Sustainable Green Chemistry Approach to Structure-Based Drug Discovery of Soursop (Annona Muricata) Bioactive Compounds: Anticancer Efficacy through Quantum Chemical Calculations, Molecular Docking, and ADMET Studies with 7SA9 and 4ZFI Proteins

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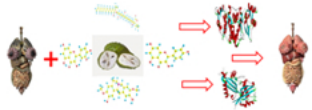
INTRODUCTION

Soursop has recently attracted scientific interest for its potential anticancer properties. The rich content of bioactive compounds in soursop, such as Annonacin, Kaempferol, Coreximine, Quercetin, acetogenins, alkaloids, and flavonoids, positions it as a promising candidate for cancer treatment (Mutakin et al., 2022). This study aimed to explore the anticancer potential of bioactive compounds from Soursop with cancer-related proteins Human MUC16 SEA5 Domain (7SA9) and Mouse Double Minute 2 (4ZFI) using a structure-based drug discovery approach.

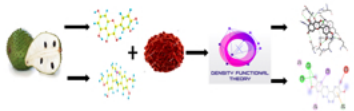


METHODOLOGY

Molecular Docking Simulation (Autodock Vina and Biovia Discovery Studio)
In this study, we conducted a molecular docking analysis to investigate the potential interactions of Annonacin, Kaempferol, Coreximine, Quercetin, with Human MUC16 SEA5 Domain (7SA9) and Mouse Double Minute 2 (4ZFI) proteins

Quantum Chemical Studies (Gaussian 09 suite program)

Density Functional Theory (DFT) was used in the Quantum Chemical Calculations. The optimization and frequency calculation of were executed employing the B3LYP functional and 6-311*G (d, p) basis set
ADMET Studies (SwissADMET and pkCSM)
ADMET studies were employed for predictive evaluations of drug-likeness and bioavailability



RESULTS

3D Visualization of Proteins
Annonacin

Figure 1: Protein-Ligand Interactions between Annonacin and 7SA9

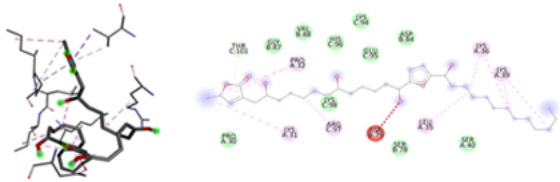


Figure 2: Protein-Ligand Interactions between Annonacin and 4ZFI

Quercetin

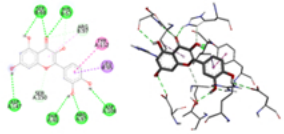


Figure 3: Protein-Ligand Interactions between Quercetin and 7SA9 protein

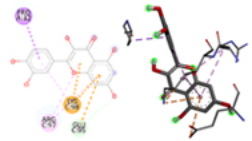


Figure 4: Protein-Ligand Interactions between Quercetin and 4ZFI protein

Kaempferol

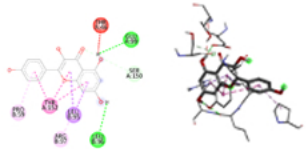


Figure 5: Protein-Ligand Interactions between Kaempferol and 7SA9 protein

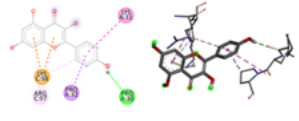


Figure 6: Protein-Ligand Interactions between Kaempferol and 4ZFI protein

Coreximine

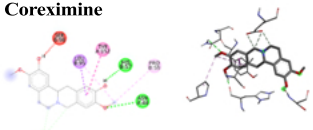


Figure 7: Protein-Ligand Interactions between Coreximine and 7SA9 protein

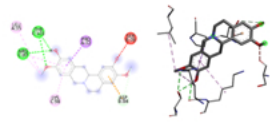


Figure 8: Protein-Ligand Interactions between Coreximine and 4ZFI protein

Results of Quantum Chemical Calculations

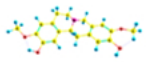


Figure 9: Optimized Geometry of Coreximine

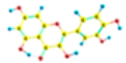


Figure 10: Optimized Geometry of Quercetin

Figure 11: Optimized Geometry of Annonacin

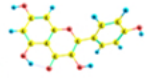


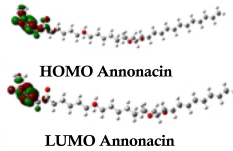
Figure 12: Optimized Geometry of Kaempferol

Table 1: Quantum chemical parameters for Coreximine, Annonacin, Kaempferol and Quercetin

Parameter	Coreximine	Quercetin	Annonacin	Kaempferol
Zero Point Energy (kcal/mol)	248.127	148.287	715.387	141.350
Polarizability (A.U)	150.561	150.294	211.242	216.534
Dipole Moment (Debye)	2.871	4.926	2.589	4.974
Enthalpy of Formation (Kcal/mol)	261.813	160.144	745.768	152.519
Free Energy (kcal/mol)	216.780	119.246	653.715	113.448
Entropy (kcal/mol)	0.151	0.137	0.309	0.131

Table 2: HOMO-LUMO Energies of Coreximine, Annonacin, Kaempferol and Quercetin

Molecule	HOMO Energy(ev)	LUMO Energy(ev)	Energy Difference (ev)
Coreximine	-3.0923	2.7726	5.8649
Annonacin	-8.1578	6.5297	14.6875
Kaempferol	-6.0434	-2.0420	4.0014
Quercetin	-3.0434	0.6134	3.6568



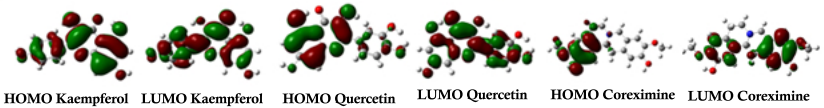


Table 3: ADMET Results of Annonacin, Coreximine, Kaempferol, and Quercetin

Property	Annonacin	Coreximine	Kaempferol	Quercetin
Physicochemical				
LogS	-2.067	-1.696	-3.624	-3.671
Medicinal Chemistry				
Lipinski Rule	Accepted	Accepted	Accepted	Accepted
Pfizer Rule	Accepted	Accepted	Accepted	Accepted
PAINS Alerts	0	0	0	1
Absorption				
HIA	---	---	---	---
Distribution				
BBB Penetration	---	+++	---	---
Metabolism				
CYP1A2 Inhibitor	+	-	+++	+++
CYP2C19 Inhibitor	-	---	---	---
CYP2C9 Inhibitor	+	---	+	+
CYP2D6 Inhibitor	++	++	++	-
CYP3A4 Inhibitor	+	---	+	-
Excretion				
CL	-0.385	18.126	6.868	8.284
T1/2	0.087	0.843	0.905	0.929
Toxicity				
AMES Toxicity	++	---	+	+

CONCLUSION

Quercetin emerged as the strongest binder to target proteins (7SA9 and 4ZFI), forming multiple hydrogen bonds (e.g., with ARG97: 1.99 Å), π-stacking, and metal chelation. Kaempferol showed balanced interactions but weaker affinity than quercetin, while annonacin relied on hydrophobic contacts and coreximine exhibited the weakest binding. Future research should focus on expansion of the compound screening to include additional Annona muricata constituents, experimental validation of the predicted activities through cell-based and animal studies, and development of optimized formulations to enhance bioavailability and target specificity.

REFERENCE

Mutakin, M., Fauziati, R., Fadhilah, F. N., Zuhrotun, A., Amalia, R., & Hadisaputri, Y. E. (2022). Pharmacological activities of soursop (Annona muricata Lin.). Molecules, 27(4), 1201.