“IN SILICO STUDY TO DETERMINE THE POTENTIAL OF ALLIUM SATIVUM TO PREVENT ISCHEMIC STROKES”

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SUBMITTED IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE
OF

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

Submitted by:

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CANDIDATE'S DECLARATION

I, Sanya Arora, 2K22/MSCBIO/44 of MSc. Biotechnology, hereby declare that the project Dissertation titled "In silico study to determine the potential of Allium sativum to prevent Ischemic strokes" which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science is an authentic record of my own carried out work under the supervision of professor Yasha Hasija. The matter presented in this report has not been submitted by me for the award of any other degree of this or any other Institute/University.

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CERTIFICATE

I hereby certify that the Project Dissertation titled "**In silico study to determine the potential of Allium sativum to prevent Ischemic strokes**", which is submitted by Sanya Arora, 2K22/MSCBIO/44, Delhi Technological University Delhi, in partial fulfilment of the requirement for the award of the degree of Masters in Science, is a record of the project work carried out by the students under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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CERTIFICATE BY THE SUPERVISOR

Certified that Sanya Arora (2K22/MSCBIO/44) has carried out their search work presented in this thesis entitled " In silico study to determine the potential of Allium sativum to prevent Ischemic strokes " for the award of Master of Science from Department of Biotechnology, Delhi Technological University, Delhi, under my/our (print only that is applicable) supervision. The thesis embodies results of original work, and studies are carried out by the student herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

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ABSTRACT

Blood clots are the double-edged swords. They are extremely important to prevent bleeding events which can be fatal. But on the flip-side they are the reasons for deaths and disabilities due to strokes and heart attacks. Formation of a clot is a multistep process that involves a number of proteins and signaling molecules. Platelets, also call thrombocytes, are one of the major components of a blood clot. Thrombus is actually another term for clot. The Anti-platelets drugs, as the name suggests, interfere with the ability of platelets to form a clot and are prescribed for the treatment of acute ischemic strokes as well as myocardial infarction. Aspirin is one of the well-known examples of such drugs. Interestingly, *Allium sativum* commonly called as Garlic has shown to have numerous beneficial pharmacological properties such as antioxidant, anti-inflammatory, anti-atherosclerotic, antihypertensive, antidiabetic and even anticarcinogenic. Several studies have also demonstrated the anti-platelet activities of garlic extracts by inhibition of several proteins involved in platelet aggregation. The purpose of this study is to investigate the potential of phytochemicals from garlic to be used as a dietary supplement for preventing occurrence of stroke in high-risk patients. Molecular Docking and ADMET analysis were performed using various computational tools such as BioVia Discovery Studio, UCSF Chimera and PyRx Virtual Screening Tool, as well as web tools – SwissADME and Pro-Tox 3.0. Alliin was the one test ligand that had comparatively highest binding affinity with all the platelet membrane proteins. All the test ligands were comparatively less toxic than the control drugs. More research including in vivo experimentations and other downstream preclinical and clinical drug development procedures are required. Phytoconstituents in garlic definitely have potential to be used as natural supplements helping people live a healthier life.

ACKNOWLEDGEMENT

I'd like to express my heartfelt gratitude to everyone who assisted me in completing my thesis. Firstly, starting from my supervisor, Professor Yasha Hasija, for her guidance, mentorship and valuable insights and constant support. I would also like to thank all the professors from the Department of Biotechnology, Delhi Technological University, for their advice and constant assistance during my time at the university. I am also thankful to my senior PhD scholars Ms. Neha Kumari and Ms. Khushi Yadav for all their help and support.

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Thank you

Sanya Arora

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CHAPTER 1: INTRODUCTION

1.1 Strokes

Strokes, especially ischemic strokes, are one of the leading causes of mortality as well as disability worldwide. It was first considered as a cardiovascular disease but later was classified as a neurological disorder due to the nature of its symptoms [1]. Strokes are characterized by the obstruction of blood flow in the internal carotids or vertebral arteries that are responsible for supplying blood to the brain leading to neuronal death in less than 5 to 10 minutes due to lack of oxygen [1]. Stokes can be of two types –

1. *Hemorrhagic stroke*: As the name suggest hemorrhagic strokes are caused by the damaged or leaky blood vessels, may be due to congenital malformation or some other factors such as injury, that lead to a sudden onset of neurological deficits. The blood from ruptured cerebral vessels seeps into or around the brain tissue. Hemorrhagic strokes are of two types based on the location of blood accumulation – Intracerebral hemorrhage and subarachnoid hemorrhage [1].

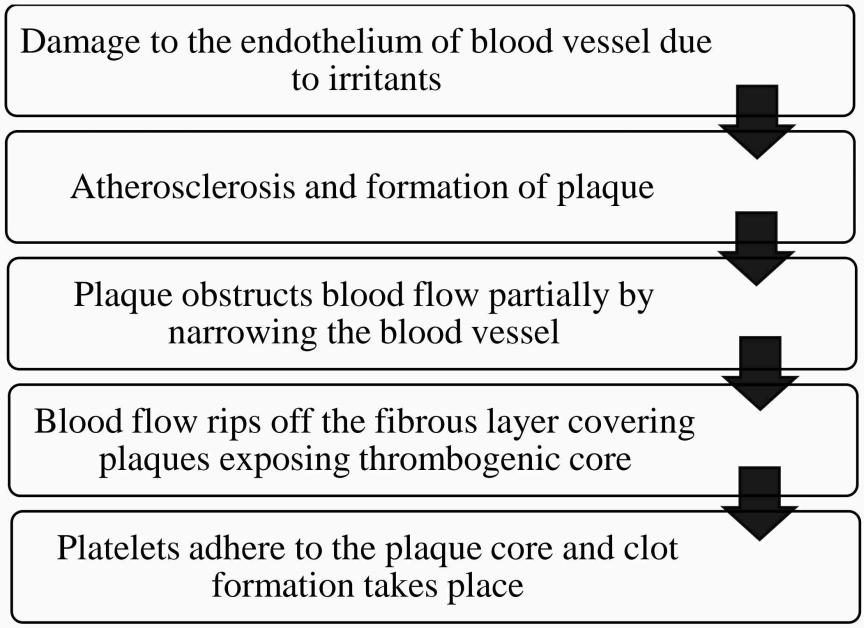
   The causes of non-traumatic Intracerebral hemorrhage may include hemostasis and coagulopathy in individuals with acquired or congenital coagulation factor deficiencies or platelet abnormalities. Therefore, treatment involves administering the absent factors or platelets [2]. When hemodynamic stresses are exerted on arterial walls it results in intracranial aneurysm which leads to accumulation of blood between the meninges -arachnoid and pia mater- the subarachnoid space, thus called subarachnoid hemorrhage. It often requires surgical interventions to prevent rebleeding and delayed cerebral ischemia (DCI). The medications such as antiepileptics, anticoagulants, antibiotics, pain control are given to provide symptomatic treatment [3].

2. *Ischemic stroke*: Ischemic stroke can either be caused by intravascular thrombosis or due to embolism. In thrombotic stroke arteriosclerotic plaque buildup in cerebral vessels obstructs the blood flow. On the other hand, when an already existing clot from the heart enters brain circulation and obstructs the blood flow it is called as Cardiogenic cerebral infarction (Cardioembolic stroke). The events in the thrombotic and cardioembolic stroke are explained in Fig.1a and Fig.1b respectively. Another reason for strokes are the lacunar infarcts developed as a result of hyaline arteriosclerosis making arterial wall thicker and reducing the size of lumen [4].

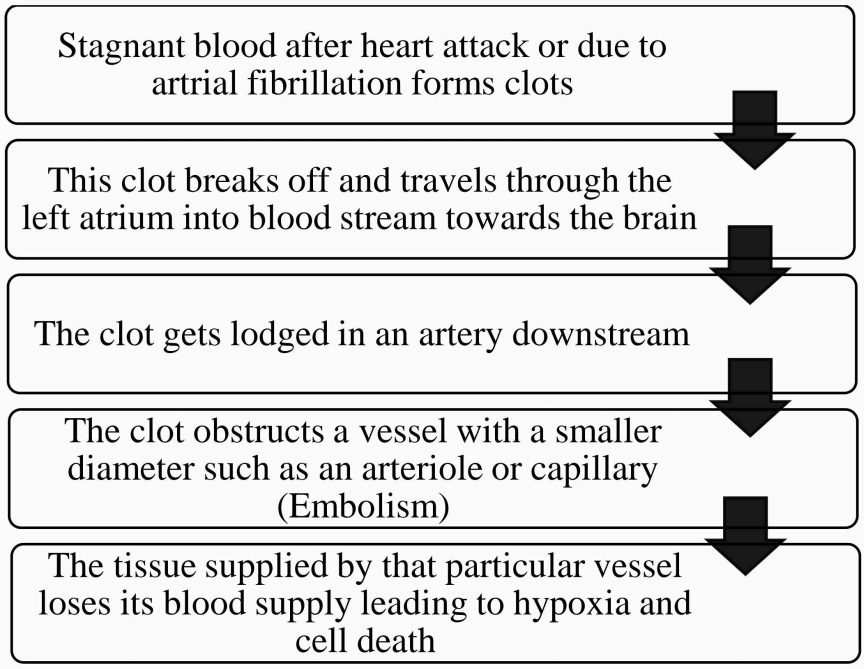
   The treatment involves bringing back blood flow to the affected regions in the brain (reperfusion) to prevent death of neurons in the ischemic penumbra and relieving the symptoms caused by the neurological damage in ischemic core. Ischemic core is the region where neuronal cells undergo necrosis due to hypoxia whereas the ischemic penumbra is the region surrounding the core where neurons are structurally intact however have lost their functionality. Such neurons remain viable for few hours due to hypoperfusion by collateral flow and the damage is reversible[5].

