Prediction on Binding Affinity of Nordentatin and Quercetin Against Anti-apoptotic BCL-2 Protein

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Abstract

Targeting apoptotic cell-death pathways has been a subject of growing interest in discovery of novel anti-cancer agents. Bcl-2 is a member of Bcl-2 family protein that is crucial for cell survival by supressing apoptosis and its overexpression is frequently detected in many type of cancers. Inactivation of Bcl-2 has been considered as an ideal strategy in anti-cancer therapies. A large number of bioactive compounds derived from natural source including Nordentatin and Quercetin have been reported to possess anticancer activities. Here we report the binding affinities of Nordentatin and Quercetin in silico against anti-apoptotic Bcl-2 protein using molecular docking programs. We demonstrate for the first time that Nordentatin showed optimum binding affinity with Bcl-2, similar to those shown by Quercetin. As the Quercetin has been previously known to play a role in cancer cell apoptosis through down-regulation of Bcl-2, the result indicated that Nordentatin could also be proposed as a prospective anticancer molecule via inhibition of Bcl-2 protein.

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Introduction

Dysregulation of apoptosis-cell death is a common event in human cancers and it plays a role in resistance against most conventional chemotherapies which rely on their ability to induce apoptotic cell death in cancer cells.[1] Therefore, restorations of apoptosis pathways have been exploited for cancer treatment, particularly in anti-cancer drug developments.

The B-cell lymphoma (Bcl-2) family protein are important regulators in mitochondrial apoptosis pathway.[2] They include six anti-apoptotic proteins and a number of pro-apoptotic interacting proteins, which regulate and mediate the intrinsic apoptosis pathway. Bcl-2 is the most studied anti-apoptotic member, known to restrict apoptosis and facilitates the survival cell independently by promoting the division of cell.[3] The protein is excessively expressed in a number of cancers and have been attributed to the resistance of cancer to conventional treatment.[4] Inactivation of Bcl-2 restored the apoptosis function in cancer cells. Therefore, targeting Bcl-2 has been proposed as a promising anticancer strategy.[5]

Phytoconstituents, such as anthraquinone, coumarins, flavonoids, and terpenoids might serve as active therapeutic agents due to their wide range pharmacological effects, including anticancer.[6] However, many of their molecular targets have not been completely understood. Nordentatin ($C_{19}H_{20}O_4$) is one of coumarin extracted from Clausena. excavata. Previous study showed that Nordentatin has strong cytotoxicity against on several cancer cell lines.[7-9] Quercetin (3,3′, 4′, 5, 7- pentahydroxy-flavone) is a natural flavonoid found in fruits and vegetables which plays an important role in a number of biological functions.[10] It also exhibits significant anti-neoplastic activities against various cancer cell lines.[11] The compound binds directly to the BH_3 domain of Bcl-2 and Bcl-xL proteins, and

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inhibits their activities and promotes the apoptosis of cancer cells.[12]

Molecular docking is a current method used to plan and design various novel of drugs. This method predicts the binding mode and affinity of a small molecule within the binding site of the receptor target.[13] This study aimed to identify the binding affinity of Quercetin and Nordentatin against Bcl-2 protein in silico with docking method.

Materials and methods

Software and program

The crystal structure of the investigational scaffold protein Bcl-2 was downloaded from RCSB protein data bank (http://www.rcsb.org), encoded with PDB code 4IEH. Ligands Nordentatin and Quercetin were downloaded in sdf file format, from PubChem Compound Database, the National Center for Biotechnology Information.

PyMol (DeLano Scientific LLC, USA) and Discovery Studio Biovia 2017 were used to visualize and modify the receptor and ligand structures. AutoDock Vina was the main software utilized in this work. The preparation of the Bcl-2 pdbqt file and selection of the grid box size were performed using AutoDock Tools version 1.5.4 (The Scripps Research Institute, La Jolla, USA). Post docking analysis was done using The PyMol and DS Biovia 2017.

