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**Original Research Article**

# Molecular Docking Studies and ADME-Tox Prediction of Phytocompounds from *Punica granatum* Peel as a Potential Anti-Alopecia Treatment

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**Abstract:** ***Background*:** Alopecia is a condition in which some or all of the hair from the scalp is lost. One recent preventative measure is the inhibition of the enzyme 5-α-reductase. Inhibition of the enzyme 5-α-reductase converts circulating testosterone to its more potent metabolite, dihydrotestosterone. *Pomegranate (Punica granatum L.)* peels are widely employed in industry and to treat a variety of illnesses. However, accurate identification is necessary to improve efficacy, repeatability, and quality. Pomegranate, or Punica granatum L., is a member of the Punicaceae family. It is known as "anar" or "dadima" on the Indian subcontinent. For hundreds of years, P. granatum has been used to treat conditions like peptic ulcer, dental disorders, diabetes, hypertension, hyperlipidemia, and numerous types of cancer. ***Method*:** Further scientific validation of the current investigation was done by computational based molecular docking study of lead molecules of *P.granatum* Peel against *5α-reducatase(SRD5As)* enzyme. 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*:** Punica found to be effective anti-alopecic agent and their lead molecules effectively binds to be target protein *5α-reducatase (SRD5As)* with binding energy -7.15, -7.66 & -7.07 kcalmol$^{-1}$ for Apigenin, luteolin and taxifolin respectively. ***Conclusion*:** The results demonstrated that every lead compound that was chosen for further study exhibited strong *5'-reductase (SRD5 As)* inhibitory activity, hence eliciting the anti-alopecic potential.

**Keywords:** Punica granatum peel, molecular docking, Apigenin, luteolin and taxifolin.



## INTRODUCTION

Hair loss is a side effect of the medical illness alopecia. The underlying abnormalities that cause hair loss in alopecia patients are typically detected on the scalp, though they can affect any part of the body [1, 2]. Worldwide, 35 million men and 21 million women suffered from alopecia in 2014. Genetics, environmental factors, and dietary factors are only a few of the reasons of alopecia [3]. Finasteride, a synthetic medicine, is used to suppress the enzyme 5-reductase in an effort to prevent hair loss; nevertheless, long-term finasteride use can have dangerous adverse effects, such as a decrease in libido [4]. Other treatments for alopecia can be employed in addition to synthetic medications, one of which is using the ingredients in the Punica granatum peel to treat dandruff and promote hair growth.

*Pomegranate (Punica granatum L.)* peels are widely employed in industry and to treat a variety of illnesses. However, accurate identification is necessary to improve efficacy, repeatability, and quality. Pomegranate, or Punica granatum L., is a member of the Punicaceae family. It is known as "anar" or "dadima" on the Indian subcontinent. The plant, which can be either evergreen or deciduous, produces deep pink or crimson, globose or oval-shaped fruits with crunchy seeds [5].

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**Punic granatum**

**Pharmacological Potential of Peel**

The arils are divided by a thin membrane that is located inside the peel. The pomegranate peels make up 43% of the overall fruit. Traditional uses of the peel extracts include the treatment of ulcers, diarrhoea, and the prevention of ribonucleic acid (RNA) replication. They are also used as ruminant feeds. Numerous pharmacological properties of pomegranate peels have been discovered, including anti-proliferative, anti-inflammatory, and anti-cancerous effects. Fruit peel antioxidant potential against breast cancer was investigated. A total of 48 different chemical components, including alkaloids, anthocyanins, anthocyanidins, tannins, flavonoids, phenolics, proanthocyanidins, sterols, terpenes, and xanthonoids, are also present in pomegranate peels [6, 7].

**Experimental work**

As per literature survey *Punica granatum* peel contained higher amount of flavonoid and plant phenolic as current investigation as well as demonstrated by Nhlanhla Maphetu [8]. The methanolic peel extract showed high amount of apigenin, luteolin and taxifolin. So, these flavonoids compounds were selected as lead molecule for computational based docking studies against 5α-reductase (SRD5 As) enzyme to explored hair growth efficacy of methanolic peel extract of *P. granatum*.