1.2 Currently available therapeutic strategies against Ischemic Strokes

FDA approved treatment for strokes is administration of Synthetic tissue Plasminogen Activators such as Tenecteplase and Alteplase intravenously within 3 to 4.5 hours of onset of stroke symptoms. Unfortunately, drawback of plasminogen activation is that it is associated with a significant risk of symptomatic hemorrhage [6]. To overcome these drawbacks, dual antiplatelet therapy is employed. Aspirin is administered in combination with clopidogrel as a standard care method. The findings from a number of clinical trials suggest that results from combination or dual-platelet therapy were better than results when given aspirin only with no significance increase in risk of hemorrhage. The risk of recurrent stroke was much lesser [6].



(a)



(b)

Fig.1 Mechanism of Ischemic strokes (a) Thrombotic (b) Cardioembolic

1.3 Garlic and its Medicinal Properties

Garlic (*Allium sativum*; Family: Amaryllidaceae) is a medicinal plant used in ayurvedic medicines. The medicinal properties of garlic have been authenticated at multiple incidences including in-vitro, in-vivo as well as in human clinical trials. It contains many sulfur containing compounds such as allicin, the most biologically active molecule in garlic, Alliin, that is the precursor of Allicin, Ajoenes, sulfides such as Diallyl trisulfide in abundance. Allicin was reported to have antibacterial, antifungal, antiprotozoal and antiviral properties against a number of pathogens [7]. Anti-oxidant and anti-hypertensive activities are attributed to Alliin. Inhibition of ACE and ACh were seen indicating its positive effect in hypertension and Alzheimer Disease respectively[7]. It prevents lipid accumulation and lipid peroxidation, reduces triglyceride levels and increases HDL levels as well. Diallyl Trisulfide has cardioprotective and anti-apoptotic activities [8].

Garlic has many direct and indirect effects leading to its anti-platelet and anti-coagulation properties. Compounds in garlic not only directly affect the platelet proteins inhibiting its activation, they pose some indirect effects such as enhancing production of Nitric oxide, preventing atherosclerosis and hyperlipidemia [7]. NO is released from endothelial cells and leads to vasodilation and it also stimulates the production of cGMP, which prevents the platelet plug formation [9].

Objective of this study

- To identify the phytochemicals from garlic having anti-platelet activity and analyze their drug likeness
- To investigate whether garlic can be a potential dietary supplement for protection against strokes.

CHAPTER 2: REVIEW OF LITERATURE

2.1 Hemostasis

Hemostasis is a biological phenomenon that repairs a bleeding blood vessel. There are three stages in hemostasis – Vasospasm, Platelet plug formation and coagulation [10]. In response to an injury the blood vessels get constricted (Vasoconstriction) to minimize the blood loss. The platelets come to the rescue and form a platelet plug that covers the injured area. Fibrin fibers attach to the platelets and further seal it creating what we call a clot. The detailed mechanism of the whole hemostasis is given in figure X in the form of a flowchart. A number of proteins, agonists and signaling molecules are involved in the process that are basis of antiplatelet or thrombolytic therapies. Aspirin which is one of the most well-known drugs acts by inhibiting COX1 responsible for converting Arachidonic acid into Prostaglandins. Arachidonic acid pathway is shown in figure 2. The downside is that Aspirin binds to its target irreversibly thereby having a longer duration of action or drug response.

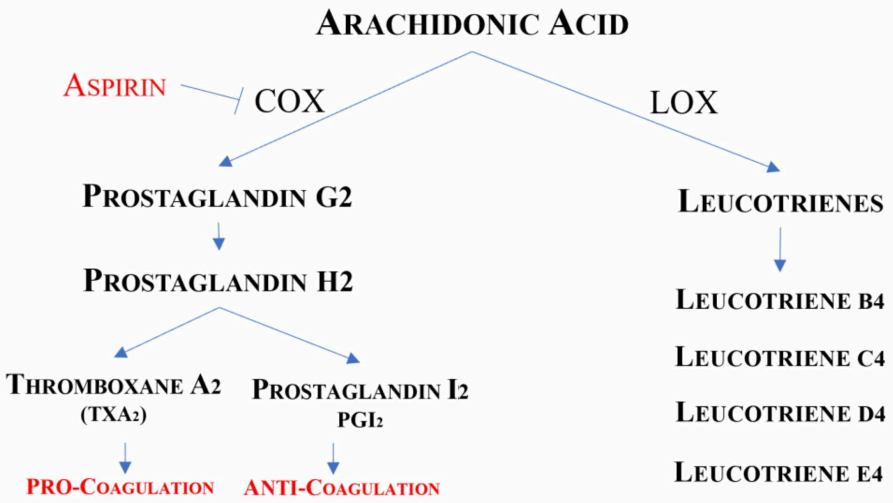


Fig. 2. Arachidonic Acid Pathway

Fig. 3. Flowchart of Hemostasis

2.2 Target Receptors for Platelet Activation and Aggregation Inhibition

a) Thromboxane A2 receptor

Thromboxane A2 receptor is a G-protein coupled receptor that binds Thromboxane A2. Thromboxane A2 is a metabolic product of arachidonic acid produced by action of enzyme thromboxane synthase on prostaglandin H2. It acts as an agonist and activates adjacent platelets during platelet plug formation thereby causing signal amplification. Major functions include platelet activation, shape change and degranulation which all occurs as a result of Gq pathway activation via Thromboxane A2 receptor [11]. The Gq pathway is illustrated in fig. X . Terutroban and Ridogrel are TP receptor agonists under clinical trials [12].

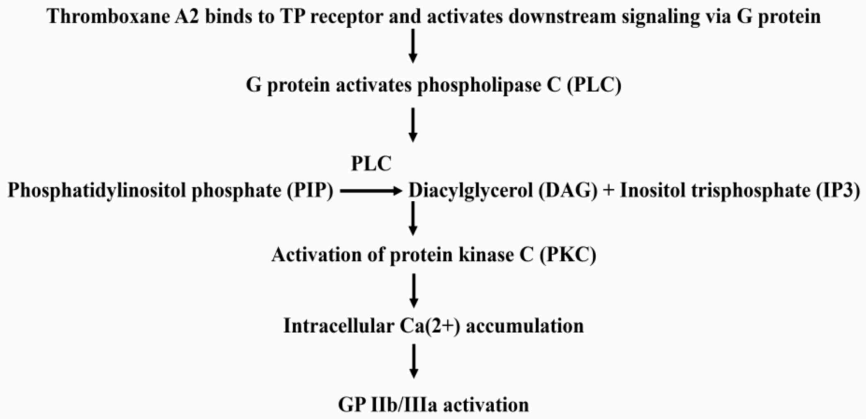


Fig. 4. Activation of G_q pathway leading to Platelet Activation

b) Glycoprotein IIb/IIIa fibrinogen receptor

Glycoprotein IIb/IIIa is a transmembrane receptor involved in adhesion of platelets to the fibrinogen. This protein requires to form disulfide bonds during its interaction with fibrinogen. Activation of this receptor leads to intracellular signaling events that further stabilize the growing thrombus. Small molecule drugs -eptifibatide and tirofiban are Glycoprotein IIb/IIIa blockers. 80% blockade of these receptors leads to complete inhibition of platelet aggregation [13].

c) ADP Receptors

ADP is released as a result of degranulation of platelets and acts on the purinergic receptors $P2Y_1$ and $P2Y_{12}$ which are also couple to Gq protein following the same pathway of platelet activation as the Thromboxane A2. $P2Y_{12}$ receptor is present almost exclusively on platelets and in abundance that makes it a suitable target for anti-thrombotic drugs [12]. The drugs clopidogrel and ticagrelor examples of drug that bind to P2Y12 receptor and are approved to be used in clinical settings [12], [13].

d) Thrombin Receptor

Thrombin receptors are called PAR (Proteinase Activated receptors). Around 1000 to 2000 PAR-1 receptors specifically, are present on the platelets that are involved in transient downstream signaling. Synergic interactions between these PAR and P2Y12 receptors further strengthens the platelet aggregation to make it stable [12]. Aspirin does not interfere with the thrombin mediated platelet aggregation. This makes this receptor an important target for potential antagonists. Vorapaxar is a reversible inhibitor of PAR-1 Receptors [12].

e) cAMP- specific Phosphodiesterase

The cAMP is an inhibitor of platelet aggregation as it activates cAMP dependent protein kinase which in turn mobilizes the calcium into the dense tubular system. With the unavailability of calcium in the cell cytosol, the activation of the glycoprotein IIb/IIIa fibrinogen receptor does not occur [14]. Adenylate cyclase and Phosphodiesterase are involved with cAMP regulation. Adenylate cyclase produce cAMP molecules and phosphodiesterase degrade it. During platelet aggregation Adenylate cyclase enzyme is inhibited by Gi protein thus unable to produce any cAMP molecules. cAMP-specific phosphodiesterase breaks down the cAMP molecules helping in platelet aggregation[15]. The drug Roflumilast is a cAMP PDE inhibitor undergoing clinical trials to be used in the treatment of COPD [16].