Preparation of ligands nordentatin and quercetin

The chemical structure of Nordentatin and Quercetin in sdf format was converted into pdb file format, using Discovery Studio Biovia 2017. Furthermore, Autodock Tools 1.5.2 (ADT) was used for subsequent procedures on the ligand structure: combined with non-polar hydrogen, added with Gasteiger changes, and prepared for rotatable bonds. The "ligan.pdb" structure was changed to "ligan.pdbqt" by using ADT and made it eligible for using the AutoDock4 (AD4) and AutoDockVina.[14]

Preparation of Bcl-2 structure

Bcl-2 structure of target proteins was retrieved from the Protein Data Bank [PDB: 4IEH] (http://www.rcsb.org). The protein structure inhibitors are separated by releasing the atomic coordinates of the pdb file. The atomic coordinates of water molecules, including in the structure of co-crystallized protein were also removed. ADT software were used to prepare the required files for AutoDock Vina with the following procedure: hydrogen polar assignment, Gasteiger charges calculation to protein structure, and protein structure conversion from pdb file format to pdbqt format.[15-17]

Molecular docking

Molecular docking was performed using AutoDock Vina program. Each ligand was docked to the receptor with grid coordinates (Grid Center) and Grid Box in a certain size for each receptor. The ligand was in a flexible condition when interacted with macromolecules under rigid conditions. The configuration file was arranged by opening notepad to run AutoDock Vina. AutoDock Tools was required to prepare the input pdbqt file for Bcl-2 and to set the size and the center of the grid box. Kollman charges and polar hydrogen atoms were included to the Bcl-2 structure. The grid size was set to 30 x 30 x 30 xyz points and grid center was designated at dimensions (x, y, and z): 9.92, 20.528 and 19.532 with grid spacing of 1000 Å. The program saves the prepared file in pdbqt format. The predicted binding affinity (kcal/mol) showed how strong a ligand binding to the receptor. This binding affinity was calculated based on the AutoDockVina scoring function.[14] The more negative, the stronger its binding affinities. The docking was validated by redocking the Bcl-2 active ligands into binding sites.[16] The docking simulation results were visualized using PyMOL and Discovery Studio Biovia 2017, which displayed the size and location of the binding site, the interaction of hydrogen bonding, hydrophobic interaction, and bonding distance with interaction radius <5Å from the position of the docked ligand.[15-18]

Results

The Nordentatin and Quercetin ligands used in the study followed the Lipinski's rule of five, or known as Lipinski's rule of drug-likeness. The rule is a guideline for the structural properties of a molecule compound whether it has similar pharmaceutical effects and oral bioavailability as an active oral drug, based on its

physicochemical profiles. The hydrogen-bond of donors and acceptors, and the molecular mass are crucial parameters to the structure of protein target and ligand binding sites.[20] The poor absorption or permeation of a compound is predicted more likely to bind when there are >5 hydrogen-bond donors, >10 hydrogen-bond acceptors, the molecular mass is >500, and calculated log P (CLog P) is >5.[21,22]

The docking protocol was validated by redocking n-heteroaryl sulfonamides to co-complex Bcl-2 [PDB: 4IEH].[23] The size and center of the coordinates in the grid box in molecular docking have to be validated to convince the binding of ligands ties to the binding pocket in the right conformation.[16] The result showed that the redocking n-heteroaryl sulfonamides position was similar with the crystallographic position (Figure 1) indicating that the AutoDock docking parameters used are applicable to this system.

The lowest binding energy was -10.8 kcal/mol showed by n-heteroaryl sulfonamides, Nordentatin compound has an equally strong affinity with quercetin, each show a binding affinity -7.3 kcal/mol against Bcl-2 [PDB: 4IEH] (Table 2).

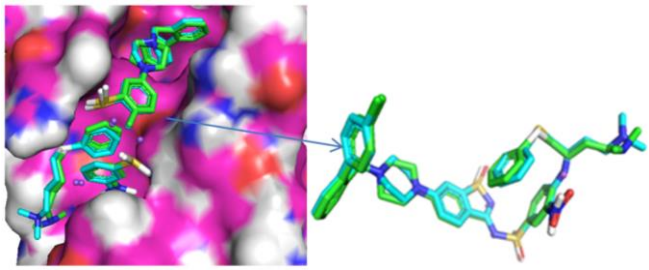

Figure 1. Redocking n-heteroaryl sulfonamides to the binding site. Crystallized conformation is shown in blue color. The best redocked pose of n-heteroaryl sulfonamides is shown in green carbon.

Relating ligands binding affinity shows its specific interaction with amino acid residues at the vicinity of the receptor site.[24] Table 3 shows the amino acid residues involved in hydrogen bond interaction, hydrophobic interactions and electrostatic interaction with the investigating ligands.

