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Molecular Docking Based Study and Analysis of Phytochemicals with TNF-α in Search of Anti-Inflammatory and Anticancer Agents

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ABSTRACT

This study has investigated the possible mode of action of several phytochemicals known to possess anti-inflammatory and anti-cancer properties. It was found by molecular docking studies that ferulic acid, gallic acid, pcoumaric acid, vanillin, myrecene, 4-vinyl phenol and catechol interacted with the binding sight of TNF-α which is the chief regulator of inflammation. This study suggest a possible role of these phytochemicals as anticancer and anti-inflammatory agents.

KEYWORDS

Anticancer, Anti-inflammatory, Molecular docking, Phytochemicals, Tumor necrosis factor-alpha (TNF-α).

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INTRODUCTION

Inflammation is a limited physical condition in which a part of the body or an organ becomes hot, swollen and reddened with pain. It is a self-immune response of the body especially as a reaction to injury or infection. Inflammation may be beneficial in certain conditions such as when the knee sustains a blow and tissues need care and protection. However persistence of inflammation for long periods causes more harm than benefit [1]. Several gene, protein and metabolic factors are involved in causing inflammation and its related diseases. Tumor necrosis factor-alpha (TNF-α) is a chief regulator of inflammation and a major player in the cytokine network [2,3]. Several studies have reported strong pro-cancer actions of TNF-α [4] and is highly involved in pathological process of chronic inflammation, autoimmunity and in several malignant diseases. Due to its high involvement and contribution to all stages of malignancies, TNF-α is considered to be a possible drug target for cancer therapy [5]. However, several toxicities are reported in cancer therapy and other diseases, substantially diminishes the enthusiasm for its application in a clinical settings [6-8]. It is well established that several phytochemicals have anti-angiogenic, anti-inflammatory and antioxidant activities [9].

Several phytochemicals such as vanillin, 4-vinylphenol, catechol, myrcene, *p*-coumaric acid, ferulic acid and gallic acid are well known to have antioxidant and anti-tumor properties. Vanillin exhibits anti-inflammatory, anticancer and antitumor properties and it has been shown to support with the significant

decrease in the production of nitric oxide and pro-inflammatory cytokines. Interleukin (IL)-1β, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), INOS, COX-2, suppresses activation of microglial via inhibiting phosphorylation of ERK1/2, p38 and NF-κB and hence are natural therapeutic agents for cancer neuroinflammatory diseases [10,11]. Leung *et al*. [12] reported the anti-cancer activity of 4-Vinylphenol *via* β-catenin, EGFR and AKT signaling pathways. In a similar manner, the naturally occurring polyphenol, catechol (1,2-dihydroxybenzene) carries anti-inflammatory activity by inhibiting cyclooxygenase and lipooxygenase that have a pivotal role in cancer formation and also act as a target in the therapy [13-15]. Myrcene a hydrocarbon known for its anti-inflammatory, anti-catabolic and pro-anabolic activity in human [16]. *p*-Coumaric acid is a strong antioxidants [17] and is reported as a strong therapeutic candidate for treating pulmonary inflammatory diseases [18]. Ferulic acid exhibits a possible role as a hypoglycemic, antioxidant, anti-inflammatory and anti-apoptotic compound [19]. Gerin *et al*. [20] has reported it as a promising hepatoprotective agent against formaldehyde toxicity. Gallic acid and its derivatives have been reported to have antioxidant, anticarcinogenic, antimutagenic, antimicrobial properties but also provide protection to the cells against oxidative stress [21-23].

In this study, selected phytochemicals were investigated based on molecular docking analysis with known drug target TNF-α as a possible anti-inflammatory and anticancer activities.

EXPERIMENTAL

Synthesis of ligand: The selected ligands were downloaded in the form of Smile notations from Pubchem and sketched using Chemsketch "structure generation from smile notation tool", all the structures were saved in .mol format. The structures were geometrically optimized using UFF in Arguslab and saved in .pdb format. Using Autodock tool all the rotatable bonds in the ligands were made flexible and saved in .pdbqt file format as an input format for molecular docking in Autodock Vina.

Preparation of receptor: Pdb-id 2AZ5 is TNF-α crystallized structure considered as a receptor in the study. Prior to docking calculations all solvent molecules, co-factors and the co-crystallized ligands were removed from the complex structure. Due to the presence of co-crystallized inhibitor in the structure, considering the pharmacophoric interactive amino acid residues for the indigenous inhibitor the binding site was selected, using the grid base application in Auto-Dock tool the cavity dimension was manually scripted with the following range: X-axis: -19.409; Y-axis: 74.650 and Z-axis: 33.849 and grid dimension of X: 40 Å; Y-40 Å and Z: 40 Å.

