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Computational molecular docking simulation study of Kojic acid glucoside as antibacterial agents

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Abstract

Kojic acid is a fungal metabolic product produced by a few species of Aspergillus, especially by A. oryzae, which has the Japanese common name koji. This compound is an inhibitor of growth of bacteria and multiplication of viruses. In this study, kojic acid derivative, Kojic acid glucoside, was evaluated as DNA gyrase activity inhibitors. DNA gyrase has long been known as an attractive target for antibacterial drugs. In order to investigate the mode of interaction of the compound with DNA gyrase active site, the chemical structures of kojic acid glucoside wase designed using ChemDraw program, then transferred into Hyperchem software for energy minimization. Docking study was performed by AutoDock 4.2 program and the resulting docking poses were analyzed in AutoDockTools, DS Visualizer 3.5 and Ligplot software. Binding model and the best docked pose of this compound showed Kojic acid glucoside formed a hydrogen bond with Asp73, Asn46, Glu50, Thr165, Val71, Arg136 of DNA gyrase in active site. The insilico molecular docking study results showed that, Kojic acid glucoside have minimum binding energy and good affinity toward the active pocket, thus, this may be considered as inhibitor of DNA gyrase.

Key words: Enzyme inhibition, Molecular Docking, Kojic acid glucoside, DNA gyrase

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Introduction

DNA gyrase, or simply gyrase, is an enzyme within the class of topoisomerase and is a subclass of Type II topoisomerases (Garrett and Grisham, 2013) that are involved in the control of topological transitions of DNA and also reduces topological strain in an ATP dependent manner while double-stranded DNA is being unwound by elongating RNA-polymerase (Sutormin et al., 2018) or by helicase in front of the progressing replication fork (Wigley et al., 1991; Morais et al., 1997).

The enzyme causes negative supercoiling of the DNA or relaxes positive supercoils. It does so by looping the template so as to form a crossing, then cutting one of the double helices and passing the other through it before releasing the break, changing the linking number by two in each enzymatic step. This process occurs in bacteria, whose single circular DNA is cut by DNA gyrase and the two ends are then twisted around each other to form supercoils. Because of their essentiality in all cells and the fact that their reactions proceed via DNA breaks, topoisomerases have become important drug targets; the bacterial enzymes are key targets for antibacterial agents. its inhibition results in the disruption of DNA synthesis and, subsequently, cell death. Gyrase is also found in eukaryotic plastids: it has been found in the apicoplast of the malarial parasite Plasmodium falciparum (Dar et al., 2007; Dar et al., 2009) and in chloroplasts of several plants (Evans-Roberts et al., 2016). Bacterial DNA gyrase is the target of many antibiotics, including nalidixic acid, novobiocin, and ciprofloxacin. DNA gyrase is a remarkable enzyme, catalysing the seemingly complex reaction of DNA supercoiling. As gyrase is essential in prokaryotes, it is a good target for antibacterial agents. These agents have diverse chemical structures and interact with gyrase in a variety of ways (Maxwell, 1997). DNA gyrase is a tetrameric enzyme that consists of 2 GyrA ("A") and 2 GyrB ("B") subunits (Vanden et al., 2019). Structurally the complex is formed by 3 pairs of "gates", sequential opening and closing of which results into the direct transfer of DNA segment and introduction of 2 negative supercoils. N-gates are formed by ATPase domains of GyrB subunits. Binding of 2 ATP molecules leads to dimerization and, therefore, closing of the gates. Hydrolysis, on the contrary, opens them. DNA cleavage and reunion is performed by a catalytic center located in DNA-gates build by all gyrase subunits. C-gates are formed by GyrA subunits (Bush et al., 2019) (Fig. 1).

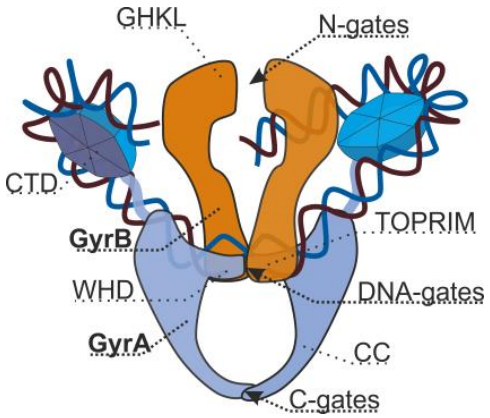

Fig. 1. Structure of DNA gyrase

The kojic acid scaffold has an excellent structure in medicinal chemistry research, due to its vast biological activities. Kojic acid is a chelation (a type of bonding of ions and molecules to metal ions) agent produced by several species of fungi, especially Aspergillus oryzae, which has the Japanese common name koji (Bentley, 2006; Yabuta, 1924; Parvez et al., 2006).

Kojic acid also has antibacterial and antifungal properties. The cocrystals of kojic acid with quercetin were found to have two times better cytotoxic activity to human cervical cancer cells (HeLa) and human colon cancer cells (Caco-2) in comparison with quercetin itself (Veverka, 2015).

