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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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ABSTRACT

The ongoing quest for less harmful and more effective anticancer drugs has prompted scientists to look at natural substances made from plants. The bioactive substances Annonacin, Quercetin, Coreximine, and Kaempferol from Soursop (*Annona muricata*) and their possible anticancer effects are the main subjects of this investigation. To anticipate the interactions and binding affinities of these compounds with cancer-related proteins, Human MUC16 SEA5 Domain (7SA9) and Mouse Double Minute 2 (4ZFI), we used molecular docking experiments in conjunction with a structure-based drug discovery strategy. Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and density functional theory (DFT) calculations were carried out. According to the ADMET results, annonacin poses toxicity hazards while coreximine is the safest. Although they need to be optimized for solubility and toxicity reduction, quercetin and kaempferol exhibit intermediate potential. Quercetin has the greatest binding interactions (hydrogen bonds, π-stacking, and electrostatic contacts) according to the DFT findings. In contrast, Annonacin and Kaempferol have weaker, less specific interactions, while Coreximine has a high affinity but hydrophobic-driven binding to 4ZFI. According to the research, *Annona muricata* has bioactive chemicals that could be used to create novel cancer medications.

KEYWORDS: Molecular-Docking; Anti-cancer; Soursop; Pharmacokinetics; Natural Compounds

1. INTRODUCTION

Cancer continues to be a major cause of death worldwide, indicating the urgent need for less harmful and more effective treatment options. [1, 2] The potential of natural plant-based chemicals in cancer treatment has drawn a lot of attention because of their varied bioactive qualities and comparatively reduced toxicity when compared to manufactured medications.[3] Although soursop is well-known for its antidiabetic, analgesic, and anti-inflammatory activities, it has recently drawn attention from scientists due to possible anticancer effects.[4, 5] According to preclinical research, gallic, chlorogenic, 4hydroxybenzoic, protocatechuic, syringic and ellagic acids, epicatechin, lutein, tocotrienol, tocopherols, annonacin, kaempferol, coreximine, and quercetin are among the bioactive components found in soursop but annonacin, kaempferol, coreximine, and quercetin that have demonstrated the most promise.[6] The biological significance of the 7SA9 and 4ZFI proteins to cancer pathways and their potential as therapeutic targets for drug development led to their selection as the study's main targets.[7] The majority of prior research on soursop has been on its many therapeutic uses, with multiple studies examining its antidiabetic, analgesic, and anti-inflammatory qualities.[8] However, most studies have focused on in vitro and in vivo experiments without a detailed computational investigation of the molecular interactions between bioactive compounds and target proteins.[9] The novelty lies on employing quantum chemical calculations to analyse the electronic properties of these compounds, molecular docking to predict their binding affinities with 7SA9 and 4ZFI proteins, and ADMET studies to evaluate their drug-likeness and pharmacokinetic properties.

2. COMPUTATIONAL DETAILS

2.0 Computational Details 2.1 Molecular Docking Simulation

To examine the interactions between bioactive chemicals from Soursop and the 7SA9 and 4ZFI proteins, this study used the AutoDock tool to perform molecular docking simulations. The required PDB and PDBQT formats of the four bioactive chemicals and proteins were created using Auto dock Tools.[10] Biovia Discovery Studio 2021 was used to visualize the docking results, enabling a thorough examination of the interactions and binding affinities between the target proteins and the bioactive chemicals.

2.2 Quantum Chemical Studies and ADMET Studies

The B3LYP functional and the 6-311* (d, p) basis sets were selected for their balance of computing cost, efficiency, and accuracy in the widely used density functional theory (DFT). Gauss view 6.0, a molecular modelling program, was used to create the initial molecular structures using databases. The most stable conformations were then found by optimizing the geometry. The Gaussian 09 software package was used for all DFT calculations, and solvent effects were only taken into account when employing the Polarizable Continuum Model (PCM), when it was required to replicate physiological conditions.[11] Computational tools such as SwissADME (http://www.swissadme.ch/index.php) and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction) were utilized to predict drug-likeness and bioavailability of the compounds. [12, 13]

