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Prediction of Active Compounds From Annona Muricata Leaves As Inhibitors of the Wdr5–Myc Interaction in Breast Cancer Through A Molecular Docking Approach

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KEYWORDS
Annona Muricata; WDR5; MYC; Breast Cancer; Molecular Docking.

ABSTRACT
Breast cancer is one of the malignancies with a high morbidity rate, in which the excessive activation of the Myc proto-oncogene protein (MYC) plays a critical role in tumor proliferation and progression. MYC requires the presence of WD repeat-containing protein 5 (WDR5) to bind to its target genes; thus, the WDR5–MYC interaction represents a strategic target for the development of breast cancer therapy. This study aimed to identify leaf metabolites of *Annona muricata* with the potential to inhibit the WDR5–MYC interaction using an in silico approach. A total of 193 metabolites from the KNApSAcK database were modeled in 3D and analyzed by molecular docking using Molegro Virtual Docker (MVD) against the structure of WDR5 in complex with a MYC inhibitor fragment (PDB ID: 6UHY). Docking validation was performed by redocking the native ligand, 1-cyclohexyl-1H-benzimidazole-5-carboxylic acid, which yielded an RMSD value < 2 Å. The docking results indicated that *epicatechin gallate*, *muricatetrocin B*, and *isoorientin* exhibited the highest binding affinities, with Moldock Scores of –123.522, –115.862, and –97.3305 kJ/mol, respectively, supported by strong hydrogen-bond interactions. Interaction visualization revealed that *epicatechin gallate* formed more key interactions with critical residues in the WDR5 active site compared with the native ligand. These findings suggest that *epicatechin gallate* is a promising candidate for inhibiting the WDR5–MYC interaction and may be further developed as a natural-product-based anticancer agent.

INTRODUCTION

Breast cancer is one of the malignancies with high incidence and mortality rates in women, and one of the key molecular signatures driving its progression is the excessive activation of the Myc proto-oncogene protein (MYC). The MYC gene regulates various biological processes, including cell growth, metabolism, biomolecule synthesis, stemness, and epigenetic reprogramming; thus, its elevated expression directly contributes to the proliferation and aggressiveness of breast cancer (Hsu et al., 2015). MYC controls the expression of genes involved in cell-cycle regulation by activating positive regulators of the cell cycle such as Cyclin D, CDKs (CDK1, 2, 4, 6), Cyclin E, and Cyclin B, as well as promoting the expression of E2F target genes (García-Gutiérrez et al., 2019; Jha et al., 2023).

MYC serves as a central regulator of cellular metabolism and growth. This oncogene strongly activates a wide array of key genes implicated in ribosomal and mitochondrial biogenesis, glucose and glutamine metabolism, lipid biosynthesis, and cell-cycle progression (Goetzman & Prochownik, 2018; Huber et al., 2021; Rodríguez-Enríquez et al., 2019). When MYC expression becomes dysregulated or pathologically elevated, the resulting hyperactivation of these target genes accelerates cell growth and proliferation, thereby facilitating tumorigenesis (Chen et al., 2018; Dhanasekaran et al., 2022; Sias et al., 2025). Owing to its role as a "master regulator," the modulation of MYC or its upstream regulators—those governing its stability and transcription—represents an important strategy to suppress breast cancer development (Capasso et al., 2025; Dhanasekaran et al., 2022; Jha et al., 2023; Weber & Hartl, 2023; Zaytseva & Quinn, 2017).

Amid challenges such as drug resistance and adverse effects associated with conventional therapies, natural compounds have gained attention as potential sources of anticancer agents. One plant of considerable interest is Annona muricata (soursop leaves), which contains bioactive constituents such as acetogenins, alkaloids (e.g., coreximine and reticuline), and flavonoids (e.g., quercetin), all of which are predicted to contribute to its biological activities (Mutakin et al., 2022). Ethanol extracts of this plant have been reported to display cytotoxic activity against several breast cancer cell lines, including MCF-7, T47D, and MDA-MB-231 (Rady et al., 2018). Ethanolic, ethyl acetate, n-hexane, and aqueous fractions of A. muricata leaves have also demonstrated selective cytotoxicity toward MCF-7 cells, accompanied by apoptotic morphological changes, along with mechanisms involving reduced Bcl-2 mRNA expression and increased caspase-9 and caspase-3 mRNA levels (Hadisaputri et al., 2021).

As a further step toward understanding the anticancer potential of A. muricata leaves at the molecular level, this study conducts an in-silico analysis to identify active compounds capable of targeting MYC as a key regulator of cell-cycle pathways, thereby exploring potential mechanisms for inhibiting breast cancer cell proliferation. This approach focuses on screening compounds with the potential to disrupt MYC's interaction with its cofactor proteins, particularly WD repeat-containing protein 5 (WDR5)—a protein shown to be essential for MYC recruitment to its target genes (Chacón Simon et al., 2020). Through molecular docking, this investigation aims to identify potential hit compounds for further experimental validation.

