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MOLECULAR DOCKING OF *JUGLANS REGIA* L. DERIVED SELECTED DIETARY FLAVONOIDS WITH APOPTOTIC SIGNALING MOLECULE P53

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ABSTRACT

The p53 tumor suppressor acts to integrate multiple stress signals into a series of diverse antiproliferative responses. One of the most important functions of p53 is to activate apoptosis. Disruption of this process can promote tumor progression and chemoresistance. It apparently promotes apoptosis through transcription-dependent and transcription-independent mechanisms that act in concert to ensure that the cell death program proceeds efficiently. Moreover, the apoptotic activity of p53 is strictly controlled, and influenced by a series of quantitative and qualitative events that ultimately determine the outcome of p53 activation. Naturally occurring plant derived compounds are considered as attractive candidates for cancer treatment and prevention. Phytoconstituents can control and modify various biological activities by interacting with molecules involved in various signaling pathways. In this study, induced fit docking was carried out for understanding the binding interactions of Juglans regia L. derived pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) with p53. Favorable binding conformations between p53 and the four phytoconstituents were observed. A number of poses were generated and evaluated for understanding binding conformations and common interacting residues between ligands and proteins and the best ligands against

p53 are reported. They may be used as potential inhibitors of carcinogenesis by targeting p53 dependent pathway. Further studies need to be carried out to explore the pharmacological properties and inhibitory potentials of these flavonoids in experimental models.

Key words: apoptosis; docking; flavonoids; *Juglans regia* L.; ligand; p53.

Introduction

Apoptosis is an active suicidal machinery or programmed cell death, which participates in eliminating the unwanted or potentially harmful cells, under pathophysiological conditions. Exposure of cells to various stressors such as toxic chemicals, UV radiation etc., may lead either to activation of protective mechanisms or ultimately to apoptosis. However, damaged cells when escapes apoptotic process, may lead to the tumorigenesis also. Therefore, apoptosis is an important approach for protecting cells from the influence of various stressors (Elmore, 2007). UV radiation and other environmental toxicants induced apoptosis have two pathways *viz.*, death receptor mediated apoptosis and mitochondrion mediated apoptosis. The mitochondrial membrane permeability is mainly regulated by anti- and pro-apoptotic proteins belonging to the Bcl-2 family (Martinou and Youle, 2011). The anti-apoptotic proteins, including Bcl-2, Bcl-XL, neutralize apoptosis by interacting with some pro-apoptotic members on the mitochondrial membrane. Moreover, tumor suppressor protein p53, induced by DNA damage, can also lead to the onset of apoptosis (Pistritto et al., 2016). UVB-induced damage to the keratinocytes, could promote hot spot mutations in the p53 gene that ultimately may lead to a faulty triggering of apoptosis and can promote the non-melanoma skin cancers. Due to apoptosis, an average of 50 to 70 billion cells in adult humans and 20 to 30 billion cells in children between the age of 8-14 die each day (Karam, 2009).

Naturally occurring phytocompounds are considered as the best agents for cancer prevention and therapy especially due to their anticipated multimodal actions and limited toxicity. Phytochemicals may also affect the signaling pathways within the cells including those regulating cell proliferation and activation of apoptosis (Gupta et al., 2010). In addition, combined regimens of naturally occurring compounds with standard chemotherapeutic drugs are very promising in providing additive or synergistic efficacies. Among various naturally occurring compounds, polyphenols are known to be present in various edible fruits including grapes, berries, walnut, pomegranate, apples, etc. Among these, flavonoids consist of a large

group of natural, small molecular weight compounds, ubiquitously present in almost all fruits and vegetables (Srivastava et al., 2016). Flavonoids are a group of natural compounds with antiviral, antioxidative, anti-inflammatory and antitumoral properties. *J. regia L*. is considered as nutrient rich due to high contents of fats, proteins, vitamins and minerals. It is also a good source of flavonoids, sterols, pectic substances, phenolic acids and related polyphenols (Shah et al., 2014). The extracts from *J. regia* L. inhibit oxidative damages (Zhao et al., 2014), inflammation (Hosseinzadeh et al., 2011), tumor growth (Negi et al., 2011) and photo-aging (Joshan and Singh, 2013). In this study, we screened selected dietary flavonoids from *J. regia* L. (*Article in press*) such as pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) for their binding interaction with p53 by induced-fit docking.