3. RESULTS AND DISCUSSION

3.1 Molecular Docking Interactions

3.1.1 Annonacin

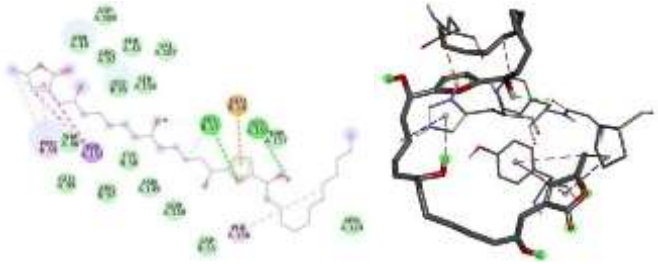

Figure 1: Protein-Ligand Interactions between Annonacin and 7SA9

The varying bond lengths underscore the flexibility and adaptability of these hydrophobic interactions, shaping the overall Bond Types as shown in **Figure 1.**

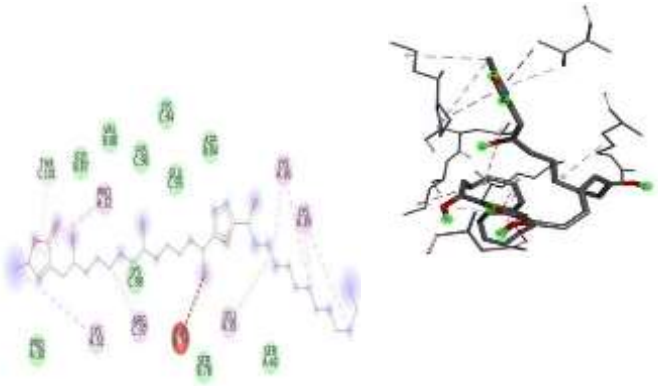

Figure 2: Protein-Ligand Interactions between Annonacin and 4ZFI

The different bond lengths highlight the hydrophobic interaction's plasticity and flexibility, forming the overall Bond Types as seen in **Figure 2.**

3.1.2 Quercetin

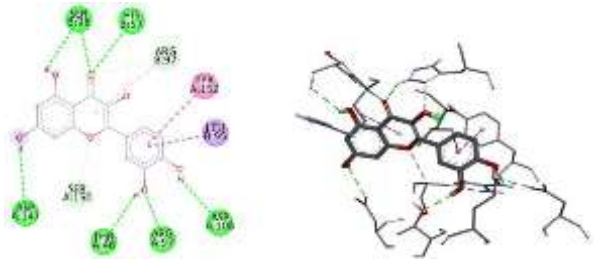

Figure 3: Protein-Ligand Interactions between Quercetin and 7SA9 protein
Conventional hydrogen bond as shown in **Figure 3** is observed with ARG97, ARG97, HIS57, SER98, THR46, ASP108, SER98, and ASP147 featuring a precise and directional interaction characterized by a bond length of 3.07406 Å, 1.99628 Å, 2.80662 Å, 2.38993 Å, 2.33035 Å, 2.82918 Å, 2.67892 Å, and 2.96446 Å, respectively

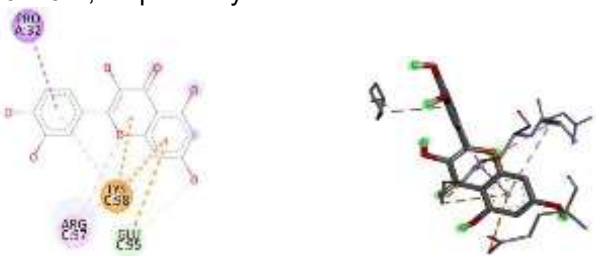

Figure 4: Protein-Ligand Interactions between Quercetin and 4ZFI protein

3.1.3 Kaempferol

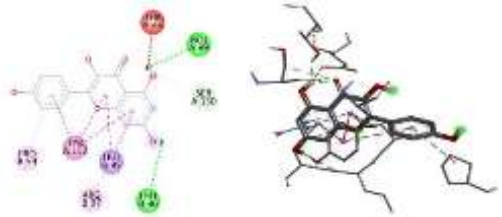

Figure 5: Protein-Ligand Interactions between Kaempferol and 7SA9 protein
As shown in **Figure 5,** distinctive conventional hydrogen bond is observed with GLU99, GLU99, and LEU96, featuring a precise and directional interaction characterized by a bond length of 2.69720 Å, 1.80097 Å, and 2.98426 Å, respectively.

