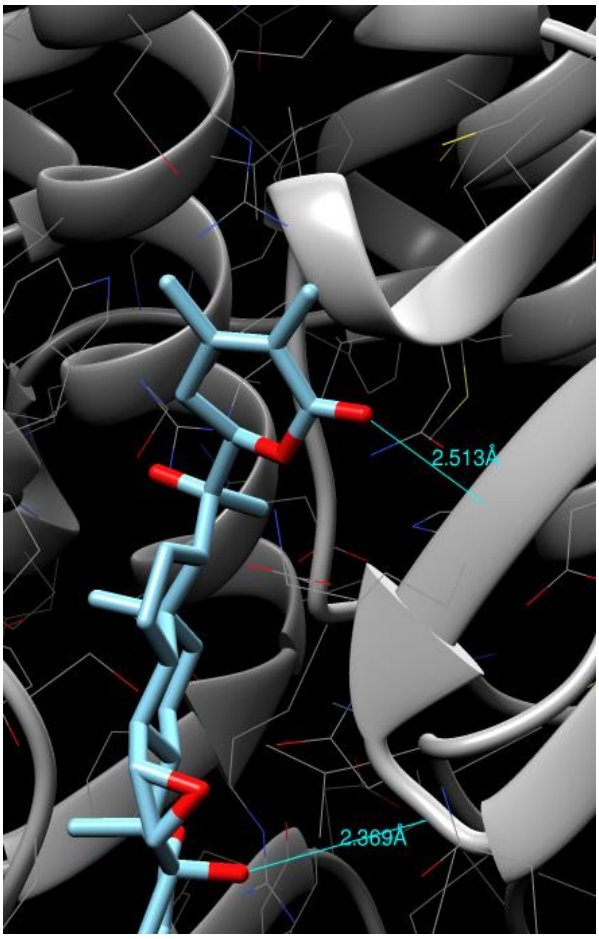

Fig 4. 52JAK3-Withanolide A with H dis

Comparison between IL6-Withanolide A and JAK3-Withanolide A

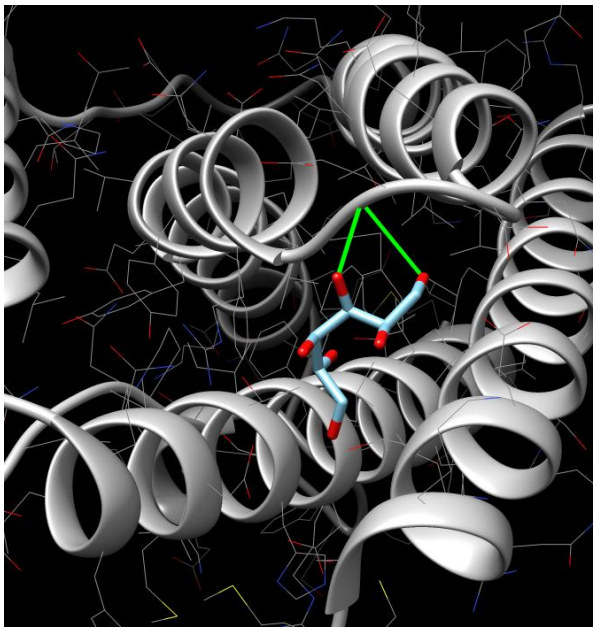

Fig 4. 53IL6-Dolcitol

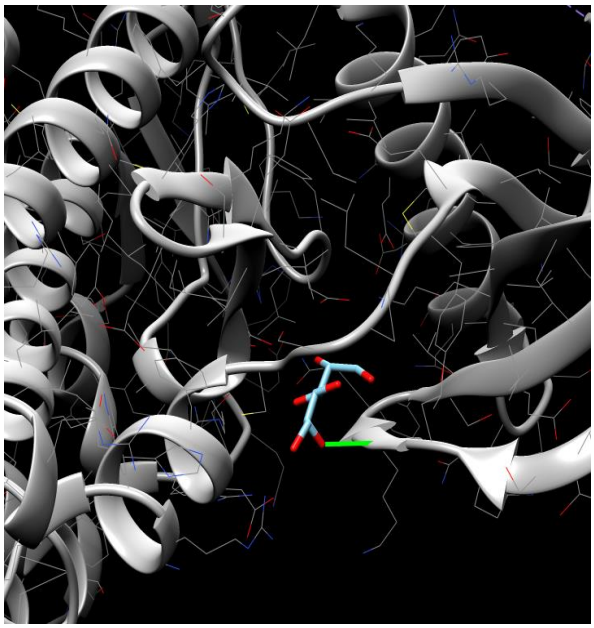

Fig 4. 54 JAK3- Dolcitol

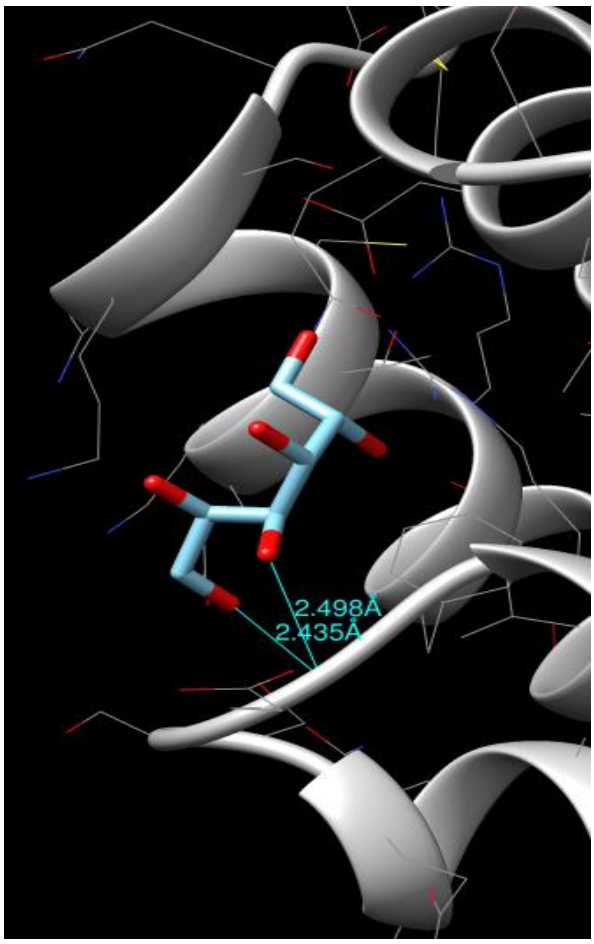

Fig 4. 55IL6-Dolcitol with H dis