MATERIALS AND METHODS

Molecular Docking

Molecular docking was performed on Centos 6 Linux workstation using Maestro (Schrodinger LLC 2009, USA). Gridbased Ligand Docking with Energetics (GLIDE-6.0) searches were performed for understanding docking interactions of compounds *viz.*, pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) with p53. All molecular modeling was carried out using Optimized Potential Liquid Simulation for All Atom (OPLS-AA) force field. Ligprep 2.3 module (Schrodinger) was employed for all compounds preparation. The three-dimensional crystal structure of p53 (PDB: 4QO1) was downloaded from the protein data bank (PDB) (http://www.rcsb.org) (Fig.1). Protein preparation wizard of Schrodinger was used for p53 preparation. No hydrogen atoms were minimized until the average root mean square deviation reached a default value of 0.3 Å. Sitemap 2.3 was used to understand binding site in the ligand-binding domain (LBD) of the above mentioned proteins. Induced fit docking (IFD) was performed to predict compound binding modes and structural movements in the LBD region of proteins using Glide and Prime modules. The prepared proteins were loaded on the workstation and the grid values were calculated to about 20 Å to cover the entire active site amino acids. About 20 conformational images were created and analyzed for the best conformation pose based on the docking score and glide energy

Molecular modeling calculations

All computational works were performed on Red Hat Enterprise Linux EL-5 workstation using the molecular modeling software Maestro (Schrodinger LLC 2009, USA). GLIDE-6.0 (Gridbased Ligand Docking with Energetics) searches were made for favorable docking interactions between one or more ligand molecules with the protein macromolecules. All the molecular modeling simulations were carried out using OPLS-AA force field [Glide 6.0] (Friesner et al., 2004). Hydrogen bond interactions and hydrophobic contacts were observed between protein and ligand using Ligplot software (Wallace, 1995).

Ligand preparation

Compounds like pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) were built using builder panel in Maestro. The four compounds were taken for ligand preparation by Ligprep 2.3 module (Schrödinger, USA), which performs addition of hydrogen, 2D to 3D conversion, measurement of realistic bond lengths and bond angles, assessing low energy structure with correct chiralities, ionization states, tautomers, stereochemistries and ring conformations.

Protein preparation and active site prediction

For the docking study, modifications were carried out in p53 (PDB: 4QO1). Missing hydrogen atoms were added and correct bond orders were assigned, and then formal charges and orientation of various groups were fixed. Following this, optimization of the amino acid orientation of hydroxyl groups and amide groups were carried out. All amino acid flips were assigned and H-bonds were optimized. Non hydrogen atoms were minimized until the average root mean square deviation reached default value of 0.3 Å. Sitemap 2.3 was used to explore binding site in the docking studies (Halgren, 2007).

Induced fit docking

Induced fit docking (IFD) is one of the main complicating step in docking studies, which predicts accurate ligand-binding modes and concomitant structural movements in the receptor using Glide and Prime modules. In IFD, when ligand binds to the receptor, it undergoes side chain or backbone conformational changes or both in many proteins. These conformational changes allow the receptor for better binding according to the shape and binding mode of the

ligand (Keskin, 2007). Here, the prepared protein was loaded in the workspace and the sitemap predicted active site was specified for IFD. Grid was calculated about 20 Å to cover all the active site residues defined by the sitemap. The van der waal's radii of non polar receptor and ligand atoms were scaled by a default factor of 0.50. IFD calculations were carried out for the pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) with the p53 (PDB: 4QO1) receptors. Following this, 20 conformational poses were calculated where the best conformational pose was selected based on the docking score, glide energy, hydrogen bonding and hydrophobic bonding interactions.

