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Identification of Antagonists of Pro-Survival Bcl-2 from *Morus alba* in Human Malignancies: An *In Silico* Approach

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Abstract

The target of most cancer chemotherapeutic agents is to drive cancer cells toward death, necessitating the need to find a fine balance between anti-apoptotic and pro-apoptotic proteins in maintaining cellular homeostasis. Any shift favoring the pro-apoptotic proteins is needed to drive cellular death in cancer chemotherapy. Therefore, this study uses molecular docking, ADMET predictions, and molecular dynamics simulations for the identification of potent inhibitors of anti-apoptotic Bcl-2 from *Morus alba* (mulberry). Our molecular docking study discovered that quercetin-3-(6-malonylglucoside) (-10.912kcal/mol) and epigallocatechin gallate (-9.750kcal/mol) recorded excellent binding affinity against human Bcl-2, better than popular standard drugs, venetoclax (-9.468(kcal/mol) and navitoclax (-9.058kcal/mol). Interactions profile summary clearly showed that hydrophobic interactions at TRP141, VAL145, and TYR105 were consistently maintained by the ligands, and all the compounds, except venetoclax, consistently maintained the hydrogen bonding at TYR105. MD simulation analysis showed that the protein and ligand RMSD for the quercetin-3-(6-malonylglucoside)-Bcl-2 complex fell within permissible range, suggesting the ligand is capable of functioning as apposite antagonists of Bcl-2. Epigallocatechin gallate also bind excellently with the target, and both ligands showed favorable ADMET parameters. Summarily, this study identifies two compounds of mulberry as potential drug candidate in the management of known human malignancies, and therefore suggest the compounds should further be assessed through *in vitro* and *in vivo* approaches to validate the reports documented here.

Keywords: *Cancer, Bcl-2, Molecular docking, MD simulation, in vitro, in vivo*

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1. Introduction

One of the classical hallmarks of cancerous cells is the evasion of apoptosis, a programmed cell death[1]. The Bcl-2 class of proteins (pro-and-antiapoptotic) are integral players in apoptosis, and since the roles of the antiapoptotic Bcl-2 members, e.g. Bcl-2 and Bcl-xL have been established in cancer, there is an important need to explore various ways of controlling the proteins[2]. Various mechanisms could be used to regulate the activities of these proteins. These mechanisms include gene expression[3], post-transcriptional regulation which uses several regulatory mechanisms to control the abundance and stability of the mRNA of Bcl-2[4], post-translational modifications, protein-protein interactions, epigenetic regulation, and protein-ligand interactions which involve the use of small molecules as the antagonists of Bcl-2 protein[5]. Inhibition of Bcl-2 in cancer has emerged as a promising therapeutic approach, particularly in hematological malignancies[6]. These inhibitors are made to target and counteract the anti-apoptotic function of Bcl-2, thus promoting the death of cancerous cells. Since the anti-apoptotic Bcl-2 proteins, such as Bcl-2 and Bcl-xL, conserve all four Bcl-2 homology (BH) domains[7], seeking to use a typeable Bcl-2 homology domain 3 (BH3) mimetic in controlling the activities of the protein represents an important area of the fight against cancer. BH3 mimetics are a class of small molecule compounds that have garnered significant attention as potent inhibitors of Bcl-2 family proteins, particularly Bcl-2 itself[8]. These inhibitors mimic the function of the BH3 domain, a critical region found in pro-apoptotic proteins of the Bcl-2 family, enabling them to selectively bind and neutralize the anti-apoptotic activities of Bcl-2[7]. A lot of these inhibitors

have been approved for their chemotherapeutic use. Very popular among these compounds are ABT-199 (Venetoclax) and ABT-263 (Navitoclax). These popular inhibitors often come with side effects, necessitating the need for unveiling natural weapon in the search for potent inhibitors with little or no side effects. Historically, plants have been used since ancient times in traditional communities for the treatment of many diseases[9]. *Morus alba* (mulberry) has a long history of use as fodder and traditional medicine. Pharmacologically, the plant has been reported to have antioxidant property, due to being a rich source of anthocyanins, compounds which are excellent antioxidant agent with strong free radical scavenging potency than known standards like vitamin C[10]. In similar manner, the cytotoxic effect of the plant has been tested by Kofujita and colleagues[11] where a flavone compound (7, 2′, 4′, 6′-tetrahydoroxy-6-geranylflavanone) isolated from the plant inhibited the growth of rat hepatoma in dRLh84 cells with an IC50 value of 53microgram per mole. Overall, two flavonioids (quercetin-3-O-β-D-glucopyranoside and quercetin-3-7-di-O-β-D-glucopyranoside) found with the plant were found to inhibit the growth of human leukemia HL-60 cells[12].
Therefore, the work presented herein was inspired by the reported therapeutic effects and safety of the plant, and a need to discover new natural blockers of Bcl-2 that could be better employed in the long fight against human cancer. Based on the above, *in silico* approaches using pharmacokinetic and pharmacodynamics properties, molecular docking, and molecular dynamics (MD) simulations were used to show that compounds from *Morus alba* are capable of inhibiting Bcl- 2, and that the inhibition of Bcl-2 is needed to drive cellular death in actively dividing and cancerous cells.

2. Methodology: Computational Approaches

All computational studies which include ligand preparation, receptor grid generation, molecular docking, molecular mechanics with generalized born surface area (MM-GBSA) and ADMET predictions were done with the various modules available in Schrodinger Maestro software according to the methods of Omoboyowa and colleague[13].

