Assessment Antiarthritic Potential of Naproxen through *In-silico* Molecular docking

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Background

Arthritis destroys the cartilage that normally protects joints. Arthritis causes not only hyperplasia of synovial cells, but also an inflammatory response. Naproxen (Np) is one of the oldest and best-selling non-selective NSAIDs, inhibiting both her COX isoforms with comparable IC50 values. Naproxen is a more potent COX-2 inhibitor than COX-I. Naproxen sodium (Ns), the sodium salt form of naproxen (Np), is more effective than other NSAIDs in treating knee osteoarthritis. It is also used to treat rheumatic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and non-rheumatoid arthritis. In a recent study, the anti-arthritic potential of naproxen was elucidated by *in-silico* molecular docking *via* binding interactions between naproxen and the NF-κβ enzyme.

Methods

In this regard, the NF-κβ enzyme has been the focus of recent research in the discovery of antarthritic agents. Docking studies were performed Molecular docking of NF-κβ enzyme with naproxen was carried out by Auto Dock.

Results

The molecular docking result revealed that naproxen showed encouraging docking score. Hence from above finding it can be predicted that naproxen exhibited good inhibitor of NF-κβ enzyme.

Key words: Naproxen, NF-κβ enzyme and *in-silico* molecular docking.

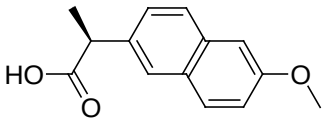
Introduction

Arthritis is one of the world's most devastating diseases, currently affecting 350 million peopl e. According to a recent report, 1 in 4 of her adults in the United States suffers from arthritis with severe joint pain [1]. Arthritis destroys the cartilage that normally protects joints. Arthrit is causes not only hyperplasia of synovial cells, but also an inflammatory response. The result ing deposition of more synovial fluid in the joint develops a layer of synovial cells that causes inflammation at the joint site. The pathology of the disease process often indicates that it also damages articular cartilage and joint alkalosis [2-3]. Ankylosing spondylitis, juvenile idiopathic arthritis, reactive arthritis, psoriatic arthritis, r heumatoid arthritis, septic arthritis, osteoarthritis, and gout are the most commonly reported t ypes of arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that have analgesic and antipyretic effects at low doses. On the other hand, high doses show anti-inflammatory effects [4]. Naproxen was chosen as the representative NSAID for this study be cause it is generally safe, well tolerated, available over-the-counter or by prescription, has a predictable pharmacokinetic profile, and known antiplatelet effects [5]. In the present study, the anti-arthritic potential of naproxen was elucidated by *in-silico* molecular docking *via* binding interactions between naproxen and the NF-κβ enzyme.

Experimental work

Ligand Preparation

2D Structure of ligand Naproxen was drawn by using ChemDraw. The two-dimensional structures of ligands were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [6].



Naproxen

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than

those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is given in table 1[6].

Table 1: The grid-coordinates of the grid-box used in the current study.

Proteins	x-D	y-D	z-D	Spacing (Å)	x center	y center	z center
4idv	46	44	46	0.375	16.134	13.917	87.361

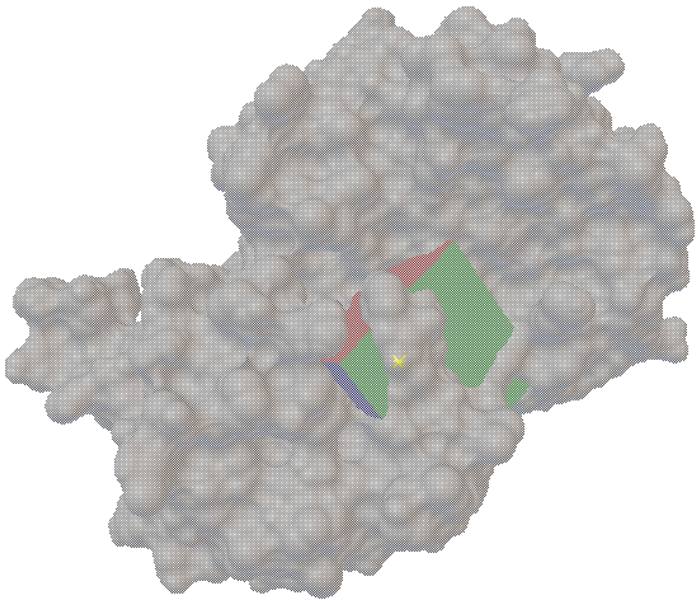


Figure 1: Grid box covering all active sites in NF-κβ inducing kinase enzyme (4idv)

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [7].

