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MOLECULAR DOCKING STUDIES OF APOPTOTIC PROTEINS CASPASE-3, CASPASE-9, BAX, BCL-2 AND BCL-XL WITH ETHYL (2S)-2-METHYL BUTANOATE AND 1-(ETHYLSULFANYL) ETHANE-1-THIOL FROM DURIAN FRUIT

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ABSTRACT

The durian fruit *Durio zibethinus* as an important source of phenolic compounds, that phenolic compound is a good natural resource of induced apoptotic properties. Hence, the present study was planned to predict the molecular interaction between the GC-MS spectral volatile compounds from *Durio zibethinus* (ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol) with apoptotic proteins (Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xl) by ARGUSLAB docking software. The result of Lipinski rule suggests that compounds as best therapeutic drug for cancer. Docking study and *in silico* toxicity results proves the application of compounds as potential and natural therapeutic agents to treat disease.

Keywords: Durian, GC-MS, Molecular Docking, ARGUSLAB and Apoptotic Proteins

1. INTRODUCTION

In silico modelling is the find-a-way around for the traditional drug testing compounds, synthesized in time consuming multi step process against biological screens. It is the new loom to clinical chemistry for the optimization of screening and testing by means of the observation on particular compound **[1]**. Computational drug discovery can help in identifying potential drug molecules and targets *via.* bioinformatics tools. They can also be used to evaluate the target structures for possible binding/active sites, generate active drug molecules, and check for their dynamic and kinetic properties **[2, 3]**. The use *in silico* methods will help us in all aspects of drug discovery today and forms the importance of structure-based drug design. There are plenty of programs which are helping us to build an active drug molecule. Meanwhile, high-performance computing, data management software and internet are helping us to generate high quality data and also transformation of huge complex biological data into accessible knowledge in current trends to discover novel drug molecules **[4, 5]**.

Generally cancer cells themselves are more prone to undergo apoptosis and a comprehensive understanding of the molecular pathways that regulate apoptosis will assist in investigating novel cancer chemotherapeutic targets **[6]** which in turn would offer new opportunities for the discovery and development of drugs **[7]**. Volatile compounds of methanol extract from durian fruit pulp identified using GC-MS spectral analysis have been tested against apoptotic proteins. The main aim of the current research was to discover the natural anticancer compounds from durian fruit pulp and also to its *in silico* docking potential against apoptotic proteins.

2. MATERIALS AND METHODS

In silico Docking Studies

To forecast the mode of action of the ligand ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol against Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xL protein, *in silico* docking studies were carried out.

Database and Tools

SwissProt

The protein sequence of Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xL were retrieved from Swiss-Prot database.

Protein Data Bank

The structure of Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xL were downloaded from PDBSum database.

RasMol

The 3-D structure of Caspase-3, Caspase-9, Bax, Bcl-2, and Bcl-xL was visualized using Rasmol Tool.

ChemSketch

The 2-D structure of ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol ligands was drawn and converted to 3-D structure in 'mol' format.

ArgusLab

Then, the docking study was carried out using ArgusLab software. Ligands ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol against Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xl protein were performed using ArgusLab docking software.

PyMol Viewer

The molecular complex formed by ArgusLab software ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol ligands and five apoptotic proteins (Caspase-3, Caspase-9, Bax, Bcl-2, and Bcl-xl) were visualized by PyMOL tool.

3. RESULTS AND DISCUSSION

The mode of action of the ligand ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol against Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xl protein was done by *in silico* docking studies. Fasta sequence of proteins *viz*., Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xl were downloaded from Swiss-Prot database. 3-D structure of Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xl were downloaded from PDBsum database and visualized *via*., RasMol tool. 2-D and 3-D structure of ethyl (2S)-2-methylbutanoate was drawn using ChemSketch tool as shown in the **Figure 1** A and 1 B. 2-D and 3-D structure of 1-(ethylsulfanyl) ethane-1-thiol was drawn using ChemSketch tool as shown in the **Figure 2**.

The 3-D structure of Caspase-3, Caspase-9, BAX, Bcl2 and Bcl-xl were docked with ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol ligands using ArgusLab software to assess the interaction between the apoptotic proteins and ligands and the docked complex is presented in **Figure 3 to 12**. The docked complexes were viewed by using PyMol Viewer visualization tool. The above result shows that there is a presence of binding site between these four proteins and two ligands. The docking study is valid by the formation of hydrogen bond between them. From the above **Table 1**, Ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol docks well to Caspase-3 and BAX proteins responsible for disease and is said to be the best compound. The result of Lipinski rule suggests the analysed compound as best therapeutic drug. Docking study and *in silico* toxicity results proves the application of compounds as potential and natural therapeutic agents to treat disease.

