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DOCKING STUDY FOR UROLITHIASIS IN *SYNADENIUM GRANTII*

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ABSTRACT: Urolithiasis, also called kidney stone, was caused by a missense mutation in the adenine phosphoribosyl transferase enzyme encoded by the APRT gene. This gene was present in human chromosome 16. In this paper, a comparative study of the effectiveness of six ligands reported in *Synadenium grantii* was analyzed by docking approach. For this purpose, the effective six ligands that were present in *Synedenium grantii* were selected, downloaded, and docked with APRT. The interactions of these ligands with APRT were analyzed by docking by using Autodock vina. The selected six ligands were phorbol ester, terpene, flavonoid, tannin, coumarin, and anthraquinone. All these ligands have anti-urolithiatic activity and are used to treat urolithiasis. A docking study by AutoDock vina reveals the interacting amino acid residues that have not been reported yet. Based on interactions of different ligands with APRT, our analysis shows that flavonoid was most effective, followed by terpene, phorbol ester, tannin and coumarin. The results show that anthraquinone was the least effective. The docking study performed by Autodock vina shows that flavonoid was most effective and anthraquinone was least effective.

INTRODUCTION: Medicinal plants have been reported to play an important role in curing many diseases. In our earlier work, we reported structure prediction for the spinach protein responsible for antioxidant property [1] and flavonoid biosynthesis [2]. Another study reported homology modeling for strictosidine synthase involved in alkaloid biosynthesis [3]. In this study, we have selected *Synadenium grantii*, which belongs to the Euphorbiaceae family. *Synadenium grantii* Hook f. is a medicinal plant popularly known as leitosinha and janaúba.

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Euphorbiaceae family contains more than 300 genera and 8900 species described worldwide [4], most of which are used for medicinal purposes. The Synadenium genus contains 19 species and is a small genus of the Euphorbiaceae family. Plants belonging to this family have developed various forms of life, including herbs, shrubs, and large trees. It has been reported that genera of Synadenium have various classes of bioactive molecules such as flavonoids, saponins, diterpenes, phorbol esters [5, 6] triterpenes [7].

Several species of this genus have been Pharmacologically evaluated against anti-inflammatory, antitumor, analgesic, immune-regulatory, and fibrinolytic experimental models [8, 9]. Species belonging to this genus are widely used in folk medicine to treat several diseases like cancer, peptic ulcers, and other health problems [10].

In folk medicine, people use its latex to treat neoplastic diseases and gastric disorders such as peptic ulcers and gastritis [11].

Urolithiasis, also termed kidney stones, results in calcification in the urinary system. This causes the formation of stones in the kidney, bladder, or urethra. A maximum of stones contain calcium. Adenine phosphoribosyltransferase (APRTase) is an enzyme encoded by the APRT gene, found in humans on chromosome 16.

This enzyme is responsible for synthesizing AMP from adenine and 5 - phosphoribosyl - 1 - pyrophosphate by salvage pathway. The deficiency of this enzyme results conversion of adenine to 2, 8-dihydroxyadenine (2,8-DHA) by xanthine dehydrogenase (XDH). It is extremely insoluble and its accumulation in the kidney can lead to crystalluria and the formation of urinary stones [12, 13].

In this disease, adenine and 2,8-DHA are secreted by the human kidney. The disease can be cured by surgery, but it is not affordable for the common man and may have some side effects. Therefore, natural drugs that were used in medicinal plants were considered the best alternative for treatment.

In this study, we have selected six ligands reported to be present in *Synedium grantii* and analyzed their interaction with APRT. The selected ligands were flavonoid, terpene, phorbol ester, tannin, coumarin, and anthraquinone. The more interactions produced by the ligand with APRT, the more it will be stable to use in the treatment of urolithiasis [14].

Flavonoids were found in most fruits and vegetables. They are responsible for their bright pigments. Wines, cocoa, and berries all contain flavonoids, considered healthy chemicals. Flavonoids have also been shown to exhibit therapeutic properties.

