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Original Research Article

Anti-Inflammatory Potential and Underlying Mechanistic of Phenolic Component from *Ziziphus jujuba* Fruit: A Molecular Docking Validation

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Abstract: The nutritious jujube fruit (*Ziziphus jujube* Mill.) is a member of the Rhamnaceous family and grows mainly in inland areas of Europe, southern and eastern Asia, Australia and especially northern China. Jujubes have a long history as fruit and medicinal. The main bioactive components are vitamin C, phenols, flavonoids, triterpenoids and polysaccharides. Chlorogenic acid (5-O-caffeoylquinic acid) is a phenolic compound of the hydroxycinnamic acid family found in the hydroethanolic fruit extract of *Z.jujuba*. This polyphenol has many health-enhancing properties, most of which are relevant for the treatment of metabolic syndrome, including antioxidant, anti-inflammatory, antilipidemic, antidiabetic, and antihypertensive effects. ***Methods:*** Molecular docking of COX2 with chlorogenic acid was carried out by AutoDock. ***Result:*** The molecular docking result revealed that chlorogenic acid showed encouraging docking score. The docking score found to be -5.15.

Keywords: Ziziphus jujuba, Chlorogenic acid, docking score, molecular docking & COX2.

INTRODUCTION

The primary purpose of inflammation, a biological response to a chain of chemical events, is to fight infection and heal tissue damage brought on by injury. The inflammatory process results in the release of many mediators. platelet-activating factor, cyclooxygenase-2, leukotrienes, nerve growth factors, inducible nitric oxide synthase, bradykinin, cytokines, and adhesion molecules are examples of the inflammatory lipid mediators that are activated [1]. The circulatory system houses the majority of the crucial elements of the inflammatory process, and the majority of the early mediators (facilitators) of inflammation speed up the flow of plasma and blood cells from the circulatory system to the tissues surrounding the injury. These substances, which are collectively referred to as exudates, shield the host from infection and encourage tissue recovery.

Cardinal Sign of inflammation [2]

- Redness
- Heat
- Swelling
- Pain
- Loss of function

Types of Inflammation [3]

Acute inflammation	Chronic inflammation
Inflammation only lasts a few hours, days, or minutes, which is a relatively short amount of time. Edema and the migration of leukocytes, particularly neutrophils, are its two key characteristics.	It typically lasts a long time and is histologically characterized by lymphocytes, macrophages, proliferation of tiny blood vessels, and fibroblasts.

Molecular Targets of Anti-Inflammatory Agents

COX enzymes (COX-1 and COX-2) catalyze the biosynthesis of prostaglandins, prostacilins, and thromboxanes from arachidonic acid. COX-1 is constitutively expressed in most tissues, whereas COX-2 is expressed in specific tissues and is induced by cytokines and growth hormone. COX-1 has regulatory effects on platelet aggregation and gastric mucosal biogenesis, and COX-2 is involved in pathological conditions such as inflammation, pain, and fever. NSAIDs exert their anti-inflammatory activity by inhibiting COX-1 and COX-2. Long-term inhibition of

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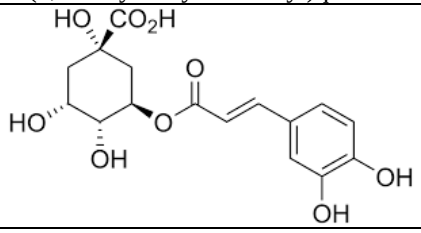
COX-1 in the gastrointestinal system causes damage to the gastrointestinal tract through ulceration and gastric bleeding. Coxibs, selective COX-2 inhibitors, are designed to inhibit COX-2 over COX-1 to achieve desired anti-inflammatory activity with minimal gastrotoxic side effects [4].COX-1 and COX-2 were nearly identical despite residues Ile434, His513, and Ile523 in COX-1, but Val434, Arg513, and Val523 in COX-2. These differences lead to increased volume of active COX-2 sites and additional side pockets away from the main channel. The structure of coxibene consists of a diarylheterocycle with a sulfonamide or methylsulfone moiety attached to the side pocket of COX-2, providing isoform-selective inhibition.

