EAS Journal of Pharmacy and Pharmacology
Abbreviated Key Title: EAS J Pharm Pharmacol
ISSN: 2663-0990 (Print) & ISSN: 2663-6719 (Online)
Published By East African Scholars Publisher, Kenya

Volume-6 | Issue-1 | Jan-Feb- 2024 | DOI: 10.36349/easjpp.2024.v06i01.003

OPEN ACCESS

Original Research Article

Scientific Validation of Flavonoids for Effective Management of Pancreatitis: *In-Silico* Molecular Docking

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Article History
Received: 03.12.2023
Accepted: 14.01.2024
Published: 17.01.2024

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: When someone develops pancreatitis, their pancreas swells up in inflammation. Pancreatic damage happens when the digestive enzymes are activated before they are discharged into the small intestine and begin attacking the pancreas. There are two types of pancreatitis: acute and chronic. Alcohol consumption and gallstones are just two of the numerous potential causes of pancreatitis. Plant medicine is an effective way to cure pancreatitis. Citrus flavonoids may offer promising bioactive molecules for treating metabolic disorders, according to some research. Hesperidin is widely consumed in the Western diet in this regard, mostly through the consumption of orange juice. Furthermore, since refined hesperidin is easily extracted or produced and is highly purified industrially, it is inexpensively available commercially. The Western diet contains little eriodictoyl, which is mostly found in lemons and is commercially available. ***Method:*** In the current work, *NF-kβ* receptor inhibitors were sought after using a molecular docking approach. The binding was determined by the Auto Dock software utilizing a grid-based docking method. Compounds' 2D structures were constructed using the chem sketch, converted to 3D, and then energetically reduced up to an arms gradient of 0.01. (MMFF). ***Result:*** Hesperetin and Eriodictoyl found to be effective anti-pancreatitis agent effectively binds to be target protein *NF-kβ* receptor with binding energy -6.9 & -6.7 kcalmol^{-1} for hesperetin & eriodictoyl respectively. ***Conclusion:*** It was discovered through a computationally based docking analysis that both lead compounds exhibit strong *NF-KB* receptor inhibiting effects. The results demonstrated a promising docking score and lead molecule's pattern of binding to the target protein's active region with strong covalent bonding. The synergistic impact of hesperetin & eriodictoyl is ability to heal pancreatitis.

Keywords: Pancreatitis, molecular docking, hesperetin & eriodictoyl.

INTRODUCTION

The pancreas is situated across the back of the belly, behind the stomach, and measures about 6 inches long. On the right side of the abdomen is the pancreatic duct, a thin tube that joins the head of the pancreas to the duodenum, the first section of the small intestine. The pancreas' narrow end, often known as its tail, extends to the left side of the body [1]. The pancreas is a large gland that is situated beneath the stomach and next to the small intestine. The pancreas primarily performs two tasks. By releasing strong digestive enzymes into the small intestine, it aids in food digestion. The hormones glucagon and insulin are released into the bloodstream as a result. These hormones are used by the body to control how it converts food into energy.

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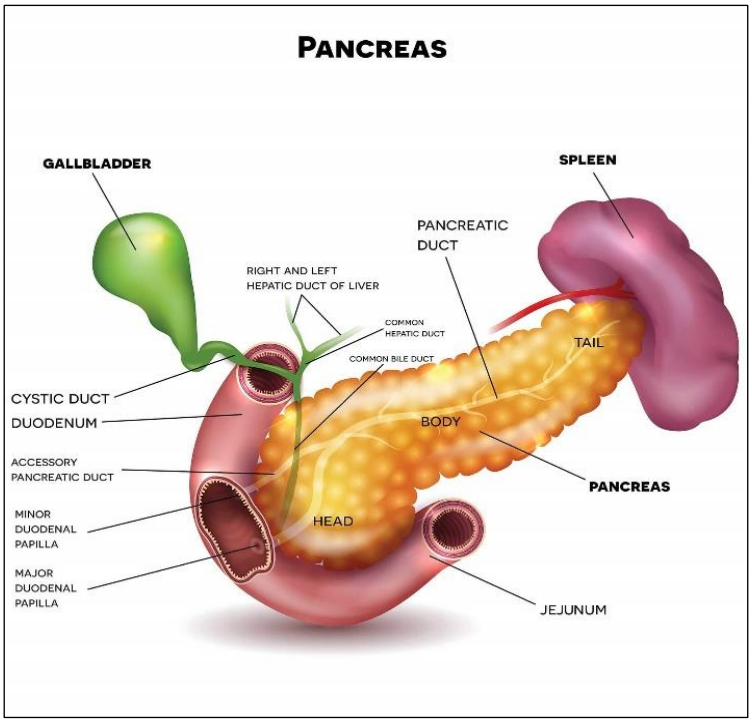
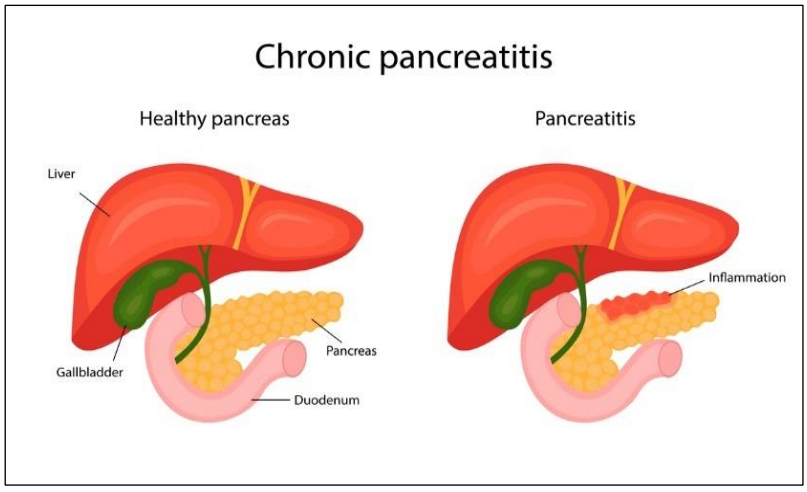