Flavonoids possess antioxidant, antibiotic and anti-inflammatory properties. Terpenes were found in every flower, herb, and fruit. They provide plants with unique scents and flavors and are considered essential oils. Phorbol esters were a class of chemical compounds found in various plants, particularly in Euphorbiaceae. Chemically, they are ester derivatives of the tetracyclic diterpenoid phorbol. Tannins are known antimicrobial biomolecules.

They bind to and precipitate protein and amino acids. Our study reveals the interacting amino acid residues of APRT with these ligands that have not been reported yet. Comparative analysis shows flavonoid was most interactive, followed by terpene, phorbol ester, tannin, and coumarin. The results show that anthraquinone was the least effective.

METHODS:

Target Selection: The mutated enzyme structure of APRT was downloaded from Research Collaboratory for structural bioinformatics protein database (RCSB Pdb) [15]. The Protein Data Bank ID of APRT was 4X45.

Selection of Ligands: The effective ligands of plants were identified through literature and downloaded from Pubchem database [16]. All the downloaded ligands of plants were docked with APRT enzyme with the help of AutoDock Vina to analyze their interactions with amino acid residues of APRT. The results were analyzed in Discovery studio 3.5.

Molecular Docking: The structures of the seven selected ligands were downloaded through pubchem. AutoDock vina was used to predict the binding modes of all selected compounds with target protein APRT.

AutoDock Vina tries a set of different conformers of the ligands to obtain the best disposition of the molecule's atoms for maximizing the scoring function that quantifies ligand-receptor interaction. The Autodock vina gives the best orientation of ligands with protein, *i.e.*, docking results. The interaction of protein and ligands was visualized by Discovery Studio 3.5.

RESULTS AND DISCUSSION: A docking study was performed to analyze the interaction of selected ligands with APRT. For this purpose, the selected ligands or chemical constituents were docked with APRT. Autodockvina was used to predict the binding mode of ligands with APRT. **Table 1** shows the data of structure and CID number of selected ligands.

TABLE 1: LIGANDS DOCKED WITH APRT ENZYME

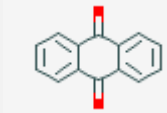
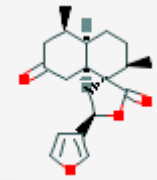
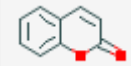
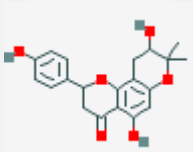
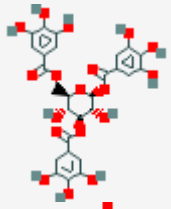
S. no	Name	Structure	CID NO.
1.	Anthraquinone		6780
2.	Terpene		186030
3.	Coumorine		323
4.	Flavonoid		44257868
5.	Tannin		129727514
6.	Phorbol ester		91899443

Fig. 1 shows the interactions of flavonoids with APRT enzyme. It was clear from the figure that flavonoids react with the B-chain protein. There were six interacting amino acids for flavonoid, THR132, LEU129, TYR101, PHE26, ARG27, and ALA131. Total 14 amino acids were involved in the interaction.

