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TO EXPLORE ANTI RHEUMATOID ARTHRITIS ACTIVITY OF *NYCTANTHES ARBOR- TRISTIS* BY USING *IN SILICO* STUDY

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ABSTRACT

Night-flowering jasmine, or Nyctanthes arbor-tristis, has long been utilized in a variety of traditional medicines due to its immunomodulatory and anti-inflammatory qualities. This study aims to investigate the potential anti-rheumatoid arthritis (RA) activity of bioactive compounds derived from Nyctanthes arbor-tristis using In silico methods. R.A. is a chronic inflammatory disorder identified by immune system dysregulation, leading to joint damage and disability.

This In silico study provides a preliminary understanding of the molecular interactions and supports the traditional use of Nyctanthes arbor-tristis in managing rheumatoid arthritis. Further experimental validation and clinical studies are recommended to confirm these findings and explore the therapeutic potential of these compounds in RA treatment.

Keywords: *Nyctanthes arbor-tristis, rheumatoid arthritis, In silico study, molecular docking, bioactive compounds*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes inflammation of the joint and synovial membranes. In addition, it results in pain, distortion, and deterioration of the bone cartilage.[1] Particularly, it has been established that inflammatory mediator are essential for the development of swelling, rigidity, and disability at the outset of RA. It is an autoimmune disease that affects the synovial joints and is constantly brought on by inflammatory mediators and viruses.[2]Severe joint and bone destruction is a hallmark of rheumatoid arthritis (RA), which is caused by an increased inflammatory response at the articular sites.[3]Instances per 10,000 people worldwide and 1% are the yearly incidence and prevalence rates of RA, respectively.[3]With about 1500 cases of RA per lakh of the global population, RA has grown to be a serious public health concern. Compared to men, women are more likely to suffer from this swelling condition (3:1).[4,5]

RA classified as follows:

Palindromic rheumatoid arthritis

Wherein recurring swelling of the monoarticular and polyarticular joints takes place.

Juvenile rheumatoid arthritis

Large joints are affected more than small joints, oligoarthritis is more common, systemic diseases are more common, rheumatic nodules and rheumatoid antinuclear antibodies, seropositivity and absence are observed. It occurs between the ages of two and four and is very intense.

Rheumatoid spondylitis

This is an inflammatory condition affecting the joints in the spine that link the vertebrae and the joints in the pelvis.[6]

The following are possible developments in the pathogenesis process

The synovial membrane, which creates the bursa surrounding the joint, is where RA starts. Synovial fluid, which is contained in these sacs, nourishes and oxygenates the cartilage covering the ends of bones while also lubricating and cushioning joints. Collagen makes up cartilage, which gives joints flexibility and stability. Persistent inflammation in the synovial system is caused by damaging chemicals produced by an aberrant immune system in rheumatoid arthritis. Cartilage destruction is rapid in rheumatoid arthritis.[7]The pannus (thickened synovial tissue) continues to develop depending on the fluid in the synovium and the immune system. Additional enzymes produced by the pannus dissolve surrounding cartilage, enlarging the region and drawing in additional WBC. It is important for swelling due to rheumatism. This inflammatory process can damage other parts of the body in addition to cartilage and bone.

When a T cell identifies an antigen as “non-self,” it releases cytokines that stimulate the growth of B cells and the production of blood-borne antibodies that help the body recognize foreign objects and ward off intruders, leading to destruction. A summary of the mechanisms underlying the inflammatory response in RA illness is provided. The following: IL-1, IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, IL-23, Among the pro-inflammatory cytokines in rheumatoid arthritis include TNF-γ, granulocyte macrophage colony stimulating factor, macrophage inflammatory protein-1, and monocyte chemoattractant protein-1.[8,9]

Steps involved in inflammation of RA

Genetic/Environmental Trigger
↓
Autoimmune Response Initiation
↓
T-cell Activation → B-cell Activation
↓ ↓
Inflammatory Mediators Release
↓
Synovial Membrane Inflammation (Synovitis)
↓
Joint Tissue Damage
↓
Chronic Inflammation and Joint Deformity

Cell adhesion molecules capable of binding to inflammatory cells are produced by endothelial cells and can induce the Placing of instigative cells to the site of swelling.