The chemical formula is C6H6O4 (Fig. 2) with melting point in range of 152 to 155 °C and 142.11 g/mol. It has a slight Solubility in water and acidity is 9.4. in addition, the IUPAC name is 5-Hydroxy-2-(hydroxymethyl)-4H-pyran-4-one Kojic acid may be used on cut fruits to prevent oxidative browning, in seafood to preserve pink and red colors, and in cosmetics to lighten skin. As an example of the latter, it is used to treat skin diseases like melisma. In this study, kojic acid derivative, Kojic acid glucoside, was evaluated as DNA gyrase activity inhibitors.

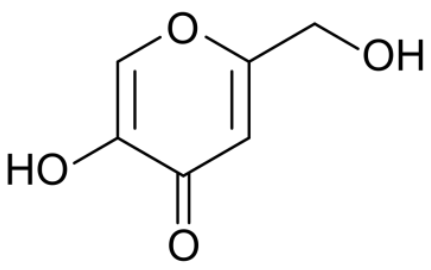

Fig. 2. Kojic acid structure

Computational techniques have been applied in the drug discovery pipeline since the 1980s. Given the low computational resources of the time, the first molecular modeling strategies relied on a rigid view of the ligand-target binding process. During the years, the evolution of hardware technologies has gradually allowed simulating the dynamic nature of the binding event. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. The aim of this research was DNA gyrase inhibition by a Kojic acid derivative (Kojic acid glucoside) using molecular docking.

Methods

For this research autodock4.2 was used. Co-crystallized ligand, water molecules of crystallization were removed from the complex using Discovery Studio Visualizer. All missing hydrogens were added and after determining the Kolman united atom charges, non-polar hydrogens were merged to their corresponding carbons using Auto docktools.9 (Wang et al., 2014).

The AutoGrid program performs precalculations for the docking of a ligand to a set of grids that describe the effect that the protein has on point charges. Using Autogrid as a part of the Auto dock package, desolvation parameters and electrostatic interactions were assigned to each protein atom. The Lamarckian Genetic Algorithm (LGA) approach was selected as the search algorithm for the global optimum binding position search among the three different search algorithms offered by AutoDock 4.2. The resulting docking poses were analyzed in Auto Dock Tools and Discovery Studio Visualizer programs.

Results and Discussion

Kojic acid glucoside successfully occupied the catalytic site of DNA gyrase. Discovery Studio Visualizer programe used to estimate possible interactions. Fig. 3-A shows that in studied compound. VAL167, THR165, ASN46, ASP73 residues of DNA gyrase were the sites for hydrogen bonding interactions. DNA gyrase (1kzn) which was obtained from RCSB Protein Data Bank (https://www.rcsb.org), was transferred into Discovery Studio Visualizer (Fig. 3-B). At the active site of the enzyme Asn46, Asp73, Arg136 residues were the sites for hydrogen bonding and it showed one Pi-cationic interaction with Arg136. DNA gyrase is a very important target for the development of novel antibiotics that target DNA replication.

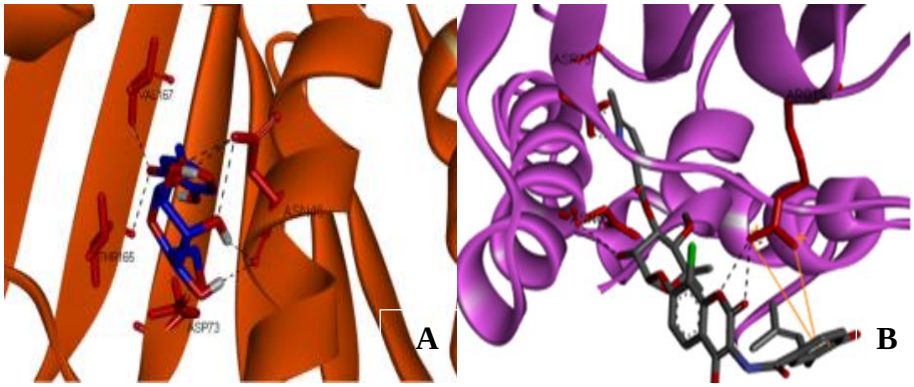

Fig. 3. A: Kojic acid glucoside successfully occupied the catalytic site of DNA gyrase. Discovery Studio Visualizer programe used to estimate possible interactions. B: Structural details of 1kzn.

Binding modes of the title compounds were compared with the binding mode of other's compounds. Clorobiocin (an aminocoumarin antibacterial that inhibits the enzyme DNA gyrase. (Pojer et al., 2003) formed hydrogen bonding interactions with criticalamino acids such as ASP 73, ASN 46, GLY 77 and ARG 136.All the compounds displayed effective binding affinity towards the target enzyme and interactions were noted with GLU 42, GLU 58, ASN 46, ASP 49, ASP 73, GLN 72and GLY 117.These observations indicated that designed compounds acquired similar binding pose as that of clorobiocin.

The in silico molecular docking study results showed that, Kojic acid glucoside have minimum binding energy and good affinity toward the active pocket, thus, this may be considered as good inhibitor of DNA gyrase.

On 2019, there is an arictle (Kumari et al., 2019) that has been docked 4-Amino-3-hydrazino-5-mercapto-1,2,4-triazole is an organic compound with the formula SC2N3H(NH2) (N2H3)) to the active site of DNA gyrase enzyme. some compounds also displayed a strong hydrogen bond with Asn46. Based on this comparison, this compound is an acceptable choice as a DNA gyrase inhibitor.

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