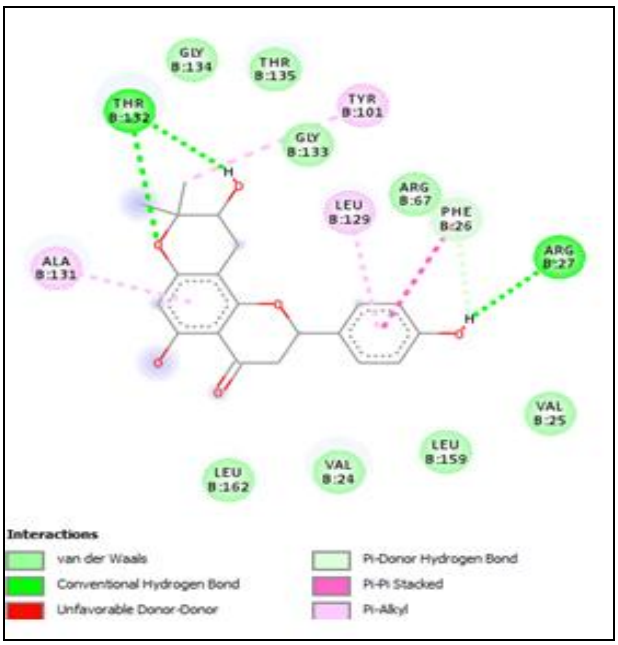


FIG. 1: INTERACTIONS OF FLAVONOID WITH APRT ENZYME

Fig. 2 shows the interactions of terpene with APRT enzyme. The result shows that terpene reacts with the target protein's A chain. The interacting amino acids of terpene were LEU159, LEU129, ARG27, PHE 26, PRO20, and VAL24. There were 10 interactions of these amino acids with terpene. Total 8 amino acids were involved in interaction.

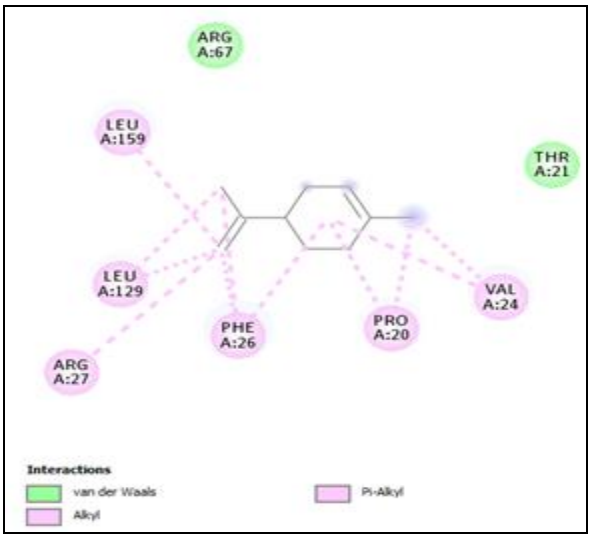


FIG. 2: INTERACTIONS OF TERPENE WITH APRT

Fig. 3 shows the interactions of Phorbol ester with APRT enzyme. The results show that there were six interacting amino acids and 10 interactions are involved for phorbol ester. It reacts with A chain of APRT enzyme. The interacting amino acid residues identified as LEU103, LEU129, LEU159, PHE26, ALA131 and PRO20. There were 7 interactions of these amino acids with phorbol ester was observed. Total 19 amino acids are involved in the interaction.

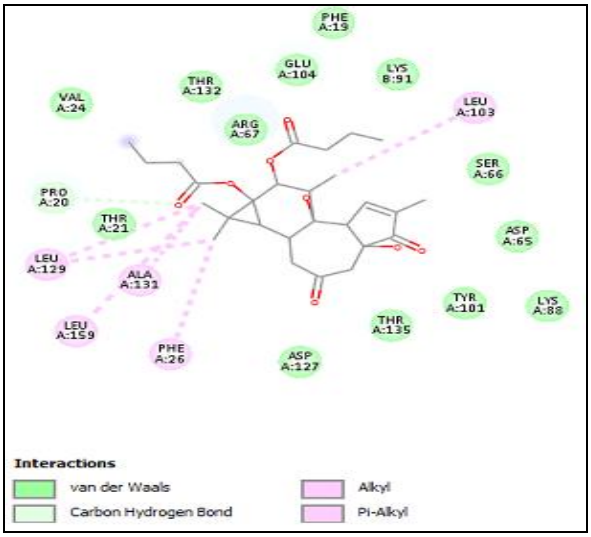


FIG. 3: INTERACTIONS OF PHORBOL ESTER WITH APRT ENZYME

Fig. 4 shows the interactions of Tannin with APRT enzyme. The results show that there were five interacting amino acids belonging to the A chain. The residues were SER161, LEU162, VAL24, GLU104, and THR21 for tannin. There were 5 interactions of these amino acids with tannin. Total 18 amino acids are involved in the interaction.