TNF-α and IL-1 help. Many types of cells found in the synovium, such as chondrocytes, dendritic cells, neutrophils, fibroblasts, mast cells, and macrophages, and osteoclasts, are activated by IL-1 and TNF-α. This activation leads to the production of additional anti-inflammatory and degradative enzymes. Both promote the growth of new cells that form the pannus. Both cytokines affect the immune system by activating T cells and B cells. A detailed explanation of the pathophysiology of RA, covering cytokines, T cells, B cells, and more. NSAIDs, or nonsteroidal anti-inflammatory medications, and DMARDs, or disease-modifying anti-inflammatory drugs. Rheumatoid arthritis medications are currently limited in their effectiveness in reducing symptoms in some sick person and are correlated with many adverse effects, including immunosuppression, which increases the risk of infection, and internal organ damage, affecting the skin, kidneys, and stomach. New research is now being done on traditional methods as herbs can be used easily over time and do not appear to be harmful or cause side effects. We believe that finding new drugs and better treatments is essential to providing long-term treatment for RA.[10,11]

PLANT PROFILE

Nyctanthes arbortristis Linn. belongs to the Oleaceae family.[12,13] It is also called “Sorrowful Path” because the flowers are less active during the day. It grows mainly in the foothills of the Himalayas in India, from China to the Godavari, Nepal, Assam, Myanmar, Bengal, and Central India.[14] One of the most powerful plants in the world. Research and business groups are interested in this plant because it can be used in food, medicine, textile, cosmetics and pharmaceutical fields. In the past, *Nyctanthes arbor tristis* has been reported in the scholarly literature for use in the treatment of fever, rheumatism, biliary tract disease, liver disease [15,16] refractory sciatica, malaria, bronchitis, wound healing, insect skin disease, stomach disease, astringency, and menstrual bleeding to be recognized.

Plant explanation

Nyctanthes arbor tristis can grow into a small tree or shrub up to 10 meters (33 feet) tall, with gray bark. Simple, opposing leaves with 17 edges measure 6-12 cm (2.4–4.7) in length and 2–6.5 cm (0.79–2.56) in width.. It is found growing in the Terai region, the Indo-Malaya region and Burma. And Ceylon. A shrub

that can tolerate some shade, dry deciduous woodlands are ideal for its growth. *N. Arbortristis Linn*.[17] A small tree or shrub with scaly, gray bark that can reach 15 to 20 feet in height. These seeds are abundant in warm, humid climates. The trunk and branches are square. The stems are white on brown, and are tough.[18] It also penetrates into plants, tree trunks and the borders of oak trees.[19] The best growing conditions for the plant are well-drained, sandy soil with enough space for the roots to spread. The tiny hairs are like tiny thorns.

Sr No.	Plant Part	Chemical Constituents	Pharmacological activity
1	Leaves	Astragaline, Nicotiflorin, Flavanol glycosides, Beta- sitosterole, Nyctanthic acid, D-mannitol, Oleanolic acid, tannic acid, ascorbic acid, glucose, fructose, carotene, lupeol, methyl salicylate, benzoic acid, iridoid glycoside	Anti-inflammatory, Antioxidant, Antifungal, Anti-pyretic, Hepatoprotective, Antibacterial, Anthelmintic, Immunopotential
2	Seeds	Arbortristoside A and B, Glycosides of linoleic oleic, 3-4 secotriterpene acid, steric, myristic and palmitic acid, lignoceric, nyctanthic acid	Immunomodulatory, Antifungal, Antibactrial
3	Flowers	Essential oils, D- mannitol, tannin and glucose, Nyctanthin, Carotenoids, Beta-monogentiobioside-beta-D monoglucoside esters of alfa-crocetin, Beta- digentiobioside ester of Alfa- crocetin Arbortristoside,	Anti-oxidant, Diuretics, Anti- inflammatory, Sedatives, Antifilarial
4	Flower oil	Alfa-pinene, phenyl acetaldehyde, p-cymene, l-hexanol methyl heptanone, l- deconol and anisaldehyde	As perfume
5	Bark Stem	Glycoside and alkaloid, Glycoside-naringenin- 4’-0-beta-glucapyranosyl-alfa-xylopyranoside and beta- sitosterol	Anti- microbial, Anti-pyretic, Antioxidant