***Ligand Preparation:***

2D Structure of ligands like apigenin, luteolin and taxifolin were drawn using ChemSketch [9], 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:

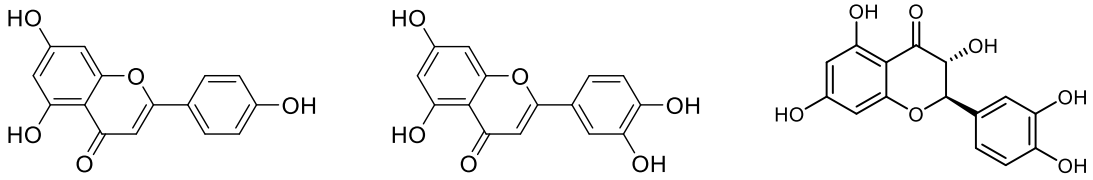



**Figure 1: 2D structure of apigenin, luteolin and taxifolin**

***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 [10].

**Table 1: Grid parameters used in current docking analysis of 5-alpha reductase.**

| S. No. | Receptor | x-axis | y-axis | z-axis | Spacing | x center | y center | z center |
|---|---|---|---|---|---|---|---|---|
| 1 | 5-alpha reductase | 58 | 40 | 44 | 0.375 | -29.547 | 15.112 | 37.14 |

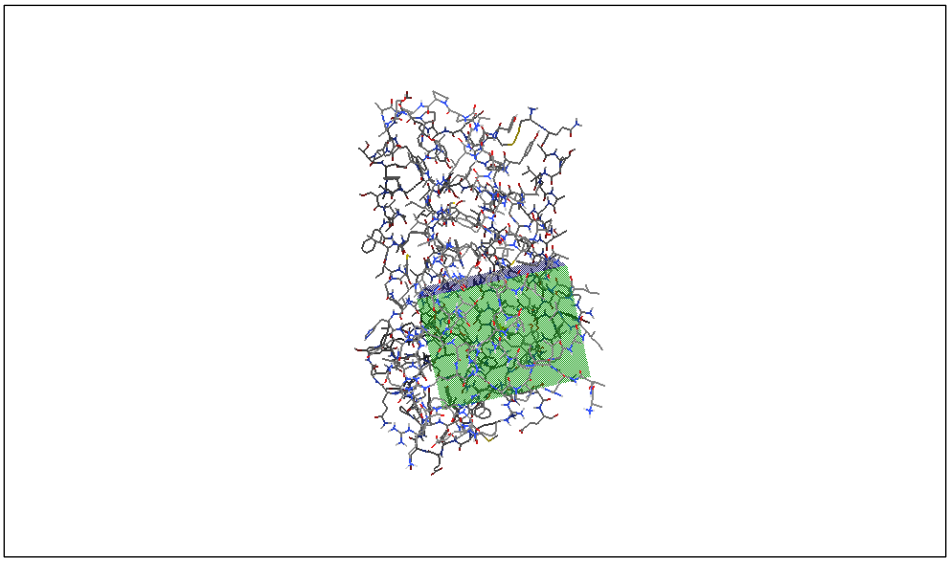


**Figure 2: Grid box covering all active sites in 5-alpha reductase receptor**

***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].

**Docking Study**

***Crystal structure***

The crystal structure of the protein consisting of 5-alpha reductase receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (7bw1.pdb) registered in the Protein data bank was used [12]. The complex ligand was separated by using Chimera software.

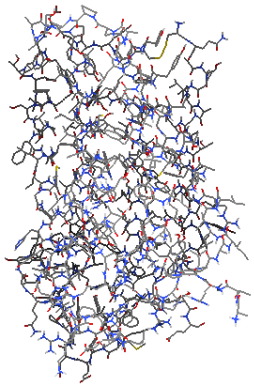


**Figure 3: Crystal structure of 5-alpha reductase receptor (PDB ID-7bw1)**

***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 [13].

**Molecular Docking Simulation Studies**

Docking of ligands like apigenin, luteolin and taxifolin against 5-alpha reductase receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [14-18].

**Toxicity & ADME-T Studies**

The ligand molecules viz. apigenin, luteolin and taxifolin 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 [19 & 21].

## RESULT & DISCUSSION

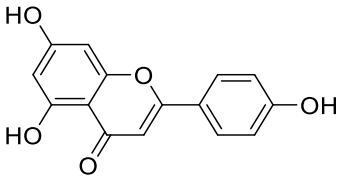
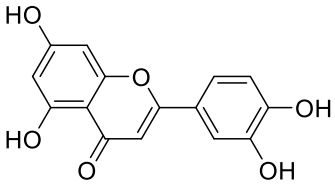
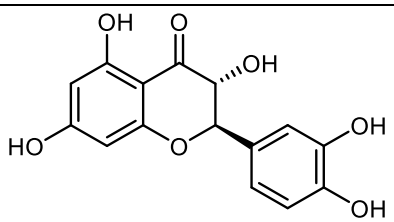
The scientific validation of the current investigation was done by computational based molecular docking study of lead molecules of *P.granatum* against *5α-reducatase(SRD5As)* enzyme. As per Chiranan Khantha *et al.,* '2021 SRD5As are dihydronicotinamide adenine dinucleotide phosphate (NADPH)-dependent and play a significant role in steroidogenesis by catalysing 4-ene-3-keto steroids into more active 5α-reduced derivatives, including the reduction of testosterone (T) to dihydrotestosterone (DHT). Dihydrotestosterone (DHT), the most potent androgen hormone, is an important aetiologic factor of androgenetic alopecia (AGA), or hair loss. Steroid 5-alpha reductases (SRD5As) increase DHT production in the scalp hair follicles, resulting in hair thinning and hair loss. Even though synthetic SRD5A inhibitors (finasteride and dutasteride) are effective in treating AGA, they cause adverse effects. This has led to an increased interest in alternative treatments from natural sources [20]. The grid parameter used in docking analysis of 5-alpha reductases (SRD5As) tabulated in table 10. The finding revealed that selected flavonoids *i.e.* Apigenin, luteolin and Taxifolin are potent inhibitor of *5α-reducatase(SRD5As)* in following manner: luteolin > Apigenin > Taxifolin.

