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Research Article

IN SILICO MOLECULAR DOCKING STUIDES OF MURICIN J, MURICIN K AND MURICIN L COMPOUND FROM A. MURICATA AGAINST APOPTOTIC PROTEINS (CASPASE-3, CASPASE-9 AND β-ACTIN)

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ABSTRACT

Background: Muricin J, Muricin K and Muricin L are isolated novel compounds present in A. muricata, which are polyphenolic in nature. Polyphenols are a good natural resource for combating cancer. Objective: The present study was planned to explore the molecular docking interaction between these compounds with apoptotic proteins (Caspase-3, Caspase-3, and β-Actin). Materials and Methods: Databases and tools such as SwissProt, Protein Data Bank and RasMol, ChemSketch, PatchDock, and PyMol Viewer were used. Results: The docking interaction as Geometrical Shape Complementary Score was predicted for Muricin J with Caspase-3 (5096), Muricin K with Caspase-3 (5068), Muricin L with Caspase-3 (5348); Muricin J with Caspase-9 (5130), Muricin K with Caspase-9 (5474), Muricin L with Caspase-9 (No Interaction); Muricin J with β-Actin (No Interaction), Muricin K with β-Actin (5646), Muricin L with β-Actin (5706). Among the three ligands, Muricin K docked well with Caspase-3, Caspase-9 and β-Actin. Muricin J docked with Caspaes-3 and Caspase-9, Muricin L docked with Caspase-3 and β-Actin. . Among the three ligands, Muricin K recorded a good Geometrical Shape Complementarity Score with Caspase-3, Caspase-9 and β-Actin. The result of Lipinski rule suggests Muricin K as best therapeutic drug. Conclusion: Docking study and *in silico* toxicity results proves the application of this compound as potential and natural therapeutic agent to treat diseases.

Key Words: Molecular docking, PatchDock, Muricin J, K, L, Apoptotic proteins

INTRODUCTION

Computational biology and bioinformatics have the potential not only of speeding up drug discovery process, thus reducing the costs, but also of changing the way that drugs are designed. Rational Drug Design (RDD) helps to facilitate and speed up drug designing process, which involves a variety of methods to identify novel compounds. [1-5] One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. [6]

*A. muricata*is a well-known medicinal tree with diuretic properties, [7] anti-bacterial, [8] anti-viral, [9] and antioxidative stress. [10] The newly isolated and elucidated Muricins J, K, and L were evaluated for anti-proliferative activity against human prostate cancer PC-3 cells. [11] In view of this, as there is no evidence of molecular docking studies in Muricin J, Muricin K, and Muricin L against cancer apoptotic proteins, the present study was designed to explore the docking interaction of Muricin J, Muricin K, and Muricin L from *A. muricata* with apoptotic proteins such as Caspase-3, Caspase-9 and β-Actin, which will pave a way for anticancer treatments by natural resources.

MATERIALS AND METHODS

In silico docking studies

Muricin J, Muricin K and Muricin L in graviola fruit were docked against Caspase-3, Caspase-9 and β-Actin protein using *in silico* molecular docking studies. Following databases and tools are used such as SwissProt, Protein Data Bank and RasMol, ChemSketch, PatchDock, and PyMol Viewer, respectively.

Retrieval of protein sequence from Swiss-Prot

The proteins of Caspase-3, Caspase-9 and β-Actin were retrieved from Swiss-Prot database. The accession numbers are: P42574, P55211 and P60709.

Retrieval of protein structure from PDB

The structure of Caspase-3, Caspase-9 and β-Actin were downloaded from PDBSum database and the PDB IDs are: 1CP3, 1JXQ and 3BYH and viewed using RasMol tool.

Retrieval of ligands from ACD/ChemSketch

2-D structure of ligands Muricin J, Muricin K and Muricin L were downloaded. The 3-D structures of Muricin J, Muricin K and Muricin Lwere drawn using ACD/ChemSketch software.