Table No.1: Phytochemical constituents with their pharmacological action:[22,23]

Structures:

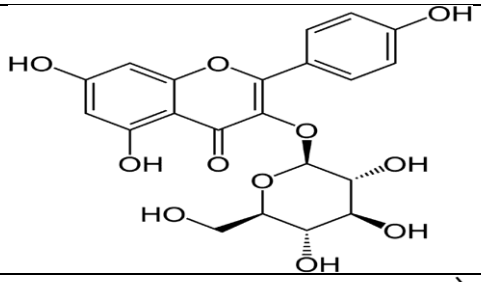
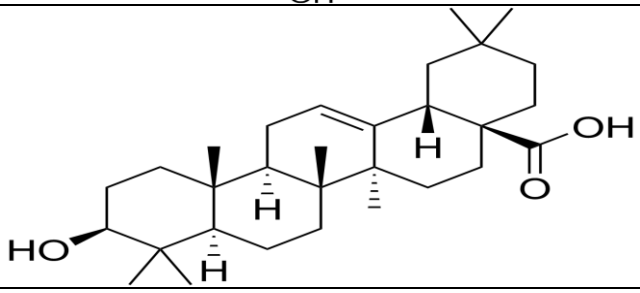
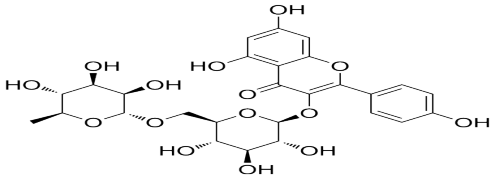
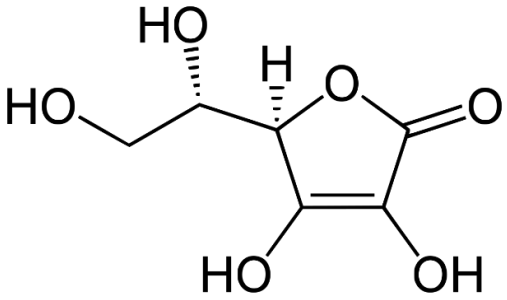
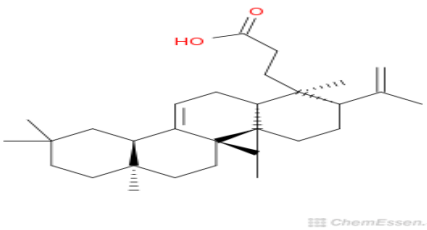
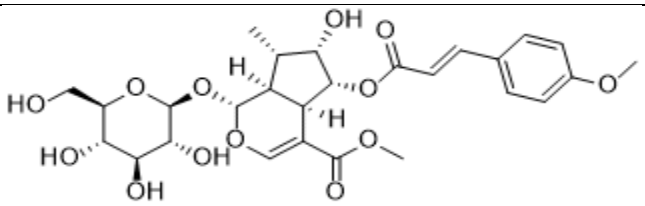
Sr No.	Phytoconstituents	Structure
1	Astragalin	
2	Oleanolic Acid	
3	Nicotiflorin	
4	Ascorbic acid	
5	Nyctanthic acid	
6	Arbortristoside A	

Table No. 2: Phytoconstituent with their structure

MATERIALS AND METHODS

SOFTWARE

The necessary software was downloaded from the internet in order to complete the docking. Versions of Python 3.11.5, MGL Tools 1.5.7, Auto Dock Tools 1.5.7 were the necessary software. Python is an advanced programming language that helps developers understand code. The software package for computational molecular biology and chemistry is called MGL Tools, or MGLTools for short. It is designed to support professionals, scientists and researchers in studies of molecular interactions and structures, especially in drug discovery and molecular modelling. A family of molecular docking techniques called Auto Docking is used in molecular biology and computational chemistry. Use BIOVIA Discovery Studio Visualizer v21.1.0.20298 to analyze the data.[24]

PyMOL (pymol)

