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Research Article

In-silico Analysis of Anti-Inflammatory and Anticancer Properties of Bioactive Compounds from *Pancratium triflorum* (*Roxb*)

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ABSTRACT

Herbal remedies with medicinal properties have been utilized in Asian countries for centuries. Recently, *Pancratium triflorum* Roxb., also known as the forest spider lily, has captured the attention of researchers due to its potential therapeutic benefits. This plant produces white flowers and contains several important phytochemicals, including lycorine, citrate, gallic acid, ellagic acid, quercetin, and kaempferol. Molecular docking, a computer simulation technique, has been used to identify potential drug candidates that can bind effectively to the active site of a protein. This study explored the anti-inflammatory and anticancer properties of *P. triflorum* Roxb.'s phyto-constituents using molecular docking with Auto dock 4.2.6. The study focused on the Vioxx-bound human Cox2 receptor and the tyrosine kinase receptor bound to gliteritinib. Standard ligands were used for redocking, and the Swiss ADME software was employed for bioavailability prediction to validate the findings. The results showed that lycorine and crinine have excellent anti-inflammatory properties, while kaempferol and quercetin have promising anticancer properties. Further research is necessary, but these findings suggest that *P. triflorum* Roxb. could be a valuable addition to the medical world. However, further research is required to validate these findings, and in vivo studies are needed to confirm the efficacy and safety of these phytochemicals as potential drug candidates.

Introduction

This study aims to screen the phytocompounds of *Pancratium triflorum* Roxb. *in-situ*. It was based on the following facts. The Amaryllidaceae family is found in various tropical regions and is known for its alkaloids that possess biological activity, including inhibitory activity of acetylcholinesterase (AChE), antifungal, antibacterial, and cytotoxic activities.[1] The genus *Pancratium,* which comprises 24 species globally, is recognized for its therapeutic potential. It contains a diverse range of alkaloids with pharmaceutical properties, including lycorine and galantamine, which hold medicinal importance.[2] The traditional medicine of several Mediterranean countries utilizes *P. maritimum* for its antimicrobial, antimalarial, purgative, antiviral, immune-stimulant, antalgic, anticancer, antifungal, and antioxidant properties.[3]

The body's innate defense mechanism is a complex process that involves inflammation, which plays a vital role in identifying and eliminating harmful foreign substances. Once inflammation subsides, the body begins the healing process, which can occur acutely or chronically, depending on the severity of the injury or infection.[4] The development of anti-inflammatory drugs involves targeting the cyclooxygenase-2 (Cox-2) receptor, with rofecoxib being a key molecule utilized in virtual ligand-based screening to achieve this goal. The Cox-2 enzyme is particularly crucial to inhibit when creating effective anti-inflammatory drugs, as it produces prostaglandins, which cause inflammation and pain.[5]

Cancer is a complex and multifaceted disease that results from uncontrolled cell growth that can spread throughout the body, originating from any part of the human body that contains trillions of cells.[6] The receptor tyrosine kinase

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(RTK) plays a pivotal role in cellular processes, such as growth, differentiation, and metabolism. Humans have approximately 58 known RTKs with similar structures consisting of an extracellular region and a carboxyl 'C' terminal. Dysregulation of RTK signaling can lead to various human diseases, including cancer, as it can cause cells to grow and divide uncontrollably, forming tumors that invade nearby tissues and organs.[7]