Ziziphus jujuba Mill is a fruit tree of the *Rhamnaceae* family. It is mainly distributed in subtropical and tropical regions of Asia and America. This plant is rich in bioactive components such as vitamin C, flavonoids, triterpenoids, and polysaccharides [5]. It is used in traditional Chinese and Korean medicine as an antifungal, antibacterial, antiulcer, anti-inflammatory, and antioxidant remedy [6]. Jujube is a blood purifier, hematopoietic promoter, viscous disposition promoter, expectorant, cough suppressant, anti-asthmatic, laxative, wound healing, aphrodisiac, semen suppressant, blood and bile coolant, itching. It has been introduced as a sedative for kidney and bladder pain. It also contributes to the treatment of rectal and intestinal ulcers/diseases and liver disease. Ripe jujube fruits have laxative properties, while unripe jujubes cure diarrhea.

Chlorogenic acid is a phenolic compound from the hydroxycinnamic acid family. The compound's chemical structure consists of a caffeic acid moiety and a quinic acid moiety; therefore, it is also known as 5-O-caffeoylquinic acid (5-CQA) [7].

Description of Chlorogenic acid [8]

IUPAC Name	3-(3,4-Dihydroxycinnamoyl)quinic acid 3-O-Caffeoylquinic acid
Structure	
Mol. Wt.	354.31
Mol. Formula	$C_{16}H_{18}O_9$
M.P.	205 - 209 °C
Appearance	solid
Taste	Astringent, sweet, and sour tastes, which change with the concentration.
Class	Polyphenolic

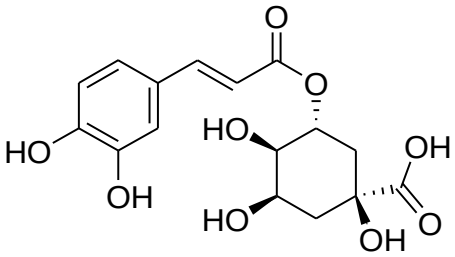
The present research work was planned to design the molecular docking of Chlorogenic acid as dual inhibitors COX2 enzyme.

EXPERIMENTAL WORK

Molecular Docking Studies

Ligand Preparation:

2D Structure of ligand Chlorogenic acid was drawn by using ChemDraw [9-10].The two-dimensional structures of ligand was converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [11].



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 [12].

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
5ikr	46	44	46	0.375	38.042	2.131	61.28
4idv	46	44	46	0.375	16.134	13.917	87.361
3elo	40	40	40	0.442	-15.237	-31.016	-7.715

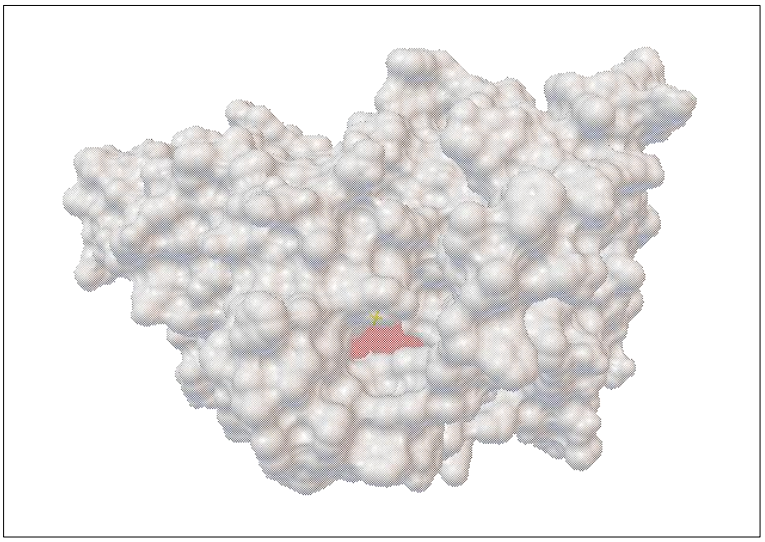


Figure 1: Grid box covering all active sites in COX2 enzyme (5ikr)