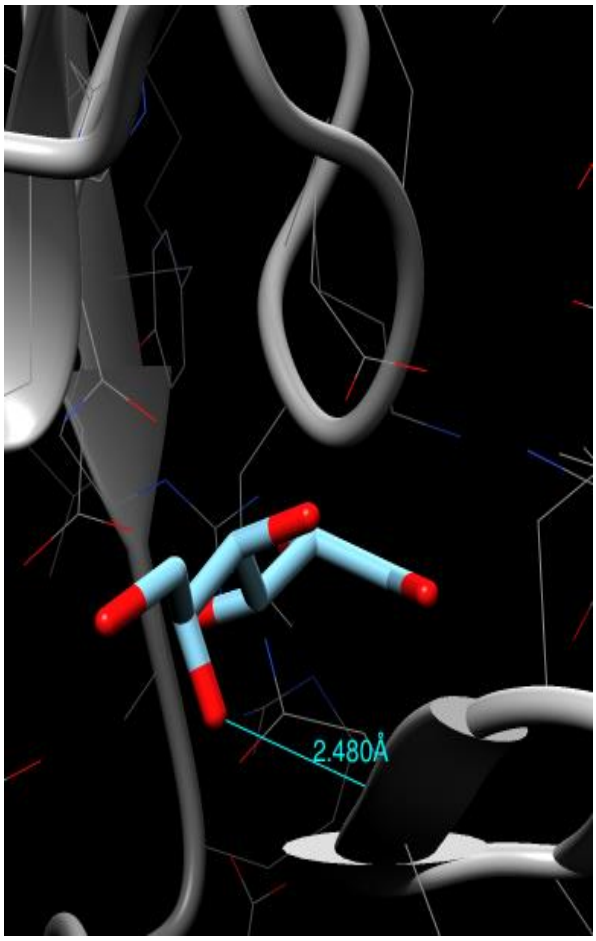

Fig 4. 56 JAK3-Dolcitol with H dis

Comparison between IL6-Dolcitol and JAK3-Dolcitol

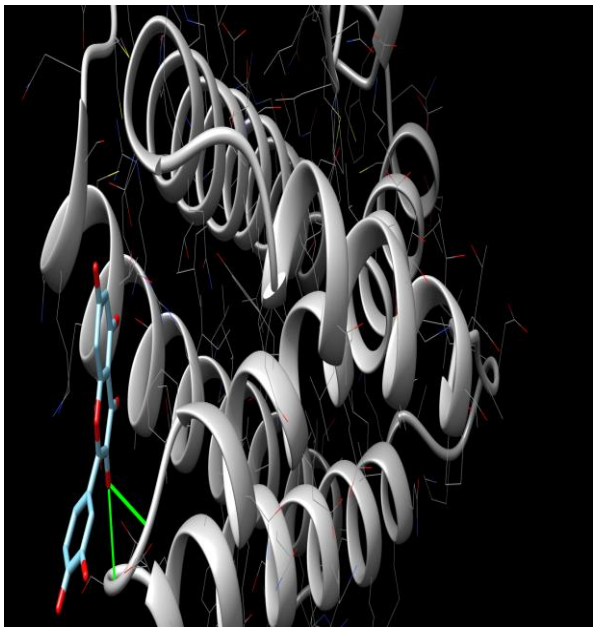

Fig 4. 57 IL6-Anaferine

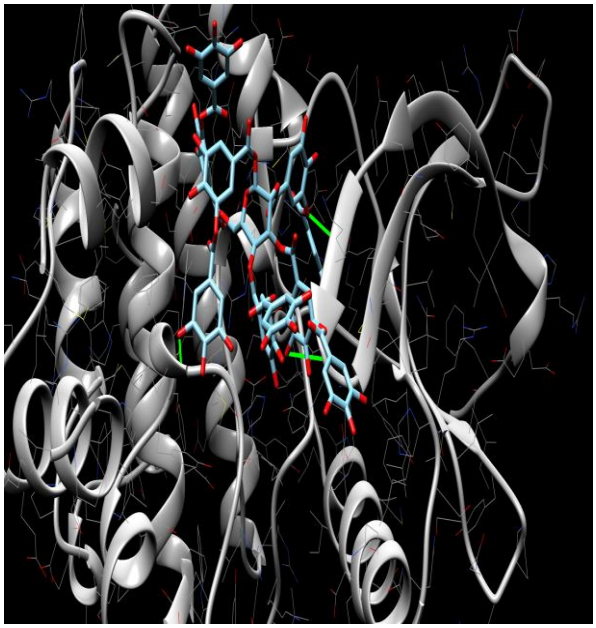

Fig 4. 58 JAK3-Anaferine

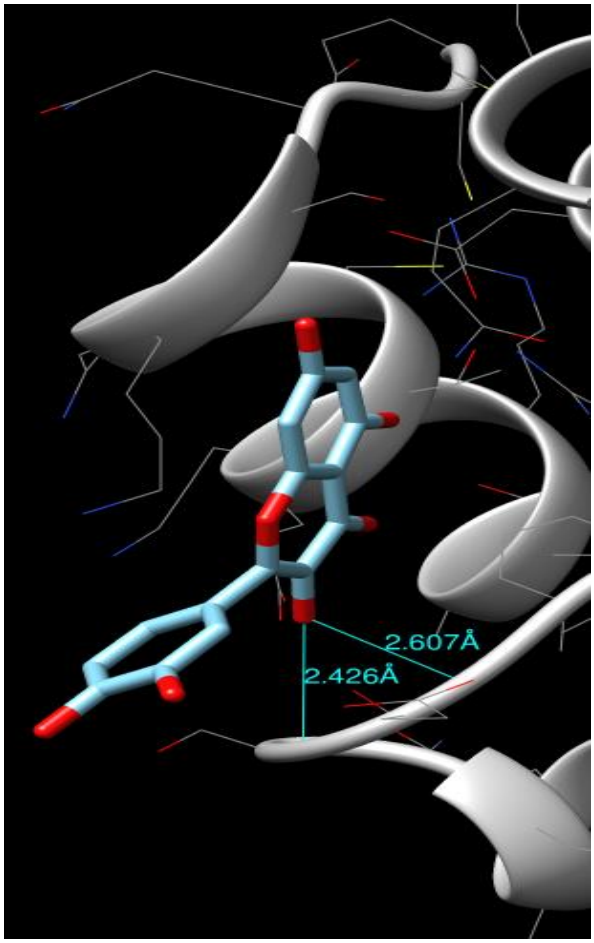

Fig 4. 59IL6-Anaferine with H dis

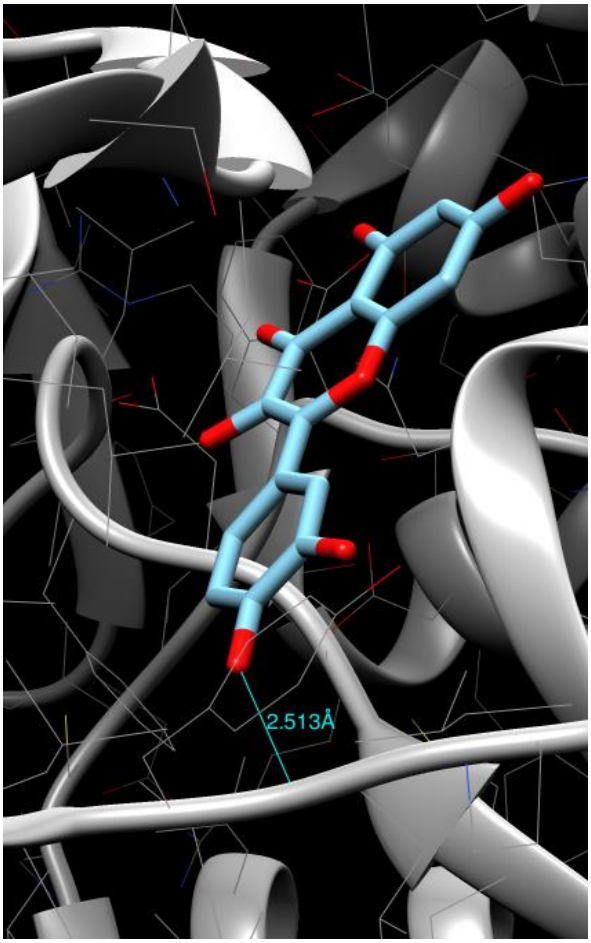

