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In-silico docking study of phytochemicals identified from the roots of *Ardisia paniculata*, *Bridelia tomentosa* and *Smilax ovalifolia* for the hepatoprotective activity

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ABSTRACT

The liver plays a significant role in the detoxification, digestion and metabolic functions but many factors cause liver damage leading to the development of hepatic cirrhosis and liver cancer. The transcription factor Nuclear Factor kappa-light-chain-enhancer of activated B cells is the major regulator of inflammation and cell death leading to liver fibrosis and liver cancer. Root of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* are being used traditionally to treat various ailments including liver disorders. High performance liquid chromatographic analysis of these roots have shown many phytochemicals however, Gallic acid, Rutin and Quercetin were the major phytochemicals. The present study was aimed to perform *in-silico* docking of phytochemicals identified from the roots of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* for the hepatoprotective activity. Silymarin was used as standard and it is well-known for hepatoprotective activity. The phytochemical Quercetin, Rutin and Gallic acid have shown significant NF-κB inhibitory activity. However, Rutin has shown enhanced NF-κB inhibitory activity than the standard Silymarin whereas, Quercetin and Gallic acid have shown decreased NF-κB inhibitory activity than the Silymarin. Hence, the study conclude that the root of *Ardisia paniculata, Bridelia tomentosa* and *Smilax Ovalifolia* is potential for the hepatoprotective activity by inhibiting NF-κB protein.

Keywords: *Ardisia paniculata*, *Bridelia tomentosa*, Hepatoprotective activity, *In-silico* docking , NF-κB, *Smilax ovalifolia.*

1. INTRODUCTION

The liver plays a significant role in the detoxification, digestion and metabolic functions but factors including excess alcohol consumption, viral infections, environmental pollution, parasitic infections and drugs cause liver damage, which may trigger inflammatory and wound-healing responses that in long run promote the development of hepatic cirrhosis and liver cancer. The transcription factor Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) is the major regulator of inflammation and cell death leading to the development of liver damage, liver fibrosis and liver cancer. In spite of medical advances, hardly there are any drugs that stimulate liver utility, offer protection to the liver from damage or help regeneration of hepatic cell. Hence, there is an urgent need for safe hepatopotective agent [1-5].

Root of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* are being used traditionally to treat various ailments including liver disorders. High performance liquid chromatographic analysis of these roots have shown many phytochemicals however, Gallic acid, Rutin and Quercetin were the major phytochemicals (Figure 1). Testing the hepatoprotective activity of these roots by conventional method is costly and time consuming however, *in-silico* docking study offer an economical way to get a valuable information on the pharmacological activities of a chemical entity in short duration of time [6]. The present study was aimed to perform *in-silico* docking of phytochemicals identified from the roots of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* for the hepatoprotective activity

2. MATERIALS AND METHODS

2.1. Materials

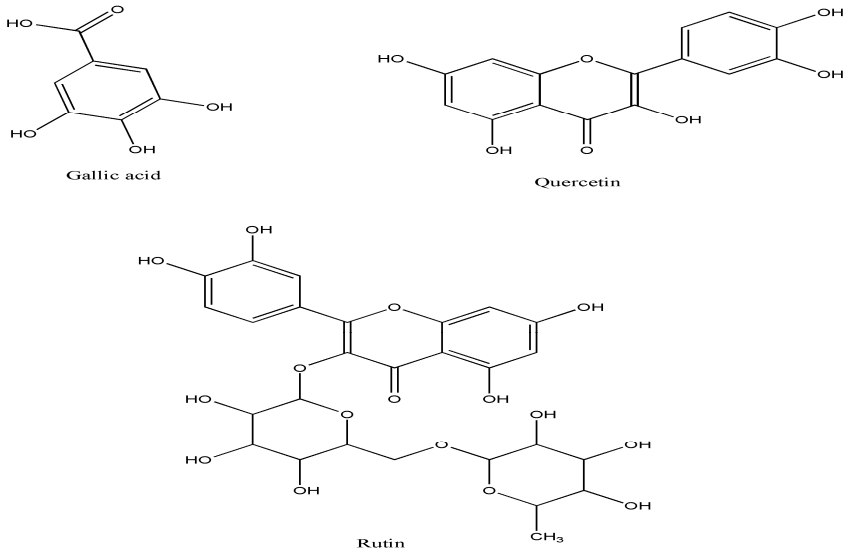

Figure -1: Chemical structures of Gallic acid, Quercetin and Rutin

Swiss PDB viewer software (v4.1) was used to view the protein NF-κB. Marveen Sketch software (v5.5) was used to draw the test ligand (Gallic acid, Rutin and Quercetin) and standard ligand (Silymarin) chemical structures. PyMol viewer software (v1.3) was used for molecular visualization. Schrödinger software [GLIDE module (v5.9), Maestro (v9.4) and QikProp (v3.6)] was used for docking procedures.