P. triflorum Roxb. is a small genus of perennial bulbous plants belonging to the Amaryllidaceae family. This genus is exclusive to the Old World, specifically Asia, Africa, and Europe.[8] These plants are fragrant flowers with perianth tubes and a corona formed by the basal connection of stamina filaments. Roxburgh identified four species, while Herbert added five species from India and described two species as *P. Malabatricum* and *P. cambyses*. The latter two are *P. triflorum* Roxb. (Fig. 1). These plants are of immense significance for their ornamental value and medicinal properties. They have been used in various traditional medicine systems to treat ailments like fever, skin diseases, and respiratory problems. Cancer is an ailment resulting from uncontrolled cell growth that can proliferate throughout the body, originating from any part of the human body and encompassing trillions of cells. Receptor tyrosine kinase (RTK) is critical in cellular growth, differentiation, and metabolism. With humans having roughly 58 known RTKs, all with similar structures consisting of an extracellular region and a carboxyl 'C' terminal, dysregulation of RTK signaling could lead to various human diseases, including cancer. *P. triflorum* Roxb. comprises fragrant flowers, perianth tubes, and a corona formed by the basal connection of stamina filaments. Roxburgh identified four species, while Herbert added five species from India and described two species as *P. malabatricum* and *P. cambyses*, the latter being *P. triflorum* Roxb.

Plants belonging to the Amaryllidaceae family are known to have a group of exclusive alkaloids. The significant alkaloids isolated are lycorine, galantamine, hazeltine, and lycorine crinine.[9] Flavonoids are Quercetin and Kaempferol, phenolics gallic, and ellagic acids.[10] *Pancratium* species are reported to have cytotoxic and antioxidant activities. It also possesses anti-inflammatory and anticholinesterase actions. They are Cox I and Cox II inhibitors.[11] Molecular docking is a vital tool in structural biology and computational chemistry. It predicts the predominant binding modes of ligands with a protein. It performs virtual rank and predicts the biological activities and mechanisms of action of various phyto and synthetic compounds. Molecular docking, a computer simulation technique, has been used to identify potential drug candidates that can bind effectively to the active site of a protein. *P. triflorum* is a plant with bioactive compounds that can be used for pharmaceutical applications. It has anti-inflammatory properties and can inhibit molecular targets involved in cancer progression. These compounds can be potential therapeutic agents for immune-mediated disorders and cancer. A previous work published by the

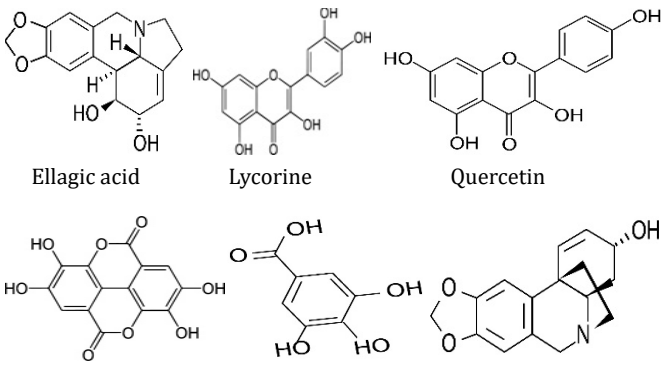


Fig. 1: *P. triflorum* Roxb. and its major phytoconstituents

Table 1: Anti-inflammatory activity on human Cox-2 receptors

Ligand	*Docking score*	*RMSD*	*Ref. RMSD*
Crinine	-7.35	0	44.91
Lycorine	-7.06	0	42.06
Quercetin	-6.05	0	52.39
kaempferol	-5.98	0	43.13
Ellagic acid	-5.20	0	44.91
Gallic acid	-4.53	0	34.00
Rofecoxib	-5.77	0	27.08

Table 2: Anticancer activity on tyrosine kinase receptors

Ligand	*Docking score*	*RMSD*	*Ref. RMSD*
kaempferol	-8.20	0	38.24
Crinine	-6.76	0	40.05
Quercetin	-5.31	0	38.20
Gallic acid	-4.58	0	43.23
Lycorine	-4.53	0	54.00
Ellagic acid	-3.90	0	48.8
Gliteritinib	-6.46	0	27.88