When someone develops pancreatitis, their pancreas swells up in inflammation. Pancreatic damage happens when the digestive enzymes are activated before they are discharged into the small intestine and begin attacking the pancreas. There are two types of pancreatitis: acute and chronic. Acute pancreatitis, a pancreatic inflammatory disorder, is brought on by an intracellular activation of pancreatic digesting enzymes. The breakdown of pancreatic parenchyma results in a systemic activation of the coagulation, kinin, complement, and fibrinolytic cascades through the production of cytokines and reactive oxygen metabolites. Shock, abrupt renal failure, and the acute respiratory distress syndrome could happen if this is severe and overpowering. Alcohol addiction affects an additional 35 percent of patients, while cholelithiasis contributes to roughly 45 percent of cases. 10% of patients can have undiagnosed conditions. In severe cases, acute pancreatitis can result in considerable tissue damage, cyst development, infection, and bleeding into the pancreatic gland. Severe pancreatitis can also harm other vital organs such the heart, lungs, and kidneys [2–3].



Pancreatitis

Symptoms of Pancreatitis	
Acute pancreatitis	**Chronic pancreatitis**
Upper abdominal pain, Abdominal pain that radiates to your back, Abdominal pain that feels worse after eating, Fever, Rapid pulse, Nausea, Vomiting, Tenderness when touching the abdomen	Upper abdominal pain, Losing weight without trying & Oily, smelly stools (steatorrhea).

The pharmacological activity of medicinal plants is typically understood as a result of millennia of trial and error, but they need to be thoroughly investigated if we wish to develop new treatments that meet the criteria of modern treatment. Since the beginning of time, man has used various plant parts for the treatment and prevention of several illnesses. All therapeutic treatments were traditionally derived from plants, whether they took the simple form of plant parts or the more complex form of crude extracts, mixtures, etc. Today, many drugs used to treat a wide range of illnesses are derived from plants. The majority of these involve extracting and then changing the chemical compound that serves as the active ingredient in a particular medicinal plant. While 25% of medical drugs in affluent countries are based on plants and their derivatives, the usage of medicinal plants is popular among indigenous people in rural areas of many developing countries [4]. A flavanone glycoside known as hesperidin ($C_{28}H_{34}O_{15}$) is abundantly present in citrus fruits like lemons, grapefruits, and sweet oranges (Citrus sinensis). Additionally, unripe sour oranges, ponderosa lemons, Citrus unshiu, and C. mitis have all been found to contain this substance. It could also be isolated from other plant genera, such as Fabaceae, Papilionaceae, Betulaceae, Lamiaceae, Zanthoxylum species (Z. avicennae and Z. cuspidatum), and Acanthopanax setchuenensis, in addition to the Citrus species. Bitter oranges include neohesperidin, an acrid chemical that is an isomer of hesperidin (Citrus aurantium). In the structure of hesperidin, rutinose [6-O-(l-Rhamnopyranosyl)-d-glucopyranose] and/or [6-O-(l-Rhamnosyl)-d-glucose] are joined by an aglycon (hesperitin or methyl eriodictyol) (Figure 1). Hesperetin can be thought of as a -7-rutinoside of hesperidin (as a non-bitter flavonoid rutinoside) [5-7].

Experimental Work

Ligand Preparation:

2D Structure of ligands like hesperetin and eriodictoyl were drawn using ChemSketch [8], the two-dimensional structures of the prepared ligands were converted into their 3-D structures optimized with 3D geometry. The optimized structures were saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligands were given below:

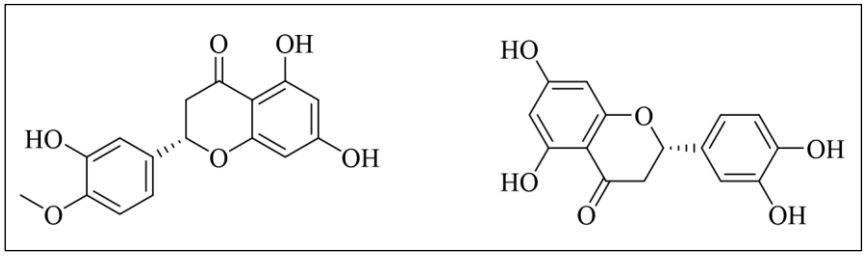


Figure 1: 2D structure of hesperetin and eriodictoyl

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 and grid points is given in table 1 [9-10].

