IN SILICO APPROACH ON SELECTIVE BIOACTIVE COMPOUNDS IDENTIFIED FROM *Catharanthus roseus* LEAVES AGAINST p38 MITOGEN-ACTIVATED PROTEIN KINASE (p38 MAPK) AND c-Jun AMINO TERMINAL KINASE (JNK)

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ABSTRACT

In silico approach is one of the most powerful techniques to discover novel ligand for proteins of known structure and thus play key role in structure based drug discovery. Hence, the purpose of the present study was to perform an *in silico* docking of nephroprotective properties of phytocompounds identified from *Cathranthus roseus* leaves namely Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid against p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino terminal kinase (JNK) using Autodock software. Present study concluded that the selected bioactive compounds can efficiently bind to the receptors and molecular docking can be successfully used in finding p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino terminal kinase (JNK) inhibitors. Among the various compounds, 9,12-Octadecadienoyl chloride and 9-Octadecenoic acid has potential binding interactions than other compounds. Hence, the studied bioactive compounds have the potential and may be used as nephroprotective agents against kidney diseases. However, these results are only preliminary screening just to facilitate subsequent *in vitro* and *in vivo* studies and thus warrants further investigation. To the best of our knowledge, this is the first report that bioactive compounds from hydro-ethanolic extract of *Cathranthus roseus* are subjected to molecular docking for screening for their nephroprotective potentials.

Keywords: *Cathranthus roseus* leaves extract; Docking; Bioactive compounds; p38 MAPK; JNK; Autodock;

INTRODUCTION

Cellular signaling pathways that involve protein kinases play critical roles in determining the balance between cell death and survival (Clarke, 2009). One such pathway is mitogen-activated protein kinase (MAPK) signaling pathway. MAPK are serine/threonine specific protein kinases that respond to varied extracellular stimuli like mitogens, osmotic stress, heat shock, proinflammatory cytokines, growth factors,

etc. and regulate various cellular activities including development, differentiation, proliferation, inflammatory responses and apoptosis. The three well-known MAPK pathways in mammalian system are extracellular signal-regulated kinases (ERKs1/2), c-Jun N-terminal kinases (JNKs1/2/3), and p38-MAPKs. MAPK1 or ERK1/2, plays an "antiapoptotic role" by the downregulation of proapoptotic proteins and upregulation of anti-apoptotic proteins through both transcriptional and posttranslational mechanisms (Yue, 2020). Nowadays, the use of bioinformatic tools, before doing wet lab activities to determine the binding of datasets of small molecules to known receptors is a major component of drug discovery as I t is cost effective and time saving (Lengauer and Rarey, 1996; Ewing *et al*., 2001; Muhammad *et al*., 2015).

Protein kinases are enzymes that covalently modify proteins by attaching phosphate groups (from ATP) to serine, threonine, and/or tyrosine residues. In so doing, the functional properties of the protein kinase's substrates are modified (Cohen, 2002; Franciosa *et al*., 2023). Protein kinases transduce signals from the cell membrane into the interior of the cell. Such signals include not only those arising from ligand-receptor interactions but also environmental perturbations such as when the membrane undergoes mechanical deformation (ie, cell stretch or shear stress). Ultimately, the activation of signaling pathways that use protein kinases often culminates in the reprogramming of gene expression through the direct regulation of transcription factors or through the regulation of mRNA stability or protein translation (Bain *et al*., 2004). Protein kinases regulate most aspects of normal cellular function. The pathophysiological dysfunction of protein kinase signaling pathways underlies the molecular basis of many cancers and of several manifestations of cardiovascular disease, such as hypertrophy and other types of left ventricular remodeling, ischemia/reperfusion injury, angiogenesis, and atherogenesis. Given their roles in such a wide variety of disease states, protein kinases are rapidly becoming extremely attractive targets for drug discovery (Thomas, 2005; Dong *et al*., 2023).

The aim of this *in silico* study was to explore the nephroprotective properties of phytocompounds from Catharanthus *roses* leaves namely Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester via molecular docking against p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino terminal kinase (JNK) using Autodock software.

MATERIALS AND METHOD
IN SILICO MOLECULAR DOCKING

Computational drug discovery technique in the recent day of Pharmaceutical research has successfully molecular modeling with different algorithm based programing software's been used. The ligand and protein binding scores according to algorithm based program thereby may use any software for protein and ligand interactions for best results (Velavan *et al.,* 2020).

Ligand and protein preparation

The ligands (Figure 1) are Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester were obtained from Pubchem database, ligands were converted in to PDB format using Open bable software and Protein obtained from PDB database. p38 mitogen-activated protein kinase (p38 MAPK) (PDB ID: 1A9U) and c-Jun amino terminal kinase (JNK) (PDB ID: 1PMN) protein preparation was generally to have a remove of all water molecules and any other Ligand molecules prior to docking, using Pymol software prepared protein was saved as PDB formed.