METHOD

Metabolite compounds of A. muricata obtained from the "Jamu of KNApSAcK" database (Afendi et al., 2012) were converted into 3D structures using DataWarrior v6.1.0 (Sander et al., 2015) and saved in SDF format. All ligands were subsequently energy-minimized using the MMFF94s+ force field in DataWarrior to obtain the most stable conformations prior to docking. The crystal structure of WDR5 in complex with a Myc site fragment inhibitor was retrieved from the RCSB Protein Data Bank (PDB ID: 6UHY) and imported into Molegro Virtual Docker (MVD v7.0.0, free trial). For molecular docking, all water molecules were removed, and corrections were made to any improper amino acid residues. The preparation steps for both protein and ligands also included assignment of partial charges and the addition of explicit hydrogen atoms to ensure chemically complete structures (Molexus ApS, 2019).

Interaction analysis between ligands and protein via molecular docking was conducted on all 3D structures of A. muricata leaf metabolites listed in the "Jamu of KNApSAcK"

database. Before docking the test ligands, a redocking procedure was performed on the 3D molecule 1-cyclohexyl-1H-benzimidazole-5-carboxylic acid (Q8G_401) into the binding site of protein 6UHY [A] to validate the docking protocol. The reliability of the docking process was verified by obtaining an RMSD value < 2 Å with 20 repetitions. Energy parameters—including the MolDock Score, Rerank Score, and hydrogen-bond contribution—were calculated for each pose, with the MolDock Score used as the primary reference (Molexus ApS, 2019).

RESULT AND DISCUSSION

Validation of the molecular docking method is summarized in Table 1. Validation was carried out by redocking the native ligand 1-cyclohexyl-1H-benzimidazole-5-carboxylic acid into the binding pocket of the 6UHY protein, a crystal structure representing WDR5 in complex with a Myc fragment inhibitor. The redocking results showed that the three ligand poses generated relatively consistent MolDock Scores, ranging from –70 to –74 kJ/mol, with Rerank Scores between –49 and –53 kJ/mol. Pose [01]Q8G_401[B] and [03]Q8G_401[B] produced low RMSD values (1.933 Å and 1.970 Å). RMSD values < 2 Å indicate that the redocked ligand position closely aligns with the native ligand orientation, confirming that the docking method used in this study is valid (Gohlke et al., 2000). Meanwhile, pose [04]Q8G_401[B] yielded a higher RMSD (6.331 Å), making it less representative as a valid pose. Hydrogen-bond energy contributions (Hbond) ranged from –2.5 to 0 kJ/mol, suggesting limited but identifiable hydrogen-bonding interactions in some poses.

Table 1. Validation of the molecular docking method using the native ligand 1-cyclohexyl-1H-benzimidazole-5-carboxylic acid redocked into protein 6UHY

Ligand Pose	Ligand Name	MolDock Score (kJ/mol)	Rerank Score (kJ/mol)	Hbond (kJ/mol)	RMSD (Å)
[01]Q8G_401 [B]	1-cyclohexyl-1H-benzimidazole-5-carboxylic acid	-72.714	-52.145	0.000	1.933
[03]Q8G_401 [B]	1-cyclohexyl-1H-benzimidazole-5-carboxylic acid	-73.478	-49.819	-1.063	1.970
[04]Q8G_401 [B]	1-cyclohexyl-1H-benzimidazole-5-carboxylic acid	-70.056	-53.103	0.000	6.331

The docking results of Annona muricata leaf metabolites against protein 6UHY—namely, the crystal structure of WDR5 in complex with a Myc fragment inhibitor—are presented in Table 2. Table 2 shows clear variations in binding affinity among the ligands. Among the 193 metabolites of A. muricata listed in the "Jamu of KNApSAcK" database, epicatechin gallate yielded the lowest Moldock Score (–123.522 kJ/mol), followed by muricatetrocin B (–115.862 kJ/mol).

More negative energy values indicate stronger binding affinity; therefore, these two compounds are predicted to have the most stable interactions within the 6UHY binding pocket. Isoorientin and annonacin exhibited moderate affinities, with Moldock Scores of –97.3305

kJ/mol and –95.484 kJ/mol, respectively, whereas (+)-reticuline showed a higher value (–90.399 kJ/mol), indicating comparatively weaker interactions.