Table 1. Grid parameters used in current docking analysis of NF-KB

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	Y center	z center
1	NF-KB	48	58	58	0.394	28.358	17.443	43.771

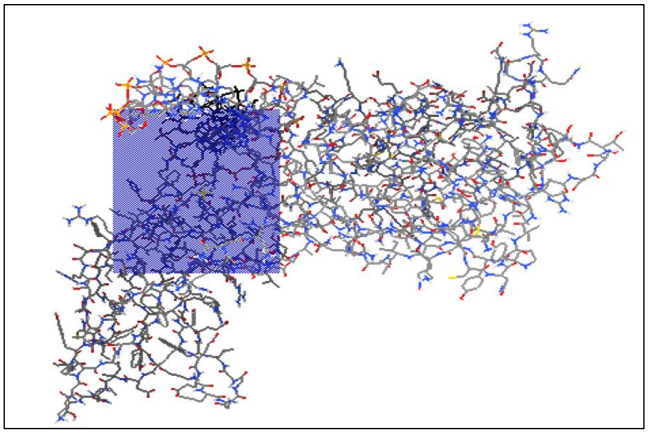


Figure 2: Grid box covering all active sites in NF-KB receptor

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 [11-14].

Docking Study

Crystal structure

The crystal structure of the protein consisting of NF-KB receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (1svc.pdb) registered in the Protein data bank was used [15-16]. The complex ligand was separated by using Chimera software.

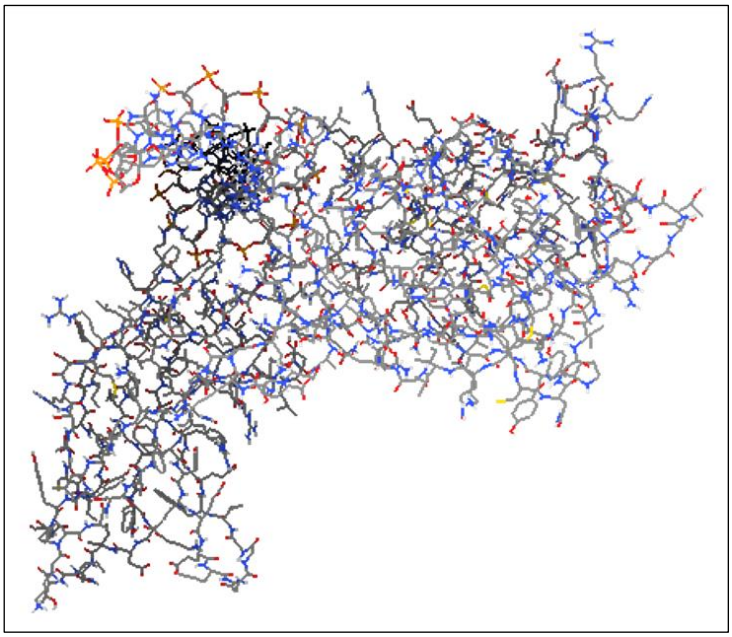


Figure 3: Crystal structure of NF-KB receptor (PDB ID-1svc)

Processing of Protein

The downloaded receptor protein is having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [17].

Molecular Docking Simulation Studies

Docking of ligands like hesperetin and eriodictoyl against NF-KB receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [18-19].