Docking: PatchDock

Docking of ligands and apoptotic proteins was carried out using PatchDock docking software.

Visualization of Protein using PyMol Viewer

The docked structures were then visualized using the PyMol Viewer software and the results were predicted.

RESULTS

Molecular Docking Studies

For molecular docking studies, the ligands Muricin J, Muricin K and Muricin L were docked against apoptotic proteins *viz*., Caspase-3, Caspase-9 and β-Actin..

Retrieval of Protein Sequences

The sequences of proteins Caspase-3, Caspase-9 and β-Actin were downloaded from Swiss-Prot database.

Retrieval of Protein Structures

The 3-D structures of Caspase-3 **(**PDB ID-1CP3), Caspase-9 (PDB ID-1JXQ) and β-Actin (PDB ID-3BYH) were downloaded from PDB database and are given in Fig. 1.

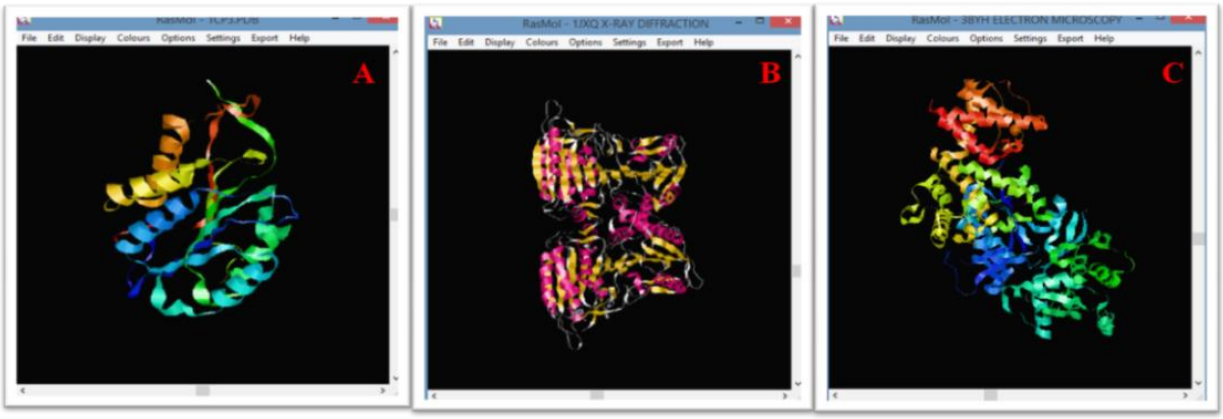

Fig. 1: 3-D Structure of Proteins

A - Caspase-3, B - Caspase-9, C - β-Actin

Retrival of Ligands

3-D structures of Muricin J, Muricin K and Muricin L were drawn using ACD/ChemSketch software after downloading the 2-D structures of respective ligands (Fig. 2).

