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Molecular Docking Study of *Annona muricata* Bioactive Compounds Against Caspase 3

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Abstract

Introduction: Soursop, or *Annona muricata*, is a plant that has long been used to treat a variety of illnesses, including cancer. The purpose of this study was to use an *in-silico* method to assess the anti-cancer activity of chemicals produced from *Annona muricata*.

Materials and Methods: To determine the bioactive substances found in *Annona muricata* that are known to have anti-cancer qualities, a thorough literature research was carried out. Following that, these substances were put through molecular docking tests against important protein targets linked to cancer, including receptors implicated in angiogenesis, apoptosis, and cell proliferation. Possible interactions between the identified *Annona muricata* chemicals and cancer-associated protein targets were discovered by the *in-silico* research.

Results: Several compounds demonstrated favorable binding interactions with Caspase-3. Coreximine showed the most favorable docking score (−6.7 kcal/mol), followed by Catechin (−6.5 kcal/mol), making these two the strongest potential bioactive or therapeutic candidates, Anomurine (−5.8 kcal/mol), Solamin (−5.4 kcal/mol), Annonacin (−4.8 kcal/mol), and Gallic acid (−4.7 kcal/mol). In contrast, the reference compound Doxorubicin displayed a weaker score (−2.2 kcal/mol). These docking values suggest potential micromolar-range affinities for several *A. muricata* compounds, which, while encouraging, indicate that they are likely to serve as lead compounds rather than direct therapeutic agents. The docking results highlighted promising candidates, although weaker docking indicates natural compounds' potential advantage; however, real-world efficacy depends on multiple pharmacological factors and their biological and clinical significance can only be established through further experimental studies, including enzyme inhibition assays, cell-based apoptosis assay and in vivo validation.

Conclusion: In summary, this *in-silico* work opens the door for the creation of innovative natural anti-cancer treatment medicines by offering important insights into the molecular mechanisms behind *Annona muricata's* anti-cancer action.

Keywords: *Annona muricata*, soursop, anti-cancer activity, *in-silico*, molecular docking, bioactive compounds.

1. Introduction

Cancer is a multifactorial disease characterized by uncontrolled cell proliferation, impaired growth regulation, and the potential for invasion and metastasis. Globally, cancer remains a major public health burden, accounting for one in every six deaths. In 2020 alone, there were an estimated 19.3 million new cases and nearly 10 million cancer-related deaths worldwide [1, 2]. Conventional therapeutic options, such as surgery, chemotherapy, and radiotherapy, have been the

mainstay of treatment for decades [3]. However, their effectiveness is often limited by severe side effects, drug resistance, and reduced quality of life for patients . These limitations have spurred interest in alternative and complementary treatment strategies, including the exploration of natural products as potential anticancer agents [4].

Cervical cancer, one of the most common malignancies among women, is caused by the uncontrolled growth of abnormal cells in the cervix In low- and middle-income countries, late diagnosis and limited access to healthcare resources often result in high morbidity and mortality rates. Early detection and preventive interventions are critical; however, in advanced cases, prognosis remains poor despite available treatment options. This underscores the urgent need to identify novel, safe, and cost-effective therapeutic alternatives [5]. *Annona muricata*, commonly known as soursop or graviola, is a medicinal plant belonging to the Annonaceae family [6, 7]. It is widely distributed in tropical and subtropical regions and has been extensively used in ethnomedicine. The plant is a rich source of secondary metabolites, including acetogenins, alkaloids, flavonoids, and phenolic compounds, which contribute to its diverse pharmacological activities [8]. Traditionally, different parts of the plant have been used to treat conditions such as fever, hypertension, parasitic infections, and inflammation [9, 10]. More importantly, accumulating evidence highlights its anticancer potential. Extracts of *A. muricata* have been shown to exhibit antibacterial, antiparasitic, antioxidant, and anticancer activities [11–13].

Among its phytochemicals, annonacin, an acetogenin, has drawn attention for its potent antitumor properties. It disrupts mitochondrial oxidative phosphorylation, leading to ATP depletion and subsequent induction of apoptosis or necrosis in cancer cells. Other compounds such as quercetin, catechin, and gallic acid have demonstrated cytotoxicity and synergistic antioxidant effects, further strengthening the case for *A. muricata* as a source of anticancer agents [14–16].