Macromolecular structure

NF-κβ inducing kinase

The crystal structure of the NF-κβ inducing kinase enzyme consisting of macromolecular receptor associated with bound ligand 13V is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (4idv.pdb) registered in the Protein data bank was used [8].

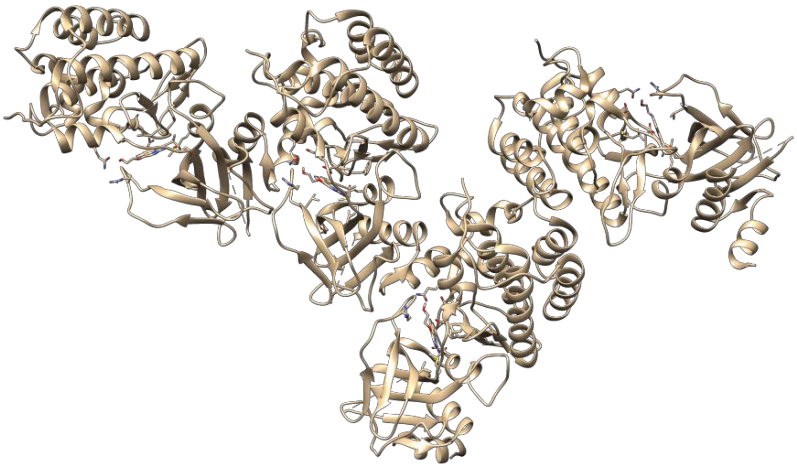


Figure 2: Crystal structure of NF-κβ inducing kinase enzyme with bound ligand 13V (PDB ID-4idv)

Molecular Docking Simulation Studies

Docking of ligand naproxen were performed against NF-κβ receptor by Autodock to establish its probable mechanism of action for their lipid lowering effect. All the bonds of ligand naproxen were kept flexible, while no residues in receptor were made flexible [9].

Toxicity & ADME-T Studies

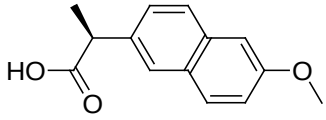
The pharmacokinetics of ligand molecule was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [10-12].

RESULTS AND DISCUSSION

Naproxen (Np) is one of the oldest best-selling non-selective NSAIDs, inhibiting both COX isoforms with comparable IC50 values. Naproxen is a more potent COX-2 inhibitor than COX-2. Naproxen sodium (Ns), the sodium salt form of naproxen (Np), is more effective in treatin g knee osteoarthritis than other NSAIDs. It is also used to treat rheumatic diseases such as rhe umatoid arthritis, osteoarthritis, ankylosing spondylitis and non-rheumatoid arthritis. *In-*

silico molecular docking results showed that the binding energy (Kcalmol-1) of naproxen was −6.61 (Table 2) and the binding affinity was 14.28 μM. Figure 3-5 shows the interaction of molecular stimuli. For the discovery of legitimate anti-arthritic activity of naproxen by reducing nuclear factor κB. Pharmacokinetic profiling of sulf asalazine and naproxen ligands showed that naproxen has a favourable pharmacokinetic profi le associated with the absence of major toxic effects such as mutagenicity, reproductive effect s, irritation and tumorigenic properties. Pharmacokinetic and toxicity profiling results for nap roxen are shown in Figure 6.