Fig 4. 60JAK3-Anaferine with H dis

Comparison between IL6-Anaferine and JAK3-Anaferine

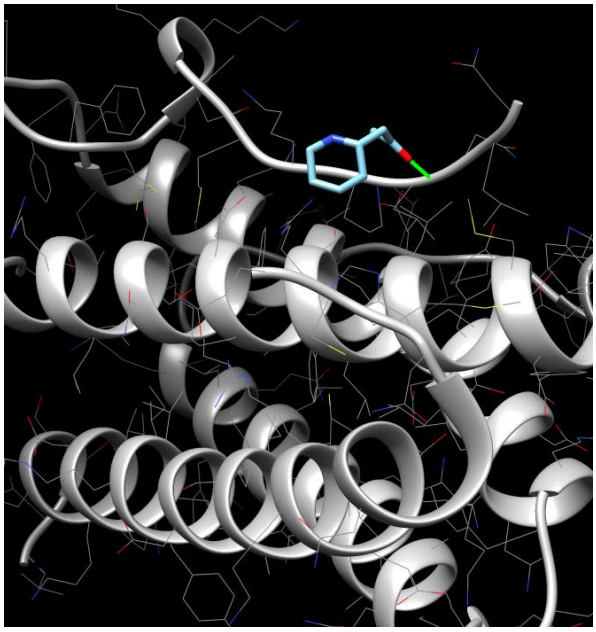

Fig 4. 61 IL6-Isopelletierine

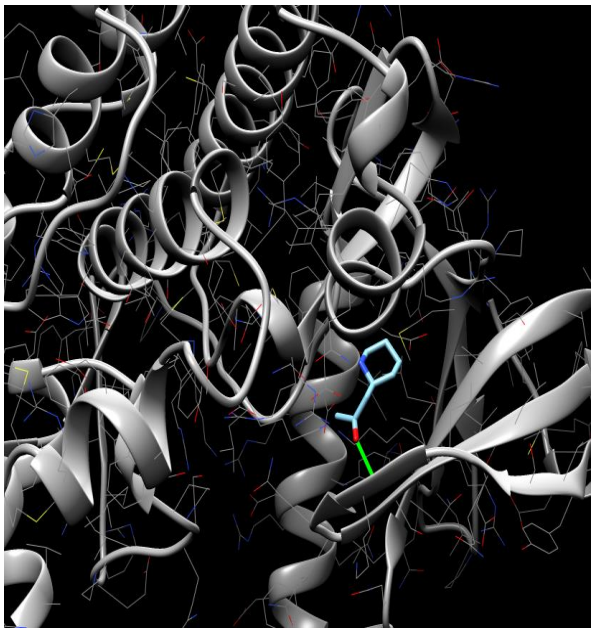

Fig 4. 62JAK3-Isopelletierine

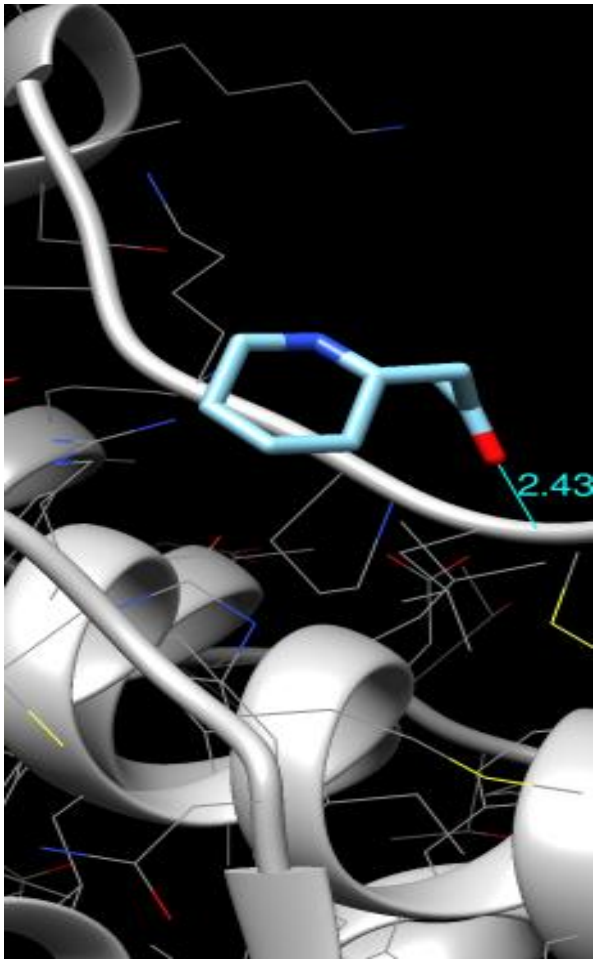

Fig 4. 63IL6-Isopelletierine with H dis