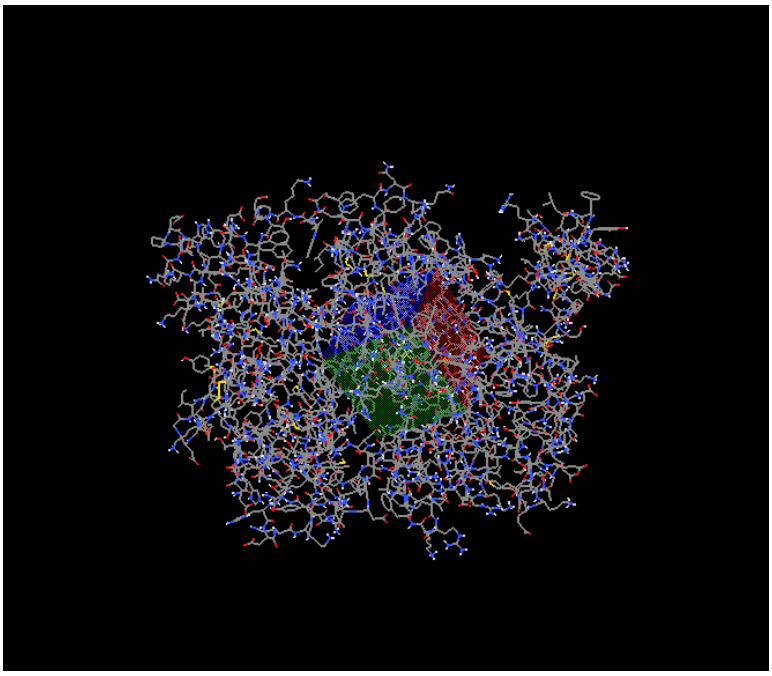


Figure 2: Grid box covering all active sites in receptor

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [13].

Docking of human COX2 with Chlorogenic Acid

Crystal structure

The crystal structure of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (5IKR.pdb) registered in the Protein data bank was used. The bound ligand mefenamic acid is found within the receptor [14].

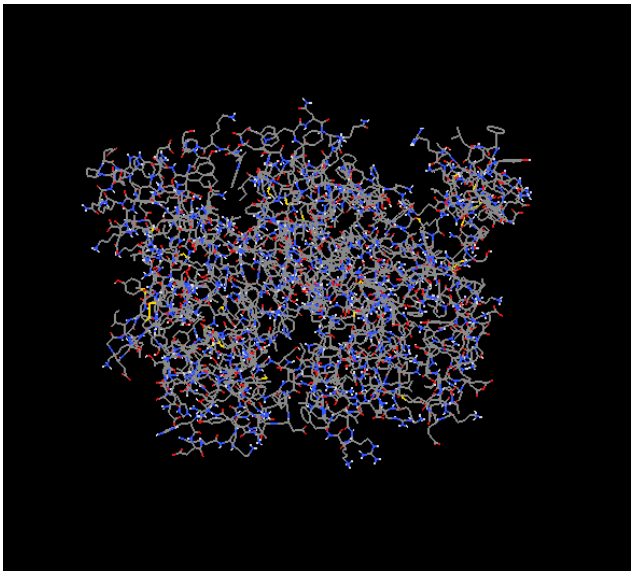


Figure 3: Crystal structure of human COX-2 enzyme with bound mefenamic acid(PDB ID-5IKR)

Processing of Protein

The downloaded receptor protein is having a single chain A, which has been selected for the experimental purpose. The bound ligand mefenamic acid was separated from the macromolecular complex by using software Chimera [15].

Molecular Docking Simulation Studies

Docking of chlorogenic acid ligand on human COX2 enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [16].

