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IN SILICO DOCKING STUDIES FOR SELECTED ALKALOID COMPOUNDS FOR NEPHROPROTECTIVE ACTIVITY

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ABSTRACT

Nephrotoxicity is defined as a sharp decline in kidney function brought on by the harmful effects of drugs and chemicals. There are several variations, and certain medications may have multiple effects on renal function. Substances that exhibit nephrotoxicity are known as nephrotoxins. Nephrotoxicity is caused by many mechanisms. Plant products have popularity in treating various diseases from ancient. The majority of alkaloids, particularly those with anti-inflammatory, anti-cancer, and anti-angiogenic properties, have definite biological effects that are frequently used in therapeutic contexts. The alkaloids Berberine and Ligustrazine have nephronprotective activity. The aim of the present study is to perform *in silico* docking studies for these alkaloids. The 3D sturcutres are collected from pubchem and the protein 3ANS collected from literature studies. Berberine, Ligustrazine, Standard (alpha tocoferol) was docked under 3ANS protein. The docking scores are -9.3,-9.1,-5.2 for standard, berberine and ligustrazine respectively. Thus berbeine has higher nephroprotection than ligustrazine. This study can help to treat various kidney diseases like Acute Kidney Disease, End Stage Renal Disease and other kidney diseases.

***Key words*:** Nephrotoxicity, Alkaloids, Berberine, Ligustrazine, *in silico* docking, Nephroprotection

INTRODUCTION

End-stage renal disease (ESRD) is mostly brought on by chronic kidney disease (CKD), which is characterised by a reduced glomerular filtration rate, an increased excretion of urine albumin, or both. Worldwide, CKD is a substantial cause of death and a large healthcare burden [1, 2]. One of the distinguishing characteristics of all types of chronic renal disease is fibrosis [3]. To delay the onset of end-stage renal disease (ESRD), this is the current goal of treating chronic kidney disease. Additionally, it has a bad prognosis, ineffective treatment plans, and a finite number of therapies [4]. So, a more effective treatment plan is needed to figure out how to stop chronic renal disease from becoming ESRD.

There is now no better medical intervention than dialysis that may consistently increase survival, prevent damage, or hasten recovery [5]. A number of causes, such as surgery [6,7], sepsis [8] and the majority of drug-induced kidney damage in clinical practise, can cause AKI.

The majority of alkaloids exhibit clear biological actions that are employed often in therapeutic settings, including those that are anti-inflammatory [09], anti- cancer [10], anti-angiogenic [11], and others. It's interesting to note that numerous star molecular alkaloids, including berberine (BBR), are crucial in renal illnesses.

Berberine

Berberine is a chemical that can be found in plants such as European barberry, goldenseal, goldthread, Oregon grape, phellodendron, and tree turmeric. It may assist to strengthen the heartbeat, which may aid those suffering from certain heart disease.

Structure:

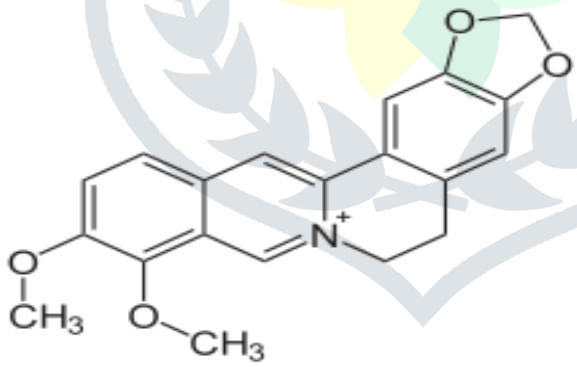


Figure 1: Structure of Berberine

Berberine is used to treat chronic kidney disease by reducing the formation of gut-derived uremic toxins in the gut microbiota. [12]

Uses

- Canker sores: Using a berberine-containing gel can help reduce pain, redness, leaking, and the size of canker sores.
- Diabetes: Berberine appears to somewhat lower blood sugar levels in diabetics when taken orally.

- A stomach infection that can cause ulcers (H. pylori). Adding berberine by mouth to several drugs commonly used to treat this illness may work just as well as other established treatments. These other treatments, too, make use of a variety of drugs.
- Hyperlipidaemia (high amounts of cholesterol or other fats (lipids) in the blood). Berberine used orally, alone or in combination with other components, may help decrease total cholesterol.

Side effects

- Berberine is possibly safe for most adults when taken orally; it has been used safely in dosage up to 1.5 grams daily for 6 months; common adverse effects include constipation, gas, and upset of stomach. Berberine is possibly safe for most adults when applied topically [13]

Ligustrazine

Ligustrazine is a chemical molecule found in fermented cocoa beans and natto. Tetra methylpyrazine is a colourless solid when refined. It belongs to the alkyl pyrazine class.