Table 2. Docking results of compounds from A. muricata leaves in the Jamu–KNApSAcK database against protein 6UHY

Ligand Pose	Ligand Name	MolDock Score (kJ/mol)	Rerank Score (kJ/mol)	Hbond (kJ/mol)
[00]107905	epicatechin gallate	-123.522	-86.414	-4.679
[00]114776	isoorientin	-97.3305	-81.202	-10.367
[02]393472	muricatetrocin B	-115.862	-68.701	-5.243
[00]439653	(+)-reticuline	-90.399	-66.202	-3.021
[02]Q8G_401 [B]	Q8G_401 [B]	-88.085	-65.662	0.000
[00]354398	annonacin	-95.484	-16.614	0.000

Hydrogen-bond energy contributions (Hbond) further support these trends. Isoorientin and epicatechin gallate formed the strongest Hbond interactions (–10.367 kJ/mol and –4.679 kJ/mol, respectively), which may contribute to enhanced stability of the ligand–WDR5 complexes. In contrast, Q8G_401[B] and annonacin—one of the marker compounds of A. muricata (Kementerian Kesehatan RI, 2017)—did not exhibit detectable Hbond contributions, indicating that their stabilization within the binding pocket is dominated by hydrophobic or van der Waals interactions. Overall, these results suggest that epicatechin gallate, muricatetrocin B, and isoorientin are promising candidates for further investigation as potential WDR5–MYC inhibitors.

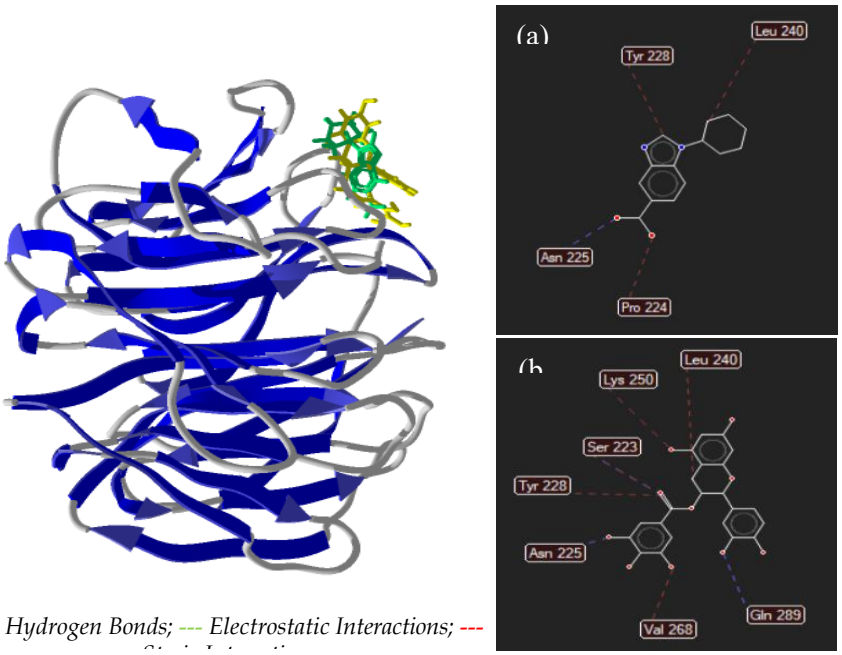

Figure 1. Interactions of the native ligand (a, green) and epicatechin gallate (b, yellow) with the active site of 6UHY based on molecular docking

Figure 1 illustrates the interactions of the native ligand (panel a, green) and epicatechin gallate (panel b, yellow) with the active site of WDR5 (PDB ID: 6UHY) based on molecular docking. Both ligands bind to the same pocket—the WDR5–Myc interaction site—indicating that the test compound may compete with the natural ligand. The native ligand forms

interactions with residues Pro224, Asn225, Tyr228, and Leu240 through hydrogen bonding and steric contacts, consistent with its orientation in the crystal structure. In contrast, epicatechin gallate displays a broader and stronger interaction pattern, including hydrogen bonds with Asn225, Ser223, and Gln289, as well as steric interactions with Tyr228, Leu240, Lys250, and Val268. The involvement of a greater number of residues indicates a more stable binding interaction and supports its lowest docking score, suggesting that epicatechin gallate has stronger affinity and high potential as an inhibitor of the WDR5–Myc interaction.

CONCLUSION

This study reveals that metabolites from *Annona muricata* leaves, particularly *epicatechin gallate*, *muricatetrocin B*, and *isoorientin*, show strong potential to inhibit the WDR5–MYC interaction crucial for breast cancer proliferation, as validated by molecular docking with an RMSD < 2 Å against the WDR5 structure (PDB ID: 6UHY). Among 193 compounds screened using Molegro Virtual Docker, *epicatechin gallate* demonstrated the highest binding affinity through multiple hydrogen bonds and steric interactions with key active site residues, outperforming others and positioning it as a lead candidate for natural-product-based therapies. For future research, in vitro assays and in vivo models should evaluate *epicatechin gallate*'s efficacy, selectivity, and pharmacokinetics to advance it toward clinical breast cancer treatment.

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