Similar docking studies of stearic acid present in *C. halicacabum* with HepG-2 cell line protein plasminogen and transferrin done by Rajesh *et al*. (2016) **[1]**, GC-MS spectral compounds in propolis against apoptotic proteins (Caspase-3, Caspase-9 and β-actin) by Flora Priyadarshini *et al*. (2018) **[8]**, Rutin compound against apoptotic proteins (Tumor Necrosis Factor, Caspase-3, NF-Kappa-B, p53, Collagenase, Nitric Oxide Synthase and Cytochrome C) by Jayameena *et al*. (2018) **[2]**, alginic acid and fucoidan compounds present in *S. wightii* against apoptotic proteins (Caspase-3, Caspase-9 and β -actin) by Jayaprakash *et al*. (2018) **[3]**, ascorbic acid, betalain and gallic acid that are present in dragon fruit against apoptotic proteins (Caspase-3, Caspaes- 9 and β-actin) by Karthika *et al*. (2018) **[5]**, pure propolis compound with Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xL by Rajini Selvaraj *et al*. (2019) **[9]**. Which supports the results if the present work? Hence, the *in silico* molecular docking studies suggests that two spectral compound can be utilized as a potential therapeutic agent to treat various diseases.

Table 1: Docking scores between proteins and ligands

S. No.	Protein	Ligand	Docking score	H-Bond
1.	Caspase-3	ethyl (2S)-2-methylbutanoate	-7.26	2
2.	Caspase-9	ethyl (2S)-2-methylbutanoate	-7.33	2
3.	BAX	ethyl (2S)-2-methylbutanoate	-8.16	2
4.	Bcl2	ethyl (2S)-2-methylbutanoate	No interaction	
5.	Bcl-xL	ethyl (2S)-2-methylbutanoate	-7.96	1
6.	Caspase-3	1-(ethylsulfanyl) ethane-1-thiol	-7.73	1
7.	Caspase-9	1-(ethylsulfanyl) ethane-1-thiol	No interaction	
8.	BAX	1-(ethylsulfanyl) ethane-1-thiol	-7.57	1
9.	Bcl2	1-(ethylsulfanyl) ethane-1-thiol	No interaction	
10.	Bcl-xL	1-(ethylsulfanyl) ethane-1-thiol	No interaction	

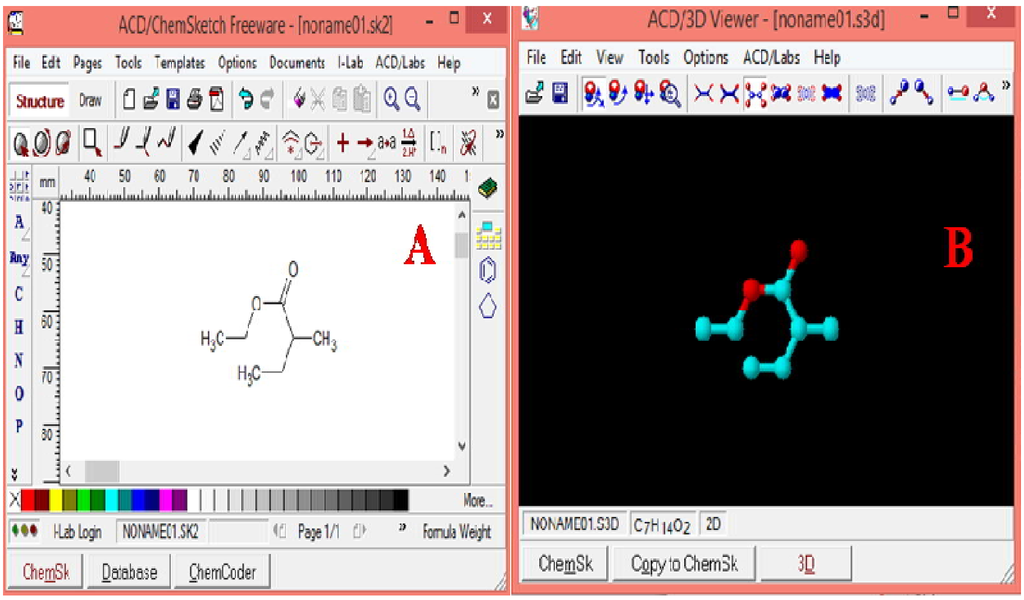

Figure 1: Structure of ethyl (2S)-2-methylbutanoate
A: 2-D structure of ethyl (2S)-2-methylbutanoate
B: 3-D structure of ethyl (2S)-2-methylbutanoate