2.1 Target identification, preparation, and receptor grid generation.

The structure of human Bcl-2 in complex with Venetoclax (ABT-199) was downloaded from the RCSB protein data bank (https://www.rcsb.org/structure/4MAN)[14]. The choice of the target was informed by the need to produce identical but better result than what has been reported. The retrieved protein was uploaded to Schrodinger Maestro and prepared. The preparation involves pre-processing, addition of bond orders, hydrogen atoms, filling loops, and removing water molecules beyond 5.00Å. The processed protein was subjected to interactive optimization to refine the crystallized protein structure and restrained minimization converging heavy atoms to RMSD at 0.30Å. Receptor grid generation defines the binding orientation and the size of the active site for protein-ligand docking. The receptor grid was generated based on the co-crystallized ABT-199 ligand present in the target protein. The grid area is determined using the receptor grid generation feature to identify the region in the system that serves as a receptor. The grid is set with the inhibitory center of ABT-199, the native ligand of PDB ID 4MAN, at the protein's active site forming XYZ center coordinates of -11.72, 9.94, and 9.02 respectively.

2.2 Ligand preparation, Lipinski's rule (LRoV) and QikProp screening of compounds.

A library of ninety-one (91) selected phytochemicals reported in *Morus alba*[15] were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov), subjected to QikProp to screen compounds with druglike characters, and further subjected to the pharmacophore hypothesis, to check compounds with matching features with crystallized protein-ligand complex. Successful ligands, during the preparation, were neutralized and just one stereoisomer was generated at most for all ligands using the LigPrep module in Schrodinger Maestro[17].

2.3 Molecular docking

Glide-XP (extra precision) was used to dock the prepared ligands into the designated active site of the prepared protein guided by the grid generated. The Van Der Waals scaling factor was set at 0.80 for the ligands atoms.

2.4 Thermodynamics calculation

To determine the binding free energy of the docked complexes, the molecular mechanics with generalized born surface area (MM-GBSA) tool integrated with prime of the Schrödinger Maestro
12.8 was used.

2.5 Pharmacophore hypothesis, ligand screening, and ADMET prediction.

Energy-optimized pharmacophore hypothesis was generated using the crystal structure of 4MAN linked to its co-crystal ligand, ABT-199. For the hypothesis settings, features that made interactions with the protein were chosen, and then a receptor-based excluded volume shell was created to mimic the receptor binding site, ignoring receptor atoms whose surfaces are within 2.00 Å of the ligand surface, and limiting excluded volume shell thickness to 5.00 Å. E-pharmacophore-based virtual screening was performed using Maestro Schrodinger 2018, version 12.8 according to the method reported by Omoboyowa and colleagues[13]. Toxicological predictions of some of the ligands were carried out using the QikProp modules of Maestro Schrodinger to see if the ligands were safe if used as human drugs. Later, they were further screened using SwissADME:
(http://www.swissadme.ch/index.php) and Protox II: (https://tox- new.charite.de/protox_II/index.php?site=compound_input). Prediction was made by writing the canonical smiles string of the ligand compound and then selecting what properties are to be predicted for example absorption (water solubility, intestinal absorption, and skin permeability) distribution, metabolism, excretion, and toxicity.

2.6 Molecular dynamics simulation

Docked complexes of the hit compounds, quercetin-3-(6-Malonylglucoside), epigallocatechin gallate, and the standard drugs (Navitoclax and Venetoclax) were subjected to molecular dynamics (MD) simulation studies using the Desmond module of Maestro Schrodinger. The primary objective of this simulation was to assess the stability of the complexes and validate the docking results obtained earlier.

During the simulation, the complexes were allowed to undergo a 100ns simulation using the NPT ensemble class, at a constant temperature of 300.0K and pressure of 1.01325 bar. The system was prepared using the System Builder module, which employed the TIP3P solvent model. An orthorhombic boundary box with dimensions of 10 x 10 x 10 Å was used, and the OPLS3e force field was employed[17]. The box was minimized, and the system charges were neutralized by the addition of Na+ and Cl- ions. To monitor the stability of the ligands and protein in their native motion, root mean square deviation (RMSD) and root mean square fluctuation (RMSF) were estimated.
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3. Results

The results obtained indicates the pharmacophore features and fitness scores of the compounds from *Morus alba*, evaluating their potential as Bcl-2 inhibitors through various computational assessments. Key findings are outlined (Figures 1-6; Tables 1-5), including pharmacokinetic properties, docking scores, and molecular interactions of the tested compounds, benchmarked against the reference drugs Venetoclax and Navitoclax. Detailed analyses of compound-protein interactions, stability through RMSD, and protein-ligand contacts are also provided.