Despite these promising findings, the translation of *A. muricata* extracts into clinical applications remains limited. Current studies often lack systematic evaluation of specific bioactive compounds, mechanistic insights, and in-silico validations to guide drug discovery pipelines. Thus, there is a clear knowledge gap regarding the molecular interactions between soursop phytochemicals and cancer-related proteins, particularly in cervical cancer. This study addresses this gap by employing in-silico molecular docking approaches to investigate the anticancer potential of *A. muricata* leaf phytochemicals against caspase-3, a key executor protein in the apoptotic pathway. The findings are expected to provide preliminary evidence for the development of novel, plant-derived anticancer therapies with minimal side effects, while strengthening the scientific basis for traditional uses of soursop.

2. Materials and Methods

The following online databases and computational tools were employed:

Databases: PubChem (for ligand structures), RCSB Protein Data Bank (for protein structure).

Software: BIOVIA Discovery Studio Visualizer v20.2.0.19295 (for ligand preparation and format conversion), AutoDock Vina (for docking), PyRx (as docking interface), and iGEMDOCK 2.1 (for validation of docking results).

In-silico Investigation by Molecular Docking of Annonacin with Caspase 3.

Protein preparation

Caspase 3 (PDB ID: 4JJ8) was selected as the target protein due to its central role as an “executioner caspase” in the apoptotic signaling pathway. Activation of Caspase 3 leads to proteolytic cleavage of essential cellular proteins, culminating in programmed cell death. Many anti-cancer agents exert their effects by upregulating Caspase 3 activity or stabilizing interactions that enhance apoptosis in malignant cells. Hence, evaluating the binding affinities of natural compounds from *Annona muricata* with Caspase 3 provides mechanistic insight into their potential apoptotic and anti-cancer activity.

The three-dimensional structure of Caspase 3 with PDB ID 4jj8 was obtained from the RCSB Protein Data Bank [http://www.rcsb.org]. Validation of the protein was done by checking for missing hydrogen, abnormal side-chains, improper bonds, etc. A pdbqt format for the protein was created when the macromolecular structure was inputted into Autodock Vina [17]. Then, the downloaded PDB X-ray crystallographic structure was imported into the software’s “prepare binding site” module for the iGEMDOCK 2.1 version [18] for the validation of docking, which was utilized to prepare the binding site.

Ligands preparation

Ten secondary metabolites were used as ligands [Table 1]. The ligands structures were downloaded in .sdf format from the PubChem databank. These structures were converted to the .pdb format for

docking purposes using Biovia Discovery Studio Visualizer v20.2.0.19295 [https://pubchem.ncbi.nlm.nih.gov/]. Energy minimization was performed to stabilize conformations using the MMFF94 force field, ensuring optimized geometry prior to docking. The optimized compounds were then imported to Autodock Vina to obtain the pdbqt formats of the structures.