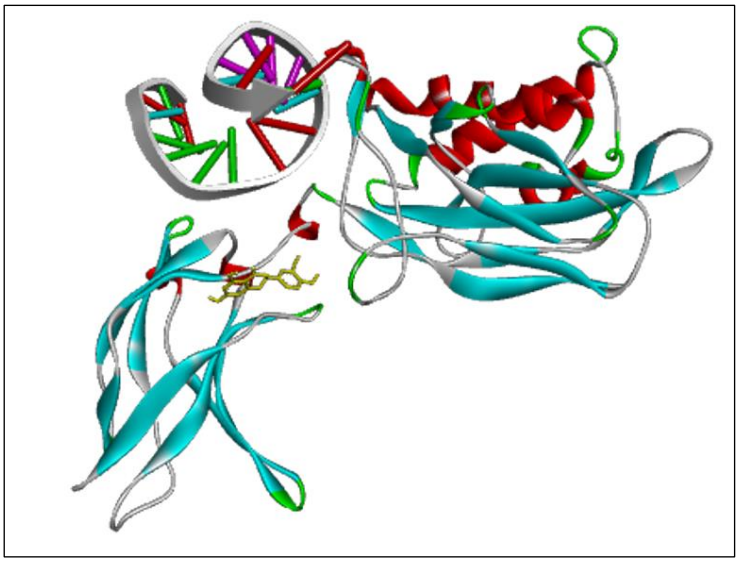


Figure 4: Binding mode of hesperetin within the active site of NF-KB receptor

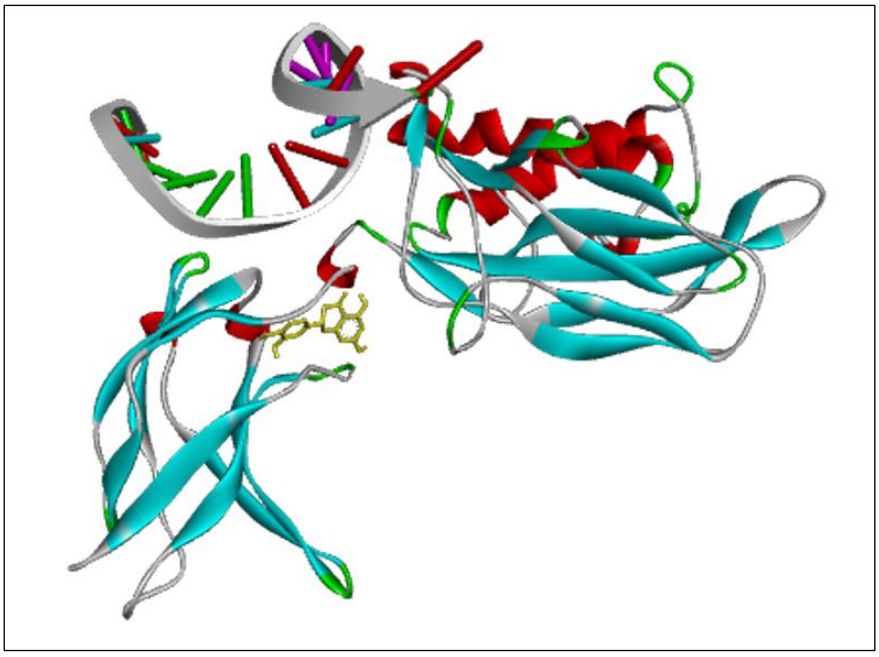


Figure 5: Binding mode of eriodictoyl within the active site of NF-KB receptor

Toxicity & ADME-T Studies

The ligand molecules viz. hesperetin and eriodictoyl were 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 [20].

RESULT AND DISCUSSION

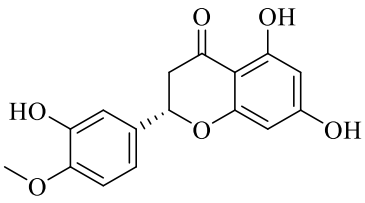
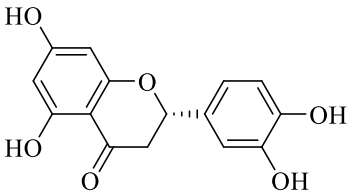
Flavonoid like hesperetin and eriodictoyl found in citrus family as per literature survey. Due to easy availability and dietary supplement hesperetin and eriodictoyl were chosen as the lead compounds for the *in-silico* validation investigation. It has long been believed that NF-kB is the archetypal proinflammatory signalling pathway because proinflammatory cytokines like tumour necrosis factor-a (TNFa) and interleukin-1 (IL-1) activate it and NF-kB is involved in the expression of other proinflammatory genes like cytokines, chemokines, and adhesion molecules [21]. Additional flavonoids like epicatechin, fisetin, genistein, and naringin have been found in numerous studies to be protective against pancreatitis-induced beta cell degeneration. The two main molecular mechanisms by which flavonoids increase beta cell survival are the reduction of oxidative stress and subsequent prevention of DNA damage and the caspase cascade. Flavonoids enhance the antioxidant capacity of beta cells by increasing both enzymatic (catalase, glutathione peroxidase, glutathione S transferase, and superoxide dismutase) and non-enzymatic (reduced glutathione). Because of their enhanced antioxidant capacity, which reduces ROS accumulation and lipid peroxidation, beta cells are protected from autophagy, apoptosis, and necroptosis.

It was discovered through a computationally based docking analysis that both lead compounds exhibit strong *NF-KB* receptor inhibiting effects. The result was tabulated in table 2 which revealed that binding energy of hesperetin and eriodictoyl was found to be -6.9 & -6.7 respectively. The binding mode showed in figure 4-5 whereas 2D & 3D interaction showed in fig.6-11. The binding interaction showed that both compound showed hydrogen binding at Asn 250& Ile 253 along with Pi-sigma binding at Glu 344 and at Lys 252 covalently.The results demonstrated a promising docking score and lead molecule's pattern of binding to the target protein's active region with strong covalent bonding. The synergistic impact of hesperetin and eriodictoyl is what gives citrus its ability to heal pancreatitis. The pharmacokinetic profile of hesperetin and eriodictoyl (figure 12 & 13) reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects.