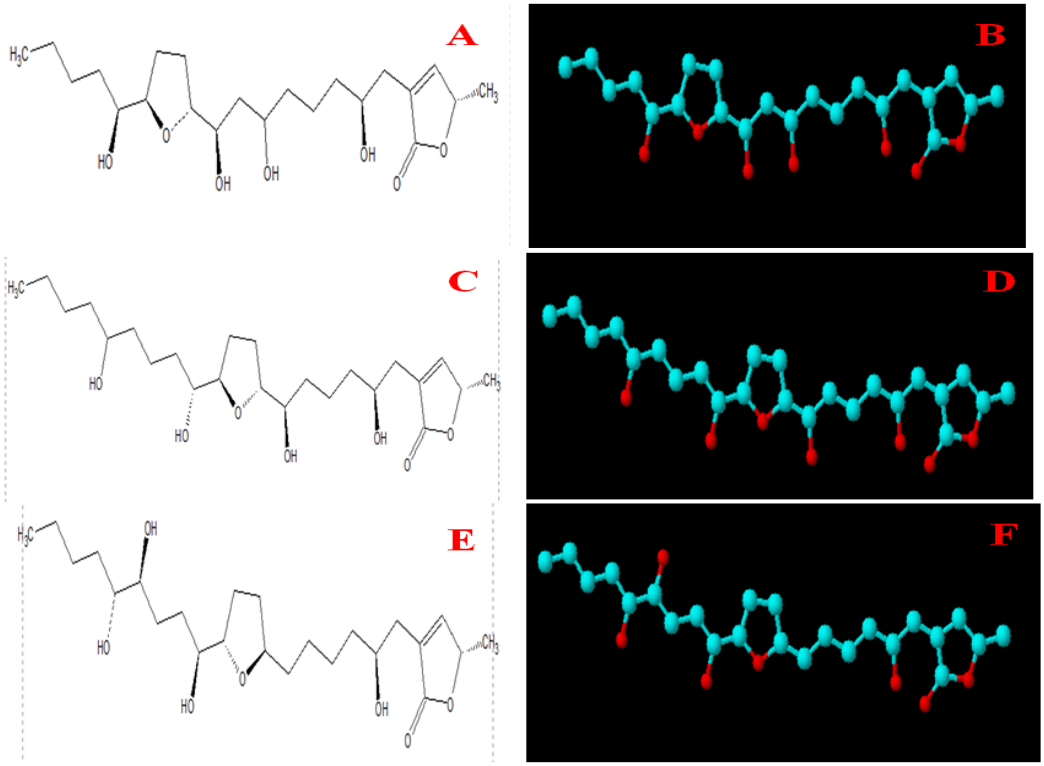

Fig. 2: Structure of Compounds

A – 2-D structure of Muricin J B – 3-D structure of Muricin J : C – 2-D structure of MuricinK :D – 3-D structure of Muricin K : E – 2-D structure of Muricin L : F – 3-D structure of Muricin L

Docking

The 3-D structure of the three inhibitors *viz*., Muricin J, Muricin K and Muricin L were docked against the apoptotic proteins Caspase-3, Caspase-9 and β-Actin using PatchDock tool. The docking results were visualized and analyzed using PyMol visualization tool (Fig. 3-5)

Caspase-3 docked with Muricin J

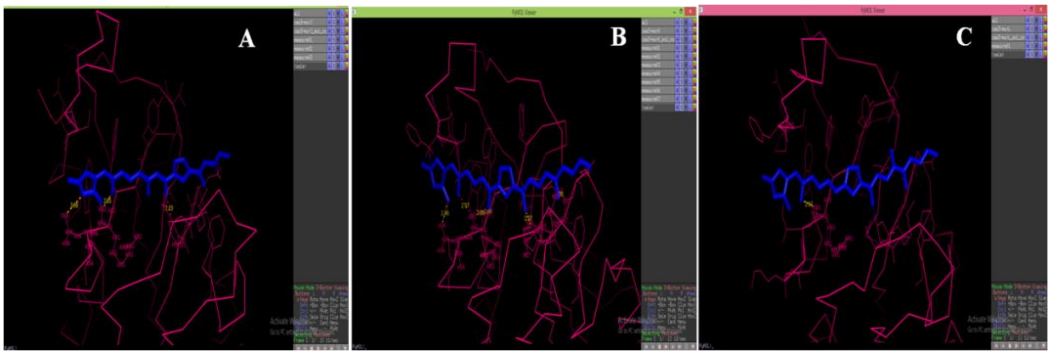

Fig. 3: Visualization of docked complex in PyMol tool

A - Caspase-3 docked with Muricin J : B - Caspase-3 docked with Muricin K : C - Caspase-3 docked with Muricin L