2.3 Inhibitory effects of Aged Garlic Extracts on Platelet aggregation

Findings from a study conducted by Rahaman et.al indicates the inhibitory effects of aged garlic extract (AGE) in platelet aggregation. Inability for the platelet to change shape was attributed to decreased fibrinogen binding as well as inhibition of reorganization of cytoskeleton, mainly actin. Inhibitory effect of AGE on PDE was also observed [9].

G.L. Allison et al also suggested that AGE inhibits platelet aggregation by inhibiting cAMP Phosphodiesterase thereby increasing cellular cAMP levels. Increased cAMP concentration causes a decrease in calcium immobilization which in turn subdues the interaction between Glycoprotein IIb/IIIa and Fibrinogen. Even the ADP activated platelets were inhibited due to AGE treatment. They also suggested that AGE as a dietary supplement might have positive effects on cardiovascular diseases [14].

About two decades ago Rahman et al. proposed that garlic can be used as a dietary supplement for cardioprotection as it inhibits platelet aggregation through a 13-week long study. Subjects were given aged garlic extract as supplement. Blood was drawn to observe platelet aggregation induced by ADP. Both the total percentage and initial rate of platelet aggregation were inhibited and Km for ADP induced aggregation was doubled [17].

CHAPTER 3: MATERIALS AND METHODOLOGY

3.1 Retrieval and Preparation of Protein

PDB files of four of the platelet membrane proteins, that are, (a) Thromboxane A2 receptor (PDB ID: 6IIV), (b) Membrane Glycoprotein IIb/IIIa (PDB ID: 3FCU), (c) ADP receptor (purinergic receptor) (PDB ID: 4PY0) (d) Thrombin receptor (PDB ID: 3VW7) and (d) cAMP-specific Phosphodiesterase (PDB ID: 1XLX) were retrieved from RCSB PDB (https://www.rcsb.org/) and downloaded in PDB format. The proteins were prepared for docking using BIOVIA Discovery Studio v21.1.0.20298 (http://accelrys.com/products/collaborative-science/biovia-discovery-studio/) by getting rid of water molecules, heteroatoms, ligands etc. from the protein structure while adding polar hydrogen. 3-D structures of the proteins are shown in Fig.5.

3.2 Retrieval and selection of Phytochemical Ligands

A library of 58 phytochemicals from the bulb of *Allium sativum* or Garlic were obtained from IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) (https://cb.imsc.res.in/imppat/), a database for phytochemicals of Indian medicinal plants. Most abundant phytochemicals were selected and were subjected to ADME and toxicological analysis. Swiss ADME server [18] was used to predict the Pharmacokinetic (ADME) properties of the molecule and the toxicological analysis was performed using the ProTox-II online tool [19]. Only the molecules that were able to cross the Blood Brain Barrier were selected for further toxicological assessment. This is because neuroactive drugs are required to cross the BBB to have their effect. Three molecules - Alliin, Allicin and Diallyl trisulfide which were abundant, BBB permeable and non-carcinogenic were shortlisted. 3D structures of these ligands were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the files were saved in .sdf format. UCSF Chimera v1.17.3 [20] software was used to converted .sdf files to .pdb format. The structures of these ligands are shown in Fig. 6 and Fig 7.

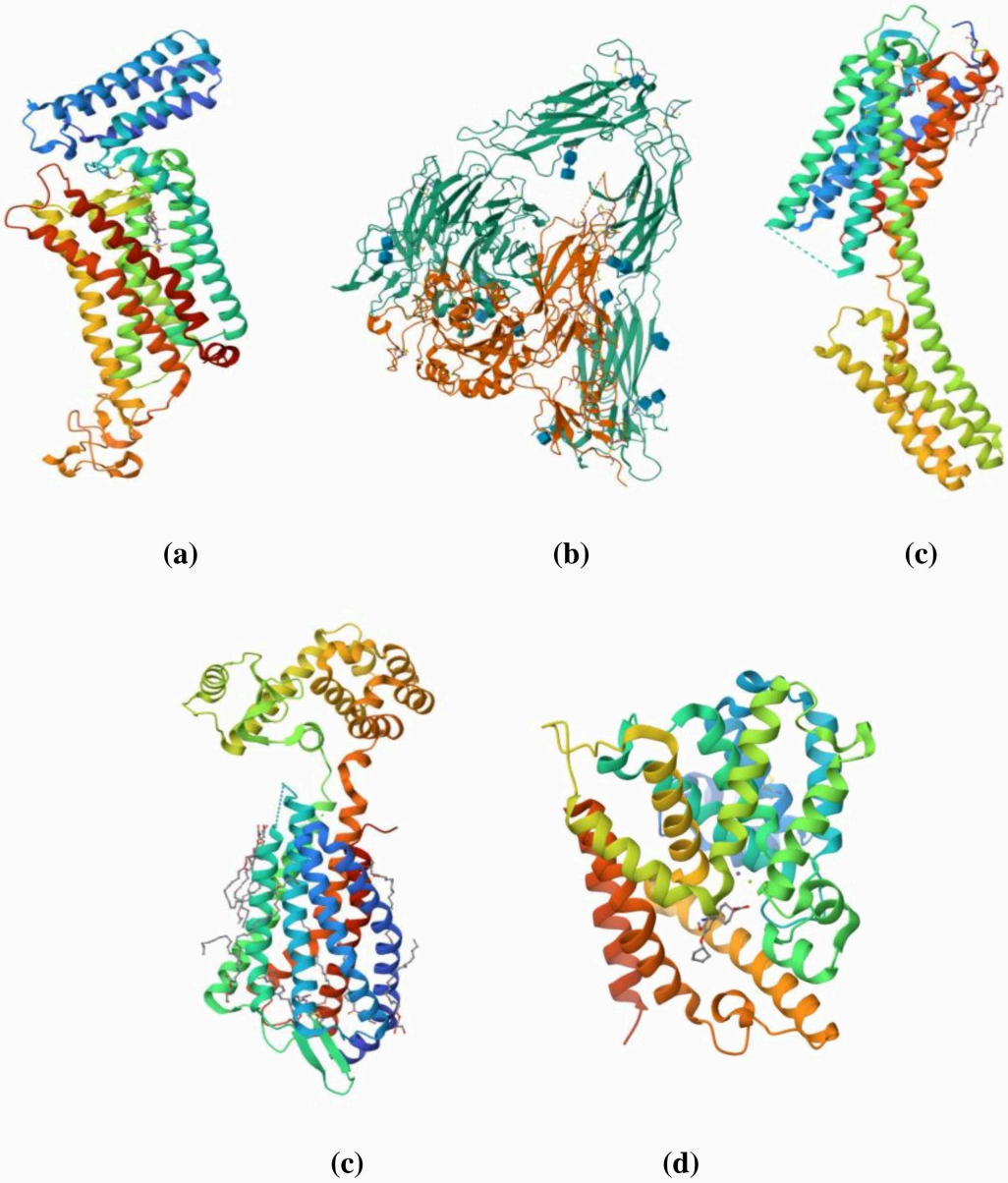
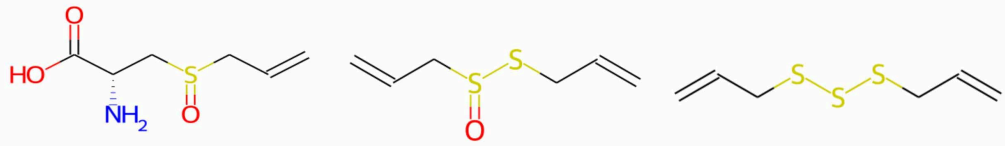
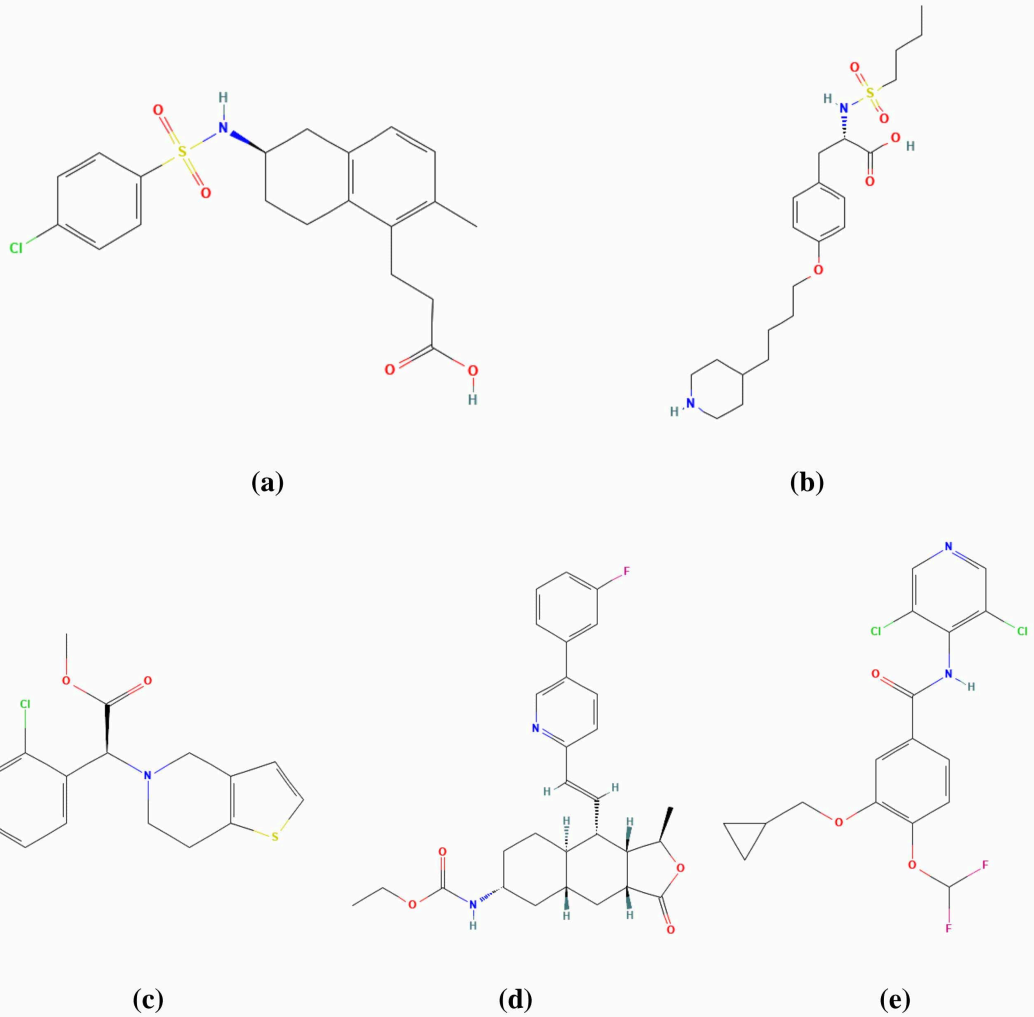