In Silico Docking Studies

Protein structures were obtained from the protein data bank (PDB) database and ligand was obtained as Pubchem. Automated docking along with a graphical user interface, Auto Dock tools was utilized to generate grids, calculate dock score and evaluate the conformers of activators bound in the active site of protein as targets. Energy minimization was done in ACD/ChemSketch. The minimized structures were then subjected to docking studies. To achieve the purpose the hetero atoms consisting of water molecules and other additional atoms were removed from the proteins. A Lamarckian genetic algorithm method, implemented in the program Auto Dock 4.1, was employed. This software used for the estimation of energy during the interaction and identify the best flexible ligand pose with minimum energy. The scoring function is based on the intermolecular interaction of ligand and protein during docking. As per genetic algorithm all the torsions were allowed to rotate during docking.

The grid map was centred at particular residues of the protein and was generated with grid dimension prepared (Center x, center y and center z). The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters   (Ghose and Crippen, 1987; Binkowski *et al*., 2007; Vidya *et al*., 2012; Shruthi *et al*., 2012). Complex structures were modeled using modeling software's Pymol (1.1 version, Delano Scientific LLC, San Carlos, CA, USA), Chimera (1.10.1 version UCSF Resources for biocomputing visualization and informatics, NIH, CA, USA) and Pose view (Trot and Olson, 2010).

RESULTS AND DISCUSSION

Molecular docking is an essential method in the improvement of new medications. Docking strategy permits describing the conduct of a test molecule in the coupling site of the receptor target of interest. A docking method must have the ability to predict the useful binding strength between the ligand and the receptor complex (Mooers, 2020). Molecular docking is a technique that is used to discover novel ligands for protein structure and plays a significant role in structure-based drug design (Paul *et al*., 2018). Molecular docking studies were performed in order to exhibit inhibitory binding mode of least energy ligands from the generated conformations with the target proteins (Xuan-Yu et al., 2011). Molecular docking analysis has directed to predict the binding attractions of different bioactive

compounds and to explain specific sites of interaction between the bioactive compounds and the target proteins. Computational advances played a significant influence in the drug development process. Virtual screening approaches are frequently and widely utilized to minimize the cost and time of drug development (Abdulfatai et al., 2017)

A consensus is emerging that protein kinase modulators will be effective treatments for a variety of diseases include kidney diseases (Thomas, 2005). Stress-induced activation of p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino-terminal kinase (JNK) signaling is a feature of both acute and chronic kidney disease and is associated with disease progression. Inhibitors of p38 MAPK or JNK activation provide protection against inflammation and fibrosis in animal models of kidney disease (Greg *et al*., 2016). to explore the nephroprotective properties of phytocompounds from *Catharanthus roseus* leaves namely Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester via molecular docking against p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino terminal kinase (JNK) (Figure 1).
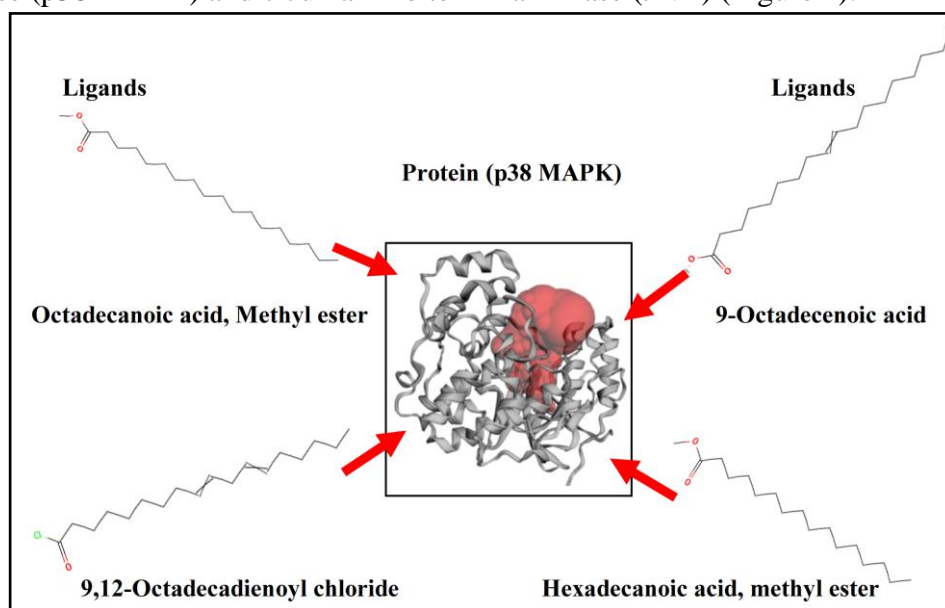

Figure 1: Molecular docking of phytochemical compounds against p38 mitogen-activated protein kinase (p38 MAPK) (PDB ID: 1A9U)
p38 mitogen-activated protein kinase (p38 MAPK) (PDB ID: 1A9U)

Active site detection: Area (SA) $Å^2$ = 838.902

Chain A was involved in active properties identified using CASTp server. The grid map was centred at particular residues of the protein and was generated with grid dimension prepared A chain (Center x = -2.59, center y = 18.85 and center z = 39.08). The predicted active site of the protein with their amino acid residues is depicted in figure 2a. The light blue color shade letters denote the active site amino