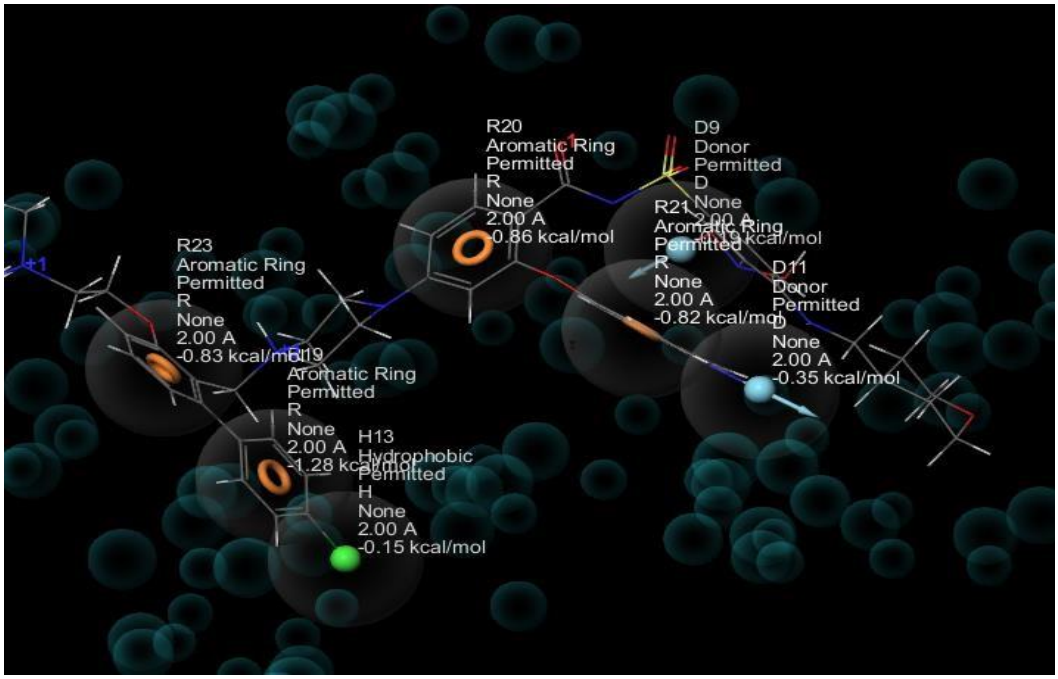

Figure 1: Pharmacophore features of the reference ligand. These features were later used to screen the compounds of *Morus alba*, where two of them came out with good fitness score. The compounds with favorable fitness scores were then researched as potential inhibitors of Bcl-2.

Table1: Fitness score of reference and test compounds

s/n	Compound	Score
1	Venetoclax	2.03
2	Navitoclax	1.96
3	Quercetin-3-(6-Malonylglucoside)	2.26
4	Epigallocatechin gallate	2.12

Table showing the fitness score of the top two compounds of *Morus alba* after being subjected to the pharmacophore hypothesis generated based on Venetoclax, the reference compound.

Table 2: *In silico* ADMETox Prediction

Compound	BBB	HIA	P-Gp Substrate	Carcinogenicity	Mutagenicity	Nephrotoxicity
Venetoclax	-	+	No	Inactive	Active	Inactive
Navitoclax	+	+	No	Inactive	Inactive	Active
Quercetin-3-(6-Malonylglucoside)	-	+	No	Inactive	Inactive	Inactive
Epigallocatin gallate	-	+	No	Inactive	Inactive	Inactive

Abbreviation: BBB, blood brain barrier; HIA, human intestinal absorption; P-Gp, plasma glycoprotein.

Table 3: Basic pharmacokinetic and pharmacodynamic properties of the tested ligands

s/n	Compound	QPlogHERG	QPPCaco	QPlogBB	QPPMDCK
1	Venetoclax (ABT-199)	-9.033	10.946	-2.879	10.308
2	Navitoclax (ABT-263)	-10.008	12.86	-1.465	64.131
3	Quercetin-3-(6-Malonylglucoside)	-3.009	0.399	-3.957	89.13
4	Epigallocatechin gallate	-5.065	1.581	-3.835	0.464

Table giving some important pharmacokinetic and pharmacodynamics properties of the standard drugs and the test compounds.
QPlogHERG: Predicted IC_{50} value for HERG K^+ Channel Blockage (concern below -5)
QPPCaco: Predicted Caco-2 Cell Permeability. (500 great)
QPPMDCK: Predicted MDCK Cell Permeability. (500 great)
QPlogBB: Predicted brain/blood partition coefficient. –3.0 – 1.2

Table 4: Docking Score, MM-GBSA, Lipinski rule of five violation (LROV)

s/n	Compound	Docking Score(Kcal/mol)	MM-GBSA	LROV
1	Venetoclax	-9.468	-68.85	3
2	Navitoclax	-9.058	-81.83	3
3	Quercetin-3-(6-Malonylglucoside)	-10.912	-71.18	3
4	Epigallocatechin gallate	-9.750	-57.89	2

Table showing the docking score, (MMGBSA) score, and violation of Lipinski' rule of five violation based on the top two ligands from *Morus alba*. The fitness of the compounds were compared to those of the standard drugs, Navitoclax and Venetoclax.