Table 1. List of ligands

S/N	Ligand	Phytochemical group
1	Anomurine COC1=CC=C[C=C1]CC2C3=CC[=C[C[=C3CCN2]OC]OC]OC	Alkaloid
2	Coreximine COC1=C[C=C2[C@@H]3CC4=CC[=C[C=C4CN3CCC2=C1]OC]O]O	Alkaloid
3	Reticuline CN1CCC2=CC[=C[C=C2[C@@H]1CC3=CC[=C[C=C3]OC]O]O]OC	Alkaloid
4	Annonacin CCCCCCCCCCCC[C@H][[C@H]1CC[C@@H][O1][C@@H][CCCC[C@@H][CCCCC[C@H][CC2=C[C@@H][OC2=O]C]O]O]O]O	Acetogenin
5	Corossolone CCCCCCCCCCCCC[C1CCC[O1]C[CCCCC[=O]CCCCCCCC2=CC[OC2=O]C]O]O	Acetogenin
6	Solamin CCCCCCCCCCCC[C@@H][[C@@H]1CC[C@@H][O1][C@@H][CCCCCCCCCCCCC2=C[C@@H][OC2=O]C]O]O	Acetogenin
7	Catechin C1[C@@H][[C@H][OC2=CC[=CC[=C21]O]O]C3=CC[=C[C=C3]O]O]O	Flavonoid
8	Quercetin C1=CC[=C[C=C1C2=C[C[=O]C3=C[C=C[C=C3O2]O]O]O]O]O	Flavonoid
9	Rutin C[C@H]1[C@@H][[C@H][[C@H][[C@@H][O1]OC[C@@H]2[C@H][[C@@H][[C@H][[C@@H][O2]OC3=C[OC4=CC[=CC[=C4C3=O]O]O]C5=CC[=C[C=C5]O]O]O]O]O]O]O	Flavonoid
10	Gallic acid C1=C[C=C[C[=C1O]O]O]C[=O]O	Tannin
	Doxorubicin C[C@H]1[C@H][[C@H][C[C@@H][O1]O[C@H]2C[C@@][CC3=C2C[=C4C[=C3O]C[=O]C5=C[C4=O]C[=CC=C5]OC]O][C[=O]CO]O]N]O	Standard drug

Molecular docking

The Autodock Vina software was used to conduct the structure-based virtual screening process, which was done at an exhaustiveness value of 8. To identify the area where the ligands would dock, a grid box was placed around the VEGF protein's active site pocket. As a result, the grid box dimension VEGF was defined as 126 x 126 x 126 [for X, Y, and Z, respectively], with a spacing of 0.375 and centered on active pocket residues. Vina evaluated the results of several ligand-receptor docking operations, calculated the binding affinities of the ligands, and clustered the resulting poses according to how much of their conformational overlaps occurred. The best pose for each cluster was picked, and the ligands were ranked according to their binding affinities [17]. The iGEMDOCK 2.1 software [18] with a separate algorithm from Autodock Vina/PyRx was used to verify uniformity in the docking results and the selection of the top-scoring chemical entities in order to validate the molecular docking-based VS. In the iGEMDOCK 2.1. version, the "prepare binding site" module of the program was used to prepare the binding site by importing the downloaded PDB X-ray crystallographic structure. Using the protein's bound ligand as a protocol for grid generation and a binding site radius of 8.0 Angstrom, the active site of the protein was identified. The "prepare compounds" module was used to prepare the ligands, which were also imported in their original

configuration [PDB]. The population size, number of generations, and number of solutions were set to 300, 80, and 5, respectively, in the docking accuracy settings for Then, the ligands' binding affinities against the target were computed. Then, a custom parameter protein was used to visualize the successful compounds using the Discovery Studio VEGF. Visualizer. To know if the docked ligand has interacted well, it was compared with the interaction of the standard drug Doxorubicin. After docking the ligands with the targeted protein, the binding energy value [kcal/mol] and ligand binding site amino acids were recorded.

3. Results

Molecular Docking

Molecular docking identified several phytochemicals from Annona muricata with stronger binding affinities for caspase-3 compared to the reference drug, Doxorubicin. The consensus docking scores revealed that Coreximine (−6.7 kcal/mol) and Catechin (−6.5 kcal/mol) were the top binders, followed by Anomurine (−5.8 kcal/mol), Solamin (−5.4 kcal/mol), Annonacin (−4.8 kcal/mol), and Gallic acid (−4.7 kcal/mol). In contrast, Doxorubicin displayed a weaker score (−2.2 kcal/mol), reflecting differences in its binding mode and mechanism of action.