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acid residues involved in the formation of binding pockets.   Figure 2 showed the 3D Cartoon view of prepared 1A9U protein.
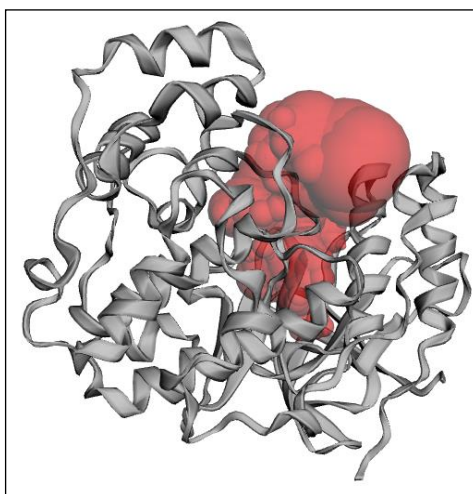

Figure 2: Protein (1A9U) 3D view using CASTp server and the sphere indicates the active site/pocket of the protein active site
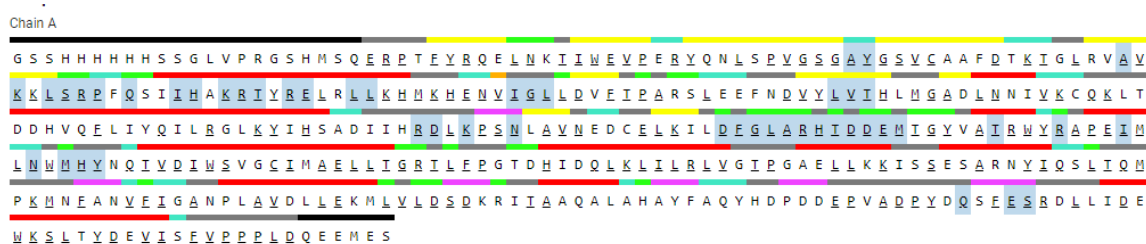

**Figure 2a: 1A9U active site**

The higher negative docking score represented a high binding affinity between the receptor and ligand molecules, showing the higher efficiency of bioactive compounds. The docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown in Table 1. The Figure 3 to 5 represent the docking of 9,12-Octadecadienoyl chloride (-5.50 kcal/mol), Hexadecanoic acid, methyl ester (-4.80 kcal/mol), Octadecanoic acid, Methyl ester (-4.60 kcal/mol) and 9-Octadecenoic acid (-4.50 kcal/mol). The binding interactions of all compounds have shown strong hydrogen bonding and hydrophobic interactions with the target protein. The docking score of Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester. The docking studies confirmed the nephroprotective activity of Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester and thereby inhibition of target protein p38 mitogen-activated protein kinase (p38 MAPK) through the binding interactions.

The highest binding energy was greatest activity. Among the various compounds, 9,12-Octadecadienoyl chloride has potential binding interactions than other compounds.

Table 1: 1A9U (p38 mitogen-activated protein kinase (p38 MAPK))

Ligand	Molecular formula	Molecular weight (g/mol)	H-bond donors / acceptors	Binding Affinity (kcal/mol)	Ligand binding site of target Amino acids
Octadecanoic acid, Methyl ester	$C_{19}H_{38}O_2$	298.50	0/2	-4.60	Lys 53, Val 105, Leu 104, Thr 106, Leu 108, Ile 84, Leu 75, Ala 51, Val 30, Val 38, Met 109, Tyr 35.
9-Octadecenoic acid	$C_{18}H_{34}O_2$	282.50	1/2	-4.50	Leu 291, Val 239, Thr 241, Gly 240, Pro 242, Leu 246, Gly 243, Glu 245, Asp 292, Lys 267, Val 290, Lys 295.
9,12-Octadecadienoyl chloride	$C_{18}H_{31}ClO$	298.90	0/1	**-5.50**	Arg 67, Ala 172, Glu 71, Phe 169, Arg 173, Tyr 35, Leu 75, Val 38, Lys 53, Leu 104, Leu 86, Thr 106, Ile 84, Ala 51.
Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270.50	0/2	-4.80	Leu 167, Met 109, Val 38, Lys 53, Ala 51, Thr 106, Asp 168, Leu 104, Glu 71, Phe 169, Leu 75, Ile 84.