Nordentatin compound forms hydrogen binding with Arg66 (3.14). There were eight residues in hydrophobic interaction found between compound Nordentatin with Tyr161 (3.82 Å), Arg66 (3.99 Å), Arg65 (3.99 Å), Arg66 (4.45 Å), Ala59 (4.10 Å), Arg66 (5.34 Å), Arg66 (5.21 Å), Tyr161(4.59 Å), Tyr161(5.46 Å). There were three electrostatic interactions involved amino acids Arg66 (3.98 Å), Arg66 (4:13 Å), Asp62 (4:08 Å).

Quercetin compound formed two hydrogen bonds involving the amino acid residues Phe63 (3.11 Å) and Arg105 (3:25 Å). There were hydrophobic interactions involved five amino acid residues of Phe63 (5:18 Å), Arg105 (5:35 Å), Arg105 (4:40 Å), Ala108 (4.97 Å), Val107 (5:27 Å). There is no electrostatic interaction between the Quercetin compound with Bcl-2.

N-heteroaryl sulfonamides compounds formed three hydrogen bonds to the binding site, involving amino acid residues Arg66 (3.29Å), Asp62 (3.70Å), Asp62 (3.64Å). Hydrophobic interactions involving 14 amino acids residues are Met74 (3.75 Å), Phe63 (5:08 Å), Phe63 (5:23 Å), Val115 (4.87 Å), Ala108 (4.99 Å), Val107 (5:26 Å), Arg105 (5:44 Å), Leu96 (4.52 Å), Ala108 (5.02 Å), Phe63 (5.42 Å), Phe63 (5.04 Å), Tyr67 (5.04 Å), Phe71 (4.62 Å), Tyr161 (4.30 Å). There was no electrostatic interaction between n-heteroaryl sulfonamides compound with Bcl-2 in the binding site.

Discussion

Molecular docking is a widely used method to predict *in silico* the binding modes and the affinity of the occurrence in molecular recognition. Molecular docking is also fast and economical computational tool to find a novel drug in the present time.[25] It is also applied to presume the conformation of a binding and its free energy for small molecule ligands toward the macro-molecular targets. Docking is considerably employed in biomolecular interactions and its mechanisms, and also to scheme the structure-based drug.[19,26] The structure-based drug is designed by docking the small molecule to the binding site of a receptor and estimating the affinity of the complex binding.[18] The process of structure-based drug discovery is highly important to develop the novel strategies by investigating drug gable cavities or pockets on a protein target.[27]

The results showed for the first time that the Nordentatin binding affinity against Bcl-2 was comparable to Quercetin against Bcl-2. However, the hydrogen binding, hydrophobic interactions

and electrostatic interactions have different amino acid residues for each interaction. Nordentatin formed a hydrogen binding, whereas Quercetin forms two hydrogen bindings. There were eight residues in hydrophobic interaction found between Nordentatin compound and Bcl-2, Quercetin formed only five residues in hydrophobic interaction. Three amino acids were involved in electrostatic interactions of Nordentatin, but there was no electrostatic interaction between the Quercetin compound with Bcl-2.

The merging of protein is a complicated process. Kauzmann[28] and Tanford[29] introduced the concept of hydrophobicity by connecting it to the tendency of amino acids alteration in different environments of protein. Hydrophobic interactions predominantly contributed in the stability of protein, higher than 50%. Hydrogen binding is also assisted in protein stability, but the percentage of hydrogen binding is lower than hydrophobic interactions even for the smallest globular proteins.[30] The role of hydrophobicity was approximately higher twice than in hydrogen binding of protein folding.[31] The hydrophobic binding is the main factor involved in folding configuration equilibrium in many native proteins.[30]

Electrostatic interactions act in determining the binding affinity, structure, chemical characteristics, stability and the biological reactivity of proteins and nucleic acids. The highly specific binding is often as a prerequisite for biological activity and electrostatics, and contributes to dissolve and form chemically the complementary interactions during binding process.[32]

The achievement of docking and structure-based design of a drug molecule for a specific target site depend largely on the quality of information regarding the architecture of active site, because the size and shape of active site or binding cavity determining the three-dimensional geometry of ligands bind within it. Pocket architecture also affects the interaction of directional and non-directional intermolecular facilitating the protein-ligand binding. A target protein may have several pockets or cavities to bind with a ligand. Some of pockets might be deeply buried in the protein interior, and others might be on the protein surface. However, the appropriate architecture of pockets does not have to be clear from standard inspection of structural data, it may be due to these cavities and protrusions are frequently interconnected via small and narrow channels, or are interspersed with numerous holes or voids. The rotation of amino acid side chains, backbone movements, loop motions, and/or ligand-induced conformational alteration determine the shape and size of binding pockets in significant various ways.[33]