3.1 Interaction Diagram of the Ligands

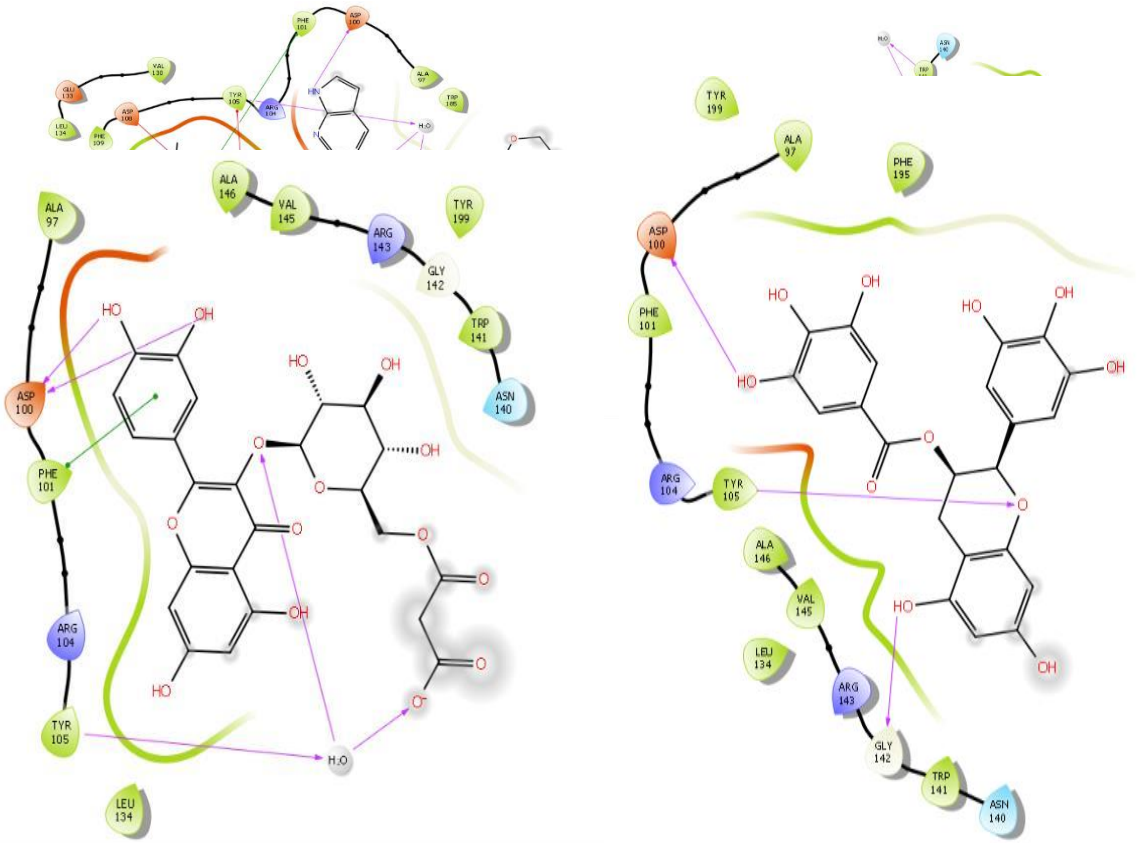

Figure 2: Figure showing the various forms of 2-dimensional interactions between the standard drugs, Venetoclax (left) and Navitoclax (right) and the crystal structure of human B-Cell lymphoma 2 (Bcl-2).

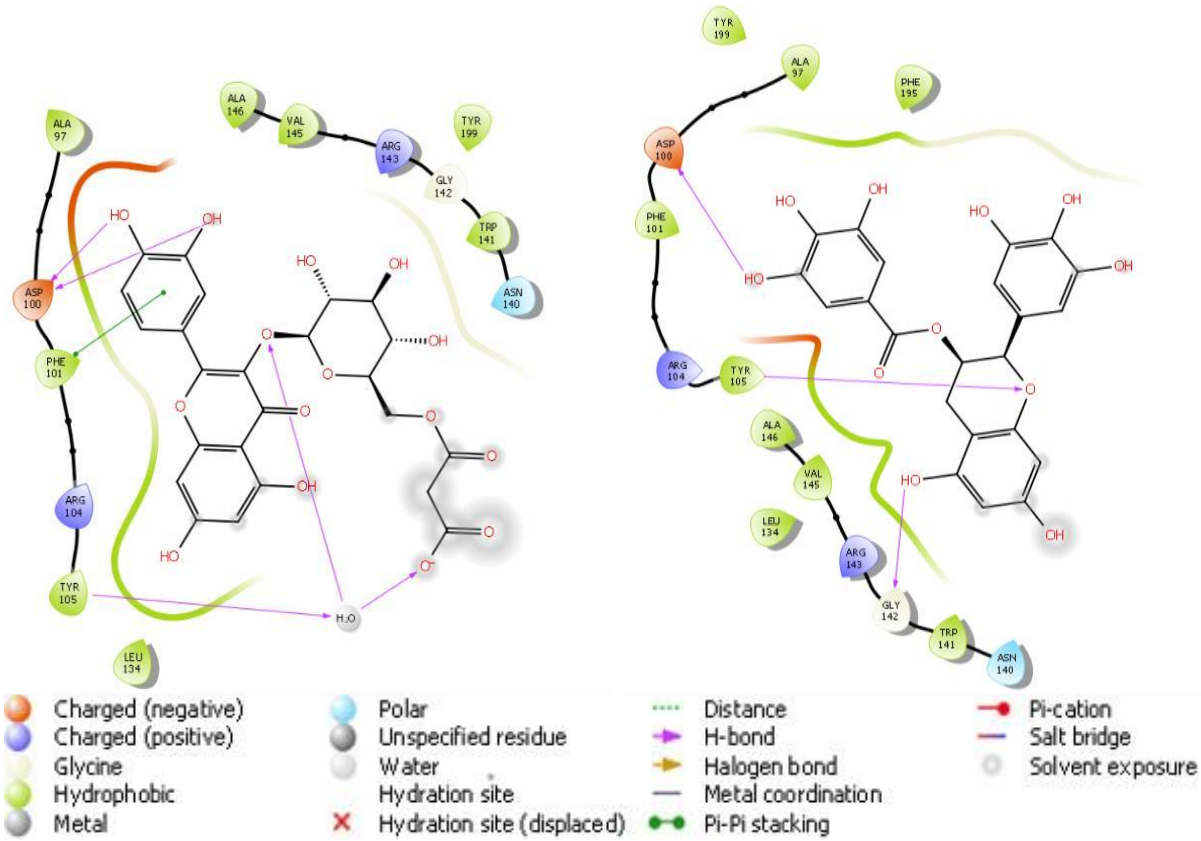

Figure 3: Figure showing the various forms of 2-dimensional interactions between the top two ligands, quercetin-3-(6-Malonylglucoside) (left) and epigallocatechin gallate (right) of *Morus alba* and the crystal structure of human B-Cell lymphoma 2 (Bcl-2).