2.2. METHODS

2.2.1. Protein structure preparation

The X-ray crystal structure of NF-κB was retrieved from the protein data bank (Figure 2). Water molecules of crystallization were detached from the composite and the protein was optimized for docking using the protein preparation and refinement software provided by Schrödinger. Partial atomic charges were computed using Optimized Potentials for Liquid Simulations-All Atom (OPLS-AA) force field.

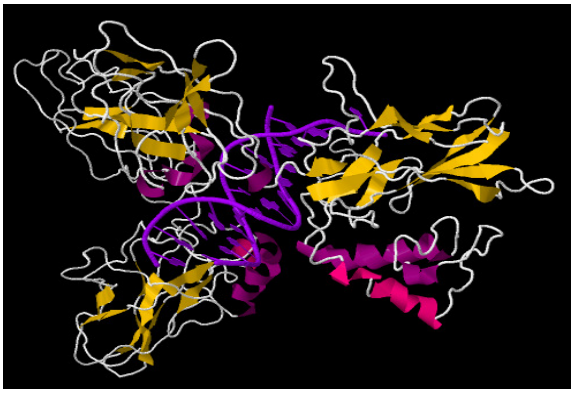

Figure - 2: X-ray crystal structure of protein NF-κB

2.2.2. Ligand structure preparation

The ligands (Gallic acid, Rutin, Quercetin and Silymarin) structure were constructed using the splinter dictionary of Maestro software using the OPLS-AA force field with the steepest descent followed by curtailed newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-AA force field.

2.2.3. Docking Protocol

Prediction of Absorption, Distribution, Metabolism and Elimination (ADME) properties of chemical entity prior to expensive experimental procedures can eliminate unnecessary testing on compounds that will ultimately fail. ADME prediction can also be used to focus lead optimization efforts to enhance the desired properties of a given compound. QikProp software efficiently evaluates pharmaceutically relevant properties of the ligands. All docking calculations were performed using the ‘‘Extra Precision’’ (XP) mode of GLIDE program. The binding site for which the various energy grids were calculated and stored, which is defined in terms of two concentric cubes (1) Bounding box, which contain the center of any acceptable ligand pose, and (2) Enclosing box, which contain all ligand atoms of an acceptable pose with a root mean square deviation of less than 0.5 Å and a maximum atomic displacement of less than 1.3 Å were eliminated as redundant in order to increase diversity in the retained ligand poses. The scale factor for van der Waals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein,

respectively. The max keep variable which sets the maximum number of poses generated during the initial phase of the docking calculation were set to 5000 and the keep best variable which sets the number of poses per ligand that enters the energy minimization was set to 1000. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of conjugate gradient. Upon completion of each docking calculation, at most 100 poses per ligand were generated. The best docked structure was chosen using a GLIDE score (G score) function. Another scoring function used by GLIDE is E-model, which itself derived from a combination of the G score, Coulombic, van der Waals and the strain energy of the ligand [7].

3. RESULTS AND DISCUSSION

The ADME properties of the ligands (Gallic acid, Rutin and Quercetin) were predicted using QikProp. The compounds prepared were subjected to drug-likeness filter. The acceptance criteria of the filter includes molecular weight (i.e. 170 to 610), number of hydrogen bond donors (i.e. 4 to 9) and number of hydrogen bond acceptors (i.e. 4 to 20). All the ligands (Gallic acid, Rutin and Quercetin) conformed to the above mentioned acceptance criteria and they were evaluated for docking using GLIDE software.