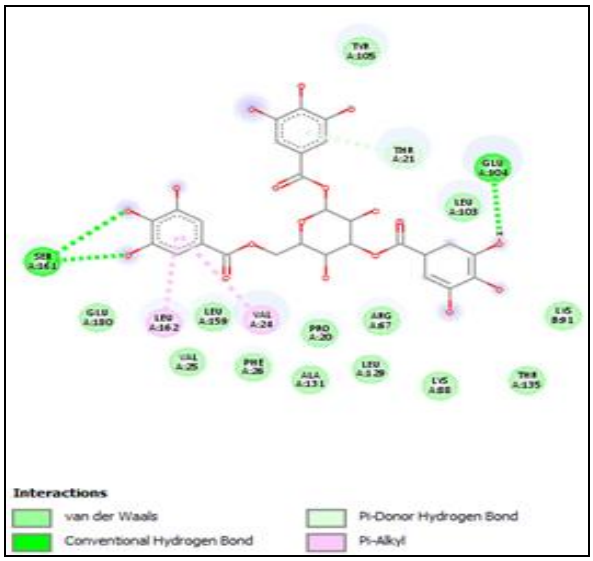


FIG. 4: INTERACTIONS OF TANNIN WITH APRT ENZYME

Fig. 5 shows the interactions of coumarin with APRT enzyme. The interacting amino acid residues was four. The four interacting amino acids of coumarin belong to A chain and are found to be THR135, THR132, GLY134, and GLY133. There were 5 interactions of these amino acids with coumarin. Total 8 amino acids are involved in the interaction.

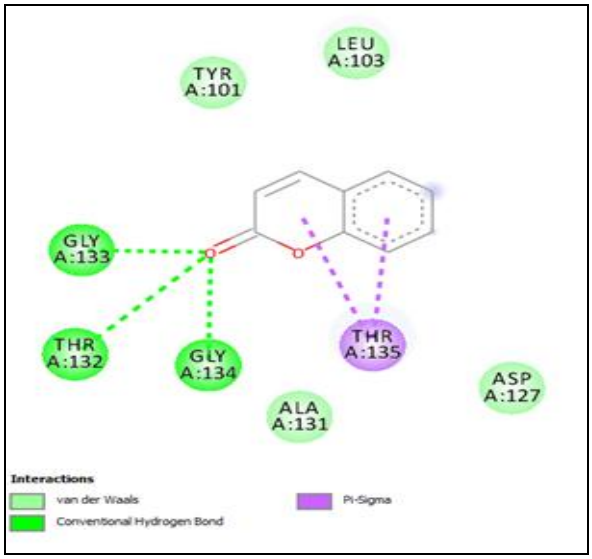


FIG. 5: INTERACTIONS OF COUMARIN WITH APRT

Fig. 6 shows the interactions of anthraquinone with APRT enzyme. Anthraquinone reacts with the B-chain of protein. The three interacting amino acids of anthraquinone were TYR101, ALA108, and LYS88. Only three amino acids were found to interact with APRT. There were 4 interactions of these amino acids with anthraquinone. Total 6 amino acids are involved in the interaction.