Molecular docking: Molecular interactions play a key role in every biological reactions. Drugs either imitate or alleviate the effect of natural ligands by binding to the receptor and achieving the pharmacological reactions. Computational simulations are used to model and understand this mode of binding, interaction and orientation of ligands into the active site of their receptors which is called as molecular docking [24]. Protein-ligand docking studies were carried out based on the crystal structures of TNF-α Pdb-id: 2AZ5. In each case, the protein is considered as a rigid part and selected ligands/phytochemicals with highest degree of flexibility. The molecular docking is carried out using Auto-dock Vina tool. For validation purpose the indigenous inhibitor of TNF-α present in the crystallized structure Pdb-id: 2AZ5 is redocked into its same binding region and identical interactions are observed. Later all the selected phytochemicals were interacted into the same binding site.

RESULTS AND DISCUSSION

The docking results revealed the 100% identical pharmacophoric interactions between the indigenous inhibitor of TNF-α and TNF-α Pdb-id 2AZ5, where the generated complex exhibited a pi-pi interaction between inhibitor and TNF-α are as follow: Tyr 119 (A), Gly 121 (A), Tyr 59 (B), Tyr 119 (B) and Tyr 151 (B) and binding energy -8.4 Kcal/mol, all the interactions are in comparison with crystallized dataset reported in Table-1 and Fig. 1.

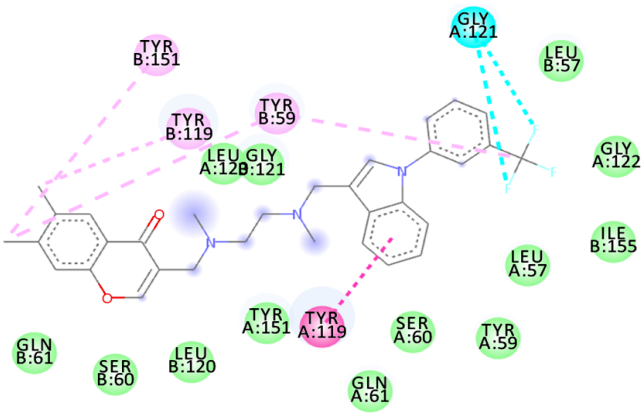

Fig. 1. Indigenous inhibitor with TNF-α

TABLE-1
MOLECULAR DOCKING RESULTS

Protein name	Ligand name	Binding energy (Kcal/mol)	H-bonds	Pi-interaction
2az5	Indigenous	-8.4	–	Tyr 119 (A), Gly 121 (A), Tyr 59 (B), Tyr 119 (B) and Tyr 151 (B)
2az5	Ferulic acid	-5.9	Tyr 151 (A), Tyr 151 (B)	Leu 120 (A)
2az5	Gallic acid	-5.8	Tyr 59 (B) and Tyr 151 (B)	NA
2az5	*p*-Coumaric acid	-5.4	Tyr 151 (A)	Leu 120 (A)
2az5	Vanillin	-5.1	Tyr 151 (B)	Leu 120 (A) and Tyr 59 (B).
2az5	Myrcene	-5.1	NA	Leu 57 (A), Leu 57 (B), Tyr 59 (B), Tyr 119 (B), Tyr 151 (B),
2az5	4-Vinylphenol	-5.0	NA	Leu 57(A), Leu 120 (A) and Tyr 59 (B)
2az5	Catechol	-4.6	Gly 121 (A), Ser 60 (B) and Tyr 151 (B)	NA

The interaction between TNF-α and ferulic acid formed by making a hydrogen bonds with Tyr 151 (A), Tyr 151 (B) and pi-pi interaction with Leu 120 (A) and binding energy score of -5.9 kcal/mol (Fig. 2). Gallic acid forms a hydrogen bond with Tyr 59 (B) and Tyr 151 (B) with a binding energy score -5.8 kcal/mol (Fig. 3). *p*-Coumaric acid exhibited a hydrogen bond with Tyr 151 (A) and pi-pi interaction with Leu 120 (A) and a binding energy score: -5.4 kcal/mol (Fig. 4).