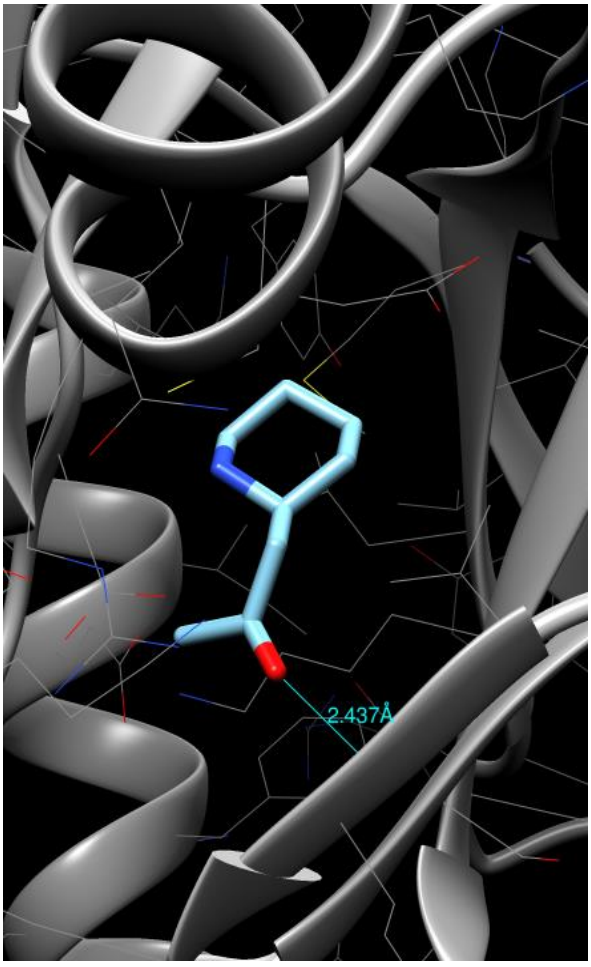

Fig 4. 64JAK3-Isopelletierine with H dis

Comparison between IL6-Isopelletierine and JAK3-Isopelletierine

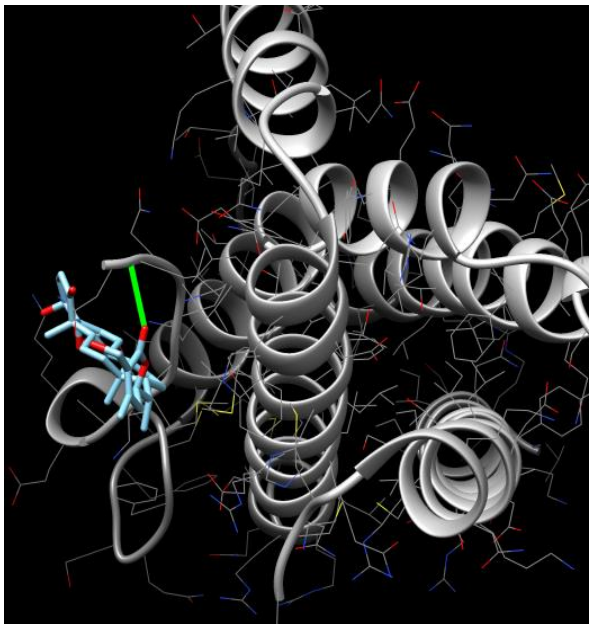

Fig 4. 65IL6-Withaferin A

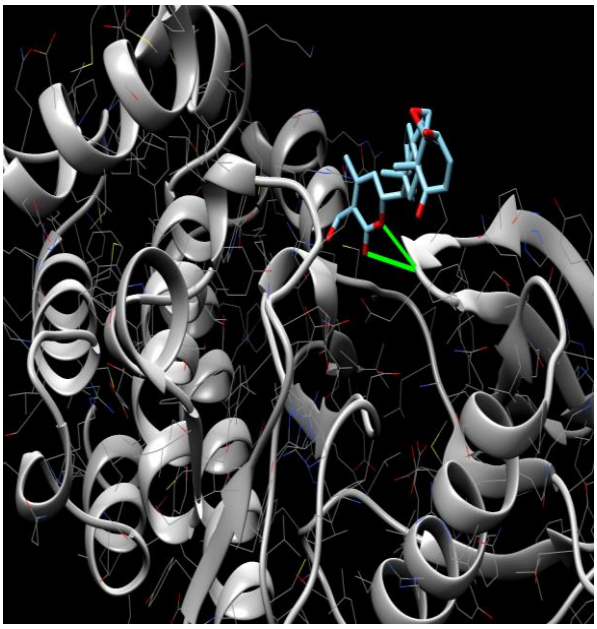

Fig 4. 66JAK3-Withaferin A

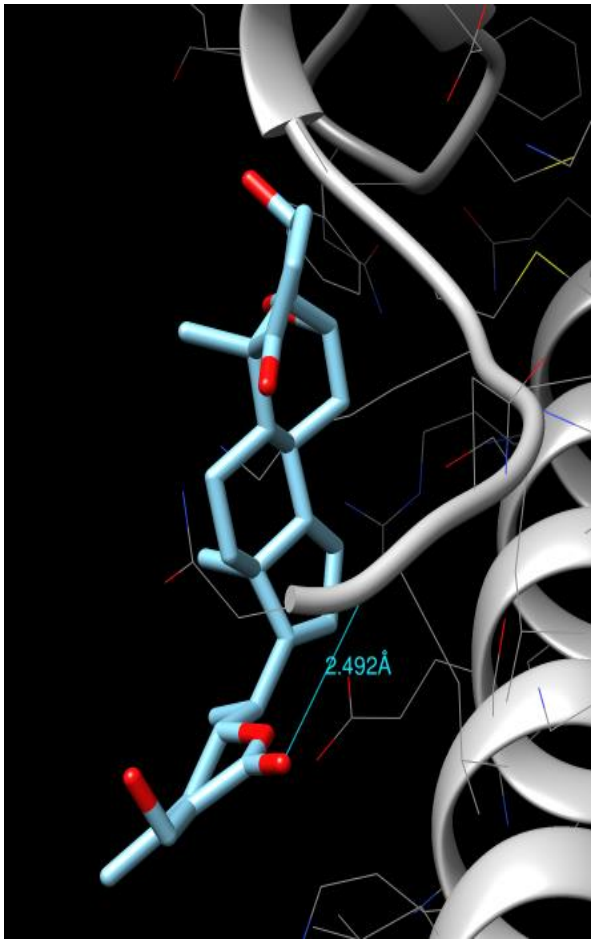

Fig 4. 67IL6-Withaferin A with H dis