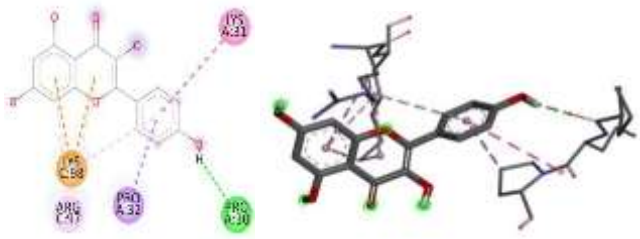

Figure 6: Protein-Ligand Interactions between Kaempferol and 4ZFI protein

Π-sigma interactions with PRO32 with bond lengths of 3.49863 Å, respectively, emphasize the involvement of aromatic systems in stabilizing the binding complex, providing additional anchoring points that reinforce the structural integrity of the binding site, as shown in **Figure 6.**

3.1.4 Coreximine

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

The π-π stacked interaction indicates a parallel arrangement of aromatic rings between TYR152 with a bond length of 4.55928 Å, and the bond length shows a relatively weak interaction as shown in **Figure 7.**

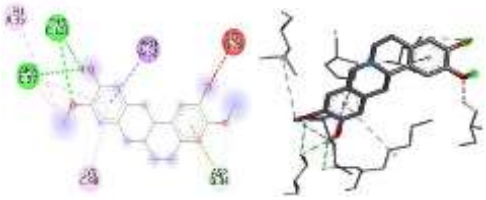

Figure 8: Protein-Ligand Interactions between Coreximine and 4ZFI protein

The hierarchy of binding strength—quercetin > kaempferol > annonacin > coreximine highlights quercetin's superior potential, though kaempferol's balanced profile warrants further exploration. **Table 1: Molecular Docking Results of Bioactive Compounds**

Parameter	Annonacin	Quercetin	Kaempferol	Coreximine
Binding Affinity (kcal/mol)				
7SA9	-7.40	-6.50	-5.30	-8.80
4ZFI	-5.20	-4.90	-4.10	-9.60
Key Hydrogen Bonds				
7SA9	HIS57 (2.56 Å)	ARG97 (1.99 Å)	GLU99 (1.80 Å)	ASN44 (2.94 Å)
4ZFI	THR101 (3.88 Å)	LYS98 (3.85 Å)	PRO30 (2.04 Å)	THR101 (2.27 Å)
Key Hydrophobic Interactions				
7SA9	π-Alkyl (TYR152)	π-π Stacked (TYR152)	π-Sigma (LEU95)	π-π Stacked (TYR152)

4ZFI	Alkyl (LEU35)	π-Alkyl (ARG97)	π-Alkyl (ARG97)	π -Alkyl (ARG97)
Electrostatic Interactions				
7SA9	π-Anion (GLU54)	π-Cation (LYS98)	–	–
4ZFI	–	π-Anion (GLU95)	π-Cation (LYS98)	π -Anion (ASP84)

When comparing the tested drugs' binding affinities to two cancer-related protein targets (7SA9 and 4ZFI), the docking results show notable differences. Coreximine was the most promising choice for additional research since it showed the greatest binding to both proteins (-8.80 kcal/mol with 7SA9 and -9.60 kcal/mol with 4ZFI). While annonacin showed a moderate but constant affinity for both targets (5.20 to -7.40 kcal/mol), quercetin demonstrated selective effectiveness against 7SA9 (-6.50 kcal/mol) but lesser binding to 4ZFI (-4.90 kcal/mol). Between -4.10 and -5.30 kcal/mol, kaempferol showed the weakest interactions of all the substances studied.