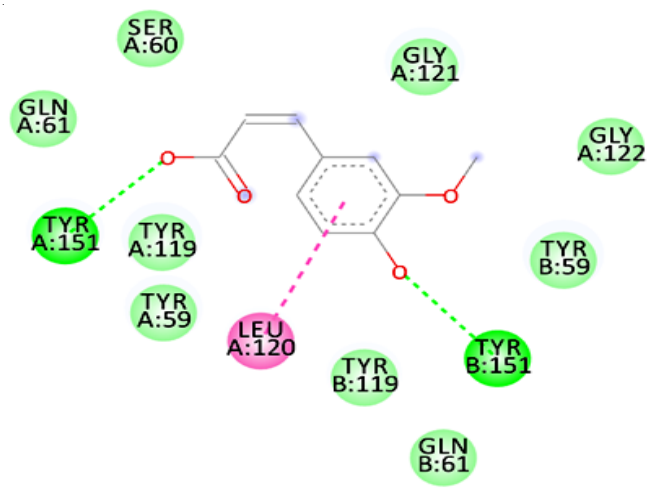

Fig. 2. Ferulic acid complex with complex with TNF-α

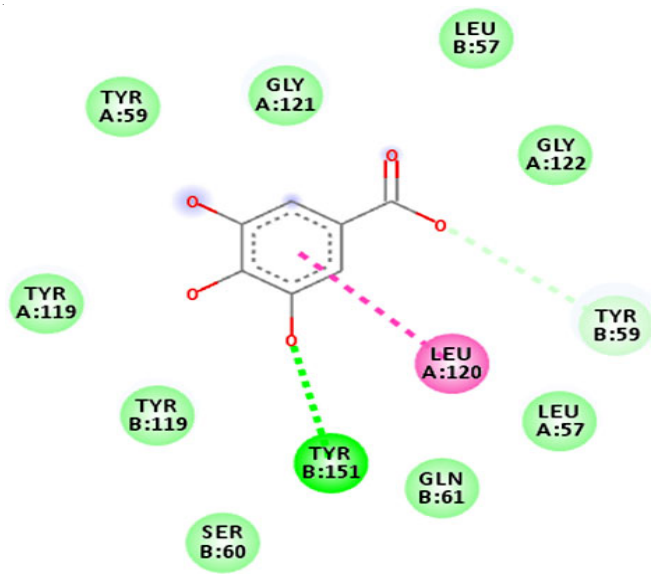

Fig. 3. Gallic acid complex with TNF-α

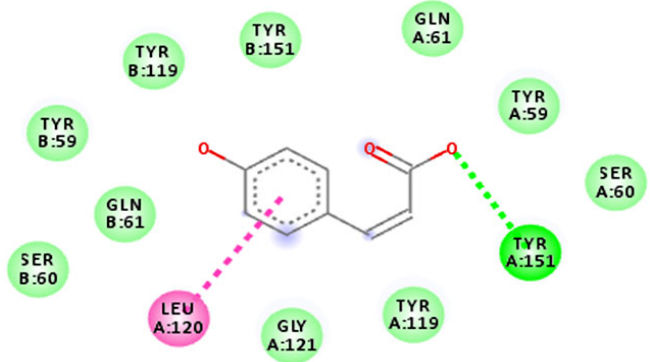

Fig. 4. *p*-Coumaric acid complex with TNF-α

Interaction between Vanillin and TNF-α generated a binding energy score of -5.1 kcal/mol with pharmacophoric interactions, hydrogen bond with Tyr 151 (B), pi-pi interactions with Leu 120 (A) and Tyr 59 (B) (Fig. 5). Myrcene interacted by forming pi-pinteraction with Leu 57 (A), Leu 57 (B), Tyr 59 (B), Tyr 119 (B), Tyr 151 (B), binding energy score: -5.1 kcal/mol (Fig. 6). Complex of 4-vinylphenol and TNF-α exhibited a pi-pi interactions with Leu 57(A), Leu 120 (A) and Tyr 59 (B) and binding energy score of -5.1 kcal/mol (Fig. 7) and catechol exhibited a strong hydrogen bonding with Gly 121 (A), Ser 60 (B) and Tyr 151 (B) with a binding energy score of -4.0 kcal/mol (Fig. 8).

