Molecular docking analysis of human JAK2 with compounds from tomatoes

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Abstract:
Janus kinase 2 (JAK2) is a tyrosine kinase receptor that belongs to the JAK family kinases is linked to oral cancer. We describe the molecular binding analysis of JAK2 with 23 compounds from tomatos. Docking data shows five compounds (rutin, quercitin, narigenin, chlorgenia acid & kaempferol) with optimal binding features with JAK2 for further consideration.

Key words: Lycopersicon esculentum, JAK2, Oral Cancer, Molecular docking

Background:
Oral cancer is the 6th frequently occurring cancer between both male and female population, and the third most common cancer in developing nations [1]. The majority of oral cancers are known as squamous cell carcinoma [2, 3] which are malignant and responsible to develop rapidly. In India, oral cancer ranked as first place among all other types of cancer in males and third commonest cancer between females in various regions [4]. Common reason for this oral cancer is tobacco and alcohol. Evading of tobacco and alcohol is the most significant precautionary action against mouth, throat and lung cancers. Oral cancer can be identified in early stage through the close interaction of the peoples who have habit of tobacco [5]. The discovery of toxic free, effective
treatment, with complementary and alternative therapies, is serious if the survival rate is to be increased. Epidemiologic studies have proposed a defensive result from some plant-derived foods and extracts [6]. Many epidemiologic reports proposed that the eating of tomatoes (Lycopersicon esculentum) decreases the risk of cancer [7]. There are many recent reports suggested that regular consumption of small amount of tomato products used to protect the cell from DNA damage in oxidant species [8] Because of notorious values, the tomatoes have their antioxidant and antitumoral properties. Computer aided drug design is one of the fastest drug designing methods; it includes various methods to discover novel compounds. One of such method is molecular docking study of drug with target protein [9]. Molecular docking is one of the best methods used to identify the orientation of compounds to the target receptor to facilitate the binding affinity and activity of the small molecules.

The Janus kinase (JAK) belongs to the family of family of tyrosine kinases and contains four members such as tyrosine kinase 2, JAK1, JAK2, JAK3, and functions as a regulator of signaling pathways activated by a number of growth factor and cytokines [10]. Among them, JAK2 kinase plays key roles many neoplastic diseases and is extremely expressed in numerous cell types [10]. Activation of the JAK2/Signal transducer and activators of transcription 3 (STAT3) signaling pathway has revealed to have vital roles of tumorigenesis and progression in different human tumor cell types [11, 12]. Therefore, the blockade JAK2/STAT3 signaling pathway inhibits cell proliferation and provokes apoptosis of numerous human cancer cells [13]. More exclusively, it has been reported that cell growth is suppressed by interference with JAK2/STAT3 signaling in OSCC [14]. So, in the present study we collected the available compounds from tomato (Table 1) and identified their effect against oral cancer target JAK2 using molecular docking approach.

Materials & Methods:

Protein Preparation:
The 3 D crystal structure of Janus Kinase 2 was downloaded from PDB with PDB code (2B7A) is downloaded from PDB and processed adequately for further analysis [15-17].

Ligand Preparation:
We used 12 reported compounds from tomato plant from literature. The structures of these compounds were retrieved in the Spatial Data File (SDF) file format from the PubChem Compound Database (National Center for Biotechnology Information at https://pubchem.ncbi.nlm.nih.gov/). All the structures were converted from SDF to PDB format with the help of the online smiles translator. PDB format were then converted to the ligand PDBQT format using ADT for use in AutoDock4 (AD4) and Auto Dock Vina [18]. AutoDock Vina was for the docking studies of compounds with the target JAK2 receptor [18]. Docked receptor-ligand complexes were visualized using PyMOL. It showed the active site, hydrogen-bond interactions, hydrophobic interactions, and bonding distances as interaction radii of the docked ligand. The binding poses of all compounds were observed and their interactions with the JAK2 were characterized, and the top most energetically good conformations of every ligand were selected.

| S.No | Compound Name          |
|------|------------------------|
| 1    | Benzoic acid           |
| 2    | Chlorogenic acid       |
| 3    | Cinnamic acid          |
| 4    | Gallic acid            |
| 5    | Glucoside              |
| 6    | Kaempferol             |
| 7    | Naringenin             |
| 8    | Protocatechuic acid    |
| 9    | Quecetin               |
| 10   | Rutin                  |

Results and Discussion:
A molecular docking study was carried out to identify the biological activity of compounds from tomato against the JAK2 receptor in oral cancer. For the selected compounds and protein the docking binding mode was recognized to link the docking score function. The binding pattern analysis among JAK2. Protein and ligands recommended that the binding pattern diverse with the ligand nature.