You can create and then view molecular structures with PyMOL, a feature-rich and potent program. It makes it possible to view various proteins and molecules in three dimensions, together with the surfaces and trajectories that correspond to them. Given the complexity of this tool, advanced features like ray tracing and 3D structure animation are also supported. Based on an open-source project, PyMOL is available for general use with additional benefits, although there is a fee for non-educational use. The original open-source PyMOL project is based on Python and is not as easily installed on Windows systems. This version, dubbed "Incentive PyMOL," comes with an installer for Windows, incentive documentation, user support, and helpful tutorials, as well as built-in tools like a molecular morphing tool."[25]

Auto Dock Tools

An automatic docking tool set is called Auto Dock. Its purpose is to forecast the way that tiny molecules, such medication candidates or substrates, would attach to a known three-dimensional receptor. [26]the process of docking the ligand to a set of grids that describe the target protein is carried out by auto dock, while auto grid computes these grids beforehand. The atomic affinity grids are not only useful for docking but also for visualizing. For instance, this can direct organic synthesis chemists in creating better binders.

BIOVIA Discovery Studio

A characteristic-rich, free molecular docking program for observing, split, and examining protein and micromolecular data is called BIOVIA Discovery Studio Visualizer. Without wasting time or scientific data, experts and their colleagues can exchange results in an easy and effective manner. A complete software suite called Discovery Studio is designed to examine and model sequences, arrangement of atoms in a molecule, and other details that is relevant to researchers studying life sciences. The program comes with implement for basic data investigation as well as attribute for observing and changing data.[27] Files created by other programs in the Discovery Studio product family can be opened using the free Discovery Studio Visualizer. It is designed to provide an interactive interface for viewing and editing text, X-ray reflectance data, sections, and other data.

Preparation of protein

The Protein Data Bank provided PDB format with the 3D structures of the following proteins: TNF protein (PDB ID:6ooy), tyrosine protein kinase protein (PDB ID:3t9t), IL6 protein (PDB ID:1alu), T cell receptor beta chain protein (PDB ID: 2axh), and IL17A protein (PDB ID:8dyg). The protein preparations were done using Python Molecular Version (PMV-1.5.7). An additional heavy hydrogen atom resulted in the formation of bonding structures. [28]

Preparation of Ligand

Ascorbic acid, oleanolic acid, nicotiflorin, and astragaline ligands' 3D formation were taken from the NCBI PubChem table and transformed using open Babel to the PDB format. [29]in order to eliminate potential interactions with the protein's TNF, IL6, tyrosine protein kinase, IL17A and T cell receptor beta chain as well as for molecular simulations, the derived ligand structures were reduced.

Target optimization

Retrieved 3D structure of the protein from PDB prepare the structure of protein by removing water molecule and ligand molecule and adding hydrogen atoms and optimizing the structure by using Discovery Studio software. The PDB format of protein is then converted into PDBQT file by using Auto dock tool to generate atomic coordination. [30]

Ligand optimization

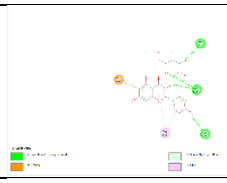
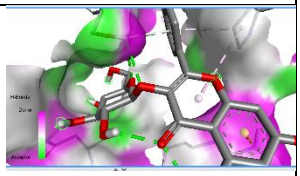
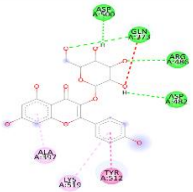
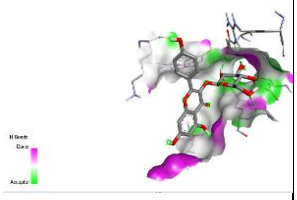
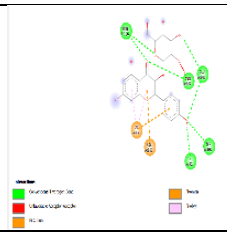
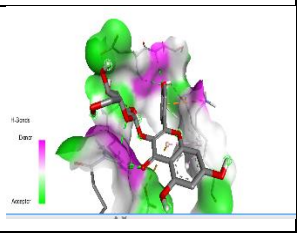
PDB coordinates of desired 3D ligand molecule were optimized for docking analysis by using PyMOL software and then converted into PDBQT file for optimization. [31]