Octadecanoic acid, Methyl ester interacted with four van der Waals type bond between the key amino acids: Val 105, Leu 104, Thr 106 and Leu 108 which are in specific positions in the study compound. Hydrogen bond interaction between Lys 53 and the hydroxyl group of study compound presented the best coupling with the p38 MAPK protein, one Pi-Sigma bond with Tyr 35 amino acid residue of p38 MAPK and six Pi-Alkyl interaction with Ile 84, Leu 75, Ala 51, Val 30, Val 38 and Met 109 amino acid residues of p38 MAPK interacted with Octadecanoic acid, Methyl ester (Table 1 and Figure 3).
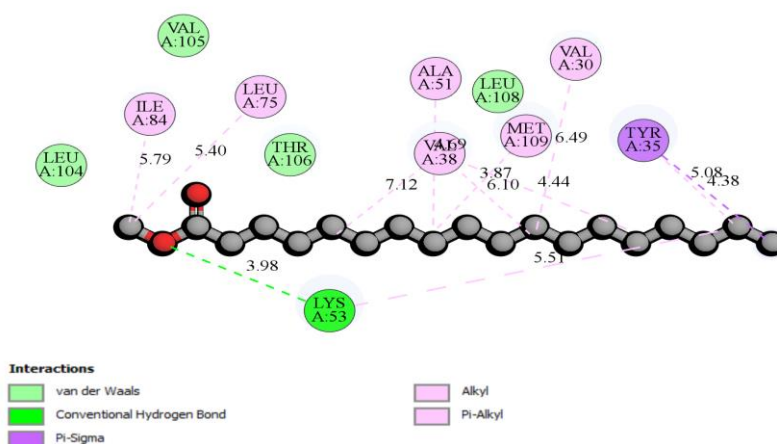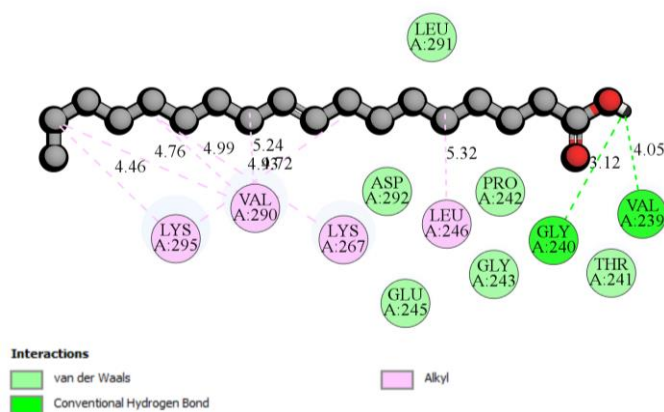

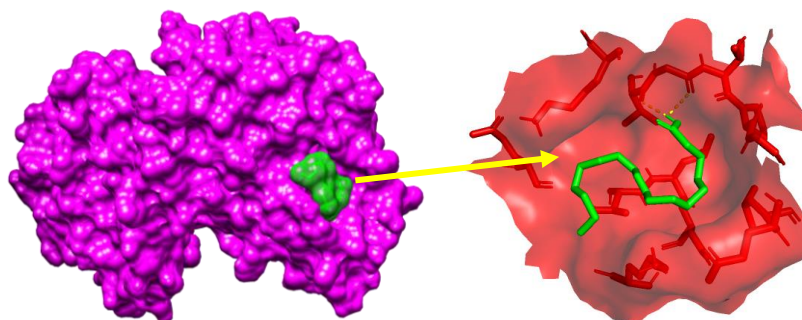**2D view of Octadecanoic acid, Methyl ester interaction with protein of 1A9U**

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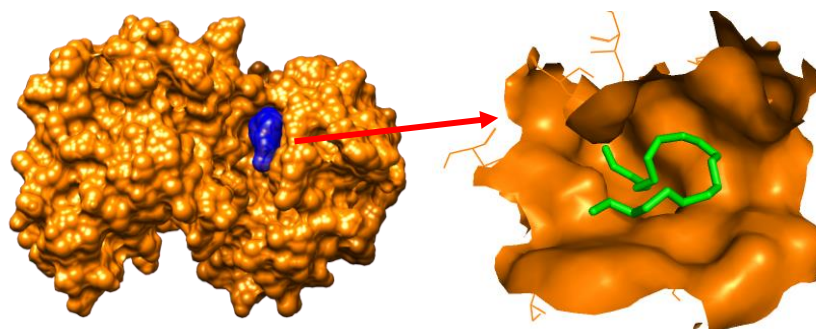
3D Surface view of protein active/binding site with ligand

Figure 3: Octadecanoic acid, Methyl ester binding with protein of 1A9U

9-Octadecenoic acid interacted with five van der Waals type bond between the key amino acids: Asp 202, Glu 245, Leu 291, Thr 241 and Thr 241 which are in specific positions in the study compound. Hydrogen bond interaction between Val 219 and Gly240 from the hydroxyl group of study compound presented the best coupling with the p38 MAPK protein and four Alkyl interaction with Lys 295, Leu 246, Lys 267 and Val 290 amino acid residues of p38 MAPK interacted with 9-Octadecenoic acid (Table 1 and Figure 4).
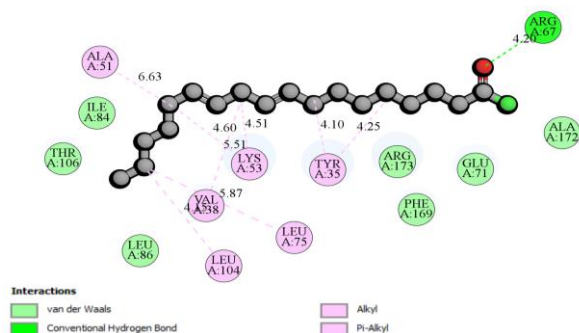
**2D view of 9-Octadecenoic acid interaction with protein of 1A9U**

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3D Surface view of protein active/binding site with ligand