Table 3: Swiss ADME prediction

Property	*Lycorine*	*Crinine*	*Kaempferol*
lipophilicity	Log p -2.57	Log p -2.06	Log p- 1.70
Water solubility	Log s-2.82	Log s-1.82	Log s-3.31
Absorption	GI -high BBB-yes	GI -high BBB-No	GI -high BBB-No
Drug likeliness	Lipinski-0 Violation	Lipinski-0 Violation	Lipinski-0 Violation
Synthetic accessibility	4.48	4.20	3.14

author states the same.[12,13] Studying bioactive compounds derived from *P. triflorum (*Roxb.) through *in-silico* analysis can provide significant pharmaceutical advantages in current circumstances. This study employs computational methods to examine these compounds' anti-inflammatory and anticancer properties, generating valuable insights into potential drug candidates. Such analysis can expedite the drug discovery process and facilitate the development of novel therapies with greater efficacy and reduced side effects, thereby addressing the pressing need for effective treatments against inflammation and cancer (Fig. 2).

Materials And Methods

Ligand Preparation

The ligands lycorine, crinine, gallic and ellagic acid, quercetin, and kaempferol of PubChem ID 72378, 398937, 370, 5281855, 5280343, 5280867, respectively, were downloaded from the PubChem database in sdf. Format. The structures were drawn using Chem Sketch software. The system was opened, and using Biova drug discovery studio, polar hydrogen and charges were added, and torsions were set and saved in PDBQT format. (Fig. 3)

Receptor Preparation

Protein as targets PDBID: 6JQR and 5 KIR were downloaded in PDB format from RCSB and saved in PDB format (Figs 4-6). We deleted the water molecules and Hetero atoms and added polar hydrogens and Kolman charges, which were saved in PDBQT format.

Redocking and Validation

The controls Gliteritinib and Rofecoxib were removed from their proteins, saved in a separate molecular window in the PDB format, and used for redocking and validation.

Running Grid and Auto dock

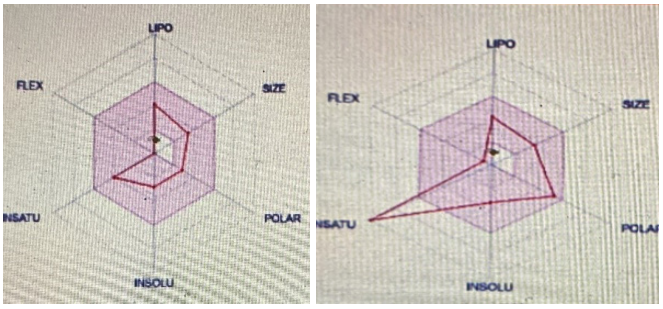
The Grid box was fixed and saved. The auto grid four was run, and map files were generated (Fig. 7). The auto dock was run using the generated executable files, and the histogram showing the docking results was opened in a notepad (Tables 1 and 2).[14]

Swiss ADME Bioavailability

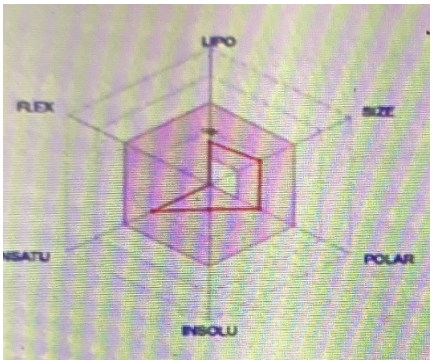
Drug-likeliness RADAR of compounds with good activity was obtained, and ADME prediction was made (Fig. 2) (Table 3).

Results And Discussion

Swiss ADME and blood-brain barrier penetration predictions revealed that crinine had no BBB effect. The log *p-value* for Crinine was -2.06, which was less than 5, which predicts drug likeliness. Lipinski's rule of 5 states that an oral drug should have a log *p-value* less than, ideally, between 1.35 and 1.8 for good oral and intestinal absorption. Its synthetic accessibility for quinine was 4.20,



Kaempferol Lycorine



Crinine

Fig. 2: Swiss ADME bioavailability radar for drug likeliness of selected compounds of *P. triflorum* Roxb.