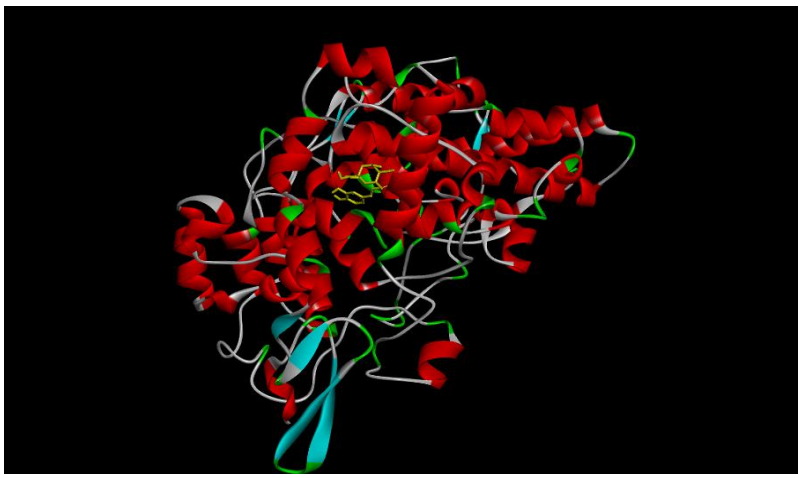


Figure 4: Binding mode of chlorogenic acid within the active site of COX2receptor

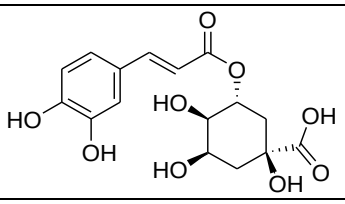
Toxicity & ADME-T Studies

The modified lead molecules are 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 [17].

RESULTS AND DISCUSSION

The proposed mechanistic insight the chlorogenic acid found in the hydroethanolic fruit extract of *Z.jujuba* was carried out by molecular docking with COX 2 receptor. Chlorogenic acid was docked and the binding energy was found to be -5.15 kcal/mol. The molecular docking of chlorogenic acid with human COX2 enzyme revealed that (Table 2), it has exhibited the chemical interaction with the amino acids in the active pockets which is showed in Figure.3. Theoretically, the ligand molecule has shown encouraging docking score. The chlorogenic acid interacts with the Tyr355, Arg120, Ala527 and Leu352 residues of COX2 to form a complex structure (Fig.4-5). The pharmacokinetic profile of chlorogenic acid reveals that it is having good pharmacokinetic profile without presence of any major toxic effects. The pharmacokinetic and toxicity profiling results of chlorogenic acid were shown in figure 6. However, further investigations are needed to confirm this suggestion.

Table 2: Results of docking of chlorogenic acid against human COX2 enzyme

S.No	Compound	Structure	Binding Energy(Kcal/mol)	Ki (µM)
1	Chlorogenic acid		-5.15	157.7