Results

In this study, IFD was carried out for pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) with p53 (PDB: 4QO1). Interaction was found to be very effective in all the flavonoids studied (Table 1). The glide energy score against p53 (PDB: 4QO1) was found to be -10.2037, -7.34659, -6.81695 and -6.01945 kcal/mol for madecassic acid; pantothenic pcid (vitamin B5); hexadecanoic acid, ethyl ester (palmitic acid); and 3,4,5-trihydroxy benzoic acid (gallic acid) respectively (Table.1 and Fig.2). All the flavonoids studied, showed comparatively high glide energy scores, docking scores and hydrogen bond interactions with p53.

Discussion

Phosphoprotein p53, the product of an important tumor suppressor gene, is recognized as the guardian of the genome as it regulates the transcription of numerous genes that code for life and death processes. However, during the last decade, the transcription-independent activity of the p53 protein has emerged as an important mechanism by which it modulates mitochondrial functions. It interacts with various proteins in the outer membrane as well as in the matrix of mitochondria, including Bax, Bcl2, p53 up-regulated modulator of apoptosis (PUMA) (Yu et al., 2003), polymerase gamma (Achanta et al., 2005) and manganese superoxide dismutase (MnSOD) (Zhao et al., 2005). It is also known as a potent transcription factor that is activated in response to diverse stresses, leading to induction of cell cycle arrest, apoptosis or senescence. Hence, the regulation of p53 is an important strategy for regulation of cell cycle arrest, apoptosis or senescence in a normal cell.

Naturally occurring compounds are considered as the most successful agents to test for cancer prevention and therapy, due to their anticipated multimodal actions and limited toxicity. Madecassic acid is a pentacyclic triterpenoid occurring naturally in many plant products. Previously the role of madecassic acid from *Centella asiatica* has been reported in the healing processes of wounds (Fu et al., 2005). Won et al., (2010), have reported the anti-inflammatory effects of madecassic acid via the suppression of NF-κB, iNOS, COX-2, TNF-α, IL-1 and IL-6 pathway in LPS-induced RAW 264.7 macrophage cells. In the present study we have analysed the interaction between madecassic acid and p53 (PDB: 4QO1) and found the glide energy score of -10.2037 kcal/mol. Pantothenic acid is also known as vitamin B5. Pantothenic acid is an essential nutrient needed for the synthesis of coenzyme-A (CoA), which is a cofactor for a variety of enzyme-catalyzed reactions involving transfer of acetyl groups. Functions of pantothenic acid include gluconeogenesis, synthesis and degradation of fatty acids, synthesis of steroids (cholesterol), steroid hormones, sphingosine, citrate, acetoacetate, and porphyrins as well as oxidative metabolism of carbohydrates. In the present study, the interaction between pantothenic acid and p53 (PDB: 4QO1) yielded a glide energy score of -7.34659 kcal/mol.

Hexadecanoic acid, ethyl ester (palmitic acid) is the most common fatty acid (saturated) found in animals, plants and microorganisms with a number of functions such as antioxidant, hypocholesterolemic, nematicide, pesticide, anti androgenic flavor, hemolytic and 5-Alpha reductase inhibitor activities (Sudha et al., 2013). The present investigation involving the interaction between hexadecanoic acid, ethyl ester (palmitic acid) and p53 (PDB: 4QO1) yielded a glide energy score of -6.81695 kcal/mol. 3,4,5-trihydroxy benzoic acid (gallic acid), a type of phenolic acid, found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants (Reynolds and Wilson, 1991) has been previously reported to have anti-oxidant as well as (Franziska et al., 2007), anti-inflammatory activities (Guan et al., 2012; Angelica et al., 2013), anti depressant (Chhillar and Dhingra 2013), antiparkinson (Chen, 2004), anti diabetic (Prasad et al., 2010), anti malarial (Griffith et al., 2002), diuretic (Ramya et al., 2014), cardioprotective (Patel and Goyal, 2010), anti-viral (Kratz et al., 2010), antifungal (Silva et al., 2014), wound healing (Nayeem and Karvekar, 2011), anthelmintic (Ndjonka et al., 2014) and anxiolytic (Dhingra et al., 2012) functions. The present study involving the interaction between 3,4,5-trihydroxy benzoic acid (gallic acid) and p53 (PDB: 4QO1) resulted in glide energy score of -6.81695 kcal/mol.