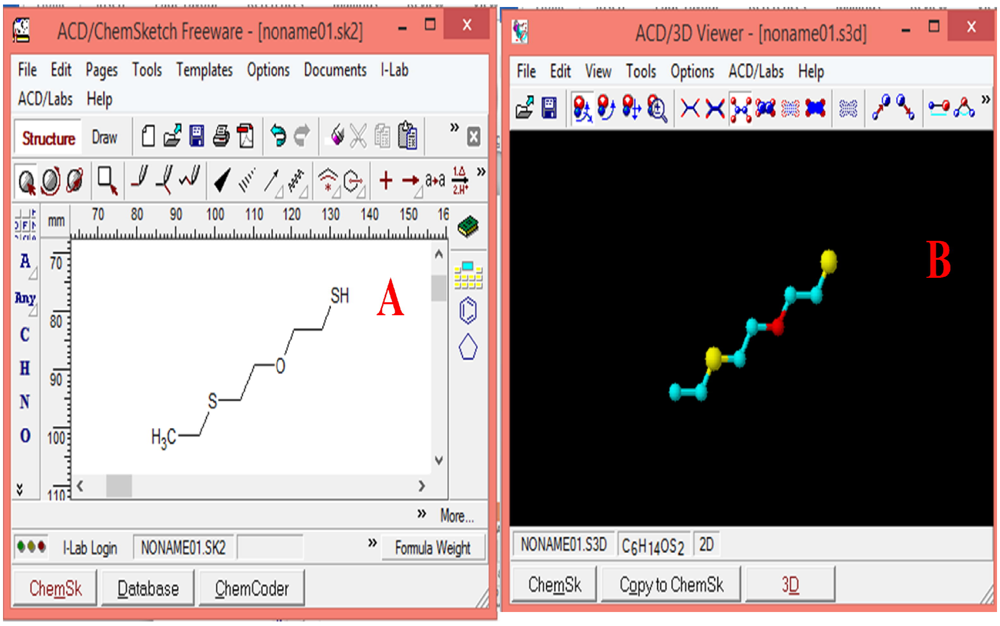

Figure 2: Structure of 1-(ethylsulfanyl) ethane-1-thiol
A: 2-D structure of 1-(ethylsulfanyl) ethane-1-thiol
B: 3-D structure of 1-(ethylsulfanyl) ethane-1-thiol

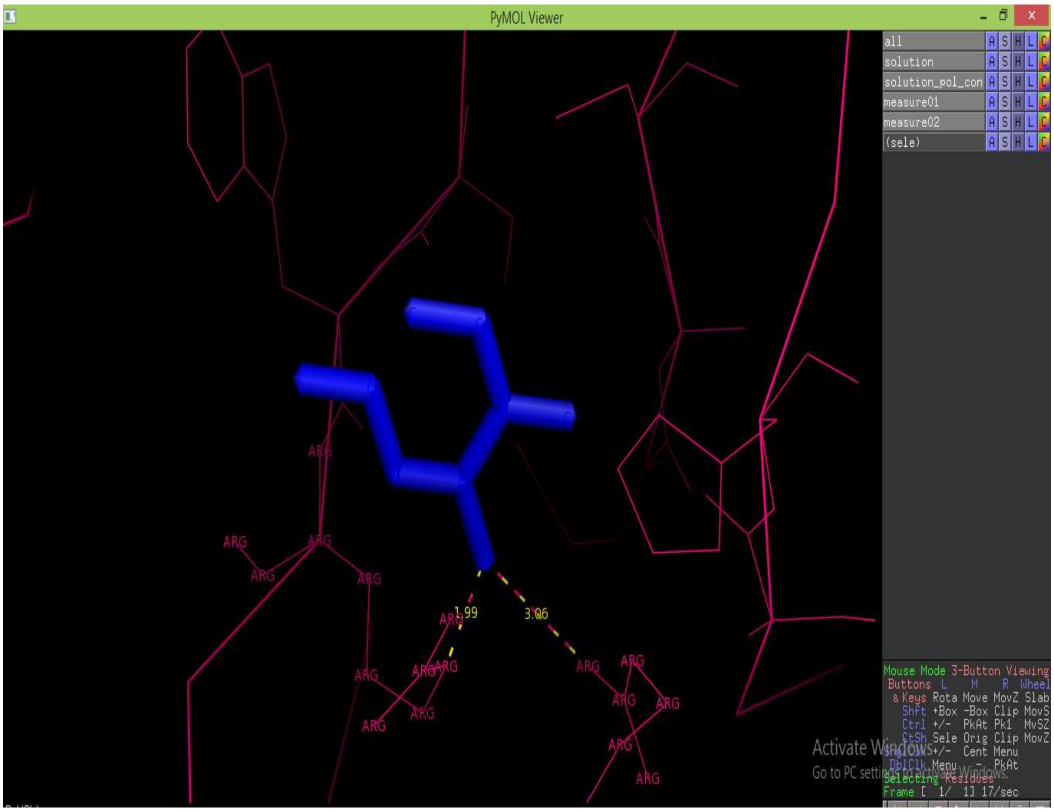

Figure 3: Visualization of docked complex of ethyl (2S)-2-methylbutanoate with Caspase-3