Divulgence of Investigation

Hesperetin and eriodictoyl, two ligands, showed chemical interaction with the amino acids in the active pockets when they were molecularly docked with the NF-KB receptor. Theoretically, all of the ligand compounds have positive docking scores and can be predicted to be effective NF-KB receptor inhibitors. Findings thus pointed to the possibility that selected flavonoids block the NF-KB signaling pathway, which in turn prevents the production of proinflammatory mediators and effectively treats pancreatitis.

Table 2: Results of docking of ligands like hesperetin and eriodictoyl against NF-KB receptor

Sl. No	Compound Name	Structure	Binding Energy
1	Hesperetin		-6.9
2	Eriodictoyl		-6.7

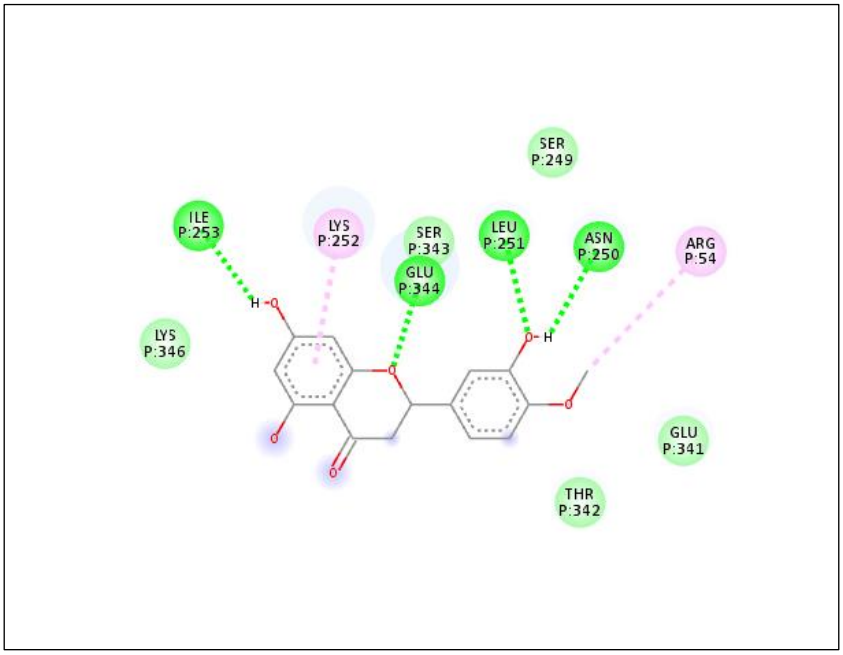


Figure 6: Two-dimensional binding mode of hesperetin within the active site of NF-KB receptor

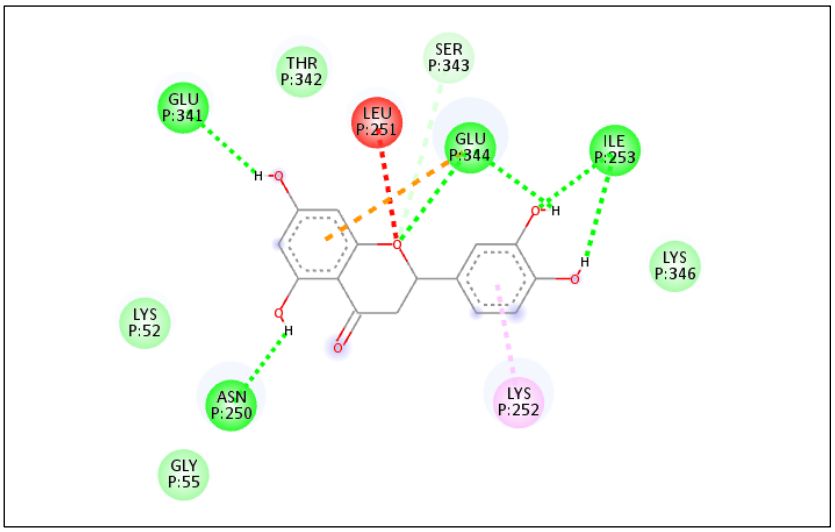


Figure 7: Two-dimensional binding mode of eriodictoyl within the active site of NF-KB receptor

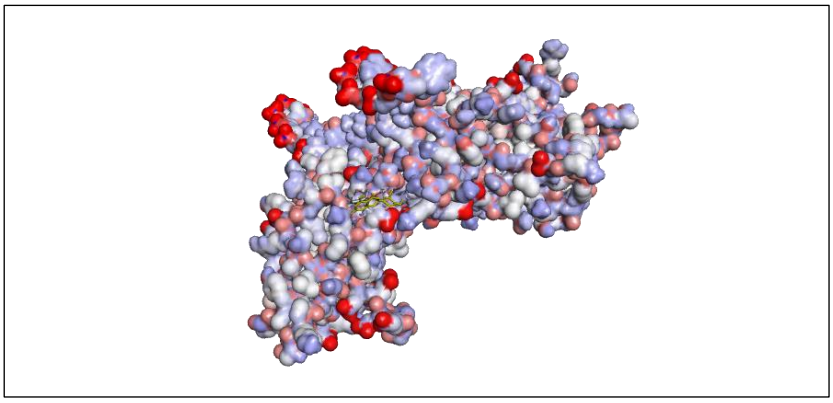


Figure 8: Three-dimensional binding conformation of hesperetin within the active site of NF-KB receptor