Table 2: Results of docking of NF-κβ enzyme

S. N	Compound Name	Structure	Binding Energy (Kcal/Mol)	Binding Affinity
1	Naproxen		-6.61	14.28 μM

Interactions

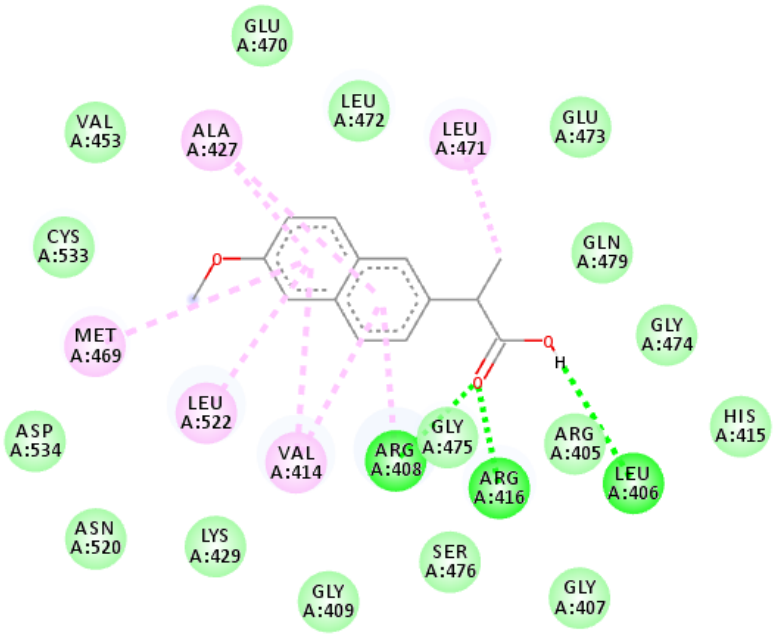


Figure 3: Two-dimensional binding interaction of naproxen with NF-κβ enzyme

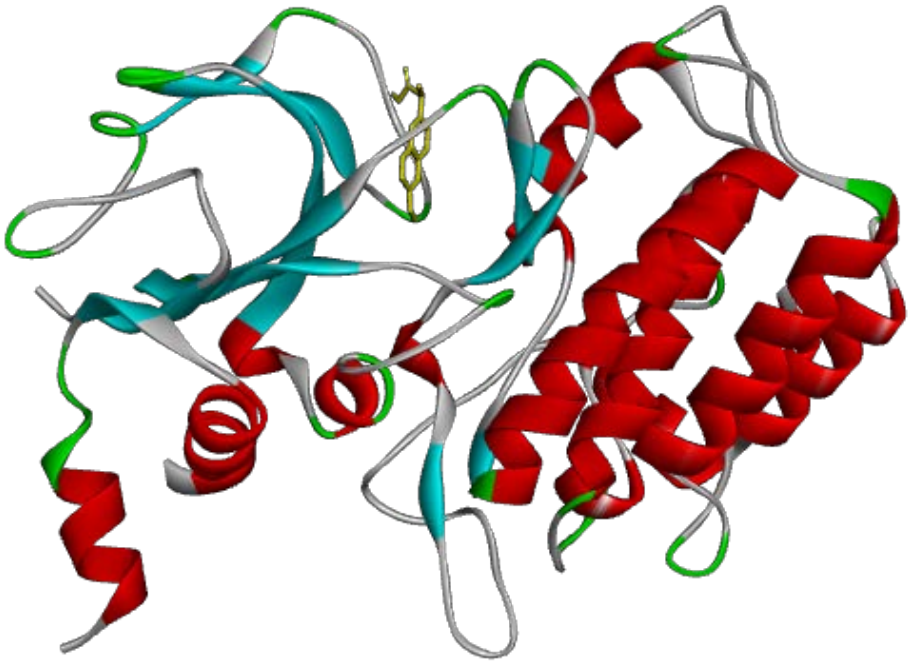


Figure 4: Three-dimensional binding interaction of naproxen with NF-κβ enzyme

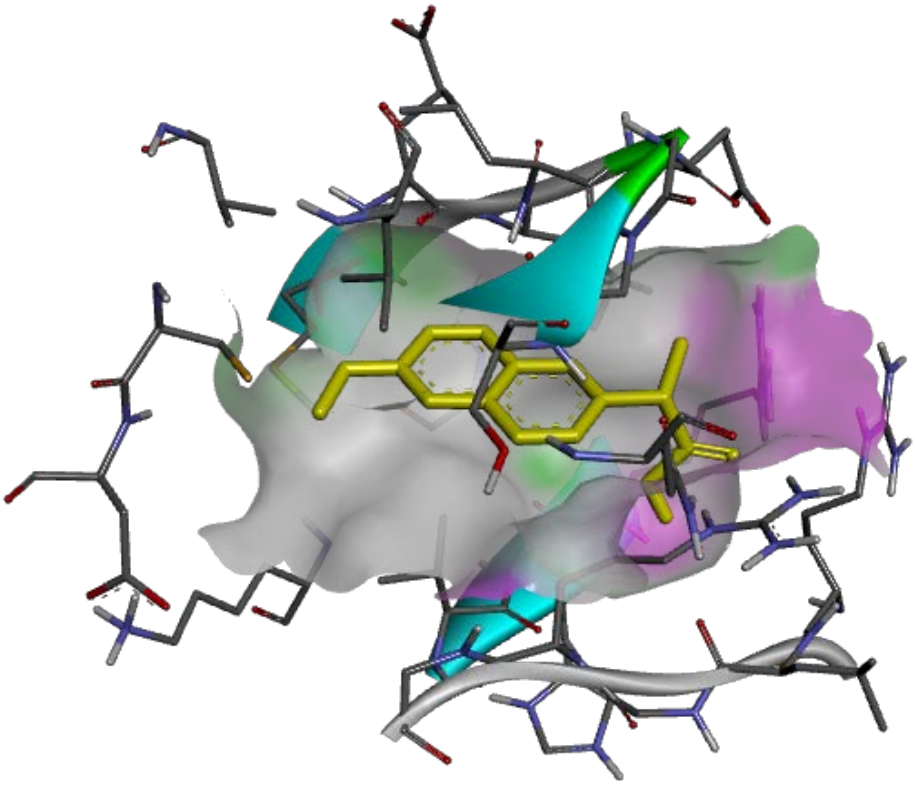


Figure 5: Binding conformation of ligand naproxen with NF-κβ enzyme

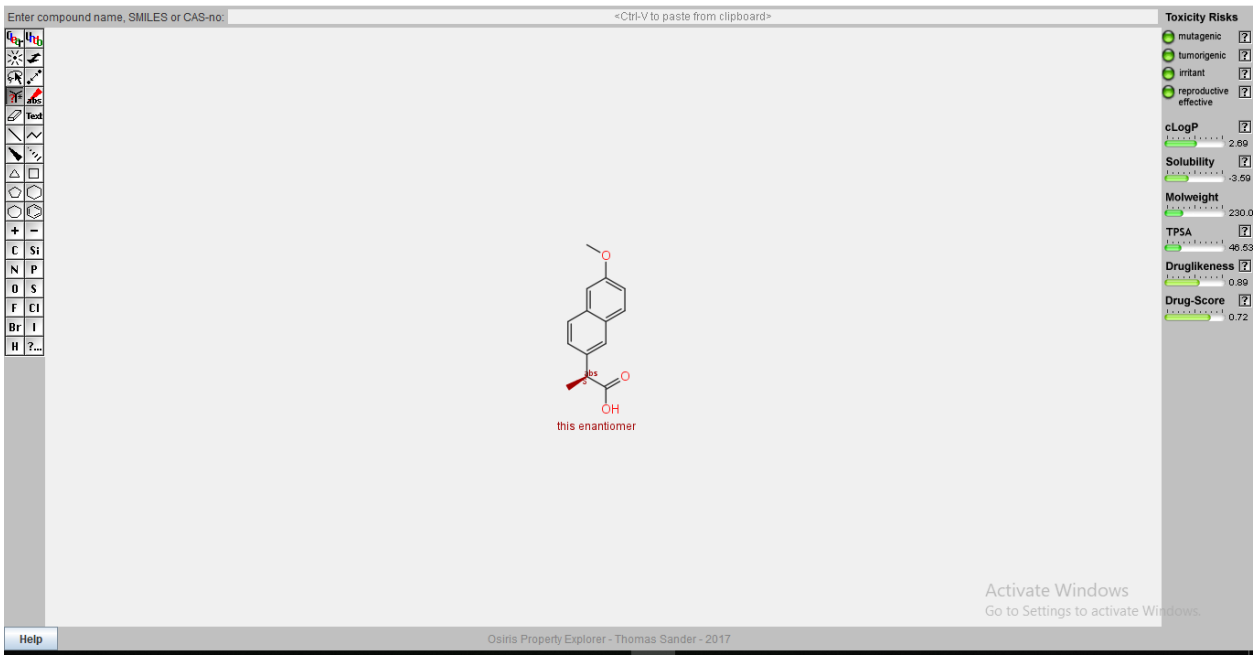


Figure 6: Pharmacokinetic and toxicity profiling of Naproxen

Conclusion

Rheumatoid arthritis (RA) is an autoimmune disease in which the immune system mistakenly attacks the joints. This causes inflammation, thickening of the synovial tissue, and swelling a nd pain around the joint. The synovial membrane responsible for this produces synovial fluid that lubricates the joints and helps them move smoothly. Over time, cartilage, elastic tissue, a nd bone in this autoimmune disease can be irreversibly damaged, narrowing the joint spaces between the bones, which can lead to severe pain and loss of mobility. There is a symmetrical effect on the joints of the hands, feet, wrists, elbows, knees and ankles. In other words, if one knee is affected, the other knee is affected as well. If the disease is untreated or untreated, it c an affect other parts of the body, such as the cardiovascular