Table 5: Summary of the various interactions of the ligands and protein

Complex	H-Bond Interactions	Hydrophobic interactions	Any other interactions
4MAN-Venetoclax	TRP 141 TYR 199	TRP 141, VAL 145, ALA 146, PHE 150, VAL 153, VAL 130, LEU 134, MET 112, PHE 109, TYR 105, PHE 101, ALA 97, TYR 199, LEU 198, PHE 195	Pi-Cation: TYR 105, ARG 104 Salt Bridge: ASP 108
4MAN- Navitoclax	ASP 100 TYR 105 ARG 143 TYR 199 GLY 142 TRP 141	TRP 185, ALA 97, TRP 141, PHE 101, VAL 145, TYR 199, TYR 105, ALA 146, VAL 130, PHE 150, PHE 109, MET 112, VAL 153, LEU 134	Pi-Cation: TYR 105 Salt bridge: ASP 108
4MAN-Quercetin-3-(6-Malonylglucoside)	ASP 100 TYR 105	ALA 97, PHE 101, TYR 105, LEU 134, ALA 146, VAL 145 TRP 141,TYR 199	Pi-pi Stacking PHE 101
4MAN-Epigallocatechin gallate	GLY 142 ASP 100 TYR 105	ALA 97, PHE 101 TYR 105, LEU 134 ALA 146, VAL 145 TRP 141, PHE 195, TYR 199	None

Figure completely summarize the various interactions between the ligands and the target protein. Such interactions are needed to keep the ligands tightly bound to the binding site of the target.