Table 1. Docking Scores of Selected Hits in Comparison with Doxorubicin

LIGAND	IGEM-DOCK [4jj8]	AUTODOCK VINA [4jj8]	Consensus scoring [average]
Doxorubicin	0.2	-4.6	-2.2
Annonacin	-8.6	-1.0	-4.8
Anomurine	-7.8	-3.7	-5.8
Catechin	-8.5	-4.5	-6.5
Coreximine	-8.7	-4.6	-6.7
Gallic Acid	-5.9	-3.4	-4.7
Quercetin	5.9	-4.3	0.8
Reticuline	11.3	-4.4	3.5
Corossolone	12.1	-2.2	4.9
Rutin	30.1	-5.1	12.5

Table 2. Consensus scoring, Conventional H-bond, and other interactions of the hit compounds and Doxorubicin [reference drug]

S/N	Ligand	Consensus Scoring [kcal/mol]	Conventional Hydrogen Bonds	Other Interactions
Drug	Doxorubicin	-2.2		GLN59, TYR60, ASN61, PHE64, GLU176, PRO178, ILE213, LYS297
1	Gallic acid	-4.7		SER143, GLY145, GLN184, ARG233
2	Annonacin	-4.8		
3	Anomurine	-5.8		

4	Quercetin	0.8	ASP255	GLN59, TYR60, ASN61, MET62, TYR100, LYS254, GLU298, LEU299, PHE301, SER302
5	Catechin	-6.5		
6	Corexmine	-6.7		
7	Reticuline	3.5		TYR60, THR57, ASN 61, ASN63, GLN59, MET62, LYS297
8.	Corossolone	4.9		
9.	Rutin	12.5		GLY105, LEU67, ALA134, ALA135
10.	Solamin	-5.4		

Coreximine and Catechin displayed the strongest interactions, forming energetically stable complexes with caspase-3. Gallic acid also demonstrated multiple hydrogen bonds, strengthening its predicted binding.

While Doxorubicin is widely used as a chemotherapeutic, its weak docking score is consistent with its distinct mechanism of action—DNA intercalation and topoisomerase II inhibition—rather than direct caspase-3 modulation. This mechanistic difference suggests that phytochemicals like Coreximine and Catechin may act through apoptotic pathway regulation and could potentially complement existing therapies.

Table 3. iGEM Result

Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
4jj8_Cleaned-Annonacin_COMPOUND_CID_354398-5.pdb	-86.1757	-86.1757	0	0	15.8571
4jj8_Cleaned-Anomurine_COMPOUND_CID_157218-4.pdb	-78.447	-78.447	0	0	19.36
4jj8_Cleaned-Catechin_COMPOUND_CID_9064-1.pdb	-84.8247	-84.8247	0	0	25.7143
4jj8_Cleaned-Coreximine_COMPOUND_CID_7037179-8.pdb	-87.1866	-87.1866	0	0	24
4jj8_Cleaned-Corossolone_COMPOUND_CID_4366126-0.pdb	120.576	120.576	0	0	12.2927
4jj8_Cleaned-Gallic acid_COMPOUND_CID_370-4.pdb	-58.8768	-58.8768	0	0	32.0833
4jj8_Cleaned-Quercetin_COMPOUND_CID_5280343-0.pdb	58.9454	58.9454	0	0	24.4091
4jj8_Cleaned-Reticuline_COMPOUND_CID_439653-0.pdb	112.807	112.807	0	0	18.4167

4jj8_Cleaned-Rutin_COMPOUND_CID_5280805-0.pdb	301.015	301.015	0	0	15.6977
4jj8_Cleaned-Solamin_COMPOUND_CID_11376469-4.pdb	-86.4862	-86.4862	0	0	13.675
4jj8_Cleaned-Conformer3D_COMPOUND_CID_31703-0.pdb	1.57326	1.57326	0	0	11.4103