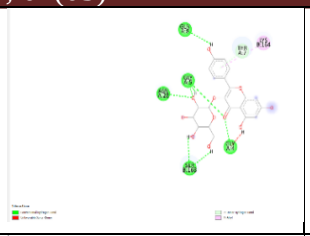
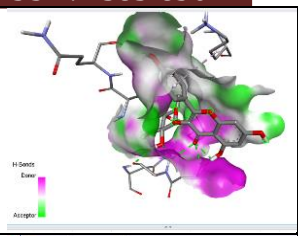
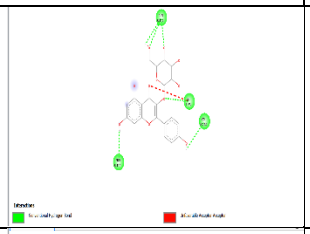
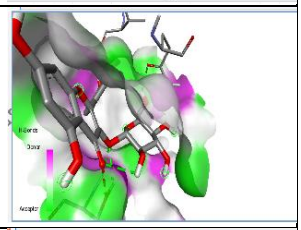
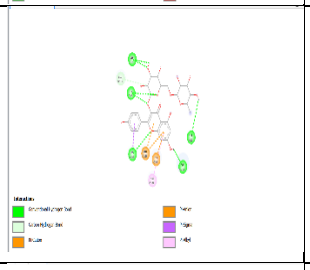
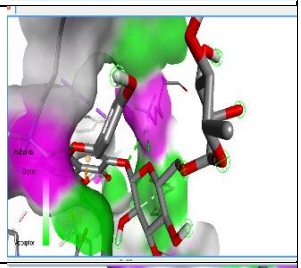
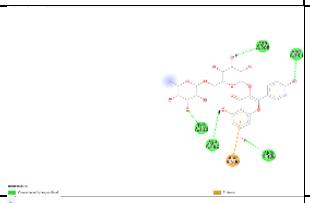
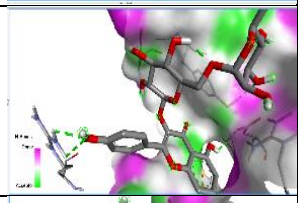
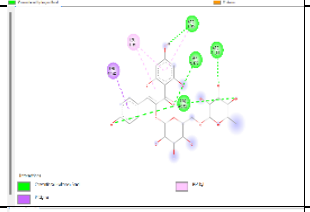
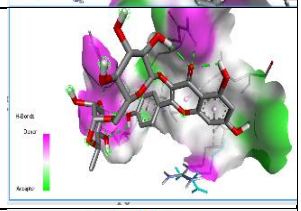
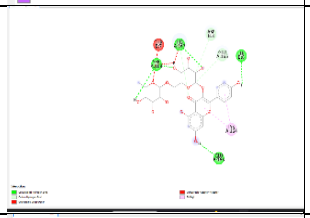
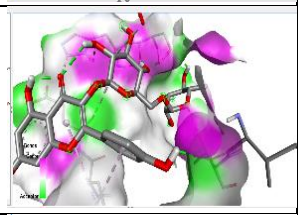
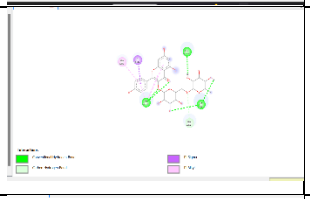
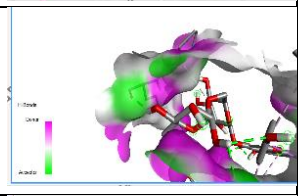
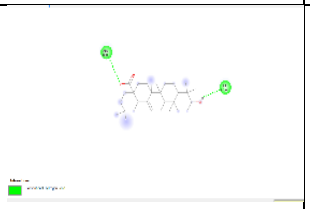
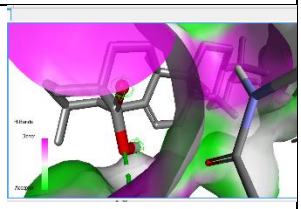
Molecular docking analysis

Molecular docking studies aim to predict the structure of ligands and receptors. The ligand is appropriately identified in the active site of the receptor target and hydrogen bonds are Create with the remaining amino acids of the selected receptor. After the protein sample is collected, water molecules are removed so as not to interfere with the port. The downloaded protein has ligands that have been removed. Polar hydrogen molecules are then added. The file is stored in PDBQT format. Search for bases in ligands and save the data in PDBQT format. [32'33]

Interaction of protein and ligand

The protein's binding energy to the ligand was obtained through molecular docking using Auto dock Tools. The bioactive substances that inhibit the target proteins the best were thought to have the lowest binding energies. The visual results and the binding energies between ligands and acceptors. A lower binding energy value indicates a stronger and more favourable affinity of the chemical for the receptors.