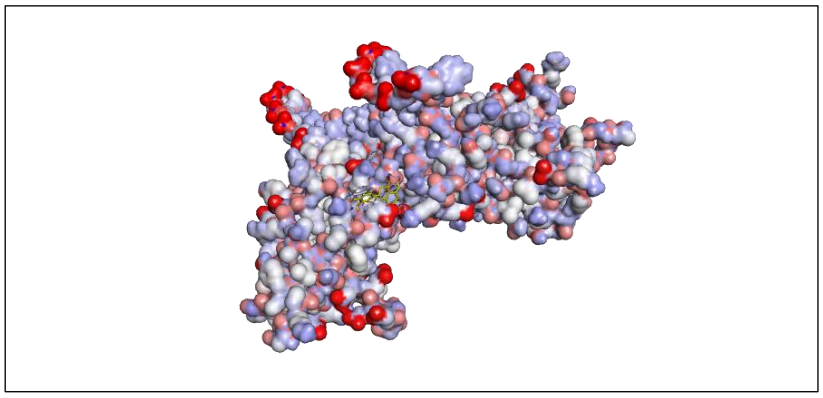


Figure 9: Three-dimensional binding conformation of eriodictoyl within the active site of NF-KB receptor

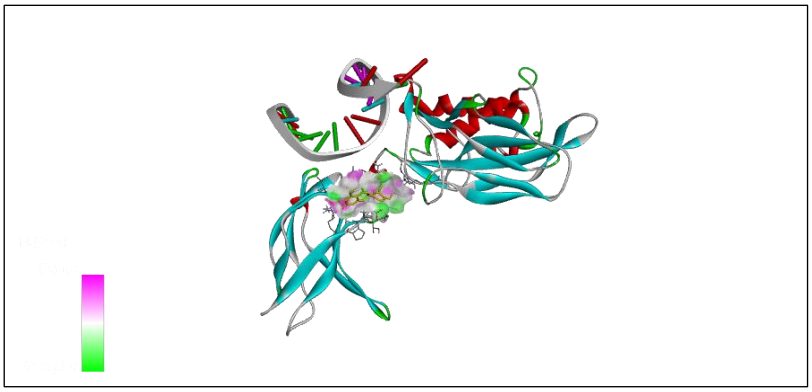


Figure 10: Three-dimensional binding mode of hesperetin within the active site of NF-KB receptor

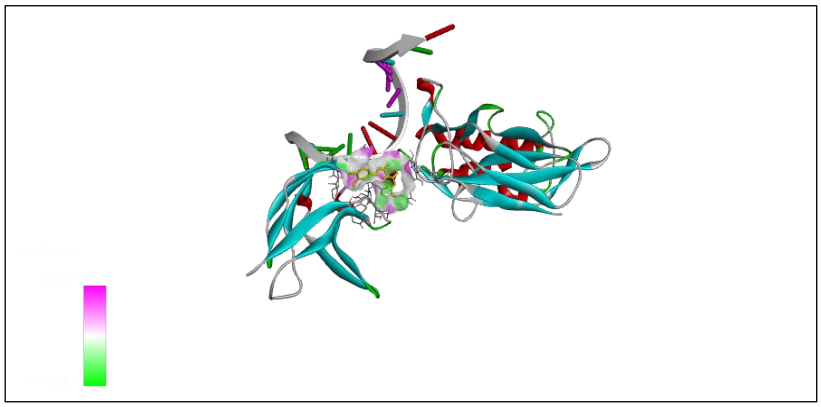


Figure 11: Three-dimensional binding mode of eriodictoyl within the active site of NF-KB receptor