and respiratory systems, or the w hole body. is a selective inhibitor of PGE2-mediated Interleukins (11)-1b and 11-6 and tumor necrosis factor in humans cause pain. It is safe and does not cause stomach irritat ion or ulcers that can occur with other NSAIDs. Naproxen is used as a disease-modifying therapy for some autoimmune diseases, including rheumatoid arthritis. It is comm only used as a chemotherapeutic agent, but in small doses. As an important result from our *in*-

silico molecular docking studies, we can conclude that naproxen has targeting efficiency agai nst RA.

Reference

1. Karimi, A.; Majlesi, M.; Rafieian-Kopaei, M. Herbal versus synthetic drugs; beliefs and facts. *J. Nephropharmacol.* **2015**, *4*, 27–30.
2. Laev, S.S.; Salakhutdinov, N.F. Anti-arthritic agents: Progress and potential. *Bioorg. Med. Chem.* **2015**, *23*, 3059–3080.
3. Katz, J.N.; Arant, K.R.; Loeser, R.F. Diagnosis and treatment of hip and knee osteoarthritis: A review. *JAMA* **2021**, *325*, 568–578.
4. Kolasinski, S.L.; Neogi, T.; Hochberg, M.C.; Oatis, C.; Guyatt, G.; Block, J.; Callahan, L.; Copenhaver, C.; Dodge, C.; Felson, D.; et al. 2019-American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* **2020**, *72*, 149–162.
5. Zlotnick S, Oldenhof J, Schuller R, Hochberg MC, Schiff M. Effect of over-the-counter doses of naproxen sodium on inhibition of platelet cyclooxygenase-1 in healthy volunteers. *Osteoarthritis Cartilage* 2006; **14**: S63.