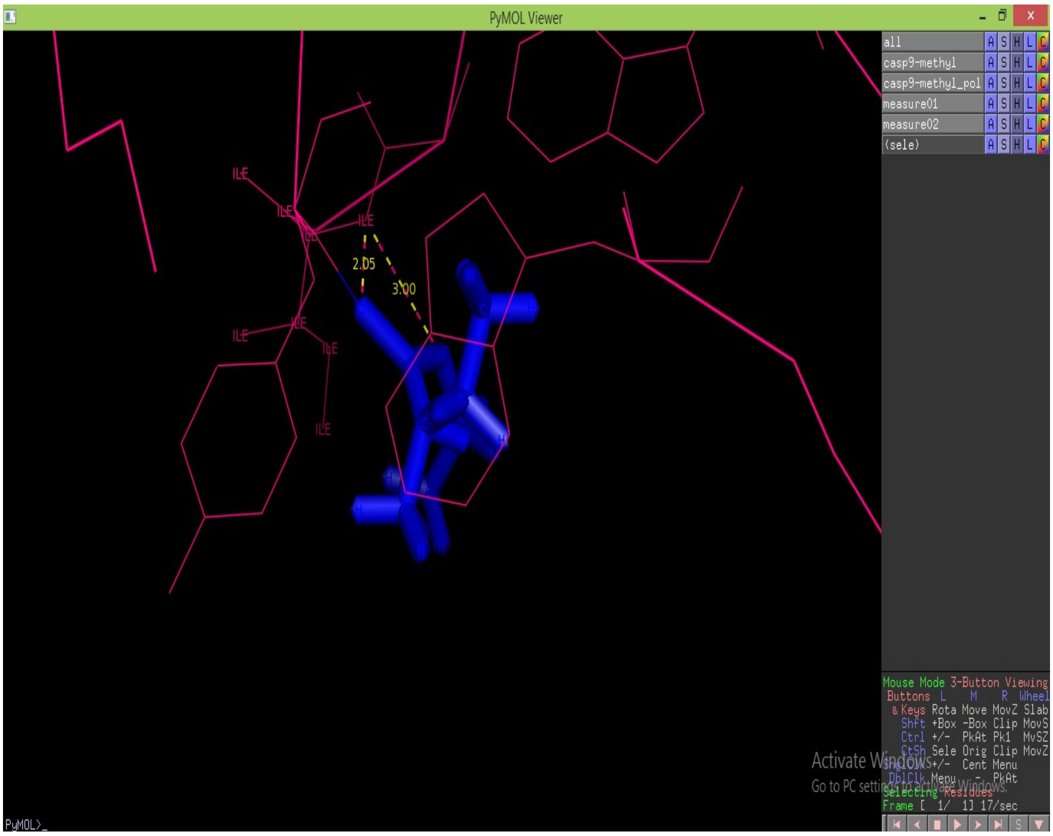

Figure 4: Visualization of docked complex of ethyl (2S)-2-methylbutanoate with Caspase-9

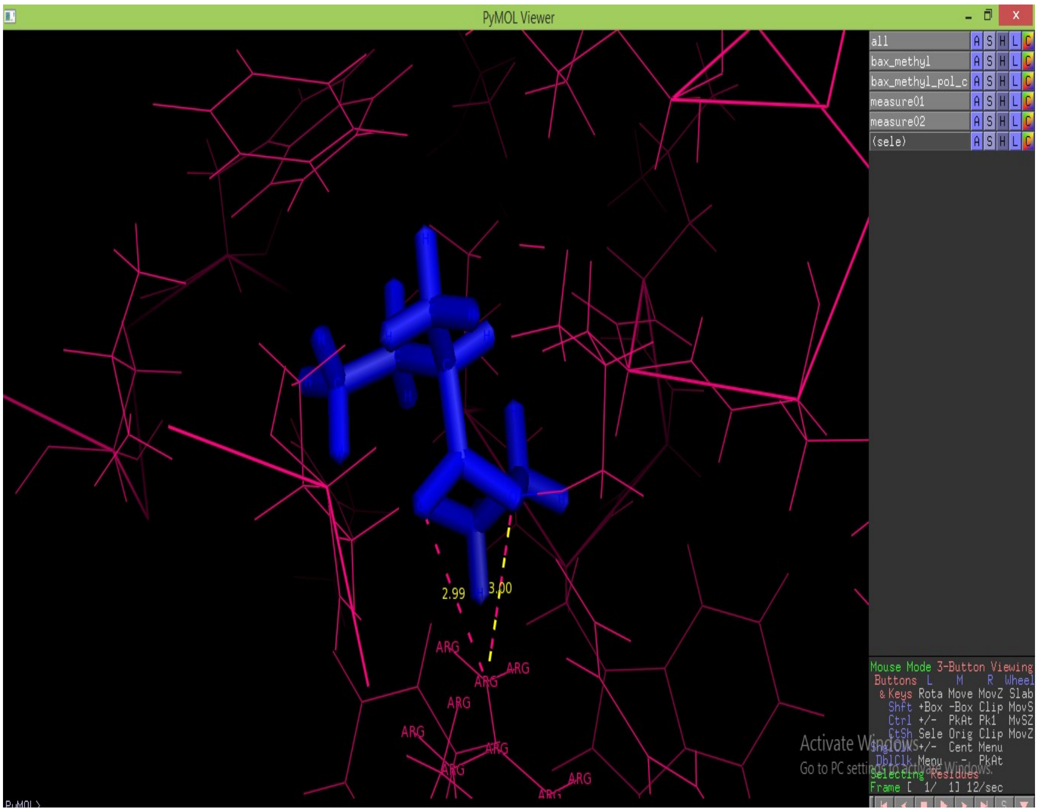

Figure 5: Visualization of docked complex of ethyl (2S)-2-methylbutanoate with BAX