Punica found to be effective anti-alopecic agent and their lead molecules effectively binds to be target protein *5α-reducatase (SRD5As)* with binding energy -7.15, -7.66 & -7.07 kcalmol$^{-1}$ for Apigenin, luteolin and taxifolin respectively. The result was tabulated in table 2. The binding mode of selected lead molecules showed in fig.4-6. The 2D and 3D interaction of selected compound displayed in fig.7-15. The interaction of Apigenin, luteolin and taxifolin with active site at *5α-reducatase(SRD5As)* showed as follows:

| Compound | Conventional Hydrogen bounding | Pi-sigma bounding | Covalent bounding | Week Vander's interaction |
|---|---|---|---|---|
| **Apigenin** | HIS$^{231}$, TYR$^{98}$, TYR$^{33}$, TRP$^{53}$, ARG$^{94}$, GLU$^{197}$ | GLY $^{34}$ | ARG$^{227}$ | ASN$^{192}$, PHE$^{194}$, TYR$^{107}$, ASP$^{164}$, LYS$^{35}$, TYR$^{178}$ |
| **Luteolin** | HIS$^{231}$, TYR$^{53}$, TYR$^{98}$TYR$^{33}$, TRP$^{53}$, ARG$^{94}$, ASN$^{160}$, ARG$^{227}$, GLU$^{197}$ | GLY $^{34}$ | PHE$^{194}$ | TYR$^{178}$, LYS$^{35}$, GLY$^{34}$, ARG$^{105}$, TYR$^{107}$, LEU$^{224,}$ |
| **Taxifolin** | ARG$^{227}$, TYR$^{107}$, ARG$^{105}$, ARG$^{171}$, TRY$^{178}$, LYS$^{35}$, ASP$^{164}$. | GLY $^{34}$ | LEU$^{167}$ | GLY$^{104}$, PHE$^{194}$, TYR$^{98}$, ASN$^{193}$, TYR$^{107}$ |

The pharmacokinetic profile reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects. The pharmacokinetic and toxicity profiling results of ligands like Apigenin, luteolin and taxifolin were shown in figure 16-18. Theoretically, all the ligand molecules have shown encouraging docking score.

**Table 2: Results of docking of ligands like apigenin, luteolin and taxifolin against 5-alpha reductase receptor**

| Sl. No | Compound Name | Structure | Binding Energy (Kcal/mole) |
|---|---|---|---|
| 1 | Apigenin |  | -7.15 |
| 2 | Luteolin |  | -7.66 |
| 3 | Taxifolin |  | -7.07 |