6. Himesh Soni *etal*. (2022). Silibin as Potent Inhibitor of COVID -19 Main Protease: In-Silico Docking Approach. Journal of Volume-4, Issue-1 (January-June, 2022)Molecular Pharmaceuticals and Regulatory Affairs.1-7.
7. Himesh Soni, Satish Sarankar, Sarvesh Sharma & Jitender K Malik. Hydroxychloroquine as Potent Inhibitor of COVID -19 Main Protease : Grid Based Docking Approach. EJMO 2020;4(3):219–226.
8. Himesh Soni, Dr. V.K. Gautam, Sarvesh Sharma, Jitender K Malik. Rifampicin as Potent Inhibitor of COVID - 19 Main Protease: In-Silico Docking Approach. Saudi J Med Pharm Sci, September, 2020; 6(9): 588-593.
9. Himesh Soni etal. (2022). Silibin as Potent Inhibitor of COVID -19 Main Protease: In-Silico Docking Approach. Journal of Volume-4, Issue-1 (January-June, 2022)Molecular Pharmaceuticals and Regulatory Affairs.1-7.
10. Saurabh Soni , Jitender K Malik , Satish K. Sarankar & Himesh Soni. Rutin as a c Potent Inhibitor of Dihydrofolate Reductase: A Computational Design and Docking. EASJ Pharm & Pharmacol; Vol-1, Iss-6 (Nov-Dec, 2019): 130-134.

11. N. Soni, K.R. Pardasani, S. Mujwar, Insilico analysis of dietary agents as hepatoprotective inhibitors of insulin like growth factor 1 receptor (IGF1R), J Pharm Pharm Sci, 7 (2015) 191-196.
12. E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng, T.E. Ferrin, UCSF Chimera--a visualization system for exploratory research and analysis, J Comput Chem, 25 (2004) 1605-1612.