Figure 4: 9-Octadecenoic acid binding with protein of 1A9U

9,12-Octadecadienoyl chloride interacted with six van der Waals type bond between the key amino acids: Thr 106, Ile 84, Arg 173, Phe 169, Glu 71 and Ala 172 which are in specific positions in the study compound. Hydrogen bond interaction between Arg 67 and the hydroxyl group of study compound presented the best coupling with the p38 MAPK protein, and six Pi-Alkyl interaction with Ala 51, Leu 75, Leu 104, Val 38, Lys 53 and Tyr 35 amino acid residues of p38 MAPK interacted with 9,12-Octadecadienoyl chloride (Table 1 and Figure 5).
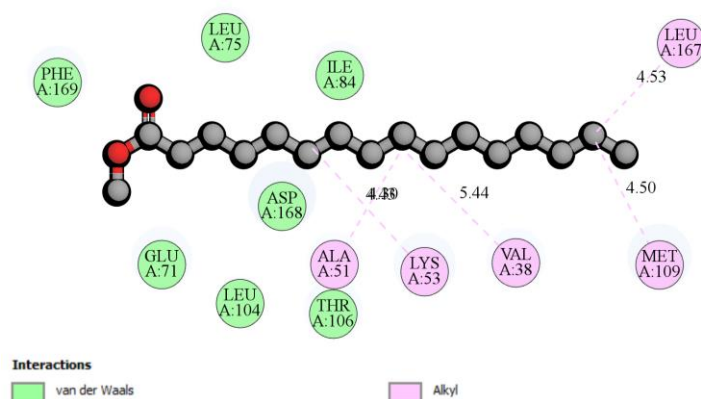

**2D view of 9,12-Octadecadienoyl chloride interaction with protein of 1A9U**
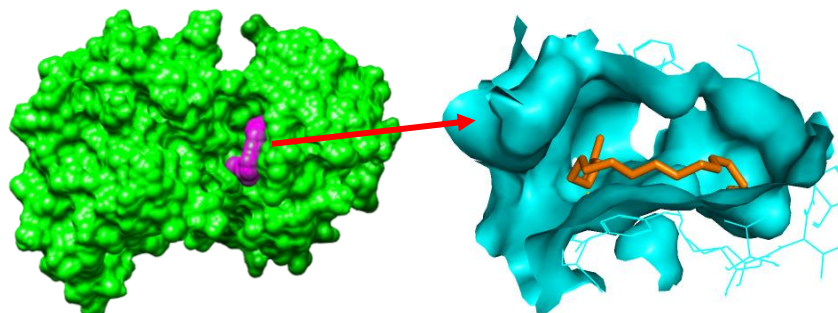
3D Surface view of protein active/binding site with ligand
Figure 5: 9,12-Octadecadienoyl chloride binding with protein of 1A9U

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Hexadecanoic acid, methyl ester interacted with seven van der Waals type bond between the key amino acids: Phe 169, Leu 75, Leu 104, Asp 168, Ile 84 and Thr 106 which are in specific positions in the study compound. The five Alkyl interaction with Lys 53, Leu 167, Ala 51, Val 38 and Met 109 amino acid residues of p38 MAPK interacted with Hexadecanoic acid, methyl ester (Table 1 and Figure 6).

2D view of Hexadecanoic acid, methyl ester interaction with protein of 1A9U
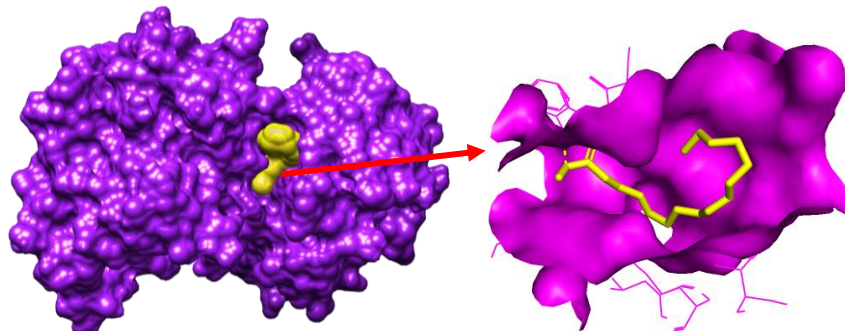
3D Surface view of protein active/binding site with ligand