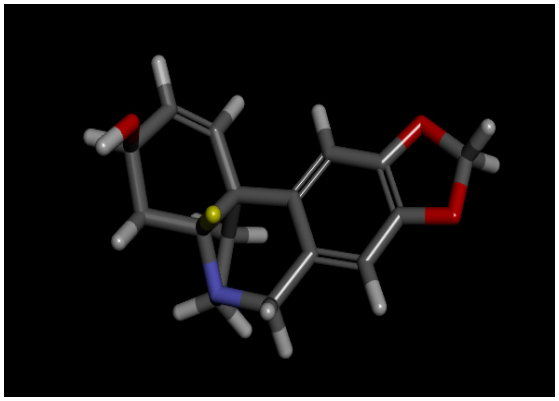


Fig. 3: Crinine ligand

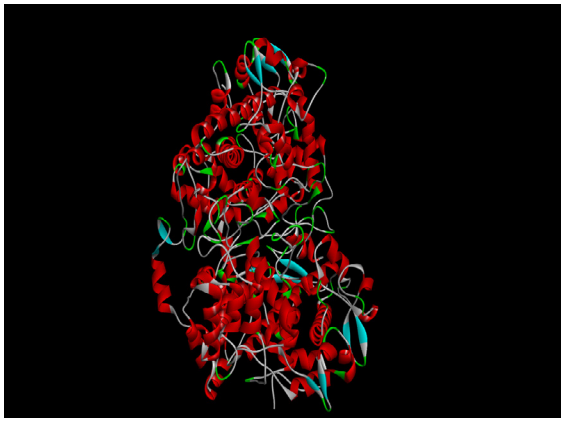


Fig. 4: Human Cox-2 receptors target - 6KIR

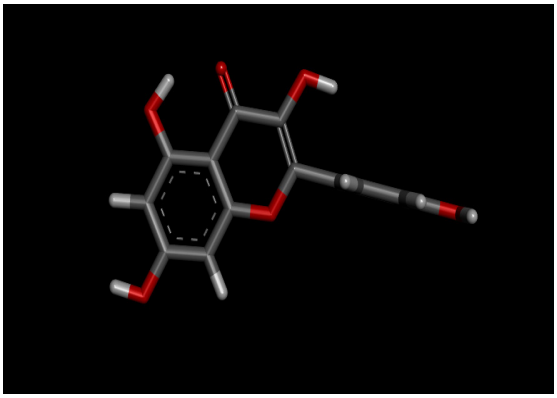


Fig. 5: Kaempferol ligand

Fig. 6: Tyrosine kinase receptor-6JQR

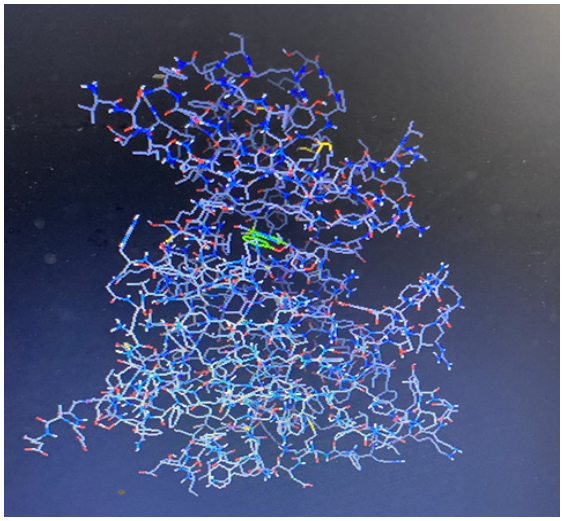


Fig. 7: Docked images of crinine with 6KIR target

which is a mid-value. This score ranges from 1-10, which is a comprehensive representation of easy-to-synthesize compounds,