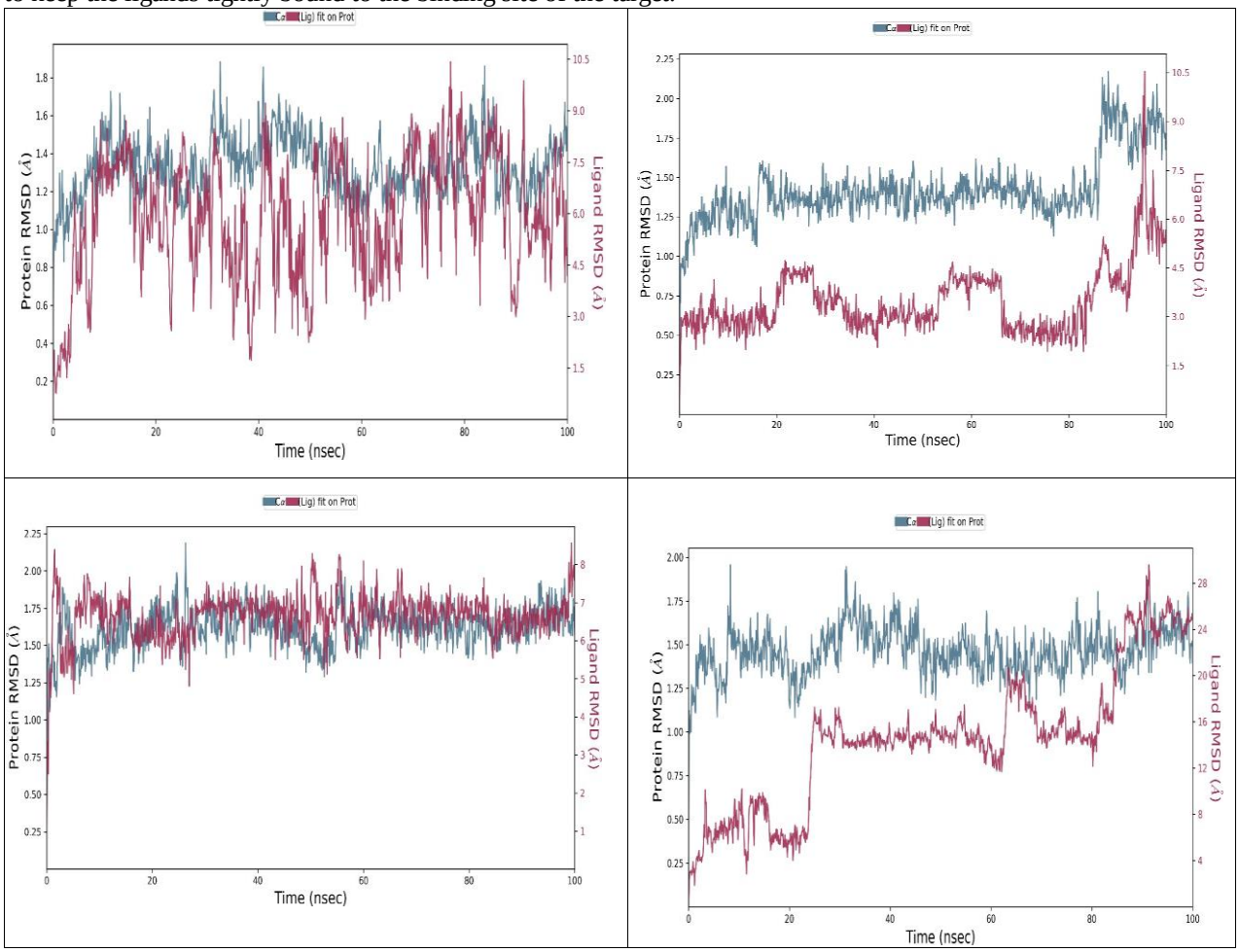

Figure 4: RMSD plot of the protein-ligand of standards and hits from *Morus alba*. Venetoclax (top left), navitoclax (top right), quercetin-3-(6-malonylglucoside) (down left), and epigallocatechin gallate (down right).

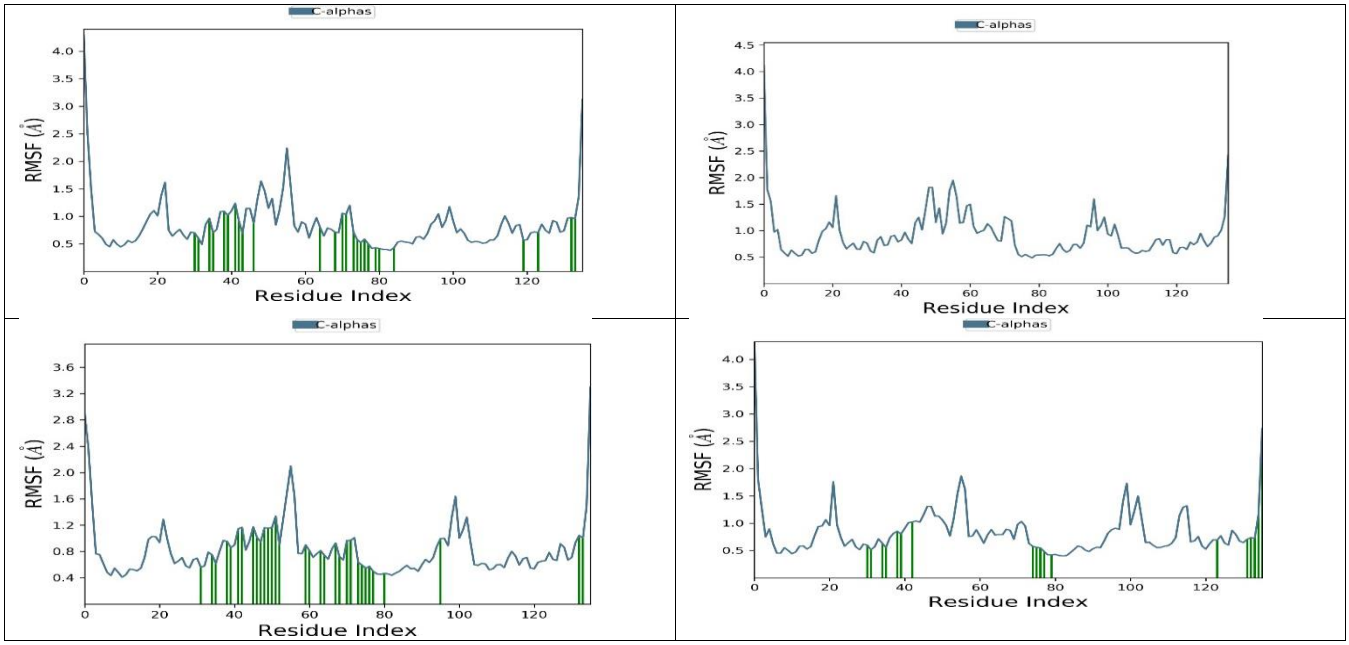

Figure 5: Protein Root Mean Square Fluctuation (RMSF). Venetoclax (top left), navitoclax (top right), quercetin-3-(6-malonylglucoside) (down left), and epigallocatechin gallate (down right)