GLIDE receptor grid was generated to determine the size of the active site. The most probable orientation of the ligands in the binding pocket is identified and a scoring function is used to quantify the strength of the interaction a molecule can make in a particular orientation. In order to provide better correlation between good poses and good scores, the GLIDE XP precision was favored over the standard mode. The docking analysis was done for the ligands (Gallic acid, Rutin, Quercetin and Silymarin) with the target protein NF-κB using the docking software GLIDE and the docked images are shown in figure 3 (a & b), 4 (a & b), 5 (a & b) and 6 (a & b). The structures docked by GLIDE are generally ranked according to the GLIDE Scoring Function (more negative). The scoring function of GLIDE docking program is presented in the G-score form. The most straightforward method of evaluating the accuracy of a docking procedure is to determine how closely the lowest energy pose (binding conformation) predicted by the object scoring function. In the present study, extra precision GLIDE docking procedure was validated by removing the inhibitor compound with NF-κB protein has been analyzed from the G-score, GLIDE energy and H-bonds. The docking result of these ligands are given in table 1. The interaction energy includes van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding were calculated for each minimized complex. Silymarin was used as standard and it is well-known for hepatoprotective activity. The phytochemical Quercetin, Rutin and Gallic acid have shown significant NF-κB inhibitory activity. However, Rutin has shown enhanced NF-κB inhibitory activity than the standard Silymarin whereas, Quercetin and Gallic acid have shown decreased NF-κB inhibitory activity than the Silymarin.