In rats, it has potential nootropic and anti-inflammatory properties. [14]

Structure

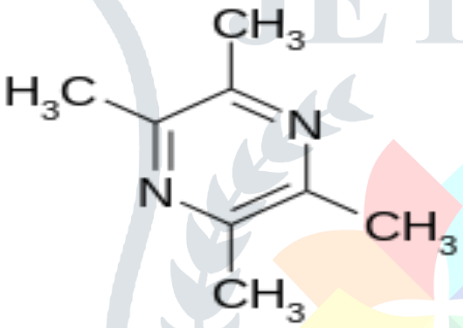


Figure 2: Structure of Ligustrazine

Uses

- Ligusticum wallichii Franch generates the alkaloid ligustrazine, which is a potent vasodilator.
- Ligustrazine is also a powerful cytotoxic oxygen free radical scavenger.
- It has been proven that ligustrazine can prevent endothelial and hepatic cell damage caused by I/R by scavenging free radicals.
- Ligustrazine has been utilised to treat acute kidney damage (AKI) in patients.

Side Effects

Adverse events were not allergic reactions, but were caused by ligustrazine's calcium channel-blocking function, which could raise heart rate and oxygen consumption. However, clinical accounts revealed that non-IgE-mediated anaphylactic responses could occur.

The purpose of the present study was to perform *in silico* docking studies for selected alkaloid compounds for nephroprotective activity.

MATERIAL AND METHODS

Ligand Preparation:

Ligands are important for the docking as they get bind to the protein molecules and show the affinity of the constituents. The alkaloids berberine, ligustrazine structures are collected from NCBI PubChem Compound database. The structures with neat confrontations are downloaded and made ready for the docking.

Protein Preparation:

The X-ray crystallographic structure of NF-B-DNA (PDB ID:1NFK) p50 homodimer (resolution 2.30) and human soluble epoxide hydrolase (resolution 1.98) in complex with synthetic inhibitor was downloaded from the Protein Data Bank (PDB) of the Research Collaboratory for Structural Bioinformatics (RCSB). The structures were stripped of the co-crystallized DNA macromolecule from 1NFK and the synthetic inhibitor from 3ANS. To obtain clean protein, crystallographic water molecules from the target proteins were removed, and then hydrogen atoms were supplied to both proteins using the CHARMm force field to stabilise the target proteins. The energy of the targets was minimised using Discovery Studio 3.5's standard dynamics cascade procedure. Binding site residues were chosen for molecular docking research.

Receptor Grid Generation:

The co-crystallized ligand was isolated from the active site of the receptor chain from the designated receptor. The partial atomic charge was less than 0.25 defaults, and the atoms had the same size as Van der Waals radii of 1.0>. The centroid of the workspace ligand serves as the active site's representation of an enclosing box. This technique was followed, and the default Glide parameters were used to create a grid centred on the ligand. The grid structure was docked with all of the ligands.

Molecular Docking Analysis:

Flexible docking was carried out on a predetermined receptor grid using the extra precision (XP) function of the AUTO-DOCK. There were no restrictions on the defined ligand-receptor interactions. To see the output of the subsequent docking studies through pose viewer, the structure output format was changed to pose viewer file.

Generation of E-Pharmacophore:

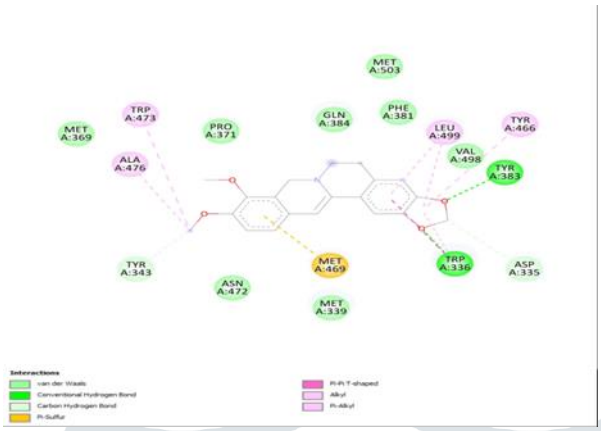
Berberine and Ligustrazine docked on protein 3ANS macromolecules, an e-pharmacophore was created. Pharmacophoric sites were created automatically with improved ligands using PHASE from Schrodinger, LLC in New York. A number of characteristics are used by PHASE, including the positive ionizable group (P), aromatic ring (R), hydrogen bond acceptor (A), hydrogen bond donor (D), negative ionizable group (N), and hydrophobe (H). Based on Glide XP descriptions, an energy value was assigned to each pharmacophoric site.

Selection of the Best-Scored Pose:

The docking scores were the primary factor considered when choosing the best docking poses for the PCNPs, but other factors included the values of various energies, the quantity of H bonds, and a visual examination of all docking poses in Maestro (Schrodinger, USA). Binding affinities can be attributed to the energy of the interaction between the protein and the ligand. To identify the optimum docked structure for each ligand, many criteria were established. The Glide GScore was then used directly to determine ranks.