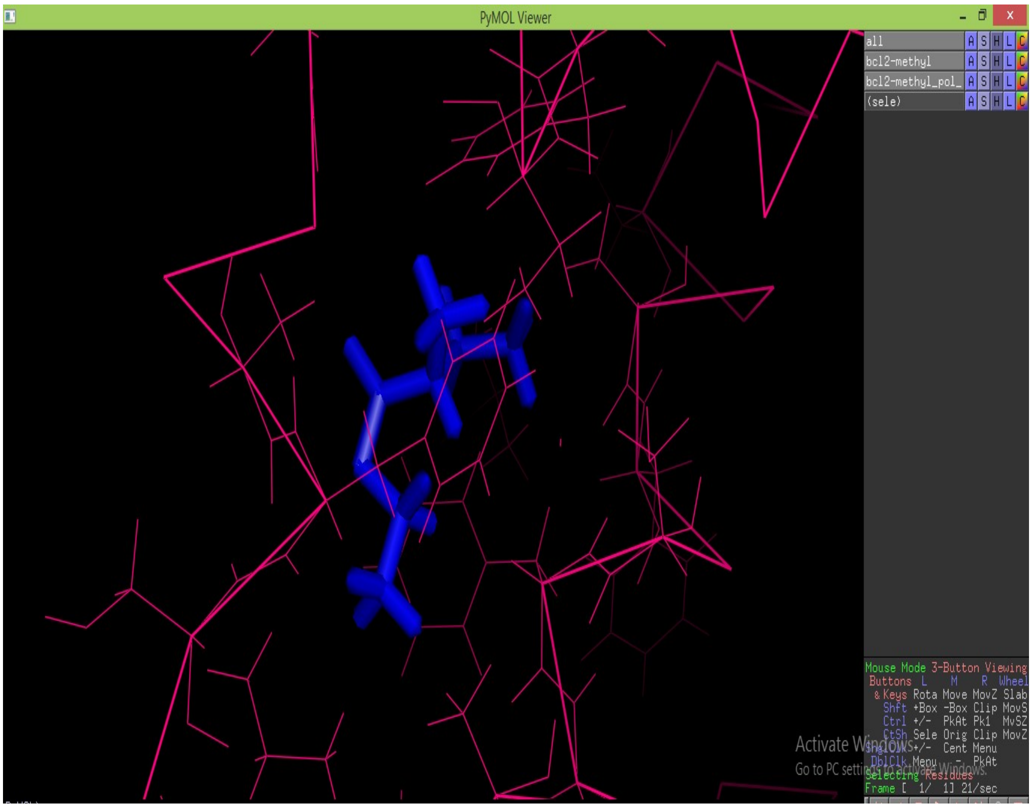

Figure 6: Visualization of docked complex of ethyl (2S)-2-methylbutanoate with Bcl2

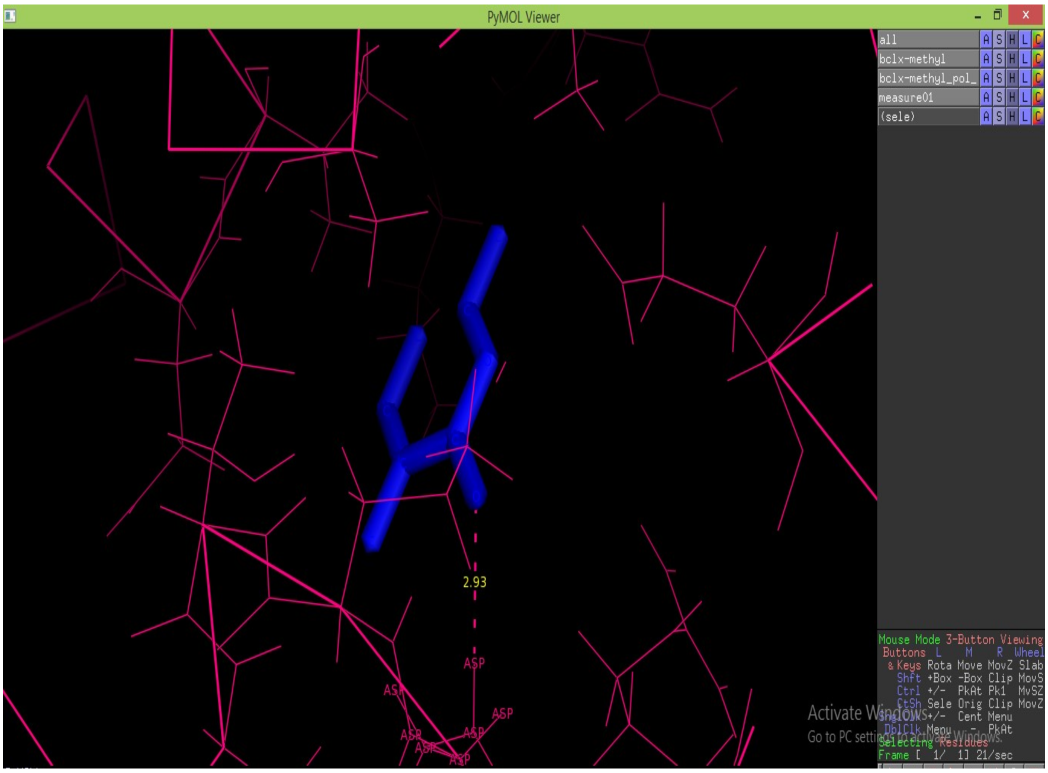

Figure 7: Visualization of docked complex of ethyl (2S)-2-methylbutanoate with Bcl-xL