Fig.5. Structures of Platelet Membrane proteins. (a) Thromboxane A2 receptor (PDB ID: 6IIV), (b) Membrane Glycoprotein IIb/IIIa (PDB ID: 3FCU), (c) ADP receptor (purinergic receptor) (PDB ID: 4PY0) (d) Thrombin receptor (PDB ID: 3VW7) and (d) cAMP-specific Phosphodiesterase (PDB ID: 1XLX)



(a) (b) (c)

Fig.6. Structures of Phytochemicals of Allium Sativum obtained from IMPPAT



(a) (b)

(c) (d) (e)

Fig.7. Control Ligands (a) Terutroban (b) Tirofiban (c) Clopidogrel (d) Vorapaxar (e) Roflumilast

3.3 Molecular Docking using PyRx

Molecular Docking in an in-silico method that enables predicting receptor-ligand interactions. It aids in drug discovery by allowing the identification of novel compounds of therapeutic interests. First step is to predict the best fit molecular orientation of a ligand within a receptor followed by estimating their binding affinity using a scoring function [21]. PyRx Virtual screening tool that allows for multiple ligand docking was used for molecular docking experiment. The steps are mentioned in Fig.8.

Protein grids were prepared according to x: 16.82, y: 154.11, z: 137.51 for 6IIV, x: -28.21, y: 330.41, z: 27.98 for 3FCU, x: -2.92, y: -7.13, z: 27.06 for 3VW7 x: -1.37, y: -11.84 z: -12.84 for 4PY0 and x: 2.06, y: 2.62, z: 1.44 for 1XLX as centers for covering the entire protein for blind docking. After completion of Docking, the most compatible protein-ligand docked complex model (with best binding affinity and RMSD value 0) was saved in PDB format to be visualized.

3.4 Visualization of Docked complexes using BIOVIA Discovery Studio

The analysis of interactions and visualization of the protein-ligand docked complexes was carried out using BIOVIA Discovery Studio wherein the Binding sites and types of interactions were observed. The PDB file of most compatible ligand-receptor complex obtained from PyRx was pasted on the protein to locate the binding sites.

3.5 ADME and Toxicological Analysis

Swiss ADME and ProTox web tools were utilized for pharmacological and toxicological analysis of the selected ligands. Pharmacological properties of the ligands such as solubility (Log S), lipophilicity (Log Po/w); Pharmacokinetic properties (absorption in the GI tract, Blood Brain Barrier penetration) and Drug likeness (Lipinski's rule of violation and Bioavailability Score) was examined followed by a toxicological assessment to predict the toxicity of the compounds in biological system. Analysis was done on the basis of all the parameters given in table 5.

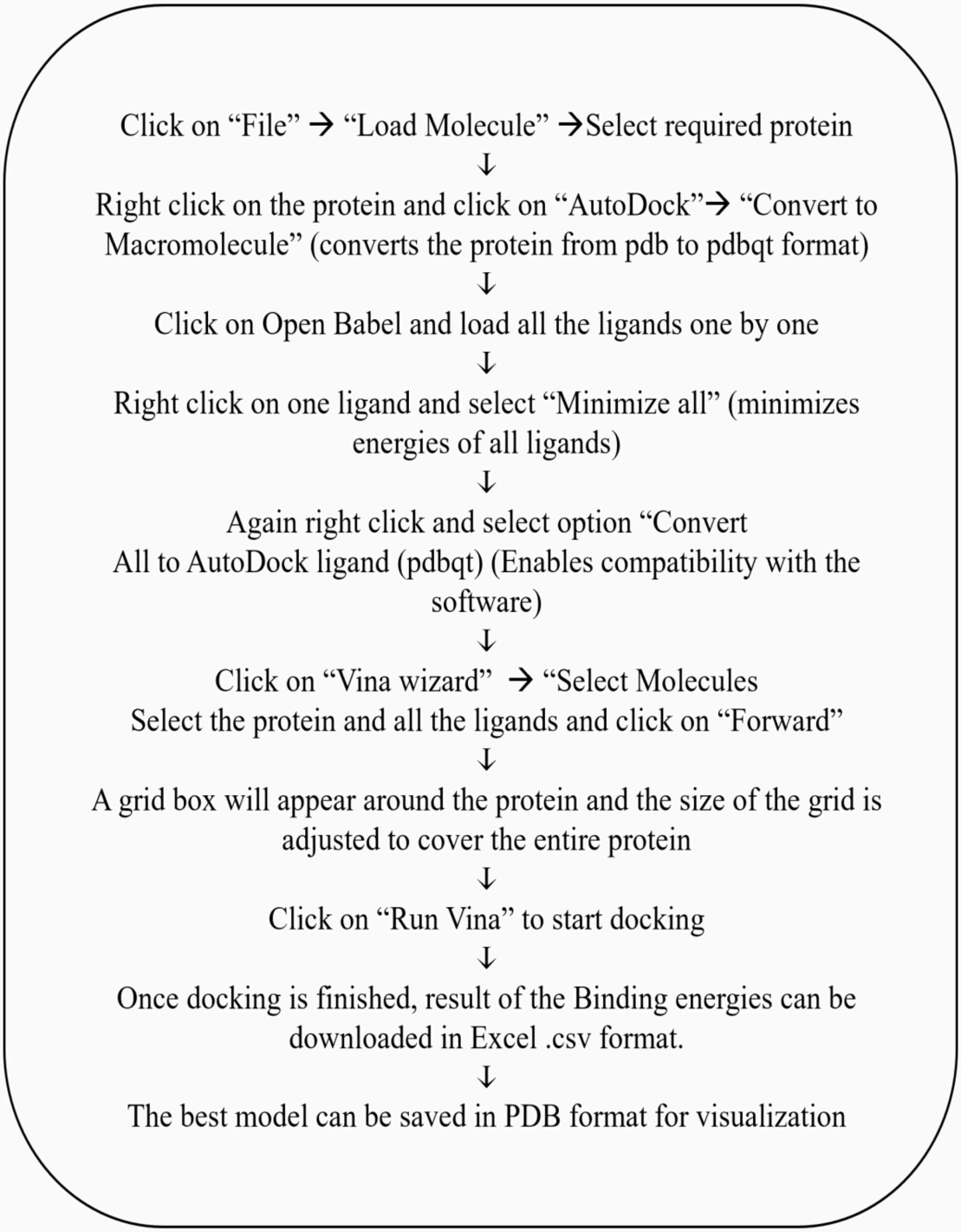


Fig.8. Workflow of Docking Steps using PyRx Virtual Screening tool

CHAPTER 4: RESULTS AND DISCUSSIONS

4.1 Molecular Docking Analysis

Molecular docking of all the five proteins with their respective controls all the three phytochemical ligands was performed using PyRx and the results were analyzed using BIOVIA discovery studio. Alliin displayed highest binding affinity with all five proteins as compared to other phytochemicals. However, the binding affinity was lesser as compared to the control ligands in each case. The binding affinity results are shown in Table. 1 and Binding sites along with type of interaction is shown in Table 2.