The protein–ligand binding occurs spontaneously only when the system of free energy change to be negative. The differentiation of free energy level between the complex state and the unbound free state (i.e., the magnitude of the negative free energy change upon binding) determines the stability of the complex, and considers that the decrease of free energy in system lead to the protein–ligand binding. In fact, both protein folding and protein–ligand binding process occurs when total Gibbs of free energy in system reduces.[34,25] The negative binding energy maximum reflects the highest binding affinity between protein and ligand. Negative binding energy indicates the stability of binding with the receptor molecule as the essential characteristics for a good drug.[35]

Quercetin efficiently bound to hydrophobic groove of Bcl-2 and changed the structure of Bcl-2 by inducing the conformation.[36] Quercetin has been shown to induce cancer apoptosis via down-regulation of Bcl-2 and Bcl-xL.[6] Since Nordentatin and Quercetin showed equal binding affinity to anti-apoptosis Bcl-2 protein, Nordentatin is also expected to work well as a Bcl-2 inhibitor. Further *in vitro* and *in vivo* studies are required to verify the *in silico* anticancer potentials of Nordentatin as a drug candidate for cancer treatment.

Conclusions

Computational molecular docking was successfully conducted to identify the interaction between Bcl-2 protein and bioactive compounds of Nordentatin and Quercetin. The docking score showed that Nordentatin exerted the similar affinity with Quercetin to Bcl-2 *in silico*. Nordentatin and Quercetin could be potential anti-cancer candidate as Bcl-2 inhibitors in apoptosis-targeting pathway.

Declaration of Interest

The authors report no conflict of interest.

Ligands	PubChem CID	Molecular Formula $C_{15}H_{10}O_7$	Molar Mass (g mol^{-1})	Hydrogen binding acceptors	Hydrogen binding donors	Log P	Rotatable bond count
Nordentatin	5320206	$C_{19}H_{20}O_4$	312.365	4	1	4.4	2
Quercetin	5280343	$C_{15}H_{10}O_7$	302.238	7	5	1.5	1

Table 1. Molecular Profiles of the Investigated Ligands.

Ligands	Mode of conformations generated at upper (9^{th}) to the lowest (1^{st}) with an RMS 0.0 Binding Affinity values at each conformation, ΔG (kcal/mol)								
	1	2	3	4	5	6	7	8	9
Nordentatin	-7.3	-7.1	-7.0	-7.0	-6.7	-6.6	-6.5	-6.5	-6.4
Quercetin	-7.3	-7.1	-6.9	-6.6	-6.6	-6.4	-6.4	-6.4	-6.3
N-Heteroaryl Sulfonamides	-10.8	-9.7	-9.6	-9.4	-8.8	-8.1	-8.1	-8.1	-8.0

Table 2. The Binding Affinity of Nordentatin and Quercetin at the Active Site of Bcl-2.

Ligands	*Binding Affinity*, ΔG (kkal/mol)	Amino acids involved and distance (Å)		
		Hydrogen binding Interaction	Hydrophobic Interaction	Electrostatic Interaction
Nordentatin	-7.3	Arg66 (3.14)	Tyr161 (3.82), Arg66 (3.99), Arg65 (3.99), Arg66 (4.45), Ala59 (4.10), Arg66 (5.34), Arg66 (5.21), Tyr161(4.59), Tyr161(5.46)	Arg66 (3.98), Arg66 (4.13), Asp62 (4.08)
Quercetin	-7.3	Phe63 (3.11), Arg105 (3.25)	Phe63 (5.18) Arg105 (5.35), Arg105 (4.40), Ala108 (4.97), Val107 (5.27)	-
N-heteroaryl sulfonamides	-10.8	Arg66 (3.29), Asp62 (3.70), Asp62 (3.64)	Met74 (3.75), Phe63 (5.08), Phe63 (5.23), Val115 (4.87), Ala108 (4.99), Val107 (5.26), Arg105 (5.44), Leu96 (4.52), Ala108 (5.02), Phe63 (5.42), Phe63 (5.04), Tyr67 (5.04), Phe71 (4.62), Tyr161 (4.30)	-

Table 3. Interaction of Amino Acid Residues - Ligands at The Receptor Sites.