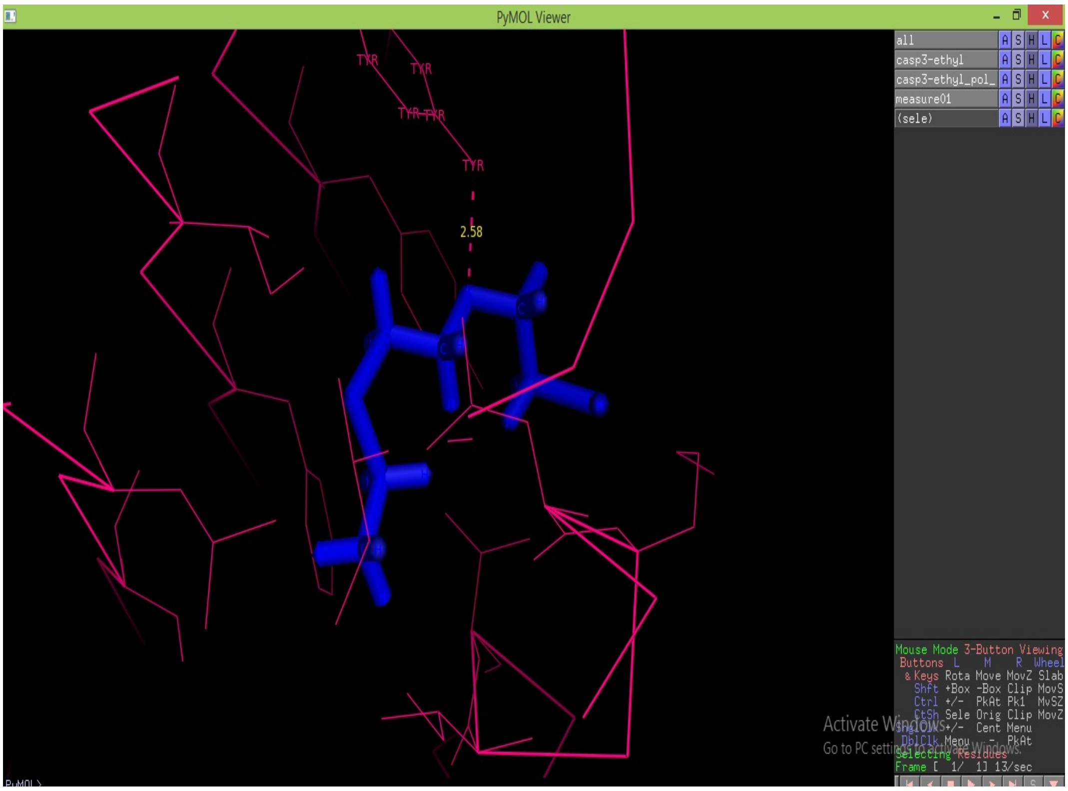

Figure 8: Visualization of docked complex of 1-(ethylsulfanyl) ethane-1-thiol with Caspase-3