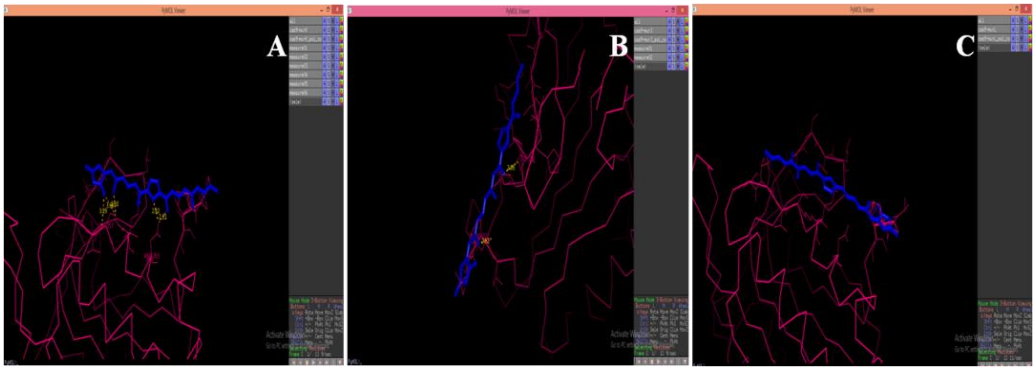

Fig. 4: Visualization of docked complex in PyMol tool

A - Caspase-9 docked with Muricin J : B - Caspase-9 docked with Muricin K : C - Caspase-9 docked with Muricin L

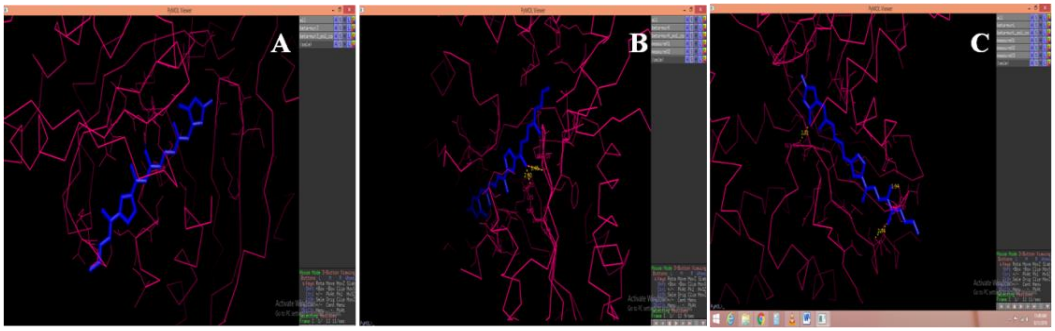

Fig. 5: Visualization of docked complex in PyMol tool

A - β-Actin docked with Muricin J : B - β-Actin docked with Muricin K : C - β-Actin docked with Muricin L

In silico docking study revealed that the interactions between ligands *viz*. Muricin J, Muricin K, Muricin L and Caspase-3, Caspase-9, β-Actin proteins when analysed by *in silico* molecular docking method exhibited the following Geometrical Shape Complementary Score between them as given in Table 1:

Table 1: Docking interactions between ligands, Muricin J, Muricin K and Muricin L and proteins Caspase-3, Caspase-9 and β-Actin

Protein	Ligand	Geometrical Shape Complementary Score	No. of H-Bond
Caspase-3	Muricin J	5096	3
Caspase-3	Muricin K	5068	6
Caspase-3	Muricin L	5348	1
Caspase-9	Muricin J	5130	2
Caspase-9	Muricin K	5474	5
Caspase-9	Muricin L	No Interaction	-
β-Actin	Muricin J	No Interaction	-
β-Actin	Muricin K	5646	2
β-Actin	Muricin L	5706	3

Table 1 shows that the interaction of Muricin J with Caspase-3 forms 3 hydrogen bond with Geometrical Shape Complementary Score of 5096; Muricin K with Caspase-3 forms 6 hydrogen bond with Geometrical Shape Complementary Score of 5068; Muricin L with Caspase-3 forms 1 hydrogen bond with Geometrical Shape Complementary Score of 5348.