**Binding Mode**

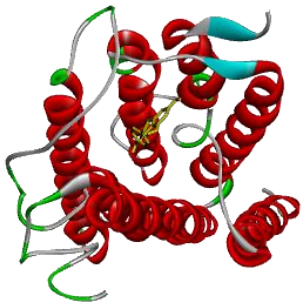


**Figure 4: Binding mode of apigenin within the active site of 5-alpha reductase receptor**

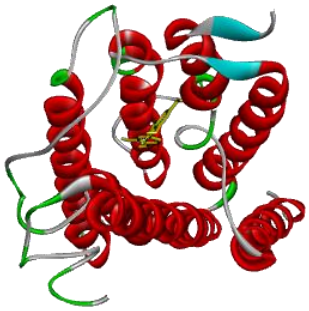


**Figure 5: Binding mode of luteolin within the active site of 5-alpha reductase receptor**

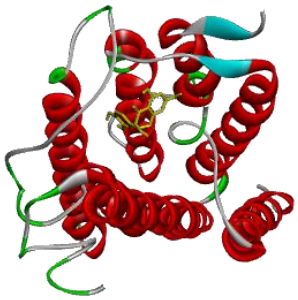


**Figure 6: Binding mode of taxifolin within the active site of 5-alpha reductase receptor**

**Interaction of Target compound with ligand**

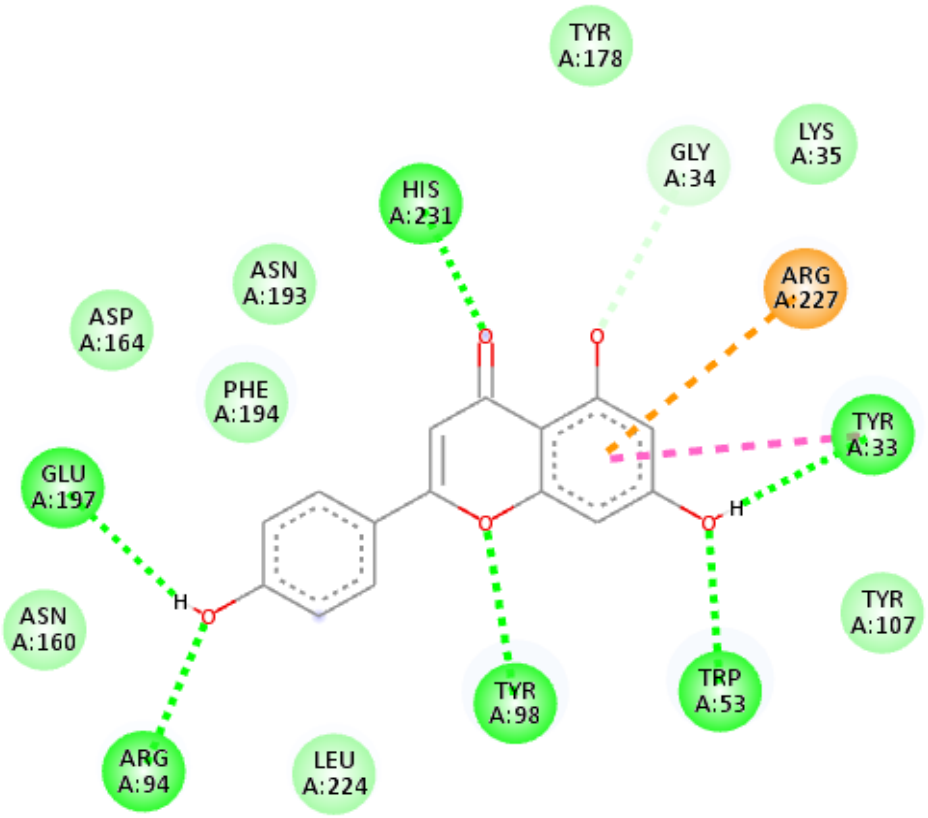



**Figure 7: Two-dimensional binding mode of apigenin within the active site of 5-alpha reductase receptor**

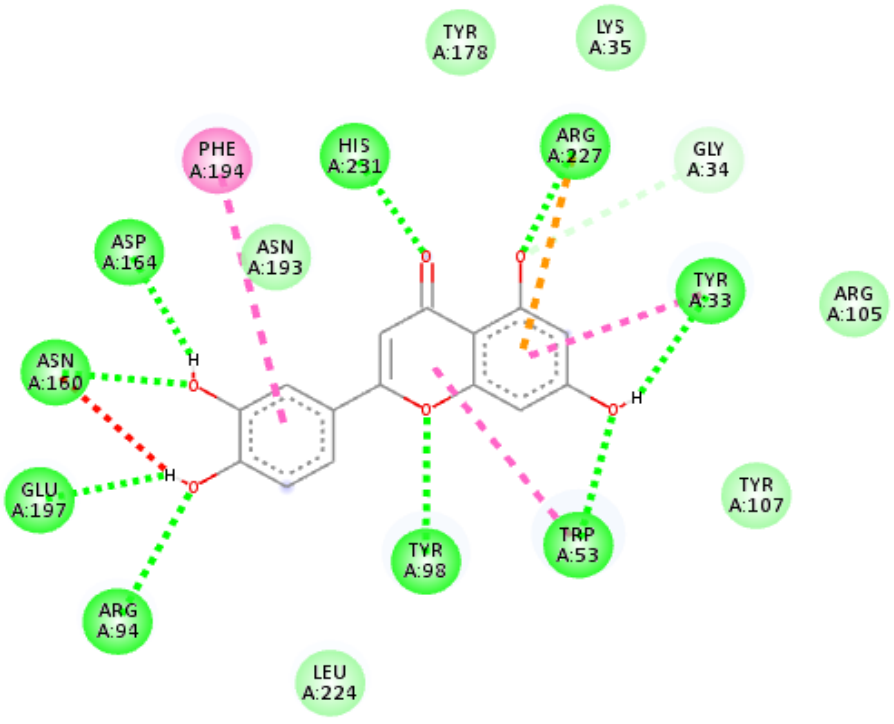



**Figure 8: Two-dimensional binding mode of luteolin within the active site of 5-alpha reductase receptor**

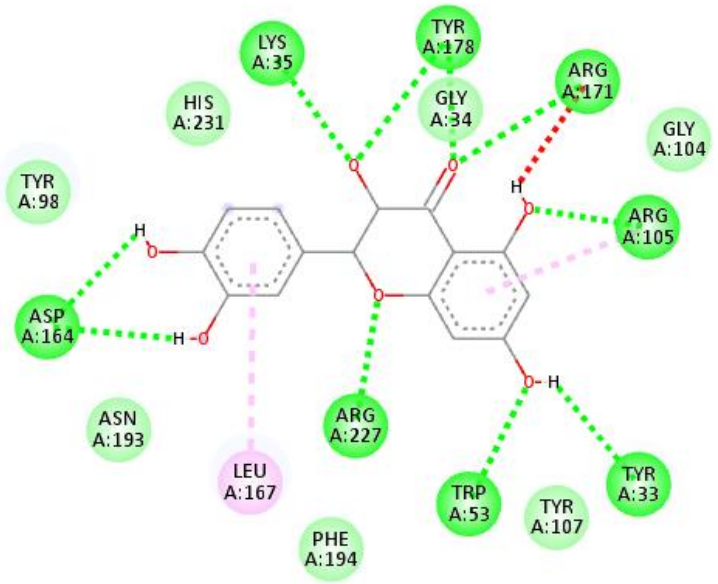



**Figure 9: Two-dimensional binding mode of taxifolin within the active site of 5-alpha reductase receptor**

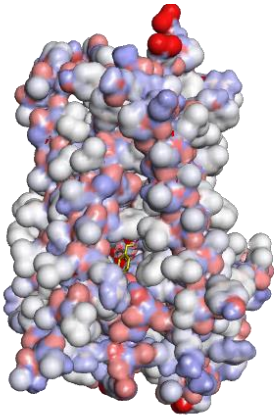


**Figure 10: Three-dimensional binding conformation of apigenin within the active site of 5-alpha reductase receptor**

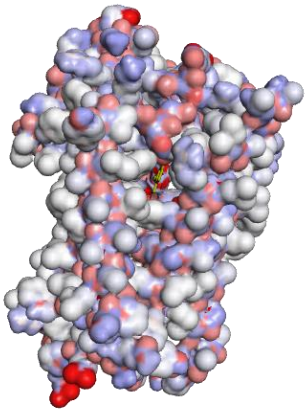