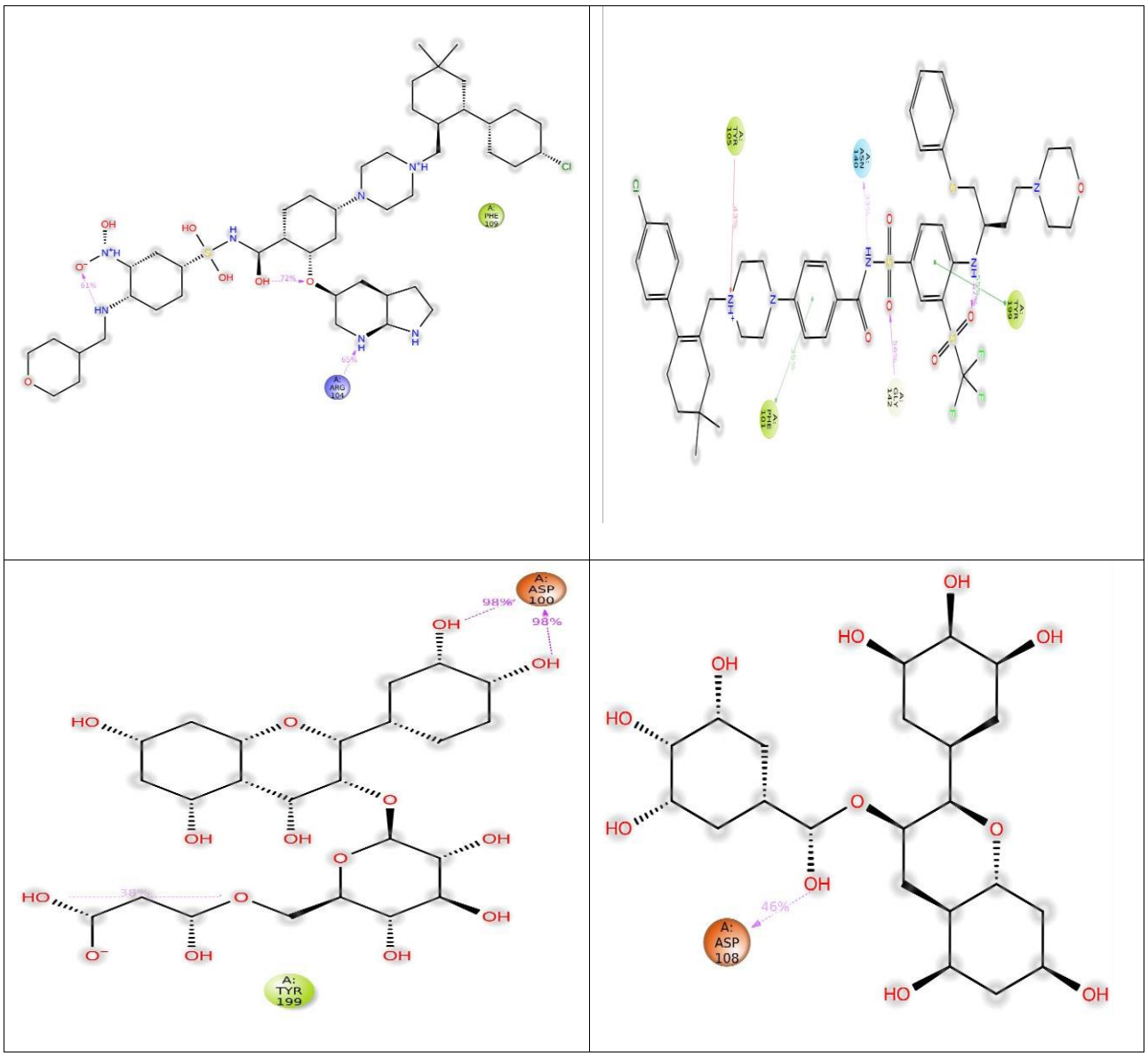

Figure 6: Protein-ligand contact. Venetoclax (top left), navitoclax (top right), quercetin-3-(6-malonylglucoside) (down left), and epigallocatechin gallate (down right).

Discussion

The target of most cancer chemotherapeutic agents is to drive cancer cells toward death, necessitating the need to find a fine balance between anti-apoptotic and pro-apoptotic proteins in maintaining cellular homeostasis[18]. *Any* shift favoring the pro-apoptotic proteins is needed to drive cellular death in cancer chemotherapy[19]. For this reason, the compounds of *Morus alba* were assessed as potential antagonists of pro-survival Bcl-2. A pharmacophore hypothesis was set to unleash which features were responsible for the stable protein-ligand interaction seen in the retrieved 4MAN-venetoclax complex (Figure 1). These observed features were then used to screen the compounds of *Morus alba* for potential drug candidacy. Compounds and their fitness scores based on the set hypothesis were reported in Table 1. As seen, the two ligands of mulberry showed excellent fitness to the protein target when compared with the two known standard drugs. New drug candidates are expected to scale ADMET parameters huddles before they could be considered as potential drugs in cancer chemotherapy. In other words, ADMET parameters are increasingly necessary in the therapeutic selection of drug candidates, as increased number of compounds were discovered as drug candidates. The high failure rate of potential drug candidate at the late development stage is highly correlated with ADMET failure, making computational techniques for ADMET prediction an integral and cost-effective model for screening potential drug candidates[20]. From Table 2, all the compounds assessed, except navitoclax, are non-blood brain barrier permeant; such indices are excellent for drugs not designed to take care of neurological disorders[20]. Importantly, all the assessed ligands remain positive to high human intestinal absorption rate, making them readily available to elicit therapeutic functions. The ligands were also assessed for their carcinogenicity; all ligands aced this huddle, placing them as likely candidate in the therapeutic development of drugs capable of serving as antagonists to pro-survival Bcl-2 protein. Several studies have suggested that changes in the plasma concentration of glycoproteins can influence cellular changes in large number of diseases[21]. However, all the ligands reported in this study are non-