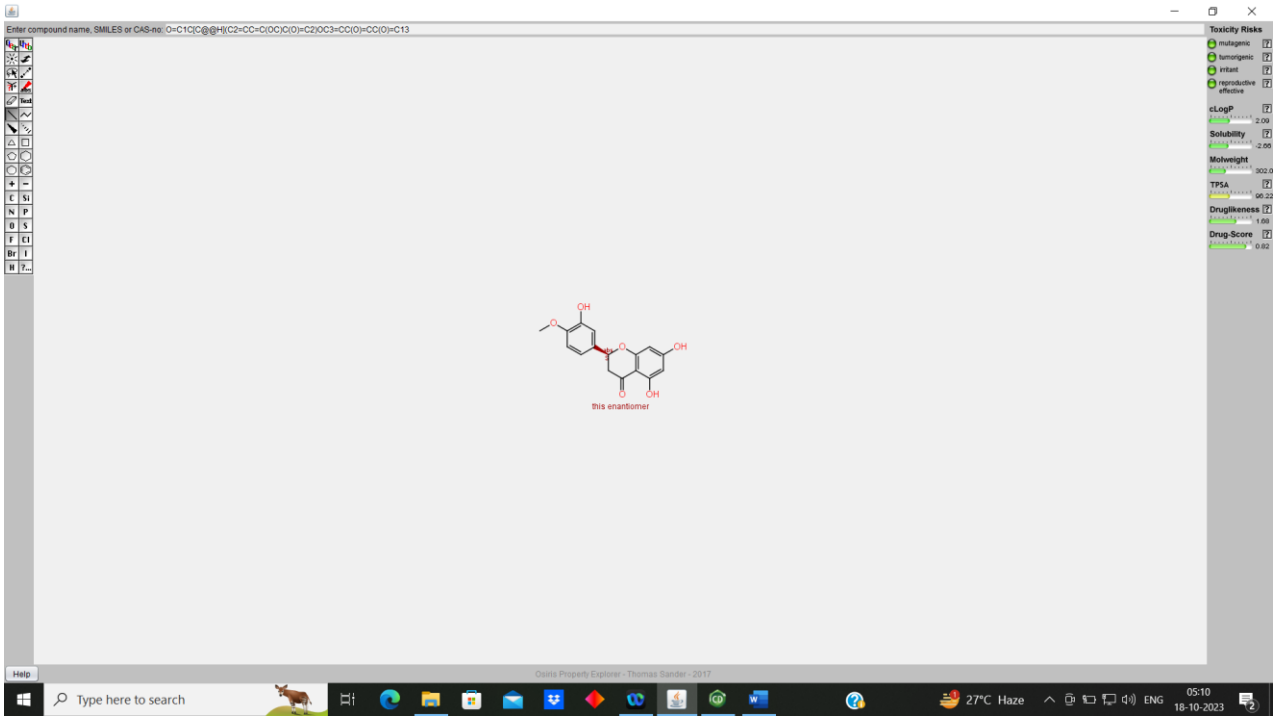


Figure 12: Pharmacokinetic Profile of hesperetin

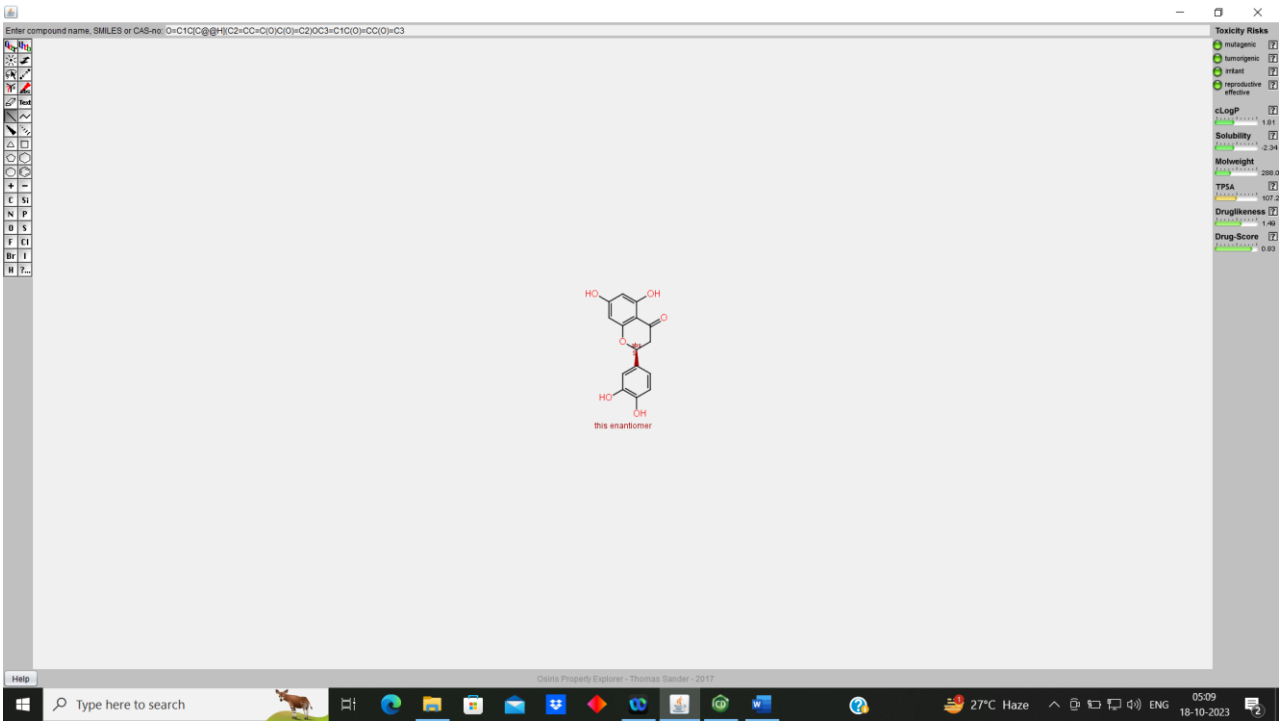


Figure 13: Pharmacokinetic Profile of eriodictoyl

REFERENCE

1. Bockman, D. E. (1993). Anatomy of the pancreas. *The exocrine pancreas: biology, pathobiology and disease. Raven Press, New York*, 1-8.
2. 2.S. BAKER Diagnosis and Management of Acute Pancreatitis. Critical Care and Resuscitation 2004; 6: 17-27.
3. Sutton, R., Criddle, D., Raraty, M. G., Tepikin, A., Neoptolemos, J. P., & Petersen, O. H. (2003). Signal transduction, calcium and acute pancreatitis. *Pancreatology*, *3*(6), 497-505.
4. Soni, H., & Singhai, A. K. (2012). A recent update of botanicals for wound healing activity. *International Research Journal of Pharmacy*, *3*(7), 1-7.
5. Hajialyani, M., Hosein Farzaei, M., Echeverría, J., Nabavi, S. M., Uriarte, E., & Sobarzo-Sánchez, E.

(2019). Hesperidin as a neuroprotective agent: a review of animal and clinical evidence. *Molecules*, *24*(3), 648.
6. Garg, A., Garg, S., Zaneveld, L. J. D., & Singla, A. K. (2001). Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytotherapy research*, *15*(8), 655-669.
7. Pawloska L. Flavonoids of B. pendula Roth and B. obscura Kot leaves. Acta. Soc. Bot. Pol. 1980; 493:281–296.
8. Soni, S., Malik, J. K., Sarankar, S. K., & Soni, H. (2019). Rutin as a potent inhibitor of dihydrofolate reductase: A computational design and docking. *EAS J. Pharm. Pharmacol*, *1*, 130-134.
9. Hurdle, J. G., O'Neill, A. J., & Chopra, I. (2005). Prospects for aminoacyl-tRNA synthetase inhibitors as new antimicrobial agents. *Antimicrobial agents and chemotherapy*, *49*(12), 4821-4833.
10. ACD, V., & Elucidator, S. (2019). Advanced Chemistry Development, Inc., Toronto, ON, Canada.
11. Soni, H., Mishra, S., Mishra, R. K., & Mishra, S. R. (2022). Silibin as Potent Inhibitor of COVID-19 Main Protease: In-Silico Docking Approach. *Journal of Molecular Pharmaceuticals and Regulatory Affairs*, 1-7.
12. Malik, J. K., Soni, H., Sharma, S., & Sarankar, S. (2020). Hydroxychloroquine as potent inhibitor of COVID-19 main protease: Grid based docking approach. *Eurasian Journal of Medicine and Oncology*, *4*(3), 219-226.