**Figure 11: Three-dimensional binding conformation of luteolin within the active site of 5-alpha reductase receptor**

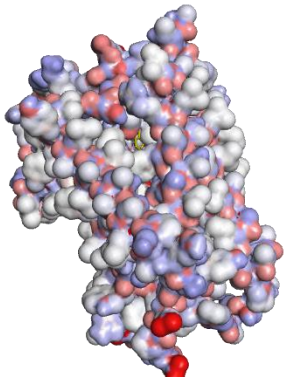


**Figure 12: Three-dimensional binding conformation of taxifolin within the active site of 5-alpha reductase receptor**

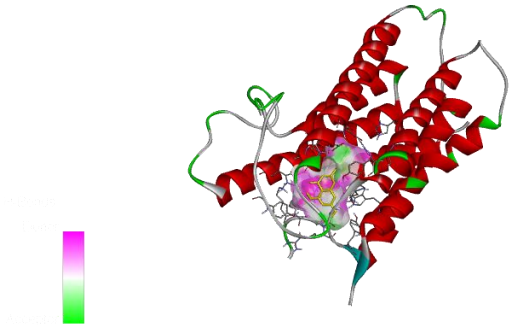


**Figure 13: Three-dimensional binding mode of apigenin within the active site of 5-alpha reductase receptor**

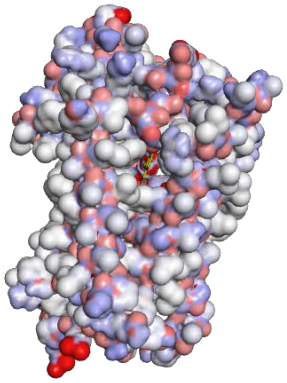


**Figure 14: Three-dimensional binding mode of luteolin within the active site of 5-alpha reductase receptor**

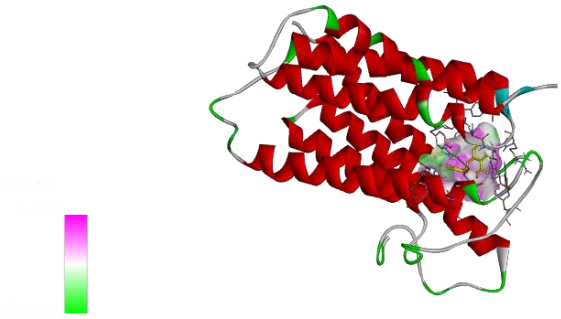


**Figure 15: Three-dimensional binding mode of taxifolin within the active site of 5-alpha reductase receptor**

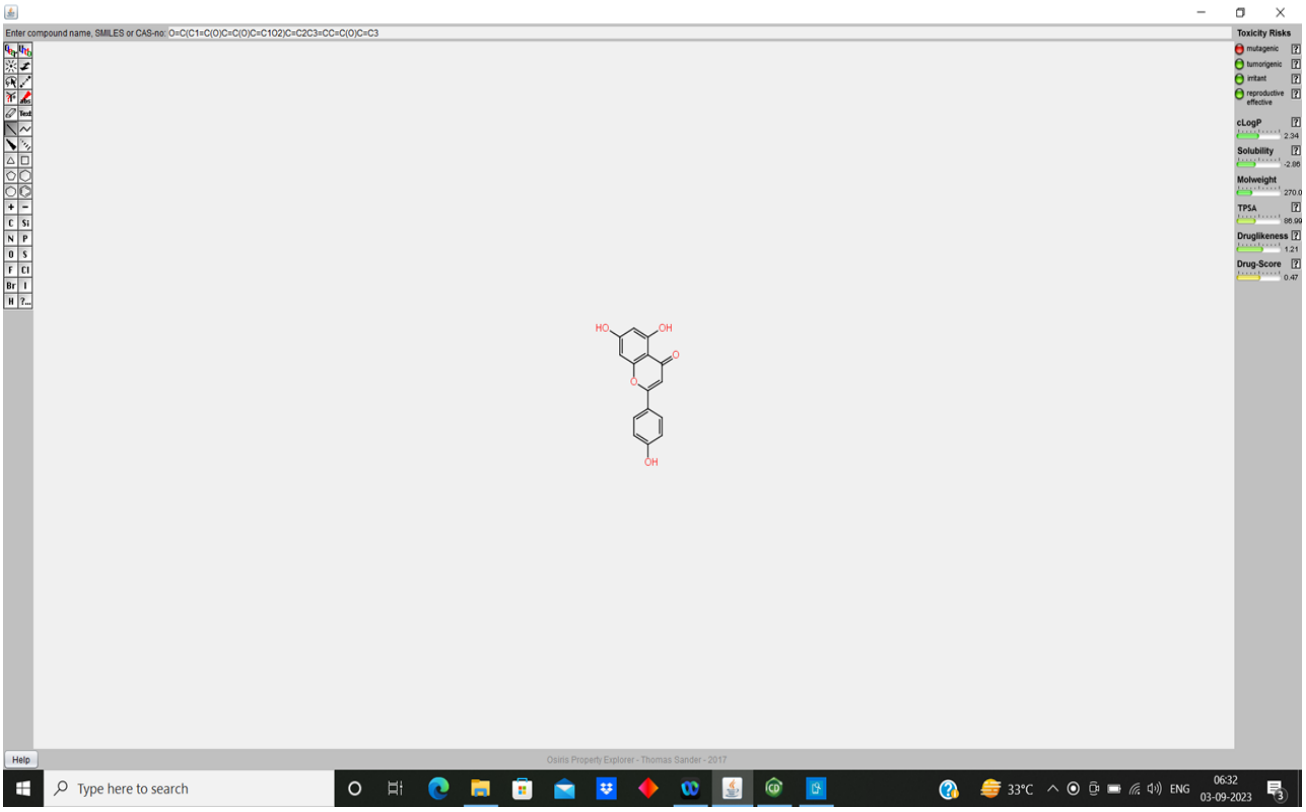



**Figure 16: Pharmacokinetic and toxicity profiling of apigenin**

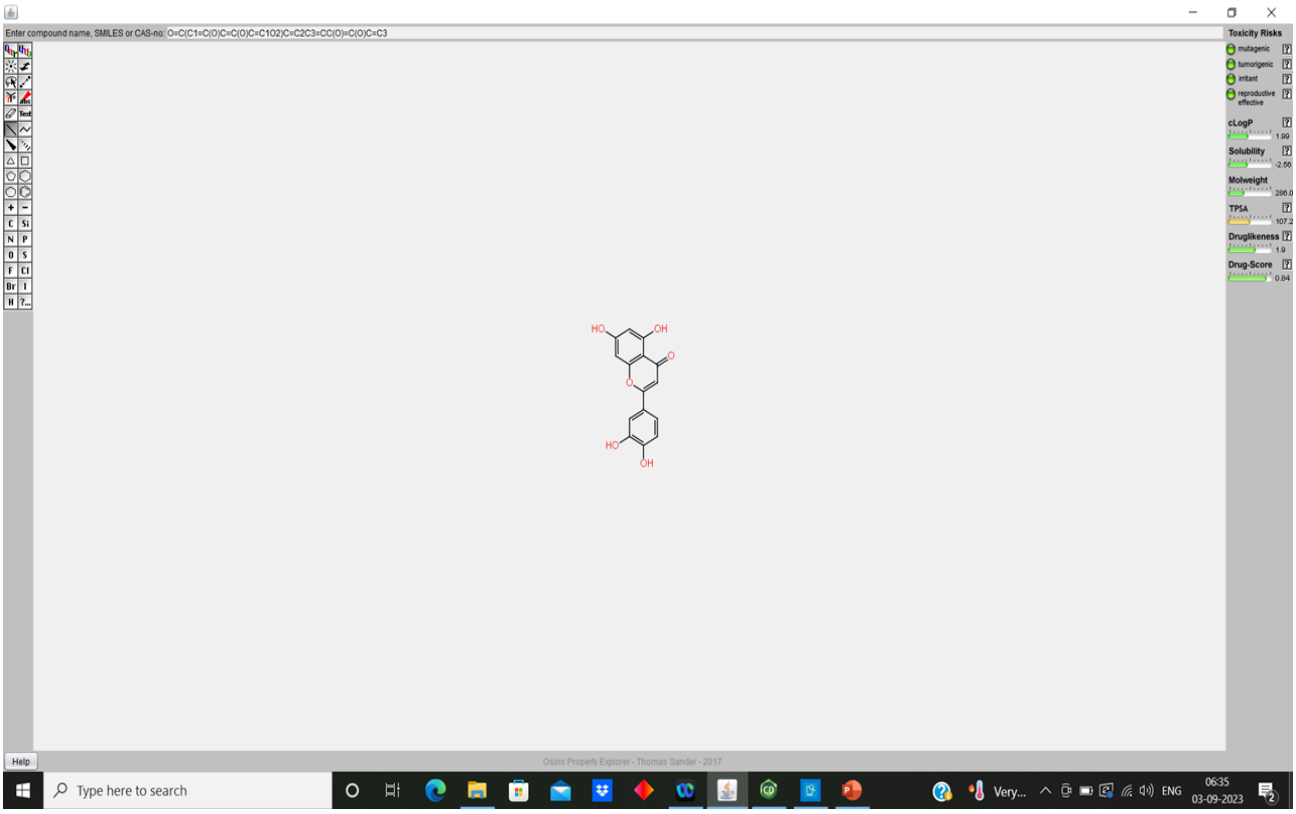



**Figure 17: Pharmacokinetic and toxicity profiling of luteolin**

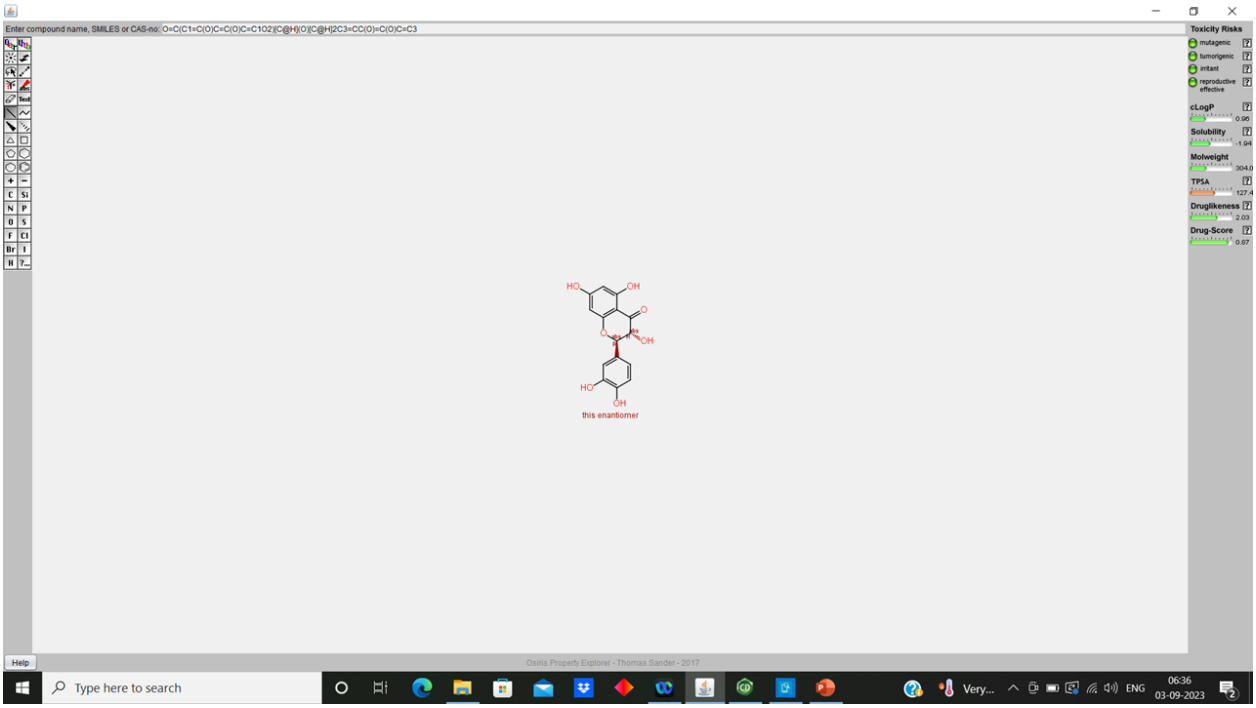



**Figure 18: Pharmacokinetic and toxicity profiling of taxifolin**

## CONCLUSION

The pomegranate is regarded as a lucky fruit that is full of enchantment. Eat one before you make a wish