Protein–ligand interaction happen naturally only if the free energy change is negative and the variation in ΔG levels of complexed and unbound free states is proportional to the stability of the protein–ligand interaction. It follows that both protein folding and protein–ligand binding occur when ΔG is low in the system [19, 20]. So negative ΔG scores showed the stability of docked protein-ligand complexes, and it is important feature for effective drugs [21]. In the present study, rutin– JAK2 complex had the more negative ΔG values, so this indicates that rutin have high binding affinity towards the target protein JAK2. Results of all other compounds also had good binding affinity with selected receptor in terms of low binding score. Molecular docking studies also used to identify the types of binding like hydrogen bond, hydrophobic, and electrostatic interactions, with essential amino acid residues are indicative of ligand docking in favorable conformations [22]. Among them hydrogen bond are the main contributors to the stability of receptor protein.
Figure 1: Molecular docking analysis of JAK2 with (a) rutin, (b) quercetin, (c) narigenin, (d) chlrogenic acid & (e) kaempferol.

Table 2: Molecular docking analysis of JAK2 with compounds from to tomatoes.
Hence, in the present study, results of docking showed that hydrogen bond, hydrophobic and electrostatic interactions are mediated through different amino acid residues in each ligand-protein interaction. Specially, the amino acids GLU-930, LEU 932 & LYS-857 alternatively form the H bond with most of the compounds. Out of 12 compounds were selected and showed in Table 2.

Compared to other compounds rutin formed six H bond interaction (LEU-855, ARG-938, ASP-939, ARG-980, LYS-857 & GLU-930) with JAK2 receptor this was showed in Table 2 and can be seen in Fig 1a. Presence of Pi-sigma (LEU-983) and Pi-alkyl (ALA-880 & VAL-863) interactions mainly participated in charge transfer of molecules and also helped to intercalating the drug in the active site of the Target protein (Figure 1a). The compound Quercetin interact with JAK2 receptor molecule satisfactorily with good docking score of -9.3 kcal/mol, making it the second most active drug. It’s showed two H-bonds with LYS-857 & LEU-932 respectively (Fig 1b). Further Quercetin also form Pi-sigma interaction with LEU-855 & LEU-932 and pi-alkyl interaction with ALA-880 & VAL-863 amino acids residues. Naringenin docked well with the JAK2 receptor with binding score of -8.9 kcal/mol. Three H-bonds were recognized between the JAK2 and Naringenin molecule. Naringenin formed the H bond with LYS-857, GLU-930 & LEU-932 amino acids residues of JAK2 protein. In addition, Leu-983 formed the Pi-sigma bond and LEU-855 & ALA-880 form pi-alkyl interaction with the receptor JAK2 (Fig 1c).

Chloregenic acid also showed efficient binding with JAK2 receptor having a docking score of -8.2 Kcal/mol. It formed the three H-bond interactions with amino acids GLU -930, ASP-994 & ARG -980 respectively. The docked complex stability also connected with extra Pi-sigma interaction (LEU-855 & LEU-983) and Pi-alkyl interactions (ALA-880 & VAL-863). All these interaction were shown in Figure 1D. Results of docking studies showed that binding score of Kaempferol with the JAK2 receptor is -7.4 Kcal/mol, this docked complex was achieved by one H bond interaction with SER-936 amino acid and one Pi-Sulfur interaction with ASP-939 and one Pi-alkyl interaction with ASP-939 (Figure 1E). All these interactions are induced the stabilizing charges responsible for intercalating the compound within JAK2 receptor. These types of interactions are also responsible for the shape of the docked complex.

Conclusion:
We describe five compounds (rutin, quercetin, naringenin, chloregenia acid & kaempferol) with optimal binding features with JAK2 for further consideration.

References: Please add initial to first author
[1] La Vecchia et al. Oral Oncol 1997 33:302 [PMID: 9415327]
[2] Elango et al. Asian Pac J Cancer Prev 2006 7:108 [PMID: 16629526]
[3] Coleman et al. JARC Sci Publ 1993 121:1 [PMID: 8258476]
[4] Parkin et al. JARC Sci Publ 1997 143: IARC, Lyon.
[5] Zhang et al. Tob Induc Dis 2019 7:40 [PMID: 31516483]
[6] Kanti et al. Oxid Med Cell Longev 2009 2: 270 [PMID: 20716914]
[7] Sesso et al. J Nutr 2003 133: 2336 [PMID: 12840203]
[8] Riso et al. Eur J Clin Nutr 2004 58:1350 [PMID: 15054415]
[9] Meng et al. Curr Comput Aided Drug Des 2011 7:146 [PMID: 21534921]
[10] Verma et al. Cancer Metastasis Rev 2003 22:423 [PMID: 12884916]
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