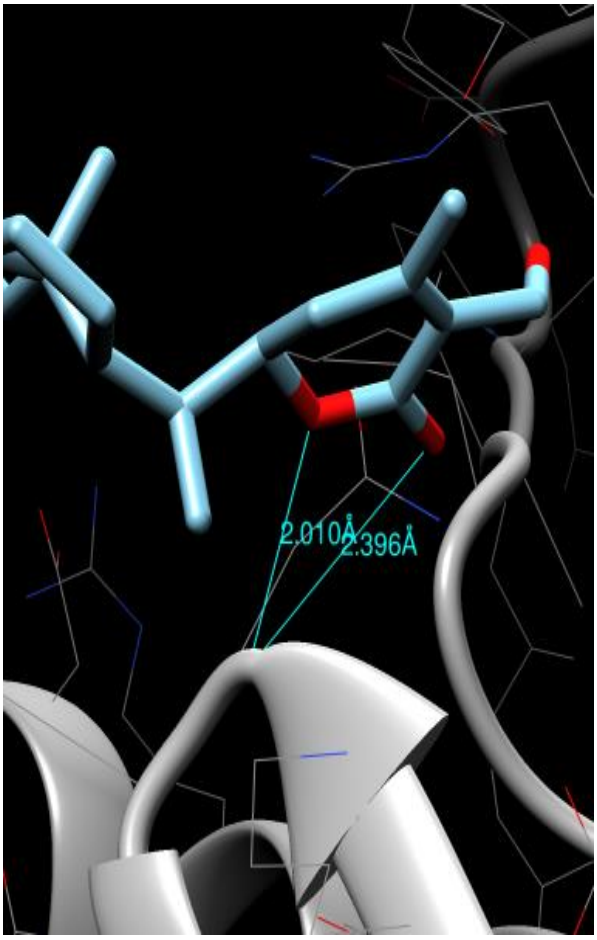

Fig 4. 68 JAK3-Quercetin with H dis

Comparison between IL6-Withaferin A and JAK3-Withaferin-A

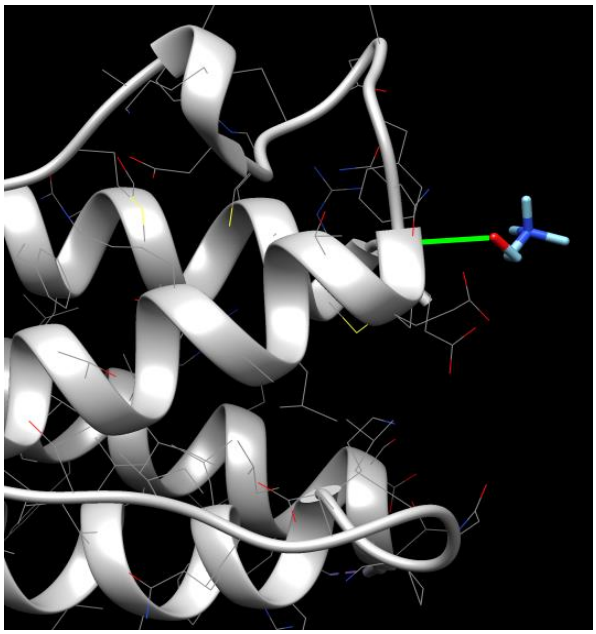

Fig 4. 69 IL6-Choline

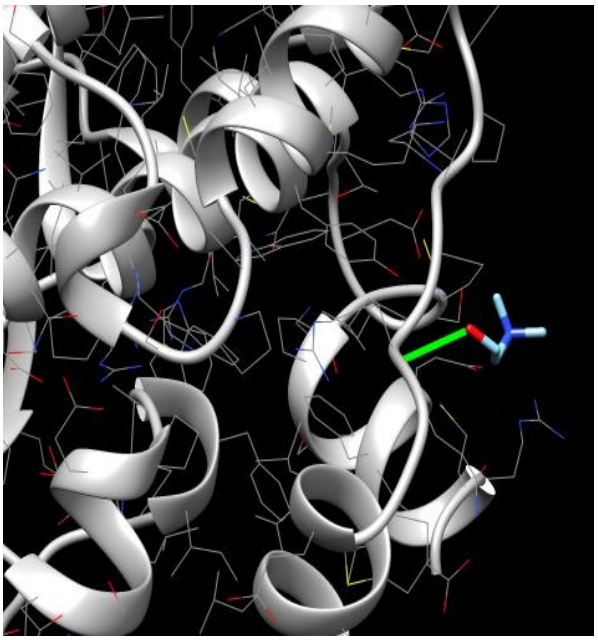

Fig 4. 70 JAK3-Choline

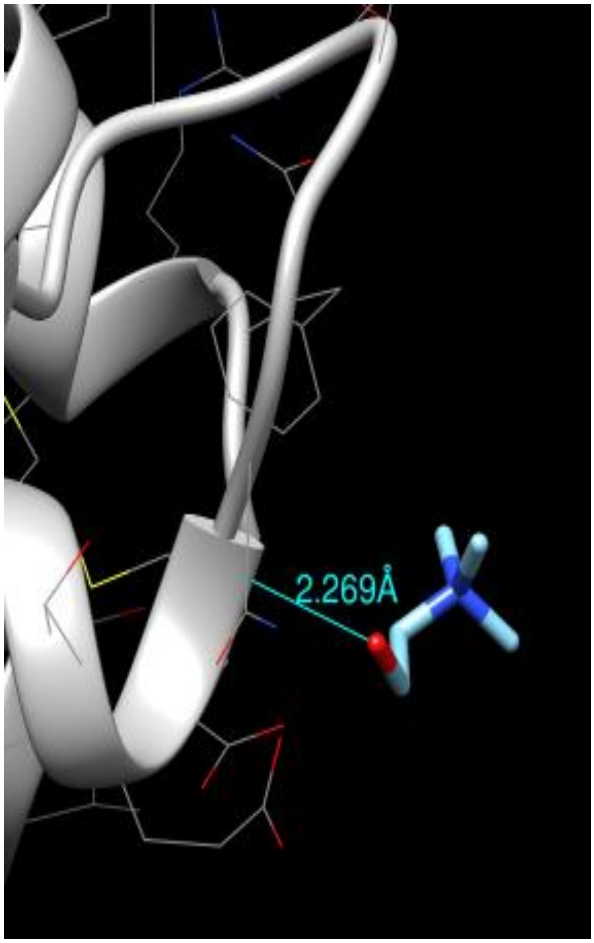

Fig 4. 71IL6-Choline with H dis

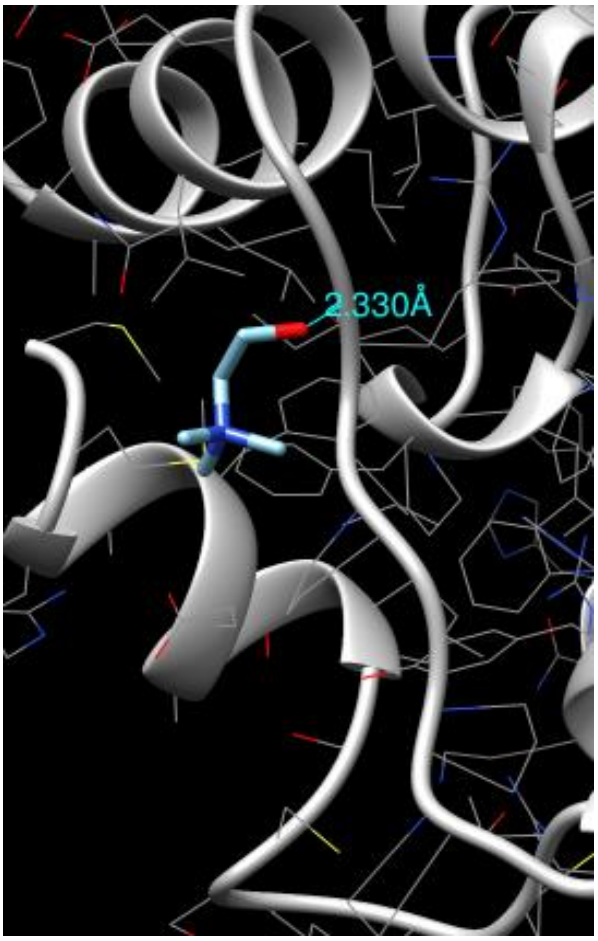

Fig 4. 72JAK3-Choline with H dis

Comparison between IL6-Choline and JAK3-Choline

4.1. Conclusion

By these molecular docking studies, it can be concluded that among the eighteen phyto constituents of Withania somnifera, Tannic acid possesses great activity against both anti-rheumatoid arthritis targets followed by Rutin (in case of IL-6) and Chlorogenic acid (in case of JAK3). Phenolics and flavonoids may have a direct action against anti-arthritis targets. Using this insilico method we may have anti-rheumatoid arthritis inhibitors to approach this inflammatory disorder RA. These inhibitors were retrieved from Withania somnifera. By summing up the whole project, outcome of the study has shown that Tannic Acid with IL6 and JAK3 targets have highest binding affinity. Phytocompound Tannic acid have great potential for drug research against RA. Further analysis and development of this drug research could be accelerated by Molecular Dynamic Simulation (MDS) and comparative modeling[34].

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