Sr. No	Bioactive compound	Protein	2D structure	3D Structure
1	Asragaline	TNF		
2	Astragaline	Tyrosine protein kinase		
3	Astragaline	IL6		

4	Astragaline	Tcell receptor beta chain		
5	Astragalin	IL17A		
6	Nicotiflorin	TNF		
7	Nicotiflorin	Tyrosine protein kinase		
8	Nicotiflorin	IL6		
9	Nicotiflorin	T cell receptor beta chain		
10	Nicotiflorin	IL17A		
11	Oleanolic acid	TNF		

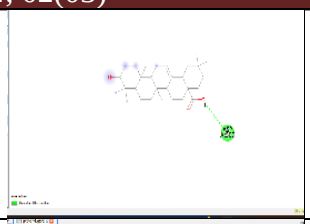
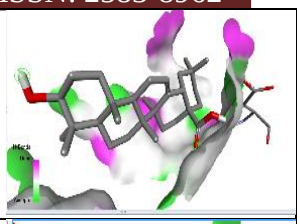
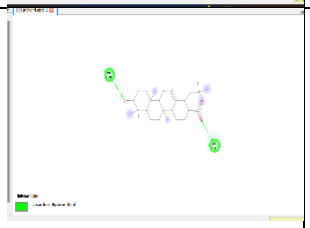
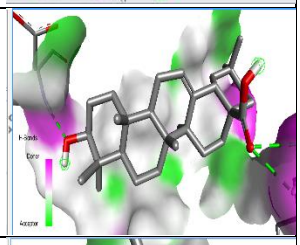
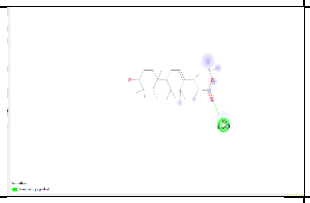
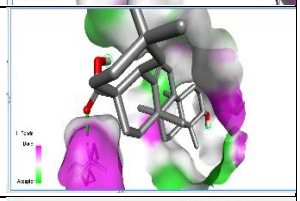
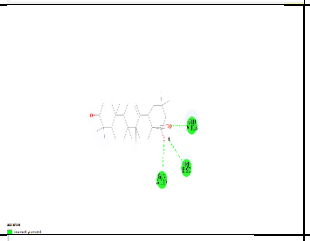
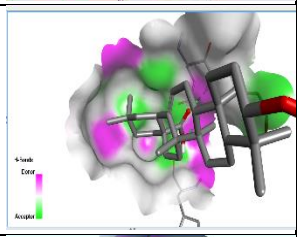
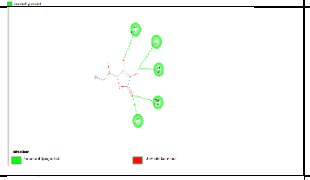
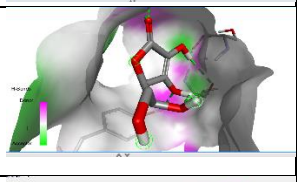
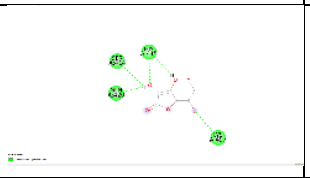
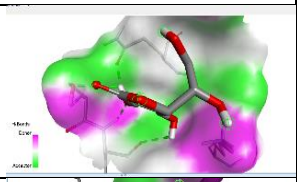
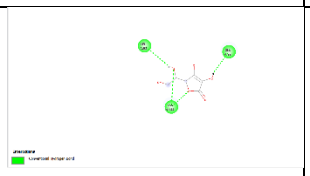
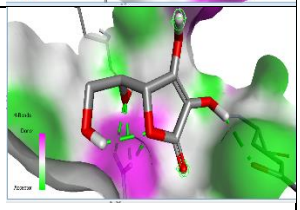
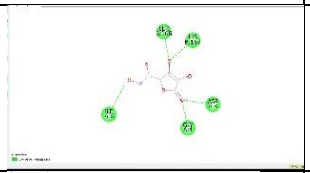
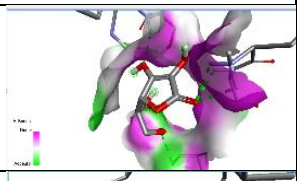
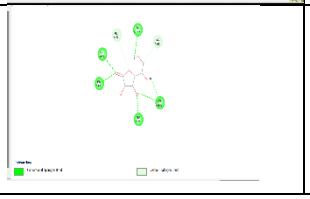
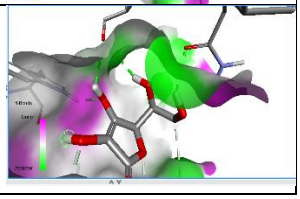
12	Oleanolic acid	Tyrosine protein kinase		
13	Oleanolic acid	IL6		
14	Oleanolic acid	T cell receptor beta chain		
15	Oleanolic acid	IL17A		
16	Ascorbic acid	TNF		
17	Ascorbic acid	Tyrosine protein kinase		
18	Ascorbic acid	IL6		
19	Ascorbic acid	T cell receptor beta chain		
20	Ascorbic acid	IL17A		