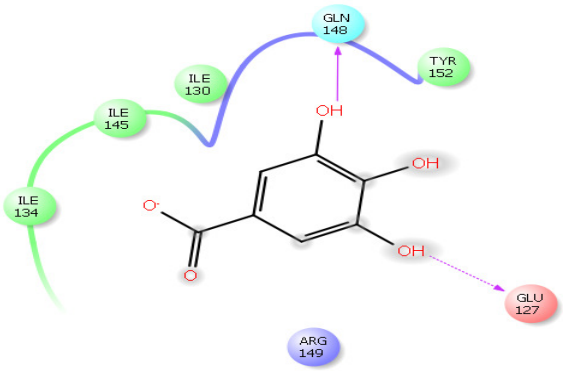

Figure - 3a: Binding interaction of Gallic acid with NF-κB

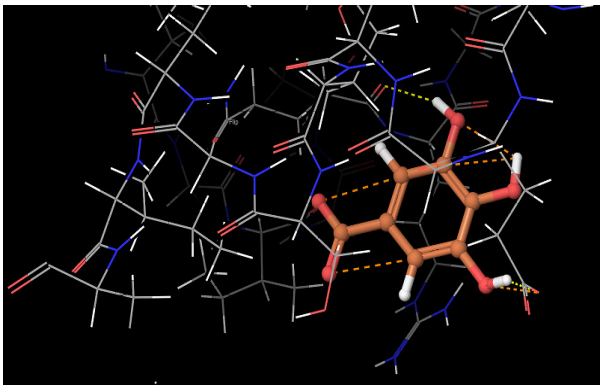

Figure - 3b: 3D image of binding interaction of Gallic acid with NF-κB

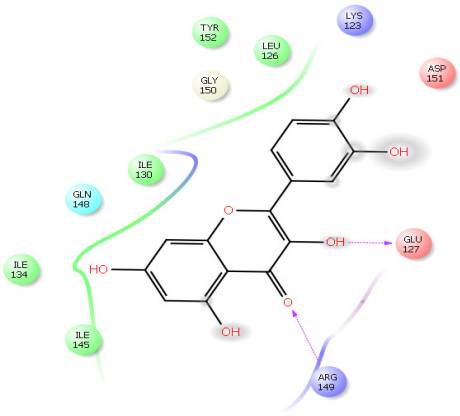

Figure - 4a: Binding interaction of Quercetin with NF-κB

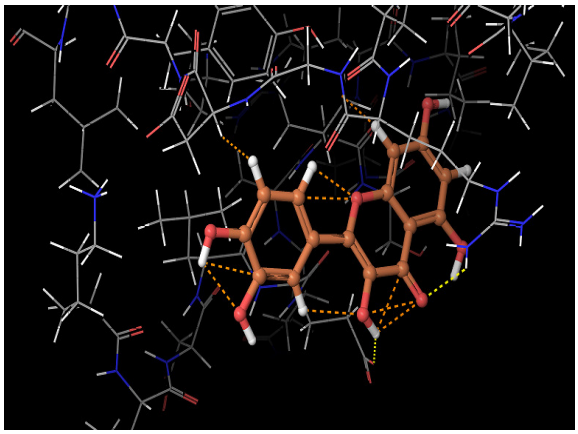

Figure - 4b: 3D image of binding interaction of Quercetin with NF-κB

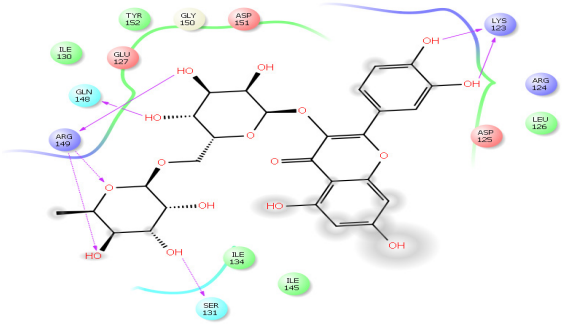

Figure - 5a: Binding interaction of Rutin with NF-κB

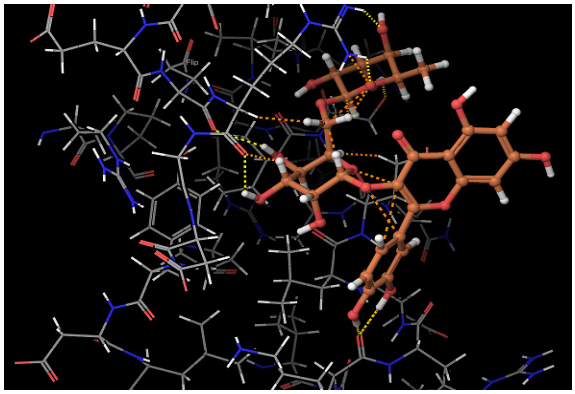

Figure - 5b: 3D image of binding interaction of Rutin with NF-κB

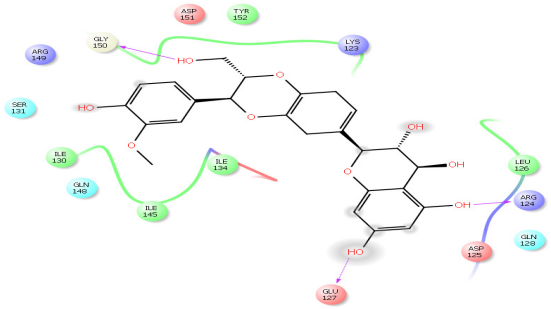

Figure - 6a: Binding interaction of Silymarin with NF-κB

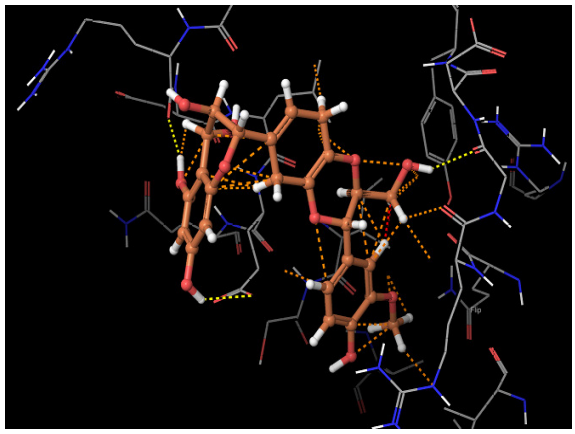

Figure - 6b: 3D image of binding interaction of Silymarin with NF-κB

Table - 1: Summary of GLIDE result of ligands against NF-κB

Ligands	Glide Score against	Glide energy
Quercetin	-5.13	-30.69
Rutin	-9.27	-44.99
Gallic acid	-4.29	-17.53
Silymarin	-6.07	-35.56

4. CONCLUSION

In the present study, *in-silico* docking was carried out for the major phytochemicals (Quercetin, Rutin, Gallic acid) present in the root of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* in comparison with standard Silymarin against NF-κB protein. Quercetin, Rutin and Gallic acid have shown significant NF-κB inhibitory activity. Of the three phytochemicals, Rutin showed maximum NF-κB inhibition than Quercetin and Gallic acid. However, the study conclude that the root of *Ardisia paniculata, Bridelia tomentosa* and *Smilax ovalifolia* is potential for the hepatoprotective activity by inhibiting NF-κB protein.

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