Kaempferol gave a better Log *p-value* of -1.70 with a better synthetic accessibility score and higher BBB and GIT absorption values. Lycorine gave the least favorable ADME prediction with a log *p-value* of -2.57, and synthetic accessibility was 4.48. The flavonoid kaempferol docked strongly with protein targets related to anticancer activity compared to positive control gliteritinib, which is an indication that this flavonoid acts as an anticancer agent with a docking score of of-8.20 which is in comparison with positive control -6.46. Another flavonoid, quercetin, gave a docking score of -6.46. The root mean square deviation value of kaempferol was 38.24. Crinine possesses a good docking score against tyrosine kinase receptor-6.76 and human COX-2 receptor-7.35. It shows that crinine is a molecule of interest. Studies suggest that anti-inflammatory agents could increase apoptosis and sensitivity of conventional therapies and decrease invasion metastasis, making them useful in cancer therapy. Cancer prevention by NSAIDS works by acting on the pathways of eicosanoids.[15] A previous study showed that *P. triflorum* extracts had different IC_{50} values for antioxidant activities.[16] The present study substantiates the previous findings. The pink-highlighted area on the bioavailability radar represents the optimal range for each property, providing a glimpse of a molecule's drug-likeliness. This tool can help assess a molecule's potential effectiveness as a drug candidate.[17] The ADME features are critical in pharmaceutical drug development

Conclusion

The present study utilized software and conformation analysis in Biova Discovery Studio to identify promising interactions between critical receptors, including tyrosine kinase and human Cox-2 enzyme, and phytochemicals such as lycorine, crinine, gallic acid, ellagic acid, quercetin, and kaempferol. These receptors could be targets for predicting phytochemicals' anti-tumor and anticancer activities. Furthermore, the bioavailability radar results indicated favorable properties of quinine and lycorine, suggesting their potential efficacy. Kaempferol exhibited the highest predicted anticancer activity, supported by superior docking scores against respective receptors (6JQR), compared to the standard gliteritinib, indicating its potential as a lead compound for anticancer therapy. Crinine exhibited maximum anti-inflammatory activity. The study's findings provide valuable insights into the pharmacological potential of phytochemicals in inflammation management and cancer treatment, warranting further investigation and development for therapeutic applications. The ADMET prediction of phytochemicals helps narrow the number of phytochemicals for further study. The ADMET prediction has revealed the lipophilicity, hydrophilicity, blood-brain, and GIT penetration of the ligand molecule of interest. It also helps the possibility of synthetic routes of compounds. *P. triflorum* Roxb. kaempferol and quercetin flavonoids showed excellent and comparable docking scores and can be considered therapeutic candidates for cancer. The four compounds listed above showed good bioavailability prediction. Hence, we consider *P. triflorum* Roxb. (Roxb.) to be a phytochemical source for various ailments.