substrate of P-glycoprotein. Since the membrane transport protein, P-glycoprotein (P-gp) inhibits the absorption, distribution and bioavailability of drugs that appear to be its substrates and release them out of circulation[22], compounds reported here are excellent since none is a substrate. The human ether-a-go-go-related gene (HERG) encodes a potassium channel that is implicated in fatal arrhythmia[23]. The HERG channel is best known for its contribution to the electrical of the heart coordinates, heart beating and appears to be the molecular target responsible for cardiac toxicity of wide range of drugs[20]. Therefore, HREG channel blockers are potentially toxic. So, improving the ability to avoid undesirable HERG activity in the early stage of drug discovery and development is significant[24]. From Table 3, the indicators showed the hits and standards showed excellent scores for HERG activity, knocking out the possibility of cardiotoxicity of hit compounds. Furthermore, several rules have been developed to examine the drug-likeness properties of drug candidates, with the most commonly used being the Lipinski Rule of Five[25] According to Lipinki's rule of 5, drug-like compounds should not violate more than one of the rules[26] Results from this study (Table 4) showed that all the hits and standards disobeyed Lipinski rule. However, Lipinski rule is not enough to screen candidates for drug-like property[27], necessitating other works done in this work to validate the drug-like character of the hits reported. Molecular docking is a computer-based tool commonly used in structure-based drug design[28]. It predicts the binding model and energy of compounds with the active pose of target proteins[29] The compounds in this study demonstrated varying degree of binding affinities for the target as shown in Table 4. The binding affinities of the standard drugs are -9.468kcal/mol, -9.058kcal/mol for navitoclax and venetoclax respectively. The two topmost compounds reported here, quercetin--3-(6-malonylglucoside) and epigallacatechin gallate, bind better to the target with binding scores -10.912kcal/mol and -9.750kcal/mol respectively. From the same table, the binding MMGBSA energies were also computed. The MMGBSA score provides a means to quickly interrogate the binding affinity of bound ligand conformations, through computationally efficient free energy measurements[30]. The interactions of the assessed ligands, standards and hits, were shown in figure 2 and 3 respectively, with a summary clearly given in Table 5. From the summary, Table 5, the interactions summary clearly showed that hydrophobic interactions at TRP141, VAL145, and TYR105 were consistently maintained by the ligands. This bonding is considered to be an integral form of interaction capable of keeping the ligands tightly bound at the interactive site of the target, Bcl-2. Moreover, all compounds, except venetoclax, consistently maintained the hydrogen bonding at TYR105. Hydrogen bonding is a special form of bonging capable of making ligands remain tightly bound at the catalytic or interactive site of target proteins. Other special interactions were seen to aid the binding of the ligands to the active site on the target. These interactions include pi-pi stacking, pi-cations, and salt bridges as shown in Table 5 and Figures 2 and 3.

The result of the docking analysis showed that quercetin-3-(6-malonylglucoside) and epigallacatechin gallate have higher binding affinities when compared with the standards, venetoclax and navitoclax. The validity and stability of these complexes were then subjected to 100ns MD simulation using the Desmond package of Schrodinger version 12.8 The RMSD of the protein provides insight into its structural conformation throughout the simulation[20]. Changes of about 1-3 angstrom are perfectly acceptable for small, globular proteins, and it is also important that the simulation converges, meaning the RMSD value must stabilize around a fixed value. From figure 4, the RMSD of Bcl-2-quercetin-3-(6-malonylglucoside) was seen to be within range from the initial, and the fluctuation analysis was stable for most of the simulation time. In contrast, the RMSD value for Bcl-2-epigallocatechin gallate fell within range from initial time, but fail to remain stable until about 90ns of the simulation time. Summarily, the MD simulation analysis showed that the ligand quercetin-3-(6-malonylglucoside) is able to serve as a potent antagonist of pro-survival Bcl-2 and remain tightly bound until a therapeutic effect is elicited. As evident in figure 4, the ligand RMSD of all the compounds, except epigallocatechin gallate, fell within values that are not too far from protein RMSD, making it easy to opine that the ligands remained tightly bound to their targets throughout the period of the simulation. From record, the ligand RMSD indicates how stable the ligand is with respect to the protein and its binding pocket, and that if the values observed are significantly larger than the RMSD of the protein, then it is likely that the ligand has diffused away from its initial binding site. Figure 5 showed the protein RMSF chart of the assessed compounds. The RMSF is useful for characterizing local changes along the protein chain(s). As seen from the figure, peaks indicate areas of protein that fluctuate during the simulation. Figure 6 represent a true picture (*in silico*) of the different contacts the ligands made with the target. Quercetin-3-(6-malonylglucoside) maintained its interaction with ASP100 for about 98% of the simulation time, epigallocatechin gallate also maintain its interaction with ASP108 for almost 50% of the simulation time. Interactions between ligand and protein during the simulation period keep the ligand tightly bound to its target, and this kind of interactions are needed by the compounds to elicit therapeutic functions.

Conclusion

Quercetin-3-(6-malonylglucoside) showed higher binding affinity against pro-survival human Bcl-2 compared to standard drugs and compounds from mulberry. Based on the docking score, evaluation of the quercetin-3-(6-malonylglucoside)-Bcl-2 complex stability by MD simulation showed stable interaction of the complex for a period of 100ns. The compound remain tightly bound to the target, showed favorable ADMET parameters, and good fit throughout the trajectory analysis. Overall, the antagonistic potential of the compounds of mulberry, particularly quercetin-3-(6-malonylglucoside), against pro-survival Bcl-2 and other pro-survival targets in cancer chemotherapy should be further explored *in vitro* and *in vivo* to validate the use of the plant in management of known human malignancies.

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Authors Declaration of Conflicting Interest.
The authors of this paper declare no conflicting interest. All authors approved the publication.

Data Availability Statement
The corresponding author will provide access to all docking structures and other documents upon reasonable request.

Author Contributions Statement
ESO conceptualize and design the study; EAO, KCN, and POA did docking and MD simulations; OOO, ESO, SNB, EFO, and AJO wrote the first draft of the manuscript. ESO, SOB, and EAO revised the manuscript. All authors read and approved the publication of this manuscript.

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