Thromboxane A2 receptor- Allin complex had a binding affinity of -4.8 kcal/mol with binding interaction with 4 residues out of which one is conventional hydrogen bond. However, binding affinity was higher with the control, that is, -7.8 kcal/mol with 2 conventional hydrogen bonds. Membrane glycoprotein IIb/IIIa-Alliin complex showed a binding affinity of -4.7 kcal/mol while with control, Terutroban, it was -7.6 kcal/mol. There were four conventional hydrogen bonds between receptor and alliin. Ligand binding site lies in the VWFA domain (135-377) where alliin had bound. Phytoconstituents of garlic are rich in sulfur containing compound that interfere with the binding of fibrinogen and Glycoprotein IIb/IIIa since their interaction requires disulfide linkages.

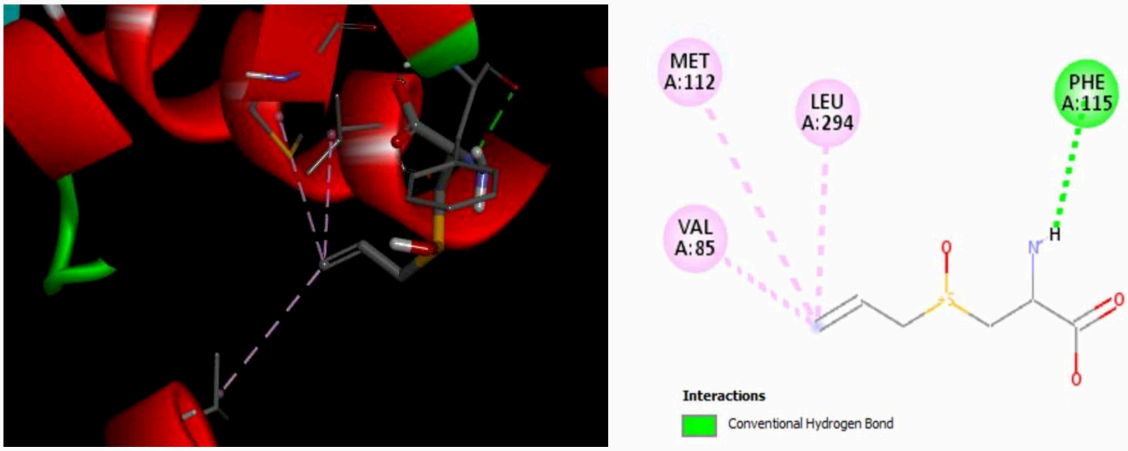
Alliin bound to the ADP receptor with an affinity of -5.2 kcal/mol pretty much comparable to -6.2 kcal/mol that was the affinity between receptor and control. There were 5 conventional hydrogen bonds between receptor and alliin. Alliin had bound to seven residues in ADP receptor out of which 5 were ADP binding sites. The binding interaction of Alliin with Thrombin receptor was via only two binding residues and both were conventional hydrogen bonds, however both were in the ligand binding domain. The binding affinity was -4.9 kcal/mol with alliin and -10.9 kcal/mol with Vorapaxar. cAMP-PDE-Alliin complex had binding affinity of -5.3 kcal/mol and between receptor and control it was -9 kcal/mol. The PDE activity lies between residues 330-659 an alliin had three binding sites in this region.

Ligand	Protein	PDB ID	Binding Affinity (kcal/mol)
Alliin Allicin Diallyl Trisulfide Terutroban (Control)	Thromboxane A2 Receptor	6IIV	-4.8 -4.1 -3.5 -7.8
Alliin Allicin Diallyl Trisulfide Tirofiban (Control)	Membrane Glycoprotein IIb/IIIa	3FCU	-4.7 -4.1 -3.5 -7.6
Alliin Allicin Diallyl Trisulfide Clopiodogrel (Control)	ADP receptor	4PY0	-5.2 -3.7 -3.3 -6.2
Alliin Allicin Diallyl Trisulfide Vorapaxar (Control)	Thrombin receptor	3VW7	-4.9 -4.2 -3.6 -10.9
Alliin Allicin Diallyl Trisulfide Roflumilast (Control)	cAMP- specific Phosphodiestrase	1XLX	-5.3 -4.2 -3.7 -9

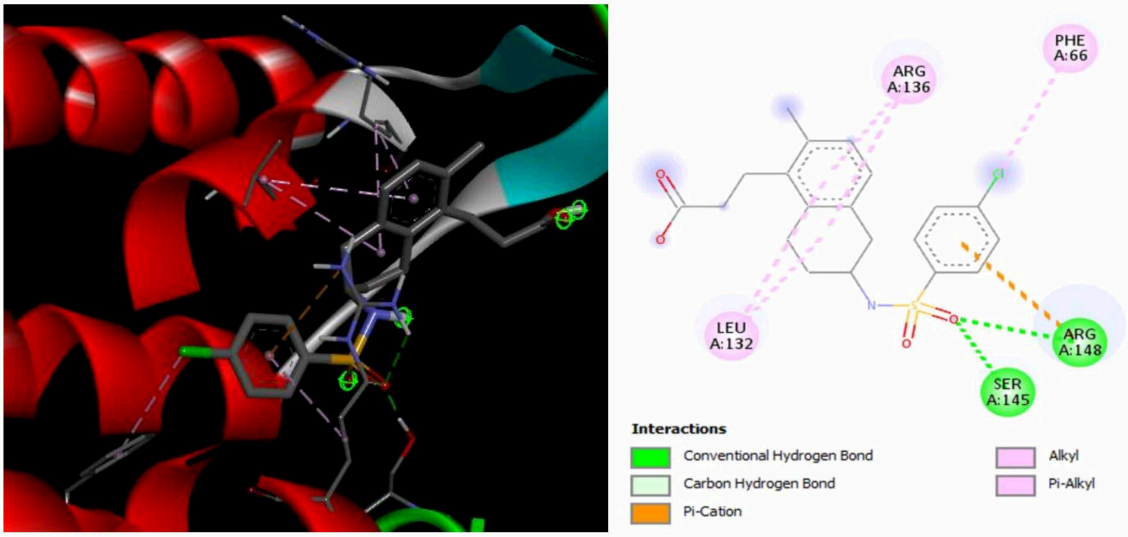
Table 1. Molecular Docking Results

Protein	Thromboxane A2 Receptor		Membrane Glycoprotein IIb/IIIa		ADP Receptor		Thrombin Receptor		cAMP-specific PDE	
Ligand	**Alliin**	**Terutroban**	**Alliin**	**Tirofiban**	**Alliin**	**Clopidogrel**	**Alliin**	**Vorapaxar**	**Alliin**	**Roflumilast**
Binding residues	VAL 85	PHE 66	PRO268	TYR122	CYS97	CYS97	LEU258	LEU332	TYR233	HIS234
	MET112	LEU132	ASN269	SER123	SER101	TYR105	TYR350	HIS336	HIS238	ASN395
	PHE115	ARG136	SER291	PHE160	VAL102	CYS175		LEU340	ASP275	TRP406
	LEU294	SER145	TYR353	TYR190	TYR105	LYS179		ALA349	ASP392	ILE410
		ARG148	ARG355	ARG214	ASN159	VAL190		ALA352	ILE410	MET431
			TYR380	ASN215	LYS179	CYS194		TYR353	PHE446	GLN443
				ALA218	HIS187	ARG256				PHE446
				ASP224						
				SER225						
				PHE231						