Interactions

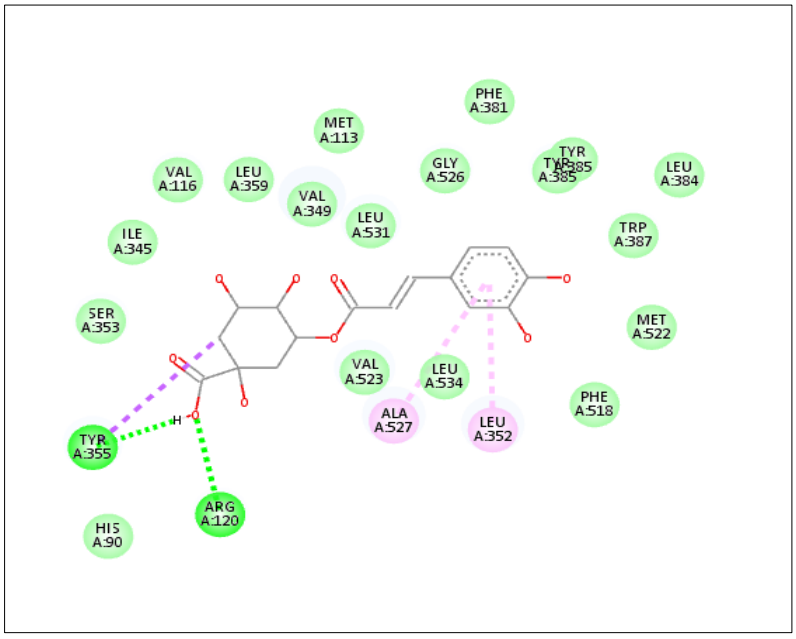


Figure 5: Binding interaction of chlorogenic acid with COX2

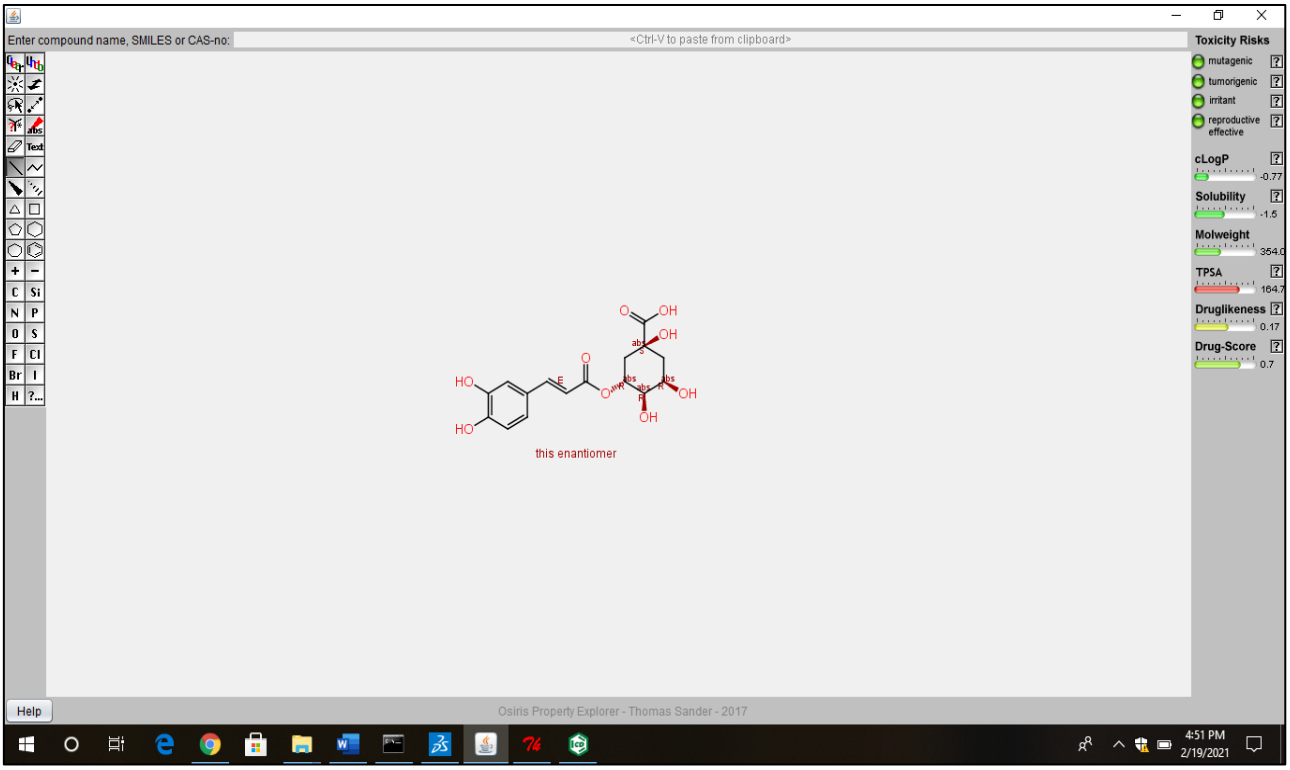


Figure 6: Pharmacokinetic and toxicity profiling of chlorogenic acid

CONCLUSION

To clarify the suggested mechanism of the chlorogenic acid discovered in the fruit extract of *Z. jujuba*, an in-silico molecular docking study was conducted. The precise mechanism of chlorogenic acid's anti-inflammatory effects is currently unknown. The docking-based computer research against the COX2 enzyme, a target for anti-inflammatory drugs, has been carried out with the intention of proposing the most likely mechanism of action of chlorogenic acid. The results of the docking study, chemical interactions, and physicochemical-based pharmacokinetic profile have shown that the chlorogenic acid suppresses COX2 to produce its anti-inflammatory effects.

REFERENCE

1. Krishna, D. H., Reddy, M. S., Rajnarayana, K., Krishna, D. R., & Prabhakar, M. C. (2003). Inflammation and novel therapeutic approaches for its management. *Indian journal of pharmaceutical sciences*, *65*(6), 565.
2. Dey, N.C., & Dey, T.K., (1970). A Text Book of Pathology. IIIrd edition, Calcutta, *Messrs Allied Agency*.
3. Soni, H., Malik, J., Singhai, A. K., & Sharma, S. (2013). Antimicrobial and antiinflammatory activity of the hydrogels containing rutin delivery. *Asian Journal of Chemistry*, *25*(15), 8371.
4. Orlando, B. J., & Malkowski, M. G. (2016). Substrate-selective inhibition of cyclooxygeanse-2 by fenamic acid derivatives is dependent on peroxide tone. *Journal of Biological Chemistry*, *291*(29), 15069-15081.
5. Haddouchi, F., Zerhouni, K., Sidi-Yekhelef, A., & Chaouche, T. M. (2016). Évaluation de l'activité antimicrobienne de différents extraits d'Helichrysum stoechas subsp. rupestre. *Bulletin de la Société Royale des Sciences de liège*, *85*, 152-159.