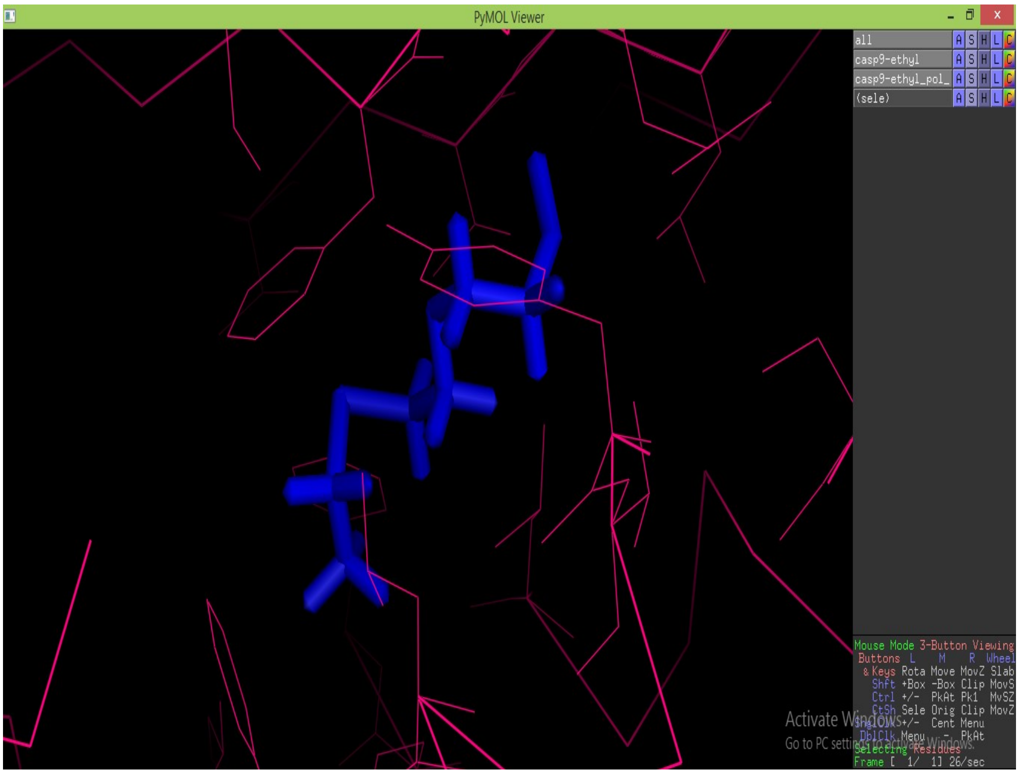

Figure 9: Visualization of docked complex of 1-(ethylsulfanyl) ethane-1-thiol with Caspase-9

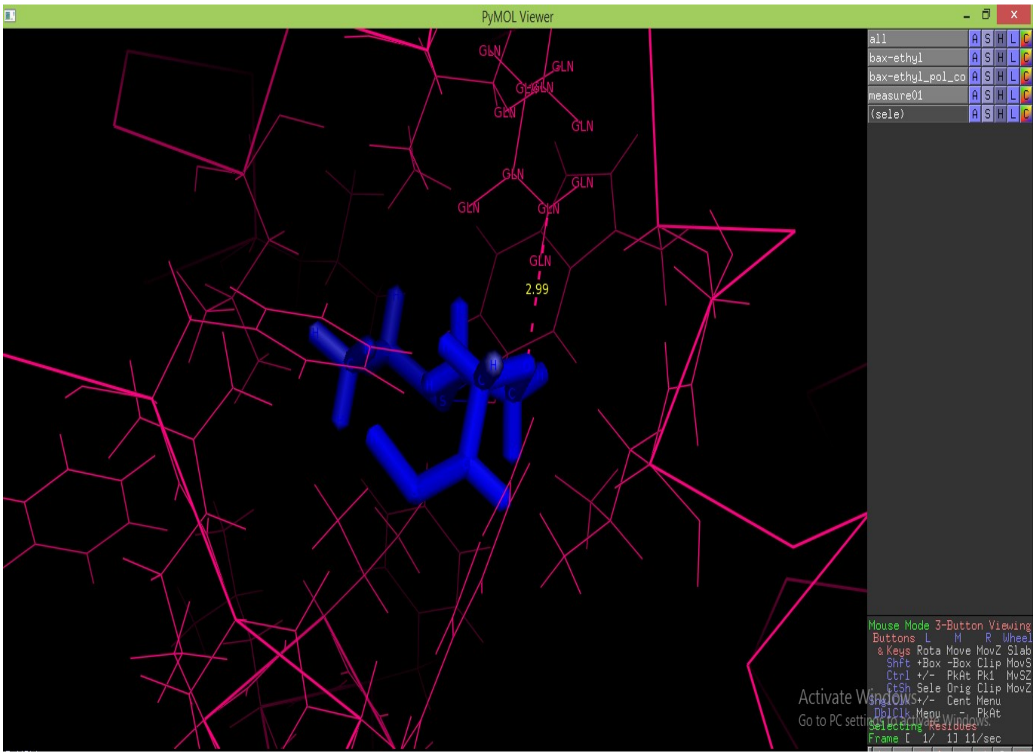

Figure 10: Visualization of docked complex of 1-(ethylsulfanyl) ethane-1-thiol with BAX