Table 2. Binding Site Analysis

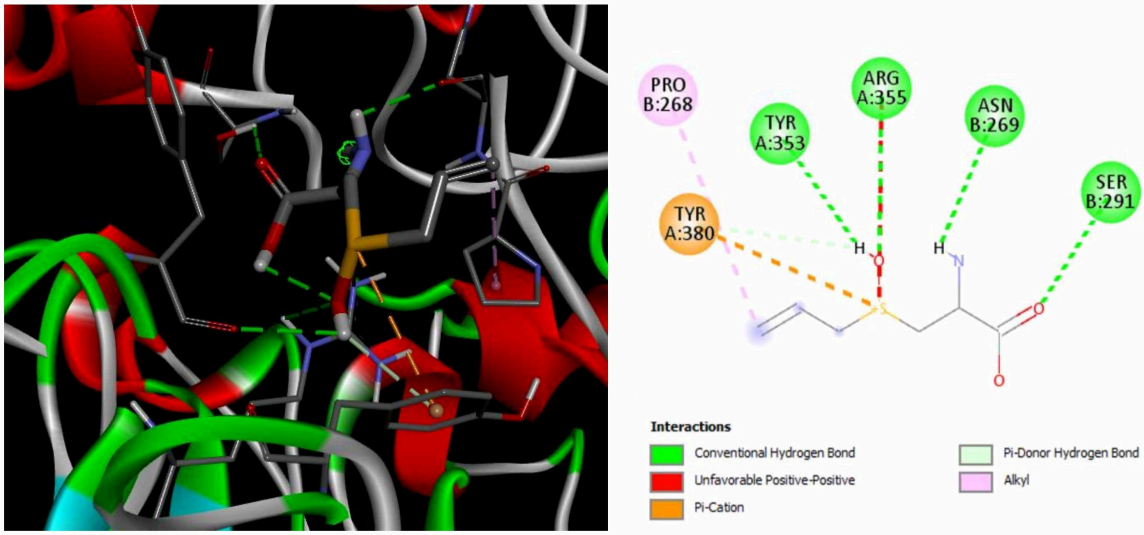


6IIV with Alliin

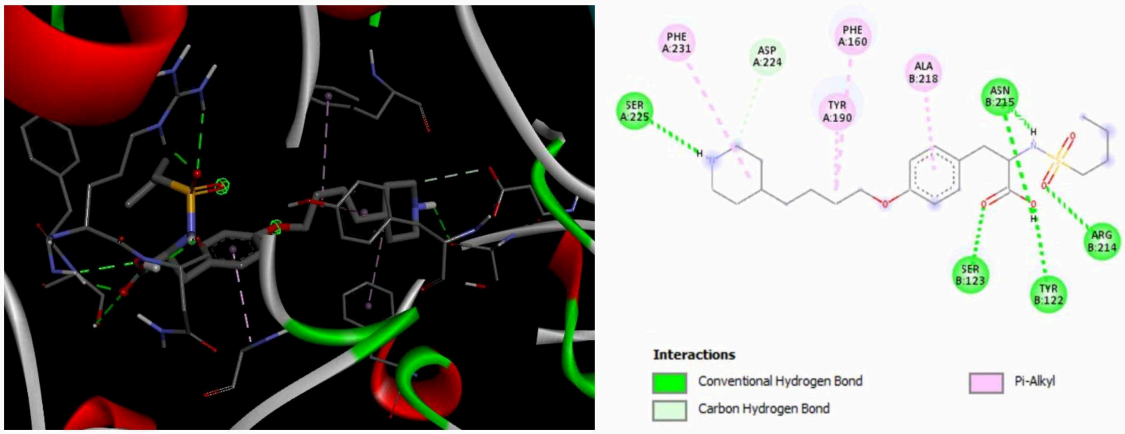


6IIV with Terutroban (Control)

Fig.9. 3-D and 2-D Thromboxane A2 receptor-Alliin and Thromboxane A2 receptor-Terutroban docked complexes visualized using Biovia Discovery Studio

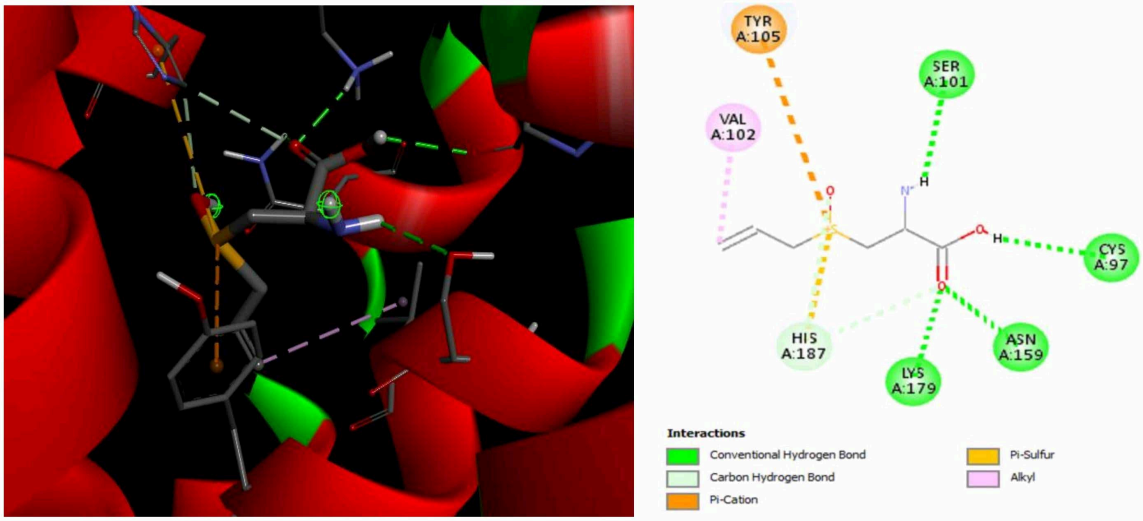


3FCU with Alliin

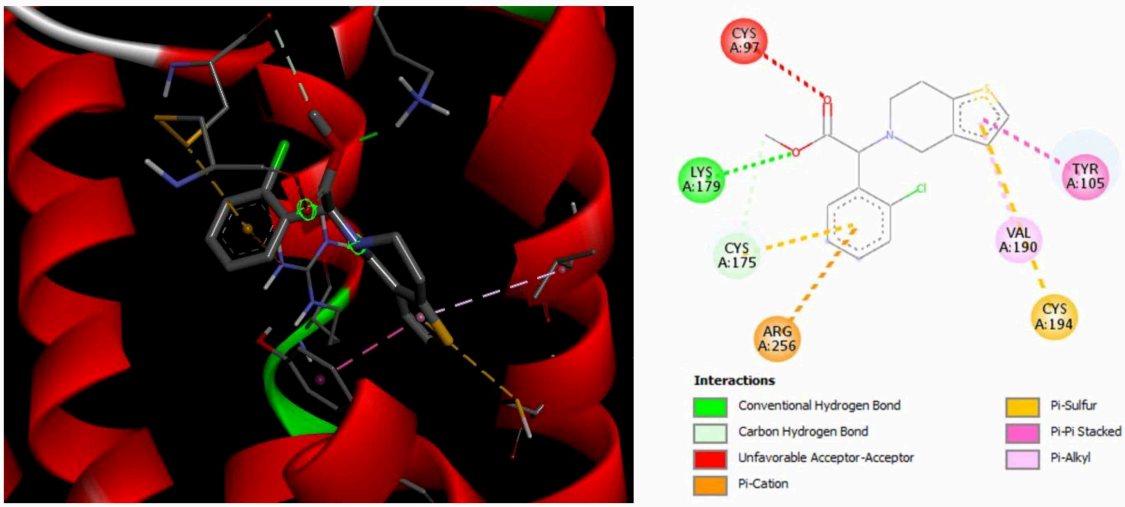


3FCU with Tirofiban (Control)

Fig.10. 3-D and 2-D Membrane Glycoprotein IIb/IIIa receptor-Alliin and Membrane Glycoprotein IIb/IIIa receptor-Tirofiban docked complexes visualized using Biovia Discovery Studio

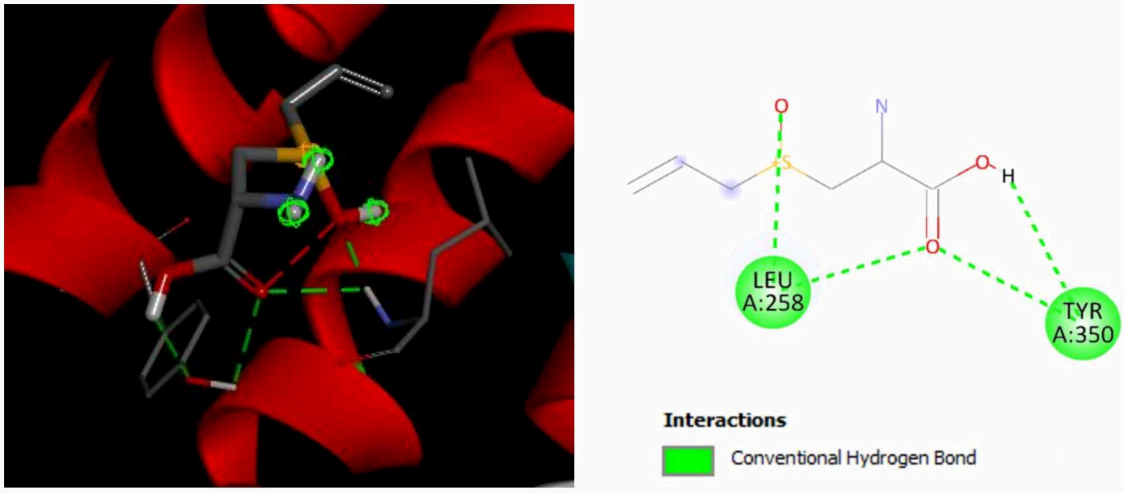


4PY0 with Alliin

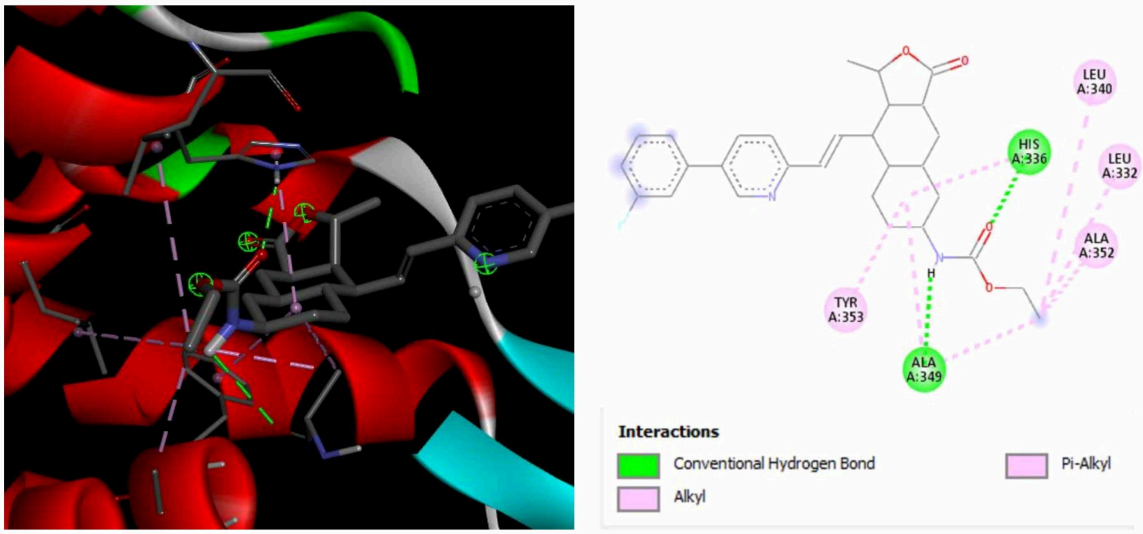


4PY0 with Clopidogrel (Control)