Table 4. AutoDock Vina Result

#Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
4jj8_Cleaned-Annonacin_COMPOUND_CID_354398-5.pdb	-86.1757	-86.1757	0	0	15.8571
4jj8_Cleaned-Anomurine_COMPOUND_CID_157218-4.pdb	-78.447	-78.447	0	0	19.36
4jj8_Cleaned-Catechin_COMPOUND_CID_9064-1.pdb	-84.8247	-84.8247	0	0	25.7143
4jj8_Cleaned-Coreximine_COMPOUND_CID_7037179-8.pdb	-87.1866	-87.1866	0	0	24
4jj8_Cleaned-Corossolone_COMPOUND_CID_4366126-0.pdb	120.576	120.576	0	0	12.2927
4jj8_Cleaned-Gallic acid_COMPOUND_CID_370-4.pdb	-58.8768	-58.8768	0	0	32.0833
4jj8_Cleaned-Quercetin_COMPOUND_CID_5280343-0.pdb	58.9454	58.9454	0	0	24.4091
4jj8_Cleaned-Reticuline_COMPOUND_CID_439653-0.pdb	112.807	112.807	0	0	18.4167
4jj8_Cleaned-Rutin_COMPOUND_CID_5280805-0.pdb	301.015	301.015	0	0	15.6977
4jj8_Cleaned-Solamin_COMPOUND_CID_11376469-4.pdb	-86.4862	-86.4862	0	0	13.675
4jj8_Cleaned-Conformer3D_COMPOUND_CID_31703-0.pdb	1.57326	1.57326	0	0	11.4103

4. Discussion

This study employed an in-silico approach to explore the anti-cancer potential of *Annona muricata* bioactive compounds by docking them against caspase-3, a central effector protein in the apoptotic pathway. Caspase-3 activation is known to mediate programmed cell death, which is often dysregulated in cancer cells. Thus, compounds capable of binding strongly to caspase-3 may help restore apoptotic signaling, making it a rational therapeutic target.

Among the screened compounds, Coreximine and Catechin showed the most favorable docking scores (−6.7 and −6.5 kcal/mol, respectively), outperforming the standard chemotherapeutic agent Doxorubicin (−2.2 kcal/mol). This suggests that these phytochemicals may stabilize caspase-3 in its active conformation, thereby enhancing apoptotic signaling in malignant cells. Similarly, Anomurine and Solamin displayed significant affinities, highlighting the therapeutic promise of alkaloids and acetogenins as apoptosis modulators. The presence of hydrogen

bonds and hydrophobic interactions with key residues further supports the likelihood of stable ligand–protein complexes.

Beyond apoptosis, several of these compounds have been reported in previous studies to exhibit antioxidant activity by scavenging reactive oxygen species (ROS) and enhancing cellular antioxidant defenses. This dual role—apoptosis induction and oxidative stress mitigation—suggests that *A. muricata* metabolites could target multiple hallmarks of cancer simultaneously, providing a mechanistic explanation for their observed docking performance.

Interestingly, Doxorubicin's weaker binding affinity highlights a fundamental mechanistic difference. While Doxorubicin acts primarily through DNA intercalation and topoisomerase II inhibition, *A. muricata* metabolites may directly influence apoptotic proteins. This indicates that phytochemicals like Coreximine and Catechin could complement standard drugs by engaging different molecular targets.

Nevertheless, some limitations of this work must be acknowledged. Docking scores provide useful predictions but cannot capture the dynamic flexibility of protein–ligand interactions. Molecular dynamics (MD) simulations and binding free energy calculations would provide deeper insights into the stability of these complexes under physiological conditions. Furthermore, pharmacokinetic and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties were not evaluated, which are crucial for drug development. In addition, in-vitro and in-vivo validation are necessary to confirm the predicted biological effects.

Taken together, this study highlights caspase-3 as a relevant molecular target for *A. muricata* phytochemicals, with Coreximine, Catechin, and Solamin emerging as promising candidates for further experimental validation. The ability of these compounds to modulate apoptosis and oxidative stress underscores their potential role in developing safer, plant-based therapeutic strategies for cancer management.

Specific interactions, such as conventional hydrogen bonds and other interactions, were also noted. For example, Quercetin formed a conventional hydrogen bond with ASP255, and Doxorubicin interacted with residues like GLN59, TYR60, and ASN61. Previous studies, such as Gyesi et al. [17] and Mutakin et al. [18], have reported the antibacterial, antiprotozoan, anti-inflammatory, antioxidant, and anticancer effects of soursop extract. This *in-silico* study complements these findings by proposing potential molecular mechanisms for the observed anti-cancer effects.