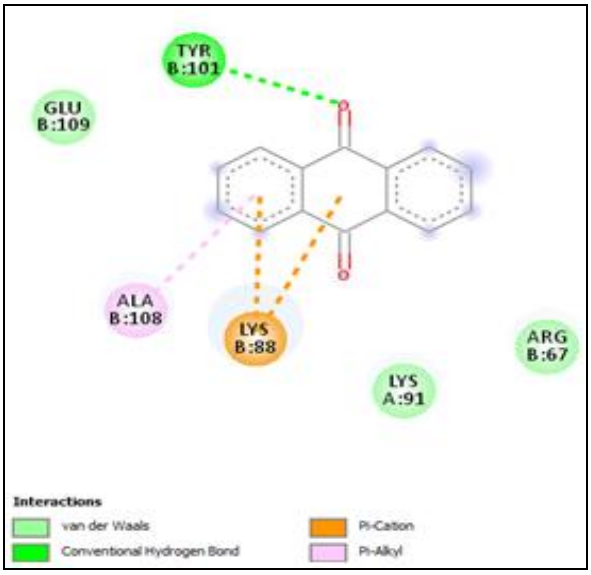


FIG. 6: INTERACTIONS OF ANTHRAQUINONE WITH APRT

Medicinal plants have been used for thousands of years in traditional medicine. It has been reported that genera of Synadenium present various classes of bioactive molecules such as flavonoids, saponins, diterpenes, phorbol esters [6], triterpenes [7]. Phytochemical results showed tannins, terpenes, coumarins, and anthraquinones in the crude bark extract and terpenes in the latex. These chemical constituents of a plant used to treat Urolithiasis [17]. In this paper six ligands were selected for this purpose to analyze their comparative effectiveness. The ligands were flavonoid, terpene, phorbol ester, tannin, caumarin, and anthraquinone. Molecular docking is also considered an important tool in structural molecular biology and computer-aided drug design.

The docking study was associated with the chemical constituent considered a ligand and a protein. This permits the characterization of chemical compound's conduct in the binding site of target proteins and additionally explains crucial biochemical procedures [18]. Docking allows us to explore databases of large chemical compounds and design effective inhibitors to cure diseases in light of interaction score [19]. The APRT enzyme was docked with the ligands by Autodock vina. This gives docking results of various orientations of ligands. It binds to the protein, which is visualized in discovery studio 3.5 and shows interacting amino acids with the ligand. In this study, docking by using Autodock vina reveals the interacting amino acid residues of APRT with selected ligands that have not been reported yet. In each docked complex, every ligand interacts with pocket amino acid residues of mutated APRT enzyme. The interaction of terpene, phorbol ester, tannin, and coumarin shows that all these compounds react with the A-chain of protein. However, flavonoids and anthraquinone react with the B-chain of protein.

Based on interacting amino acids with different ligands and amino acids involved in the interaction, this study suggests the effectiveness of different ligands with APRT. Our results show that more interaction and amino acid residues were involved with flavonoids. This was followed by terpene, phorbol easter, and tannin. Comparative analysis of the interaction of these ligands with APRT shows that there were six interacting amino acid residues for flavonoids. Phorbol ester and terpene Tannin shows five interacting amino acid residues, while coumarin and anthraquinone show four and three interacting amino acid residues, respectively. In each docked complex, chemical constituents represented a lot of interactions with the amino acid residues. The ligand fit in the pocket of the enzyme, interacted with the amino acid residues of mutated APRT enzyme, and did not leave the complex, demonstrating its stability and soundness.

The more interactions produced by the chemical constituents, the more stable the use in the treatment of urolithiasis. Therefore, our results show the comparative effectiveness of the different ligands for treating urolithiasis. Based on the interaction produced by these ligands, our study shows that flavonoid was most effective, followed by terpene, phorbol ester, tannin, and coumarin. Anthraquinone was the least effective.

CONCLUSION: In this study, our goal was to perform docking of the selected ligands with APRT enzyme to predict the binding interactions with

APRT. This has not been reported yet. Based on the interaction of APRT-selected ligands, this study shows the effectiveness of different ligands. The results suggest that flavonoid was most effective, followed by terpene, phorbol ester, tannin, and coumarin. Anthraquinone was found to be the least effective.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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