to hasten its fulfilment. The prognosis of the complex multifactorial condition alopecia is uncertain. While many individuals recover on their own, some may have a persistent illness. Although corticosteroids are thought of as the first line of defence, there are no FDA-approved therapies. It was necessary to investigate potential new therapeutic approaches. With this goal in mind, the current study was created to examine *Punica granatum's* ability to treat alopecia. The results suggested that flavonoids such apigenin, luteolin, and taxifolin found in P. granatum's methanolic peel extract showed significant 5-reductase (SRD5 As) enzyme inhibitory activity and, as a result, exhibit anti-alopecia action.

## REFERENCE

1. Obasi, C. J., Obasi, I. S., Okafor, U. C., & Uzoka, I. S. (2018). Comparison of anti-dandruff activity of synthetic shampoos and crude plant extracts on dandruff causing isolates. *J Biotechnol Biochem*, *4*, 42–6.
2. Semwal, D., Kotiyal, R., Chauhan, A., Mishra, A., Adhikari, L., Semalty, A., & Semalty, A. (2015). Alopecia and the herbal drugs: an overview of the current status. *Advances in Biomedicine and Pharmacy*, *2*(6), 246-254.
3. Guo, E. L., & Katta, R. (2017). Diet and hair loss: Effects of nutrient deficiency and supplement use. *Dermatol Pract Concept*, *7*, 1–10.
4. Kaur, H., Babu, B. R., & Maiti, S. (2007). Perspectives on chemistry and therapeutic applications of Locked Nucleic Acid (LNA). *Chemical Reviews*, *107*(11), 4672-4697.
5. Soni, H., Nayak, G., Mishra, K., Singhai, A. K., & Pathak, A. K. (2010). Evaluation of Phyto Pharmaceutical and Antioxidant potential of Methanolic Extract of Peel of punica granatum. *Research journal of Pharmacy and Technology*, *3*(4), 1170-1174.
6. Wang, D., Özen, C., Abu-Reidah, I. M., Chigurupati, S., Patra, J. K., Horbanczuk, J. O., ... & Atanasov, A. G. (2018). Vasculoprotective effects of pomegranate (Punica granatum L.). *Frontiers in pharmacology*, *9*, 351682.
7. Mishra, S., Mishra, R. K., Mishra, S. R., & Soni, H. (2022). Potential of Polyherbal Formulation in Burn Wound Model. *Sch Int J Tradit Complement Med*, *5*(1), 19-23.
8. Maphetu, N., Unuofin, J. O., Masuku, N. P., Olisah, C., & Lebelo, S. L. (2022). Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of Punica granatum L.(pomegranate) plant extracts: A review. *Biomedicine & Pharmacotherapy*, *153*, 113256.
9. ACD/Structure Elucidator, version 2018.1, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2019.
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*, *4*(1), 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. 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.
16. 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.
17. 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.
18. Mujwar, S., & Pardasani, K. (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), 326-47.
19. 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.
20. Khantham, C., Yooin, W., Sringarm, K., Sommano, S. R., Jiranusornkul, S., Carmona, F. D., ... & Ruksiriwanich, W. (2021). Effects on steroid 5-alpha reductase gene expression of Thai rice bran extracts and molecular dynamics study on SRD5A2. *Biology*, *10*(4), 319.
21. Malik, J., Jhariya, D., Ahirwar, P., Sharma, S., Upadhyay, S., & Soni, H. (2024). Mechanistic insight anti-arthritis efficacy of bio-actives of Moringa oleifera: In-silico molecular docking. *Journal of Pharmacognosy and Phytochemistry*, *13*(1), 44-48.

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