Acetogenins, like annonacin, are neurotoxic long-chain fatty acids that are present in soursop and have been shown to have anti-tumor activities. Annonacin's high binding to Caspase 3 in this study is consistent with the mechanism by which it inhibits ATP synthesis through oxidative phosphorylation, resulting in necrosis or apoptosis. Given that caspase 3 is an essential enzyme in the apoptotic pathway, a positive interaction implies that anonacin may in fact cause apoptosis. Other acetogenins like Solamin and Corossolone were also included in the study, with Solamin showing a favorable consensus score, further supporting the role of this class of compounds. Alkaloids [Anomurine, Coreximine, Reticuline] and flavonoids [Catechin, Quercetin, Rutin] were also investigated. Coreximine and Anomurine, both alkaloids, showed strong binding affinities, even surpassing Doxorubicin in some docking scores. Catechin, a flavonoid, also exhibited significant binding. This is in tandem with existing research on the anti-cancer properties of various phytochemical groups. For instance, flavonoids and phenolics, which are present in *Annona muricata*, are well-known for their antioxidant and anti-cancer activities, as noted by studies on the chemical composition and antioxidant activities of soursop [19, 20, 11].

The finding that several soursop compounds, including Coreximine and Catechin, have significantly more favorable docking scores than Doxorubicin may seem counterintuitive given the latter's status as a potent and clinically approved chemotherapeutic agent. However, this apparent contradiction is critical to understanding the limitations of computational models. A molecular docking score measures a compound's direct binding affinity to a single target protein. Doxorubicin's primary mechanism of action is not the direct activation of Caspase-3. Instead, it is a topoisomerase II inhibitor and a DNA intercalator, which leads to DNA damage. This DNA damage triggers a cascade of events that ultimately result in the activation of apoptosis and the subsequent increase in Caspase-3 activity. Therefore, Doxorubicin's effect on Caspase-3 is secondary and indirect, which would not be captured by a docking simulation targeting this specific protein. The low docking score for Doxorubicin against Caspase-3 is thus not a measure of its clinical efficacy but rather a testament to its distinct mechanism of action, highlighting the importance of considering a drug's entire pathway rather than just a single target interaction. The computational predictions for soursop compounds are significantly bolstered by a large and growing body of pre-clinical evidence for the anti-cancer effects of both

isolated compounds and whole extracts. Studies have demonstrated that soursop extracts are potently cytotoxic to a wide range of cancer cell lines, often with a dose-dependent effect. For example, an ethanolic extract of *Annona muricata* leaves showed highly effective anti-cancer activity with IC50 values of 134.6 µg/mL for breast cancer [MAD_MB_231] and 124.6 µg/mL for lung cancer [A549] cell lines. Another study found that a soursop extract was selectively cytotoxic to HER2+ breast cancer cells [HCC1954] while showing weak toxicity to normal peripheral blood mononuclear cells [21]. Beyond cytotoxicity, *in vivo* studies in animal models have provided encouraging results, with soursop extracts shown to shrink breast tumors in mice and inhibit the tumorigenicity and metastasis of pancreatic cancer in xenograft models. The plant has also shown promising effects in models of prostate, liver, and skin cancers [22].

However, the paper rightly stresses that experimental validation [*in vitro* and *in vivo*] is essential to confirm the predicted interactions and assess therapeutic efficacy. This aligns with standard drug discovery pipelines, where computational predictions must be verified experimentally. Zeweil et al. [23], for instance, conducted *in-vivo* studies on Graviola, showing its effect on breast cancer by augmenting apoptosis and antioxidant pathways. This kind of experimental validation would be a crucial next step for the compounds identified in the current *in-silico* study.

5. Conclusion

In conclusion, assessing *Annona muricata*'s anti-cancer activity in silico is a viable method for finding new natural compounds with anti-cancer therapeutic promise. Compounds from *Annona muricata* offer important information on their possible anti-cancer activities, especially in relation to Caspase 3. Strong binding affinities for substances such as Coreximine, Catechin, Annonacin, Anomurine, and Solamin are encouraging and support soursop's traditional use and previously documented anti-cancer properties. This study emphasizes how crucial it is to combine computational and experimental techniques in order to accelerate drug discovery and development.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical issues to be considered in this research.

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Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

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