Likewise, the interaction of Muricin J with Caspase-9 forms 2 hydrogen bond with Geometrical Shape Complementary Score of 5130; Muricin K with Caspase-9 forms 5 hydrogen bond with Geometrical Shape Complementary Score of 5474, while Muricin L with Caspase-9 has no interaction.

Similarly, the interaction of Muricin J with β-Actin has no interaction; Muricin K with β-Actin forms 2 hydrogen bond with Geometrical Shape Complementary Score of 5646; Muricin L with β-Actin forms 3 hydrogen bond with Geometrical Shape Complementary Score of 5706.

This result shows that there is a presence of binding site between these three proteins and three ligands. The docking is also valid by the formation of hydrogen bond between them. From the above docking results, it is pragmatic that the ligands docks well to these proteins responsible for disease. Among the three ligands, Muricin K recorded a good Geometrical Shape Complementarity Score with Caspase-3, Caspase-9 and β-Actin.

Hence, Muricin K can be taken as the best ligand among the three. The result of Lipinski rule suggests the analysed Muricin K compound as best therapeutic drug. Docking study and *in silico* toxicity results proves the application of Muricin K compound as potential and natural therapeutic agent to treat disease.

DISCUSSION

In silico docking study revealed the interactions between ligands *viz*., Muricin J, Muricin K and Muricin L and Caspase-3, Caspase-9, β-Actin protein, respectively and also the minimum binding energy (kcal/mol) between them. This result showed that there was a presence of binding site between these three proteins and three ligands. The docking was also valid by the formation of hydrogen bond between them. Similar docking results were also done by several authors. [1-5, 12-14] In addition to *in vitro* and *in vivo* methods, [15-16] *in silico* approach has also been used to predict molecules with anticancer activity. [17-18]

Likewise, 62 compounds from 9 species of *Begonia* were docked to the pocket of erlotinib binding site in EGFR-TK protein. [19] The docking result showed that the compound type of alkaloid, steroidal glycoside, triterpenoid glycoside and flavonoid glycoside (polyphenol) have higher chemPLP docking score than other compounds and co-crystallized ligand erlotinib. This result suggested the high potential anticancer activity of alkaloid and glycoside type compounds from *Begonia* species that led them to identify and isolate these types of compounds from *Begonia sp*. [19] Similar findings from other works [19-21] support the results of our study, that the phytocompounds*viz*., Muricin J, Muricin K and Muricin L present in graviola fruit might play a protective role in fighting against apoptotic proteins.

In the present investigation, from the above docking results, the ligands docked well to these proteins responsible for disease and among the three ligands, Muricin K recorded a less docking score with Caspase-3, Caspase-9 and β-Actin. Hence, Muricin K can be taken as the best ligand among the three. The result of Lipinski rule suggests that the analysed Muricin K compound as best therapeutic drug. Docking study and *in silico* toxicity results proves the application of Muricin K compound as potential and natural therapeutic agent to treat disease.

In toto, our study docking studies revealed that even though there is a presence of binding site between the ligands Muricin J, Muricin K and Muricin L, and proteins like Caspase-3, Caspase-9 and β-Actin, Muricin K shows best docking potential. The result of Lipinski rule suggests that the analysed Muricin K compound as best therapeutic drug. The docking is also valid by the formation of hydrogen bond between them. The results reveal that the methanol fruit extract of *A. muricata* is a promising potential anticancer agent for cancer therapy. The exact mechanism should be further investigated in future studies and to elucidate the medicinal properties of *A. muricata*, especially the active components *viz.,* Muricin J, Muricin K and Muricin L, there is a need for further investigation that will pave a way for finding this herbal resource as a medicine to control different types of cancers in future.

CONCLUSION

Increasing awareness, promotion and utilization of this fruit for public benefits are highly encouraged and identification of active phyto-constituents in the fruit pulp will serve as a natural cytotoxic agent against various cancers.

CONFLICT OF INTEREST

There are no conflict of interest declared

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