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References

1. Paiva MJ, Nascimento GN, Damasceno IA, Santos TT, Silveira D. Pharmacological and toxicological effects of Amaryllidaceae. Brazilian Journal of Biology. 2023 15;83:277092. Available from. https://doi.org/10.1590/1519-6984.277092
2. Otari SS, Ghane SG. Bioactive Compounds and Biological Activities of the Genus Pancratium. Bioactive Compounds in the Storage Organs of Plants. 2023 Sep 4:1-8.
3. Mariarosaria Leporini, Giorgia Catinella, Maurizio Bruno, Tiziana Falco, Rosa Tundis, Monica R. Loizzo. "Investigating the Antiproliferative and Antioxidant Properties of Pancratium maritimum L. (Amaryllidaceae) Stems, Flowers, Bulbs, and Fruits Extracts».Evidence-Based Complementary and Alternative Medicine.2018;7. Available from https://doi.org/10.1155/2018/9301247
4. Pahwa R, Goyal A, Jialal I. Chronic Inflammation. [Updated 2023 August 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493173/
5. Leão RP, Cruz JV, da Costa GV, Cruz JN, Ferreira EFB, Silva RC, de Lima LR, Borges RS, Dos Santos GB, Santos CBR. Identification of New Rofecoxib-Based Cyclooxygenase-2 Inhibitors. A Bioinformatics Approach. Pharmaceuticals (Basel). 2020; 13:20. Available from doi: 10.3390/ph13090209.
6. Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018 ;1:58.Avaliable from: https://doi:10.1186/s12943-018-0782-4.
7. What is cancer? National Cancer Institute, **[**Updated: October 11, 2021] An official United States government website.2023 April 4 https://www.cancer.gov/about-website#:~:text=Cancer.
8. Olga De Castro, Salvatore Brullo, Paolo Colombo, Stephen Jury, Paolo De Luca, Antonietta Di Maio. Phylogenetic and biogeographical inferences for *Pancratium*, emphasizing the Mediterranean species based on plastid sequence data. *Botanical Journal of the Linnean Society*. 2012;170:12–28.Available from: https://doi.org/10.1111/j.1095-8339.2012.01268.x
9. Cedrón JC, Del Arco-Aguilar M, Estévez-Braun A, Ravelo AG. Chemistry and biology of Pancratium alkaloids. Alkaloids Chem Biol. 2010; 68:1-37. doi: 10.1016/s1099-4831(10)06801-x. PMID: 20334035.
10. Leporini M, Catinella G, Bruno M, Falco T, Tundis R, Loizzo MR. Investigating the Antiproliferative and Antioxidant Properties of *Pancratium maritimum* L. (Amaryllidaceae) Stems, Flowers, Bulbs, and Fruits Extracts. Evid Based Complement Alternat Med. 2018 September 30; 2018:9301247. Available from: https://doi.org/10.1155/2018/9301247.
11. Elgorashi EE. Phytochemistry and pharmacology of the family Amaryllidaceae: An overview of research at RCPGD. Natural Product Communications. 2019: 149:1934578 -19872929.Available from https://doi.org/10.1177/1934578X19872929.
12. Thomas Kurian. Molecular docking study of epigallocatechin gallate on flt3 in complex with Gliteritinib for anticancer activity. Asian journal of pharmaceutical and clinical research.2024:17:1: 5-7. Available. from10.22159/ajpcr.2024.v17i1.48733.
13. Yuriev E, Ramsland PA. Latest developments in molecular docking. 2010-2011 in review. J Mol Recognit. 2013;26:215-39. Available from: 10.1002/jmr.2266. PMID: 23526775.
14. Huey R, Morris GM, Forli S. Using AutoDock4 and Auto Dock Vina with Auto Dock Tools: A Tutorial. California, USA: The Scripps Research Institute. Molecular Graphic Laboratory; 2012:5 -19.
15. Zappavigna S, Cossu AM, Grimaldi A, Bocchetti M, Ferraro GA, Nicoletti GF, Filosa R, Caraglia M. Anti-Inflammatory Drugs as Anticancer Agents. Int J Mol Sci. 2020 ;21(7):2605. Available from doi: 10.3390/ijms21072605.
16. Johnson M, Maharaja P, Janakiraman N, Adaikala Raj G, Menezes IRA, da Costa JGM, Verde LCL, Coutinho HDM. *Pancratium triflorum* Roxb. (Amaryllidaceae) and Molineria trichocarpa (Wight) N.P. Balakr (Hypoxidaceae). Cytotoxic and antioxidant activities. Food Chem Toxicol. 2018;119:290-295. Available from 10.1016/j.fct.2018.02.055.
17. Gonzales AL, Huang SK-H, Sevilla UTA, Hsieh C-Y, Tsai P-W. In Silico Analysis of Anti-Inflammatory and Antioxidant Properties of Bioactive Compounds from *Crescentia cujete* L. *Molecules*. 2023; 28(8):3547.Available from. https://doi.org/10.3390/

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