Fig.11. 3-D and 2-D ADP receptor-Alliin and ADP receptor-Clopidogrel docked complexes visualized using Biovia Discovery Studio

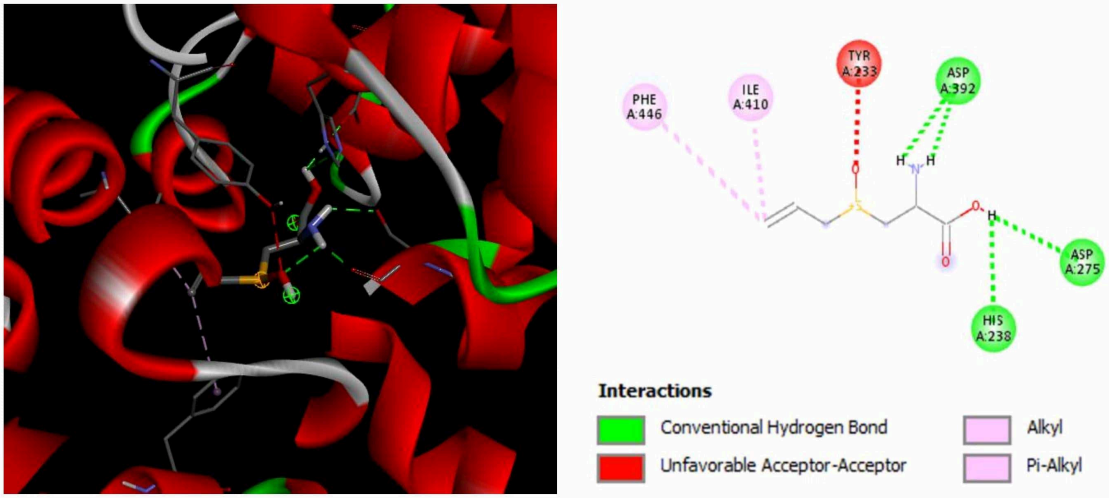


3VW7 with Alliin

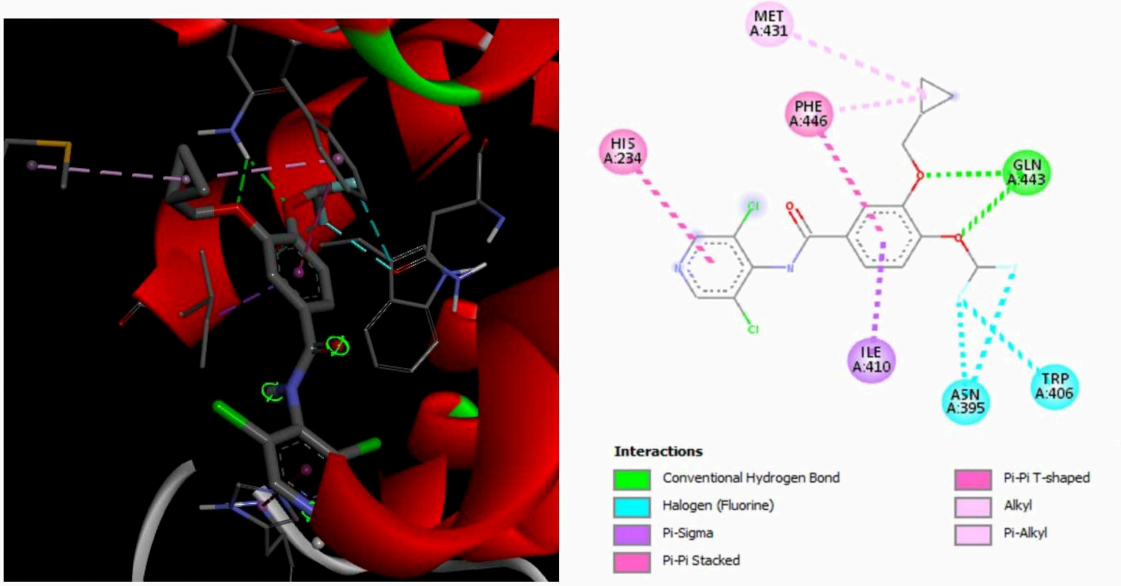


3VW7 with Vorapaxar (Control)

Fig.12. 3-D and 2-D Thrombin receptor-Alliin and Thrombin receptor-Vorapaxar docked complexes visualized using Biovia Discovery Studio



1XLX with Alliin



1XLX with Roflumilast (Control)

Fig.13. 3-D and 2-D cAMP specific PDE-Alliin and cAMP specific PDE receptor-Roflumilast docked complexes visualized using Biovia Discovery Studio

5.2 ADME and Toxicological Analysis

For ADME pharmacological analysis, Water solubility, lipophilicity, pharmacokinetics (GI Absorption, BBB Permeability) and drug likeness (Lipinski's Violations, Bioavailability) were estimated for all the test and control ligands. The results are presented in Table 3. All of the ligands except for alliin were lipophilic. All of them had high GI Absorption and followed the Lipinski rule of 5 that determines whether the drug is fit to be orally active or not. It undertakes four parameters- Molecular weight (less than 500 Da), Log of partition coefficient or Lipophilicity (less than 5) and number of Hydrogen bond donors and acceptors (less than 5 and 10 resp.)[22]. Bioavailability was also almost similar for test and control ligands.

However, only one of the control ligands, Clopidogrel, was BBB permeable. This means only clopidogrel can cross the blood brain barrier to be neuroactive and prevent the formation of clot that might cause a thrombotic stroke.

Pharmacological Analysis						
Ligand	**Water Solubility (LogS)**	**Lipophilicity (Log Po/w)**	**Pharmacokinetics**		**Drug- Likeness**	
			GI Absorption	**BBB Permeant**	**Lipinski Violation**	**Bioavailability Score**
Alliin	1.62	-1.33	High	Yes	0	0.55
Allicin	-1.34	1.61	High	Yes	0	0.55
Diallyl Trisulfide	-2.21	2.68	High	Yes	0	0.55
Terutroban	-4.85	3.64	High	No	0	0.56
Tirofiban	-2.7	2.13	High	No	0	0.55
Clopidogrel	-4.32	3.5	High	Yes	0	0.55
Vorapaxar	-6	4.89	High	No	0	0.55
Roflumilast	-5.04	4.17	High	No	0	0.55

Table 3. ADME Analysis of the test and control ligands

Toxicological Analysis was done with all the parameters given on the Pro-Tox tool. Toxicological report of Alliin is shown in Table 5 showing all the parameters as example. The phytochemicals were comparatively a lot safer and less toxic than the controls. Toxicity class was determined- 1 being most toxic and 6 being least one. The results are shown in table X. Alliin was found to be class 6 toxic with LD50 of 8000mg/kg. Such high LD50 shows that drug might cause lethality when taken at much higher dose. It had shown slight chances of respiratory and cardiotoxicity. Allicin was class 4 toxic with LD50 of 874mg/kg and had shown probable binding to Cytochrome CYP29 that is an isoform of drug-metabolizing cytochrome P450 (CYP450) enzyme [23]. Diallyl Trisulfide was predicted to be the most toxic among all the three phytochemicals having class 3 toxicity with possible interference with p53 and Cytochrome CYP29.

Among the controls Vorapaxar that binds to the thrombin receptor was most toxic with highest molecular weight, 492.58, class 2 toxicity, LD50 OF 9mg/kg which is extremely low. It was also predicted to have possible Neurotoxicity, Nephrotoxicity, Respiratory toxicity, Immunotoxicity and Clinical toxicity with probable binding to CYP2C9 and CYP3A4. Other controls were also predicted for having organ toxicities where Roflumilast even showed a probability score of 0.57 for carcinogenicity. Clopidogrel was highly probable to cause Neurotoxicity (probability score 0.92) and Respiratory toxicity (probability score 0.95). Vorapaxar was immunotoxic with 0.99 probability score which is concerning.