All the four selected phytoconstituents showed good glide energy scores, which are significant when compared with previously reported interaction of quercetin with p53 having a docking score of -4.52 KCal/mol (Muthukala et al., 2014). The present study is also comparable with the previous report of nicandrenone and ginsenosides having docking scores of -8.71093 and -6.7669 respectively, when interacted with p53 (Shaikh et al., 2012). The results of the present investigation provides a theoretical entry to use these phytoconstituents as potential inhibitors against the transcription factors involved in different stress mediated responses.

Conclusion

In this study, the binding interactions of *J. regia* L. derived four phytoconstituents *viz.*, pantothenic acid (vitamin B5); 3,4,5-trihydroxy benzoic acid (gallic acid); madecassic acid and hexadecanoic acid, ethyl ester (palmitic acid) with p53 were analysed using induced fit docking (IFD). The phosphoprotien p53 is a major signaling molecule involved in the stress mediated apoptotic pathway. All the tested phyto-constituents interacted with the target proteins through hydrogen bonding, hydrophobic interactions etc., and showed significant glide energy. Thus results of the present investigation strongly suggest the use of these flavonoids for amelioration of apoptotic responses.

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Fig.1: 3D structure of p53 (4QO1)

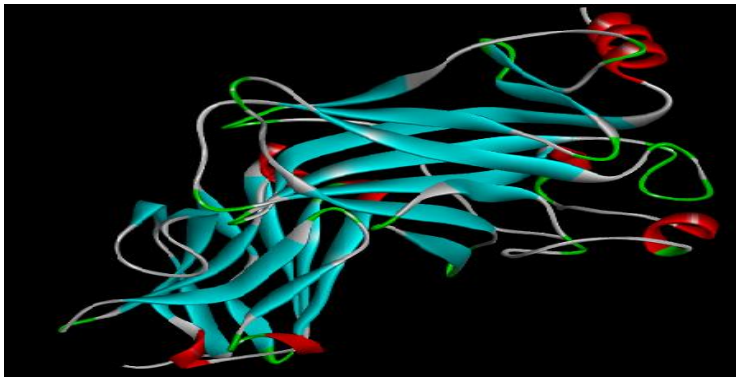

Table.1. Induced Fit Docking for selected flavonoids showing strong inter- and intra molecular interactions with drug-binding pocket residues of p53.

Proteins	**Flavonoids**	**Docking Score (kcal/mol)**	**Glide Energy (kcal/mol)**	**Hydrogen bond Interactions (No.of hydrogen bond)**
4QO1 (p53)	Madecassic Acid	-10.2037	-77.786	3
	Pantothenic Acid (vitamin B5)	-7.34659	-64.312	1
	Hexadecanoic acid, ethyl ester (**Palmitic acid**)	-6.81695	-46.563	1
	3,4,5-trihydroxy benzoic acid (**Gallic acid**)	-6.01945	-41.456	8

Fig.2:

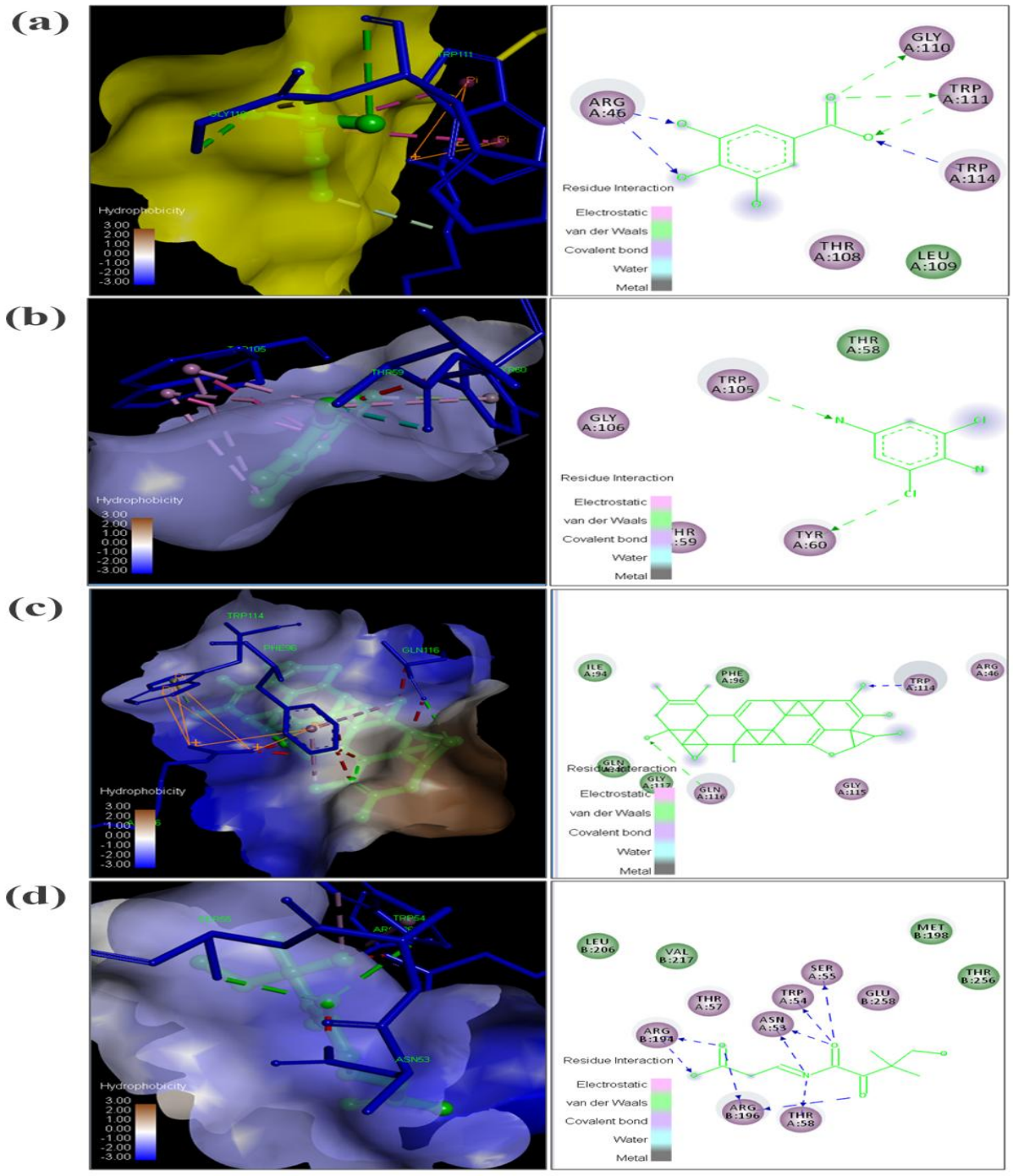

Fig.2. Induced-fit docking model of the flavonoids Madecassic Acid; Pantothenic Acid (vitamin B5); Hexadecanoic acid, ethyl ester (Palmitic acid); and 3,4,5-trihydroxy benzoic acid (Gallic acid) (a, b, c, d respectively), at drug-binding site of p53. Pymol(left side) and Ligplot(right side) view. Hydrogen bonds are shown by blue dotted lines.