6. Gao, Q. H., Wu, P. T., Liu, J. R., Wu, C. S., Parry, J. W., & Wang, M. (2011). Physico-chemical properties and antioxidant capacity of different jujube (Ziziphus jujuba Mill.) cultivars grown in loess plateau of China. *Scientia Horticulturae*, *130*(1), 67-72.
7. Santana-Gálvez, J., Cisneros-Zevallos, L., & Jacobo-Velázquez, D. A. (2017). Chlorogenic acid: Recent advances on its dual role as a food additive and a nutraceutical against metabolic syndrome. *Molecules*, *22*(3), 358.
8. https://pubchem.ncbi.nlm.nih.gov/compound/Chlorogenic-acid.
9. Kumar, R., Sharma, A., Iqbal, M. S., & Srivastava, J. K. (2020). Therapeutic promises of chlorogenic acid with special emphasis on its anti-obesity property. *Current Molecular Pharmacology*, *13*(1), 7-16.
10. 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.
11. 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..
12. 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.
13. 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.
14. 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.
15. Mujwar, S., Sun, L., & Fidan, O. (2022). In silico evaluation of food-derived carotenoids against SARS-CoV-2 drug targets: Crocin is a promising dietary supplement candidate for COVID-19. *Journal of Food Biochemistry*, *46*(9), e14219.
16. Fidan, O., Mujwar, S., & Kciuk, M. (2023). Discovery of adapalene and dihydrotachysterol as antiviral agents for the Omicron variant of SARS-CoV-2 through computational drug repurposing. *Molecular diversity*, *27*(1), 463-475.
17. Shah, K., & Mujwar, S. (2022). Delineation of a novel non-steroidal anti-inflammatory drugs derivative using molecular docking and pharmacological assessment. *Indian Journal of Pharmaceutical Sciences*, *84*(3), 642-653.

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