Toxicological Analysis					
Ligand	**Mol. Wt.**	**LD 50 (mg/kg)**	**Toxicity Class**	**Type of Toxicity**	**Probability**
Alliin	177.22	8000	6	Respiratory Toxicity	0.61
				Cardiotoxicity	0.59
Allicin	162.27	874	4	Cytochrome CYP29	0.59
Diallyl Trisulfide	178.34	100	3	p53	0.65
				Cytochrome CYP29	0.67
Terutroban	407.91	2500	5	Nephrotoxicity	0.56
				Respiratory toxicity	0.65
				Cardiotoxicity	0.51
				Clinical toxicity	0.6
				Cytochrome CYP2C9	0.68
Tirofiban	440.6	1503	4	Clinical toxicity	0.61
				Respiratory toxicity	0.73
Clopidogrel	321.82	1914	4	Neurotoxicity	0.92
				Respiratory toxicity	0.95
				Clinical toxicity	0.58
				CYP2C19	0.50
				CYP2C9	0.66
				CYP2D6	0.82
Vorapaxar	492.58	9	2	Neurotoxicity	0.65
				Nephrotoxicity	0.68
				Respiratory toxicity	0.76
				Immunotoxicity	0.99
				Clinical toxicity	0.63
				CYP2C9	0.63
				CYP3A4	0.63
Roflumilast	403.21	2000	4	Hepatotoxicity	0.51
				Neurotoxicity	0.69
				Respiratory toxicity	0.85
				Carcinogenicity	0.57
				Immunotoxicity	0.84
				Clinical toxicity	0.68
				Mitochondrial Membrane Potential (MMP)	0.53
				Achetylcholinesterase	0.51
				Cytochrome CYP2C9	0.63
				Cytochrome CYP3A4	0.52

Table 4. Toxicity Report of all the ligands

Prediction of Toxicity of Alliin			
Classification	**Target**	**Prediction**	**Probability**
Organ toxicity	Hepatotoxicity	Inactive	0.76
	Neurotoxicity	Inactive	0.68
	Nephrotoxicity	Inactive	0.59
	Respiratory toxicity	Active	0.61
	Cardiotoxicity	Active	0.59
Toxicity end points	Carcinogenicity	Inactive	0.62
	Immunotoxicity	Inactive	0.99
	Mutagenicity	Inactive	0.72
	Cytotoxicity	Inactive	0.58
	BBB-barrier	Active	0.55
	Ecotoxicity	Inactive	0.65
	Clinical toxicity	Inactive	0.52
	Nutritional toxicity	Inactive	0.6
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	Inactive	0.97
	Androgen Receptor (AR)	Inactive	0.93
	Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive	0.95
	Aromatase	Inactive	0.99
	Estrogen Receptor Alpha (ER)	Inactive	0.84
	Estrogen Receptor Ligand Binding Domain (ER-LBD)	Inactive	0.94
	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	Inactive	0.94
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Inactive	0.96
	Heat shock factor response element (HSE)	Inactive	0.96
	Mitochondrial Membrane Potential (MMP)	Inactive	0.97
	Phosphoprotein (Tumor Supressor) p53	Inactive	0.95
	ATPase family AAA domain-containing protein 5 (ATAD5)	Inactive	0.97
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	Inactive	0.90
	Thyroid hormone receptor beta (THRβ)	Inactive	0.78
	Transtyretrin (TTR)	Inactive	0.97
	Ryanodine receptor (RYR)	Inactive	0.98
	GABA receptor (GABAR)	Inactive	0.96
	Glutamate N-methyl-D-aspartate receptor (NMDAR)	Inactive	0.92
	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	Inactive	0.97
	Kainate receptor (KAR)	Inactive	0.99
	Achetylcholinesterase (AChE)	Inactive	0.76
	Constitutive androstane receptor (CAR)	Inactive	0.98
	Pregnane X receptor (PXR)	Inactive	0.92
	NADH-quinone oxidoreductase (NADHOX)	Inactive	0.97
	Voltage gated sodium channel (VGSC)	Inactive	0.95
	Na+/I- symporter (NIS)	Inactive	0.98
Metabolism	Cytochrome CYP1A2	Inactive	0.99
	Cytochrome CYP2C19	Inactive	0.97
	Cytochrome CYP2C9	Inactive	0.80
	Cytochrome CYP2D6	Inactive	0.79
	Cytochrome CYP3A4	Inactive	0.98
	Cytochrome CYP2E1	Inactive	0.93

Table 5. ProTox Report of Alliin

CHAPTER 6: CONCLUSION AND FUTURE SCOPE

One of the largest medical issues we face today is strokes and its related complications due to the prevalence of unhealthy lifestyles. Hypertension, hyperlipidemia and diabetes are the risk factors for strokes. Cigarette smokers are found to have an increase in platelet aggregation and adhesiveness as well as increased fibrinogen concentrations[9]. The current treatment strategies aim to preserve the functioning of brain tissue by maintaining cerebral blood flow and reperfusing the penumbra as well as reducing the risk of a second event [6]. Moreover, treatment using tPA is time-sensitive and patients with delayed presentation of symptoms out of treatment window are not eligible for treatment with thrombolytics. In such cases, antiplatelet therapy is the safest option for treatment and prevention of recurrent strokes [6].

Medicinal plants are less toxic-safer alternative sources of pharmacological molecules which are being used to treat ailments and stay healthy since centuries. Discovering such phytochemicals that might have the potential to prevent and even cure diseases is of utmost importance. Increasing drug resistance is alarming and requires more potential alternatives. Garlic is one such potentially amazing therapeutic herb that has several pharmacological actions against a broad range of diseases. Many clinical trials and in vitro studies have demonstrated the positive effects of garlic in many diseased conditions. This study demonstrates how the currently available drugs and drugs in clinical trials for strokes are toxic as compared to the natural phytoconstituents from garlic which are also active pharmacological molecules against the same receptors. However, the binding affinity was lesser as compared to synthetic controls. Therefore, I propose using phytoconstituents of garlic to prepare a supplemental formulation that would help prevent not only strokes but also a variety of other diseases. More pharmacological studies as well as lead optimization procedures are required to increase the binding affinities and understand their effects.

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Ms Sanya Arora

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Dear Author,

It is our pleasure to inform you that your paper entitled **Assessing the Potentiality of Natural Inhibitors from Nuphar Lutea against Nipah Virus through Molecular Docking** (Paper Id: ICMMSE-50) has been accepted for Virtual oral paper presentation at ICAAIML-2024 on 30th and 31st August 2024 and the paper has been accepted for publication in WoS and **SCOPUS** indexed journal ***AIP Conference Proceedings*** (e-ISSN No. 1551-7616).

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We are looking forward to your participation at the conference.

Thanks and Regards,

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ICMMSE 2024

Assessing the Potentiality of Natural Inhibitors from Nuphar Lutea against Nipah Virus through Molecular Docking

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ABSTRACT: In 2023 the Kozhikode district of Kerala, a zoonotic virus with a high mortality rate (40%-70%) infected six people and took two lives. And the downside is that there is no approved medicine against this virus. This offender is Nipah Virus, a 40nm – 1900nm virus of paramyxoviridae family named after village of Sungai Nipah in Malaysia where it was first discovered in 1999. It is endemic to Southeast-Asia and Western Pacific specially Bangladesh and India. The natural reservoir of Nipah Virus are the Fruit bats which can transmit the infection to both humans and animals. In this paper we conducted an in-silico assessment of the ability of 6-hydroxythiobinupharidine, 6-hydroxythiobinuphlutine B and 6,6′-hydroxythiobinupharidine to inhibit Nipah Virus Phosphoprotein. The study made use of a number of computational tools, including BioVia Discovery Studio, Auto dock Tools, UCSF Chimera and PyRx Virtual Screening Tool. The results revealed that all the three ligands were potent inhibitors of Phosphoprotein with docking score of -8.7 kcal/mol, -8.5 kcal/mol and -8.4 kcal/mol, respectively, which is better than that of the standard control Ribavirin (-5.9kcal/mol). We have also explicated the roles of various viral proteins of Nipah Virus in its pathogenicity and infection process to try to determine the likelihood of preparing efficient inhibitors against them.

KEYWORDS: Nipah Virus, Molecular Docking, *Nuphar lutea*, Natural inhibitors, Phytochemicals.

I. INTRODUCTION

Nipah virus (NiV) is a bat-borne zoonotic virus belonging to the genus Henipavirus of the family paramyxoviridae that can cause severe respiratory infection as well as lethal encephalitis (swelling of brain) in humans[1] . The initial symptoms of NiV infection may include headache, fever, sore throat, dizziness which can subsequently progress to pulmonary infection and neurological conditions like acute encephalitis followed by death in some critical cases[2]. It is either transmitted from infected pigs to humans (Malaysia outbreak) or directly from fruit bats, that are the natural reservoir of NiV, to both humans and animals due to consumption of fruits or juice like date palm sap contaminated with the urine or saliva of bat (As happened in India and Bangladesh) [3]. However, incidences of person-to-person transmission were recorded in Bangladesh and India but not in Malaysia[4].

In 1998-99, during the first Malaysia and Singapore outbreak nearly 300 cases of Nipah Virus were reported with over 100 deaths due to encephalitis and respiratory illness caused by NiV infection. Since then then several Nipah viral outbreaks have been reported in Bangladesh and India. Two different strains of Nipah virus (NiV) namely, NiV Malaysia (NiV-M) and more pathogenic NiV Bangladesh (NiV-B) have been reported. Owing to its high mortality rate, Nipah virus has been classified as a BSL-4 agent by The Centers for Disease Control and Prevention (CDC), USA[5].

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I hereby declare that the details furnished above are true and correct to the best of my knowledge and belief.