Figure 6: Hexadecanoic acid, methyl ester binding with protein of 1A9U

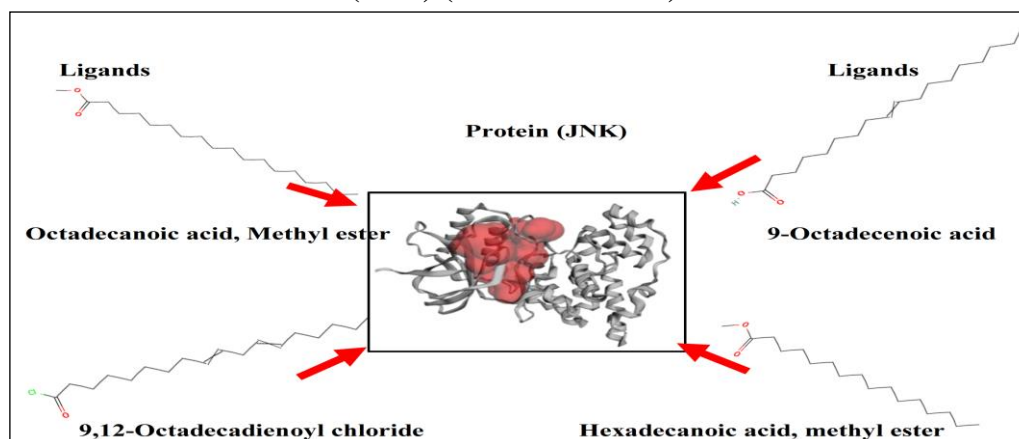**c-Jun amino terminal kinase (JNK) (PDB ID: 1PMN)**

Figure 7: Molecular docking of phytochemical compounds against c-Jun amino terminal kinase (JNK) (PDB ID: 1PMN)

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Active site detection: Area (SA) Å^2 = 1173.26

Chain A was involved in active properties identified using CASTp server. The grid map was centred at particular residues of the protein and was generated with grid dimension prepared A chain (Center x = 18.93, center y = 14.71 and center z = 24.45). The predicted active site of the protein with their amino acid residues is depicted in figure 8a. The light blue color shade letters denote the active site amino acid residues involved in the formation of binding pockets. Figure 8 showed the 3D Cartoon view of prepared 1PMN protein.
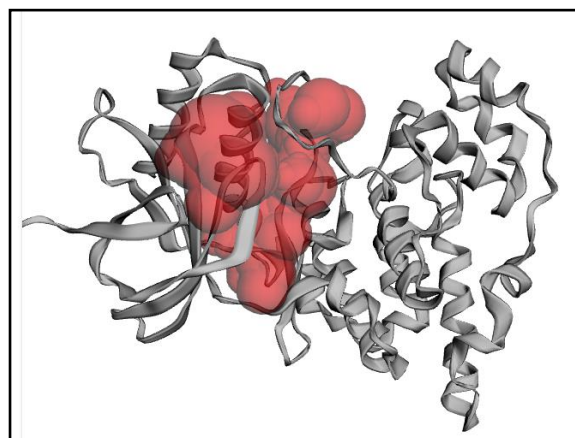

Figure 8: Protein (1PMN) 3D view using CASTp server and the sphere indicates the active site/pocket of the protein active site
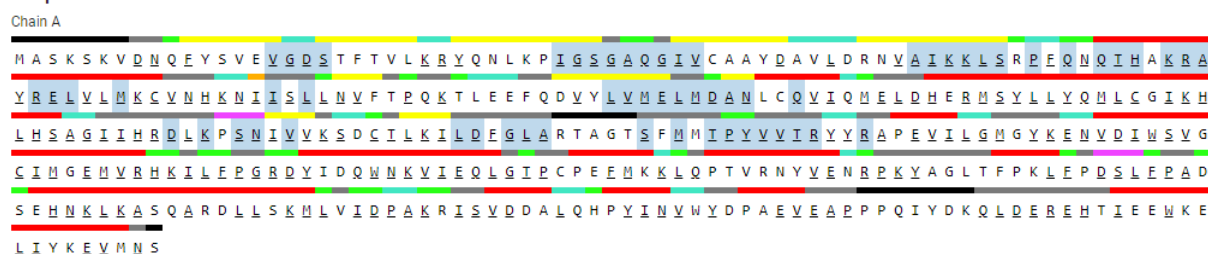
Figure 8a: 1PMN active site

The higher negative docking score represented a high binding affinity between the receptor and ligand molecules, showing the higher efficiency of bioactive compounds. The docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown in Table 2. The Figure 9 to 11 represent the docking of 9-Octadecenoic acid (-5.80 kcal/mol), 9,12-Octadecadienoyl chloride (-5.50 kcal/mol), Octadecanoic acid, Methyl ester (-5.40 kcal/mol) and Hexadecanoic acid, methyl ester (-4.80 kcal/mol). The binding interactions of all compounds have shown strong hydrogen bonding and hydrophobic interactions with the target protein. The docking score of Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and

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Hexadecanoic acid, methyl ester. The docking studies confirmed the nephroprotective activity of Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid, methyl ester and thereby inhibition of target protein c-Jun amino terminal kinase (JNK) through the binding interactions. The highest binding energy was greatest activity. Among the various compounds, 99-Octadecenoic acid has potential binding interactions than other compounds.