Table No. 3: Interaction between Bioactive compound and Protein

RESULT

The bioactive compounds found in *Nyctanthes abror tristis* such as Astragalin, Nicotiflorin, Oleanolic acid and Ascorbic acid are docked with the protein such as TNF, tyrosine protein kinase, IL6, t cell receptor beta chain and IL17A and the results are as follows:

Sr No.	Bioactive compound	Protein	H- bonding	Bond energy Kcal /mol
1	Astragalin	TNF	6	-7.4
2	Astragalin	Tyrosine protein kinase	6	-7.8
3	Astragalin	IL6	7	-6.9
4	Astragalin	T cell receptor beta chain	10	-7.5
5	Astragalin	IL17A	8	-7.7
6	Nicotiflorin	TNF	8	-7.0
7	Nicotiflorin	Tyrosine protein kinase	7	-7.4
8	Nicotiflorin	IL6	9	-6.5
9	Nicotiflorin	T cell receptor beta chain	7	-8.4
10	Nicotiflorin	IL17A	8	-8.7
11	Oleanolic acid	TNF	2	-6.2
12	Oleanolic acid	Tyrosine protein kinase	1	-7.9
13	Oleanolic acid	IL6	3	-6.7
14	Oleanolic acid	T cell receptor beta chain	1	-7.4
15	Oleanolic acid	IL17A	3	-7.5
16	Ascorbic acid	TNF	6	-5.6
17	Ascorbic acid	Tyrosine protein kinase	5	-4.9
18	Ascorbic acid	IL6	6	-5.2
19	Ascorbic acid	T cell receptor beta chain	7	-5.2
20	Ascorbic acid	IL17A	6	-5.1

Table No. 3: Interaction between Bioactive compound and Protein

DISCUSSION:

In silico study on *Nyctanthes arbor-tristis* for anti-rheumatoid arthritis activity has provided promising insights. The bioactive compounds identified within *Nyctanthes arbor-tristis* exhibit potential interactions with key targets involved in the pathogenesis of rheumatoid arthritis.

This *In silico study* provides a preliminary understanding of the molecular interactions and supports the traditional use of *Nyctanthes arbor-tristis* in managing rheumatoid arthritis. Further experimental validation and clinical studies are recommended to confirm these findings and explore the therapeutic potential of these compounds in RA treatment.

CONCLUSION

Molecular docking and virtual screening results indicate that these compounds have significant binding affinities with rheumatoid arthritis-related proteins, suggesting possible inhibitory effects.However, while in silico studies offer valuable initial insights, it is crucial to corroborate these results with *in vitro* and *in vivo* studies to fully understand the therapeutic potential and safety profile of *Nyctanthes arbor-tristis*. Future research should focus on the mechanistic pathways, dose optimization, and clinical efficacy to develop these bioactive compounds into effective treatments for rheumatoid arthritis.

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