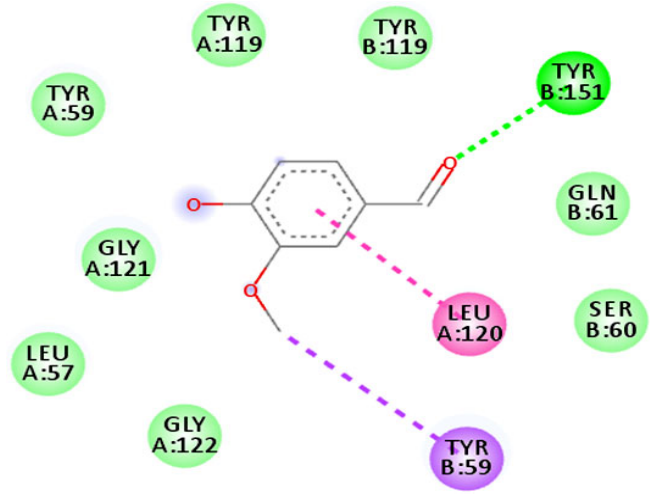

Fig. 5. Vanillin complex with TNF-α

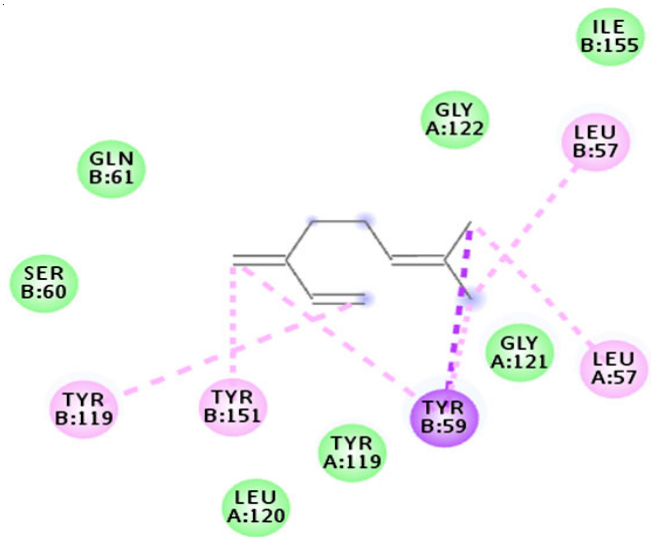

Fig. 6. Myrcene complex with TNF-α

Conclusion

The molecular docking investigations have revealed that all the selected phytochemicals interacted with in the binding site and similar pharmacophoric interactions were observed with respect to indigenous anticancer inhibitor. It is possible that the above phytochemicals exert their anti-inflammatory action by interacting with TNF-α which in itself is a chief regulator in the inflammatory process. Hence these phytochemicals could act as effective anti-inflammatory and anti-cancer agents. Further validation by *in vivo* and *in vitro* methods will elucidate

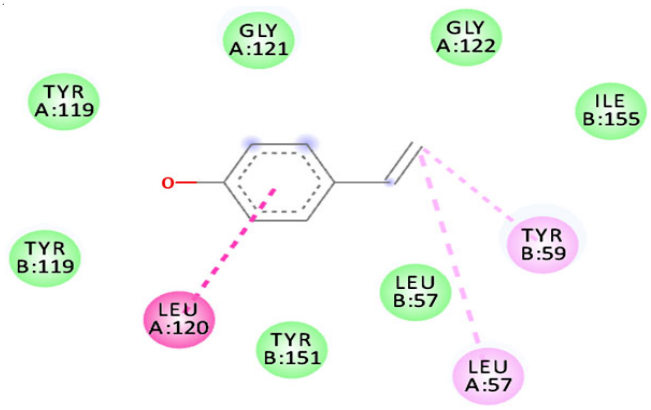

Fig. 7. 4-vinylphenol complex with TNF-α

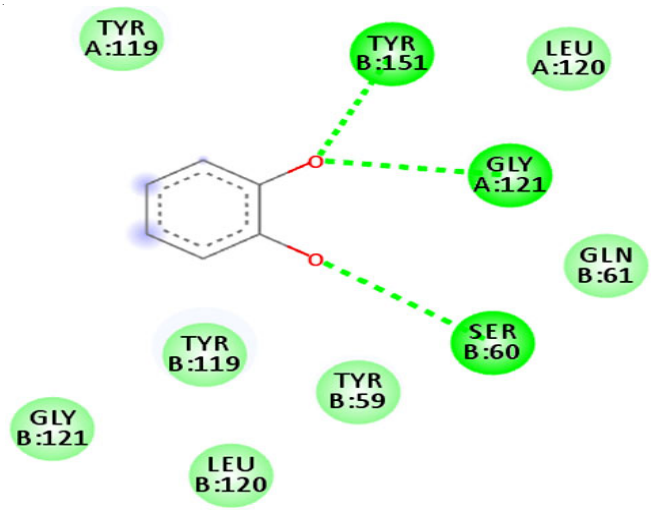

Fig. 8. Catechol complex with TNF-α

a more comprehensive mode of action of the selected phytochemicals.

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