3.2 Results of Quantum Chemical Calculations

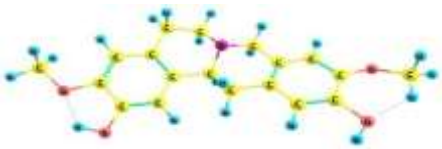

Figure 9: Optimized Geometry of Coreximine

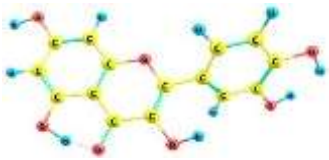

Figure 10: Optimized Geometry of Quercetin

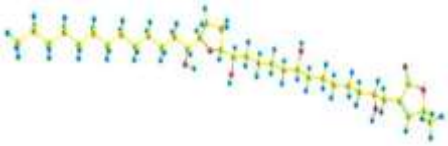

Figure 11: Optimized Geometry of Annonacin

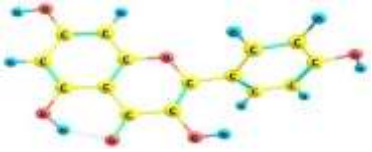

Figure 12: Optimized Geometry of Kaempferol

Table 2: 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

T**able 2** shows some quantum chemical parameters for Coreximine, Quercetin, Annonacin, and Kaempferol, and the optimized structures can be seen in **Figure, 9, 10, 11, and 12,** respectively, offering insights into their stability, reactivity, and potential anticancer properties. A molecule's zero-point energy, or ZPE, is its lowest energy state. With the largest ZPE and hence higher reactivity, annonacin may be better able to disrupt the functions of cancer cells. Quercetin may be the least reactive, as seen by its lowest ZPE value, which is followed by intermediate values for coreximine and kaempferol. When targeting cancer cells, high reactivity can be useful, but stability must be balanced. Since annonacin has the highest ZPE (715.387 kcal/mol), it is more reactive due to its higher intrinsic energy.

Table 3: HOMO-LUMO Energies of Coreximine, Annonacin, Kaempferol and Quercetin

Molecule	HOMO Energy(ev)	LUMO Energy(ev)	Energy Difference ΔE (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

Quercetin and Kaempferol demonstrate particularly favourable electronic profiles for anticancer activity, as evidenced by their relatively small HOMO-LUMO gaps (3.6568 eV and 4.0014 eV, respectively). The exceptionally large HOMO-LUMO gap of Annonacin (14.6875 eV), as shown in **Table 3** suggests high kinetic stability but potentially limited reactivity.

3.3 ADMET Results

In addition, quercetin and kaempferol exhibit reduced toxicity risks and neither hepatotoxicity nor mutagenicity (AMES−), in comparison with annonacin, which causes drug-induced liver injury (DILI+++). They also improve their safety profiles due to their balanced CYP450 interactions, which show moderate inhibition without significant interference. Both chemicals have substantial potential for drug-induced liver damage, according to their toxicity profiles, and quercetin also exhibits AMES toxicity. The most promising candidate from an ADMET standpoint is coreximine, as shown by the comparison of these four molecules in Table 4.

Table 4: ADMET Profiles of Potential Anticancer Compounds

Parameter	Annonacin	Coreximine	Kaempferol	Quercetin
Molecular Weight (g/mol)	568.250 (High)	327.150 (Moderate)	286.050 (Low)	302.040 (Low)
logP	4.506 (High lipophilicity)	2.155 (Moderate)	2.656 (Moderate)	2.155 (Moderate)
Logs	-2.067 (Low solubility)	-3.624 (Very low)	-3.624 (Very low)	-3.671 (Very low)
TPSA (Å²)	120.360	62.160	111.130	131.360
Rotatable Bonds	14 (Flexible)	2 (Rigid)	1 (Very rigid)	1 (Very rigid)
Permeability (Caco-2/MDCK)	Poor	Poor (P-gp substrate)	Poor	Poor
Plasma Protein Binding (PPB)	>100% (Very high)	82.251% (Moderate)	97.861% (High)	95.496% (High)
BBB Penetration	--	+++ (High)	--	--
CYP Inhibition	CYP1A2, 2C9, 2D6, 3A4	None	CYP1A2, 2C9	CYP1A2, 2C9