Table 2: 1PMN (c-Jun amino terminal kinase (JNK))

Ligand	Molecular formula	Molecular weight (g/mol)	H-bond donors / acceptors	Binding Affinity (kcal/mol)	Ligand binding site of target Amino acids
Octadecanoic acid, Methyl ester	$C_{19}H_{38}O_2$	298.50	0/2	-5.40	Gly 71, Asn 152, Ala 151, Ile 70, Met 149, Val 196, Leu 148, Leu 206, Val 78, Ala 91, Lys 93, Leu 144, Leu 126, Ile 124, Met 146, Ile 92, Val 145.
9-Octadecenoic acid	$C_{18}H_{34}O_2$	282.50	½	**-5.80**	Val 196, Met 149, Gly 71, Met 146, Leu 206, Val 78, Ile 70, Lys 93, Leu 144, Ile 92, Val 145, Leu 126, Ile 124, Ala 91.
9,12-Octadecadienoyl chloride	$C_{18}H_{31}ClO$	298.90	0/1	-5.50	Leu 144, Ile 124, Gly 71, Asn 152, Ile 70, Met 149, Leu 148, Ala 91, Val 196, Ser 193, Met 146, Val 78, Lys 93, Leu 206.
Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270.50	0/2	-4.80	Asn 194, Ser 193, Ser 72, Gly 73, Leu 206, Met 146, Ala 91, Leu 148, Lys 93, Val 196, Val 78, Met 149, Ile 70, Gly 71.

Octadecanoic acid, methyl ester interacted with nine van der Waals type bond between the key amino acids: Val 145, Leu 126, 148, Gly 71, Ala 151, Asn 152, Ile 70, Met 149 and Ile 192 which are in specific positions in the study compound. The eight Alkyl interaction with Val 196, Leu 206, Val 78, Ala 91, Leu 144, Lys 93, Met 146 and Ile 124 amino acid residues of p38 MAPK interacted with Octadecanoic acid, methyl ester (Table 2 and Figure 9).

2D view of Octadecanoic acid, Methyl ester interaction with protein of 1PMN

3D Surface view of protein active/binding site with ligand

Figure 9: Octadecanoic acid, Methyl ester binding with protein of 1PMN

9-Octadecenoic acid interacted with six van der Waals type bond between the key amino acids: Met 149, Gly 71, Ile 124, Lew 126, Val 145 and Ile 92 which are in specific positions in the study compound. The six Pi-Alkyl interaction with Val 196, Met 146, Leu 206, Val 78, Ile 70 and Lys 93 amino acid residues of p38 MAPK interacted with 9-Octadecenoic acid (Table 2 and Figure 10).
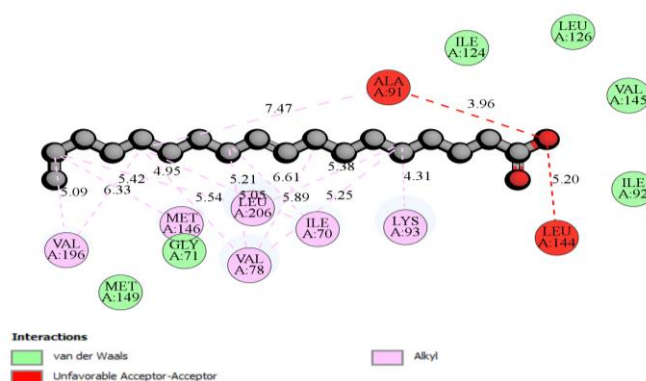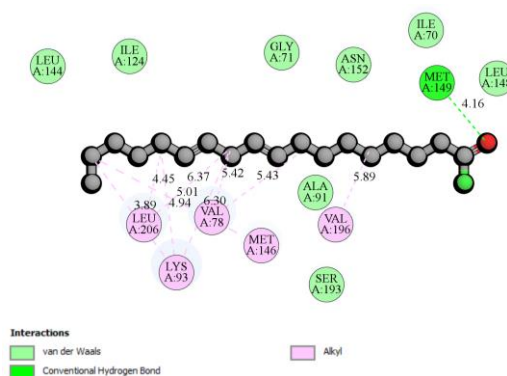

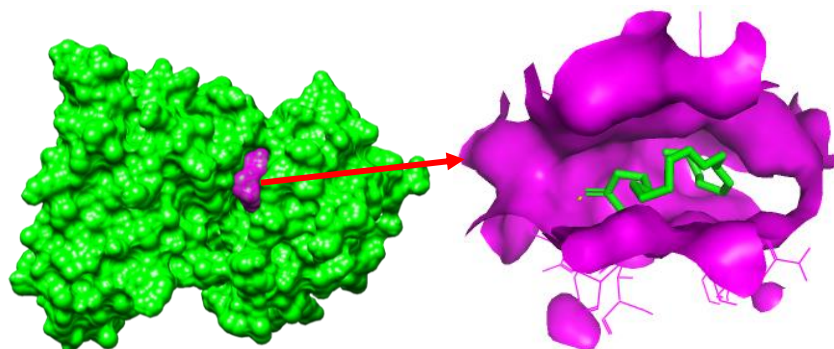**2D view of 9-Octadecenoic acid interaction with protein of 1PMN**
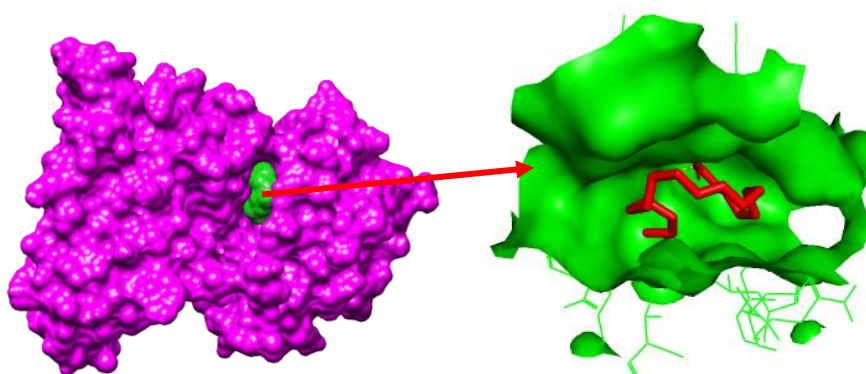
3D Surface view of protein active/binding site with ligand
Figure 10: 9-Octadecenoic acid binding with protein of 1PMN