13. Soni, H., Gautam, D., Sharma, S., & Malik, J. (2020). Rifampicin as potent inhibitor of COVID-19 main protease: In-silico docking approach. *Saudi Journal of Medical and Pharmaceutical Sciences*, *6*(9), 588-593.
14. Sander, T., Freyss, J., von Korff, M., Reich, J. R., & Rufener, C. (2009). OSIRIS, an entirely in-house developed drug discovery informatics system. *Journal of chemical information and modeling*, *49*(2), 232-246.
15. Kciuk, M., Mujwar, S., Szymanowska, A., Marciniak, B., Bukowski, K., Mojzych, M., & Kontek, R. (2022). Preparation of novel pyrazolo [4, 3-e] tetrazolo [1, 5-b][1, 2, 4] triazine sulfonamides and their experimental and computational biological studies. *International Journal of Molecular Sciences*, *23*(11), 5892.
16. Kciuk, M., Gielecińska, A., Mujwar, S., Mojzych, M., Marciniak, B., Drozda, R., & Kontek, R. (2022). Targeting carbonic anhydrase IX and XII isoforms with small molecule inhibitors and monoclonal antibodies. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *37*(1), 1278-1298.
17. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, *30*(16), 2785-2791.
18. Mujwar, S., & Pardasani, K. R. (2015). Prediction of Riboswitch as a potential drug target for infectious diseases: An Insilico case study of anthrax. *Journal of Medical Imaging and Health Informatics*, *5*(1), 7-16.
19. Mujwar, S., & Pardasani, K. R. (2015). Prediction of riboswitch as a potential drug target and design of its optimal inhibitors for Mycobacterium tuberculosis. *International Journal of Computational Biology and Drug Design*, *8*(4), 326-347.
20. Shah, K., Mujwar, S., Gupta, J. K., Shrivastava, S. K., & Mishra, P. (2019). Molecular docking and in silico cogitation validate mefenamic acid prodrugs as human cyclooxygenase-2 inhibitor. *Assay and drug development technologies*, *17*(6), 285-291.
21. Jakkampudi, A., Jangala, R., Reddy, B. R., Mitnala, S., Reddy, D. N., & Talukdar, R. (2016). NF-κB in acute pancreatitis: Mechanisms and therapeutic potential. *Pancreatology*, *16*(4), 477-488.

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