Major Toxicity Concerns	Hepatotoxicity, Mutagenicity,	Skin sensitization (++) Carcinogenicity	DILI (+++), Skin sensitization (++)	DILI (+++), Skin toxicity (+), Skin sensitization (+++) AMES
Drug-Likeness	Fails some rules	Compliant (QED = 0.888)	Compliant	Compliant (with alerts)

4. CONCLUSION

This study has demonstrated the strong anticancer potential of the bioactive compounds, including Annonacin, Quercetin, Coreximine, and Kaempferol, that are present in soursop (*Annona muricata*). When it came to creating many hydrogen bonds (e.g., with ARG97: 1.99 Å), π-stacking, and metal chelation, coreximine was the most effective binder to target proteins (7SA9 and 4ZFI). Kaempferol showed balanced interactions but a lower affinity than quercetin, whereas coreximine had the lowest binding, and annonacin depended on hydrophobic contacts. Additional *Annona muricata* ingredients should be screened for in future investigations, and cell-based and animal studies should be used to experimentally validate the anticipated action and development of optimized formulations to enhance bioavailability and target specificity.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

(1) Weth, F. R.; Hoggarth, G. B.; Weth, A. F.; Paterson, E.; White, M. P.; Tan, S. T; & Gray, C. Unlocking hidden potential: advancements, approaches, and obstacles in repurposing drugs for cancer therapy. British J. Cancer. 2024, 130(5), 703-715.

(2) Boshuizen, J.; Peeper, D. S. Rational cancer treatment combinations: an urgent clinical need. Mol. cell, 2020, 78(6), 1002-1018.

(3) Dehelean, C. A.; Marcovici, I.; Soica, C.; Mioc, M.; Coricovac, D., Iurciuc, S.; & Pinzaru, I. Plantderived anticancer compounds as new perspectives in drug discovery and alternative therapy. Mol. 2021, 26(4), 1109.

(4) Santos, I. L.; Rodrigues, A. M; Amante, E. R.; & Silva, L. H. Soursop (*Annona muricata*) properties and perspectives for integral valorization. Foods, 2023, 12(7), 1448.

(5) Abdul Wahab, S. M.; Jantan, I.; Haque, M. A.; Arshad, L. Exploring the leaves of *Annona muricata* L. as a source of potential anti-inflammatory and anticancer agents. Frontiers in pharm. 2018, 9, 344514.

(6) Ilango, S.; Sahoo, D. K.; Paital, B.; Kathirvel, K.; Gabriel, J. I.; Subramaniam, K.; Nirmaladevi, R. A review on *Annona muricata* and its anticancer activity. Cancers, 14(18), 4539.

(7) Bio Smart Notes. Biological significance of proteins. *Bio Smart Notes*. 2025, https://biosmartnotes.com/biological-significance-of-proteins/

(8) Coria-Téllez, A. V.; Montalvo-Gónzalez, E.; Yahia, E. M.; Obledo-Vázquez, E. N. *Annona muricata*: A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. Arabian J. chem, 2018, 11(5), 662-691.

(9) Lin, J.; Sahakian, D. C.; De Morais, S. M.; Xu, J. J.; Polzer, R. J.; Winter, S. M. The role of absorption, distribution, metabolism, excretion and toxicity in drug discovery. *Current topics in medicinal chemistry*, 2003, *3*(10), 1125-1154.

(10) Trott, O.; & Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J. com. Chem. 2010, 31(2), 455-461.

(11) Wang, Y.; Cheng, X.; Yang, X.; & Yang, X. DFT study of solvent effects for some organic molecules using a polarizable continuum model. J. solution chem. 2006, 35, 869-878.
(12) Riviere, J. E. Absorption, distribution, metabolism, and elimination. Veterinary pharmacology and therapeutics, 2009, 9.
(13) Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. reports, 2021, 7(1), 42717