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9,12-Octadecadienoyl chloride interacted with eight van der Waals type bond between the key amino acids: Leu 144, Ile 124, Gly 71, Asn 152, Ile 70 Leu 148, Ala 91 and Ser 193 which are in specific positions in the study compound. Hydrogen bond interaction between met 149 and the hydroxyl group of study compound presented the best coupling with the p38 MAPK protein and five Pi-Alkyl interaction with Leu 206, Val 78, Met 146, Lys 93 and Met 146 amino acid residues of p38 MAPK interacted with 9,12-Octadecadienoyl chloride (Table 2 and Figure 11).
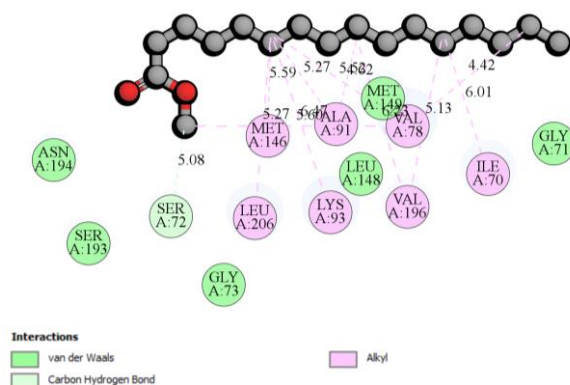

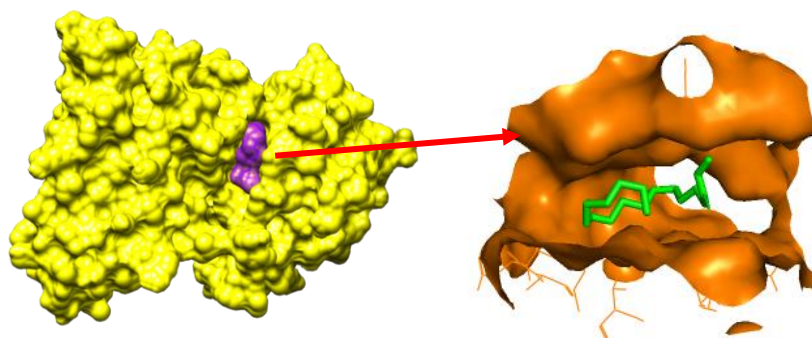**2D view of 9,12-Octadecadienoyl chloride interaction with protein of 1PMN**

3D Surface view of protein active/binding site with ligand

Figure 11: 9,12-Octadecadienoyl chloride binding with protein of 1PMN

Hexadecanoic acid, methyl ester interacted with six van der Waals type bond between the key amino acids: Asn 194, Ser 193, Gly 73, Met 149, Leu 148 and Gly 71 which are in specific positions in the study compound. Hydrogen bond interaction between Ser 72 and the carbon group of study compound presented the best coupling with the p38 MAPK protein and seven Alkyl interaction with Met 146, Ala 91, Leu 206, Lys 93, Val 78, Val 196 and Ile 709 amino acid residues of p38 MAPK interacted with Hexadecanoic acid, methyl ester (Table 2 and Figure 12).

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2D view of Hexadecanoic acid, methyl ester interaction with protein of 1PMN

3D Surface view of protein active/binding site with ligand
Figure 12: Hexadecanoic acid, methyl ester binding with protein of 1PMN

CONCLUSION

In silico approach is one of the most powerful techniques to discover novel ligand for proteins of known structure and thus play key role in structure based drug discovery. Present study concluded that the selected bioactive compounds (Octadecanoic acid, Methyl ester, 9-Octadecenoic acid, 9,12-Octadecadienoyl chloride and Hexadecanoic acid) can efficiently bind to the receptors and molecular docking can be successfully used in finding p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun amino terminal kinase (JNK) inhibitors from *Cathranthus roseus* leaves extract. Among the various compounds, 9,12-Octadecadienoyl chloride and 9-Octadecenoic acid has potential binding interactions than other compounds. Hence, the studied bioactive compounds may have the potential to be used as nephroprotective agents against kidney diseases. However, these results are only preliminary screening just to facilitate subsequent *in vitro* and *in vivo* studies and thus warrants further investigation. To the best of our knowledge, this is the first report that bioactive compounds from hydro-ethanolic

extract of *Cathranthus roseus* are subjected to molecular docking for screening their nephroprotective potentials.

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