RESULTS AND DISCUSSION:

The Molecular Docking of Berberine and Ligustrazine was performed with the protein human soluble epoxide hydrolase (PDB ID: 3ANS), Vitamin E (alpha tocopherol) was taken as standard drug. The docking results are as shown below:



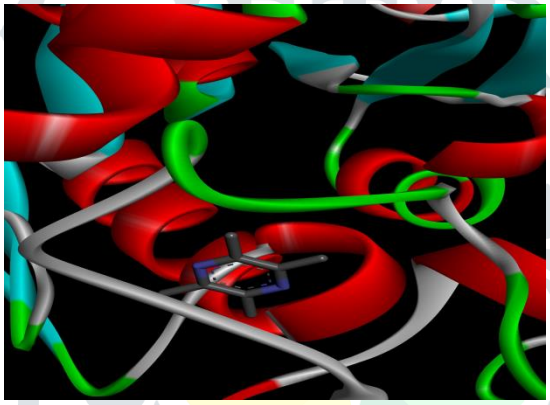


Table 1: Docking scores of the components

S.NO	Name of Component	Docking Score
1.	Standard	-9.3
2.	Berberine	-9.1
3.	Ligustrazine	-5.2

BERBERINE 3ANS COMPLEX

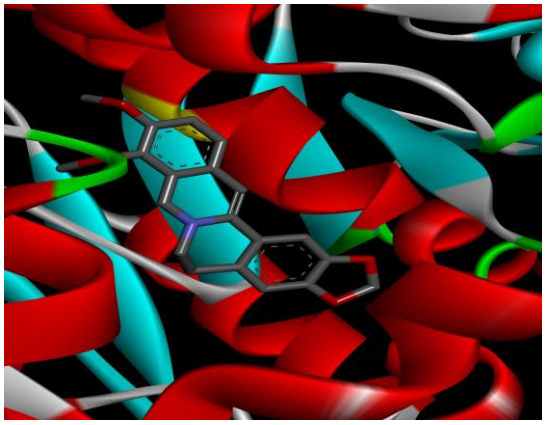


Figure 3: interaction of berberine with protein 3ANS

LIGUSTRAZINE 3ANS COMPLEX

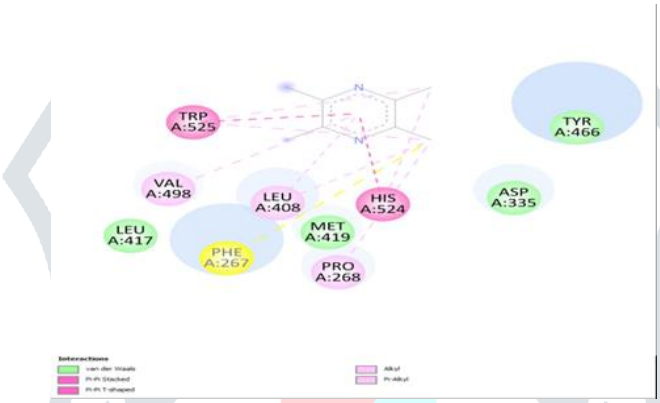


Figure 4: interaction of Ligustrazine with 3 ANS

DISSCUSSION

NF-B is a critical mediator of signal transduction that is activated by a number of pro-inflammatory cytokines; hence taking part in the effector phase of inflammation.NF-B is also triggered by many pathophysiological events in renal cells and is responsible for Inflammation is associated with renal illness. Chronic inflammatory disease and oxidative stress, activities that are linked to NF-B activation play an important role in the development and progression of chronic renal disease. Cisplatin nephrotoxicity has also been linked to NF-B. There have been beneficial benefits in experimental renal damage. Agents that block or antagonise NF-B activating stimuli have been reported. Many herbal remedies have been shown in investigations to protect against CP-induced kidney impairment by blocking NF-B activation. As a result, it is obvious that addressing inflammation (NF-B) is an appealing therapeutic approach in treatment of various kidney diseases [15, 16].

Initially, it was thought that soluble epoxide hydrolase (sEH) was only engaged in xenobiotic metabolism. Fatty acid epoxides are now well established as suitable substrates for this enzyme as a component of the arachidonic acid cascade, sEH plays a key role in eicosanoid epoxide metabolism. sEH is produced in a variety of cells and organs, including the liver, kidney, vascular endothelium, leukocytes, and adipocytes, and catalyses the hydrolysis of epoxyeicosatrienoic acids (EETs) into the equivalent dihydroxyeicosatrienoic acids [17, 18].

Several studies have revealed that EETs have nephroprotective properties due to their antioxidative, anti-inflammatory, and antiapoptotic properties. sEH inhibitors are a unique strategy in the treatment of

nephrotoxicity. The findings stated above motivated us to explore the molecular docking and dynamic behaviour of berberine and ligustrazine bioactive chemicals reported from the title plant against NF-B and sEH. Berberine inhibited NF-B and sEH proteins with greater binding affinity and structural stability inside the binding pockets during the dynamic simulation period, according to the *in-silico* investigations [19, 20].

CONCLUSION

Berberine and Ligustrazine were docked under protein 3ANS and the docking score was found to be -9.1 and -5.2 respectively, when compared with the standard we can conclude that the berberine having higher nephroprotection. This study can help to treat various kidney diseases like Acute Kidney Disease, End Stage Renal Disease and other kidney diseases.

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