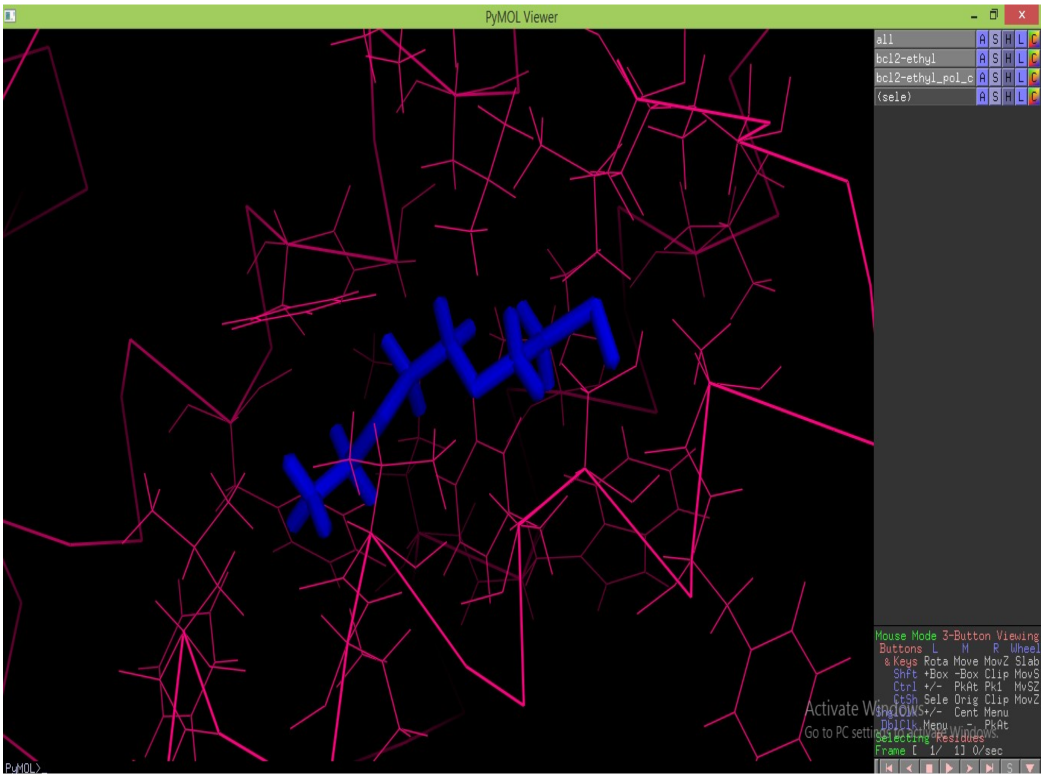

Figure 11: Visualization of docked complex of 1-(ethylsulfanyl) ethane-1-thiol with Bcl2

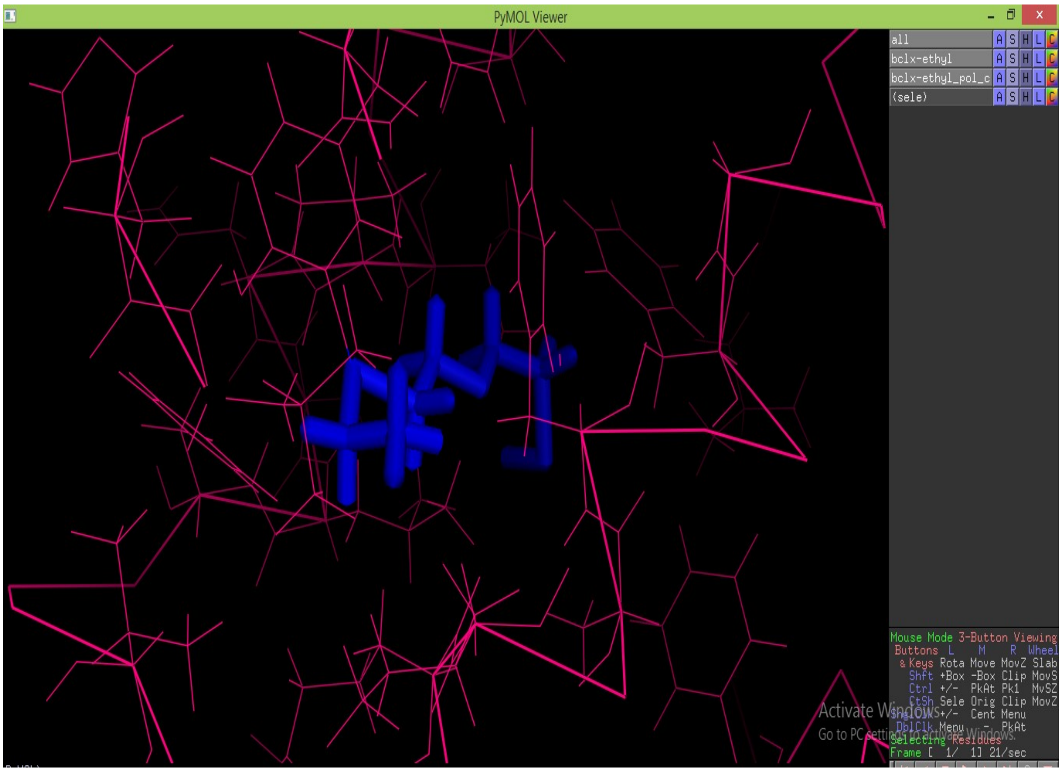

Figure 12: Visualization of docked complex of 1-(ethylsulfanyl) ethane-1-thiol with Bcl-xL

4. CONCLUSION

Current researches have been focused on the identification of cancer inhibitors from natural sources, and clinical trials with such tropical fruits have begun. Our study concludes that ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol GC-MS spectral compound of methanol extract from durian fruit pulp will be effective to control the over expression of anti-apoptotic proteins such as Caspase-3, Caspase-9, Bax, Bcl-2 and Bcl-xL demonstrating that these agents may be used in cancer treatment. From the results ethyl (2S)-2-methylbutanoate and 1-(ethylsulfanyl) ethane-1-thiol should be subjected to further experimental study in order to confirm these findings.

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