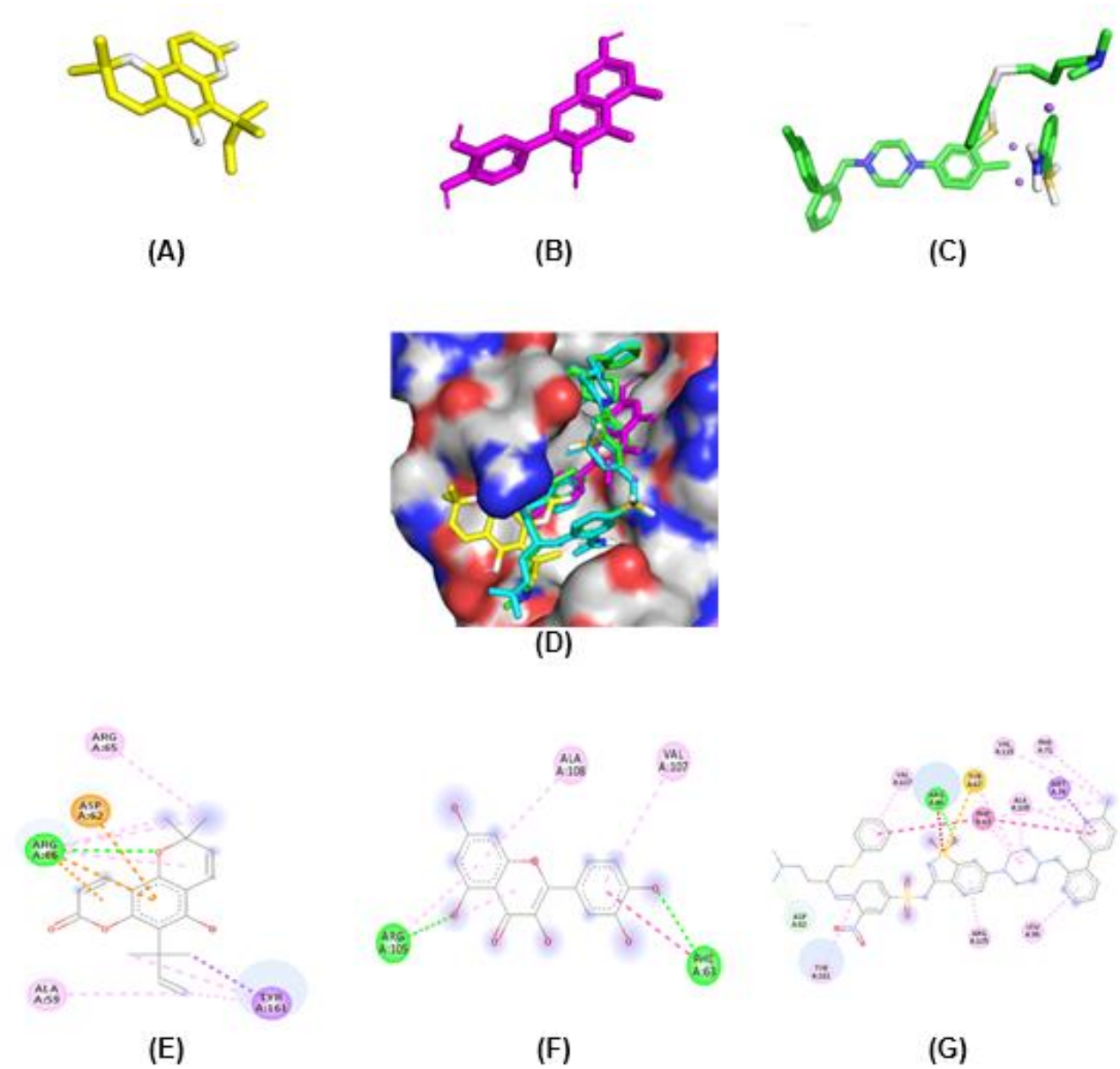

Figure 3. Binding conformation of the compounds in binding site. (A) Nordentatin is shown in yellow carbons. (B) Quercetin is shown in magenta carbons. (C) Compound n-heteroaryl sulfonamides is shown in green carbons. (D) Superimposition of Nordentatin, Quercetin and redocked of n-heteroaryl sulfonamides discovered compounds, crystallized conformation of n-heteroaryl sulfonamides is shown in cyan. (E) Nordentatin ligand and Bcl-2 receptor interaction. (F) Quercetin ligand and Bcl-2 receptor interaction. (G) n-heteroaryl sulphonamides ligand and Bcl-2 receptor interaction. Note: The E, F, and G of 2D diagrams were visualized by DS Biovia 2017.

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