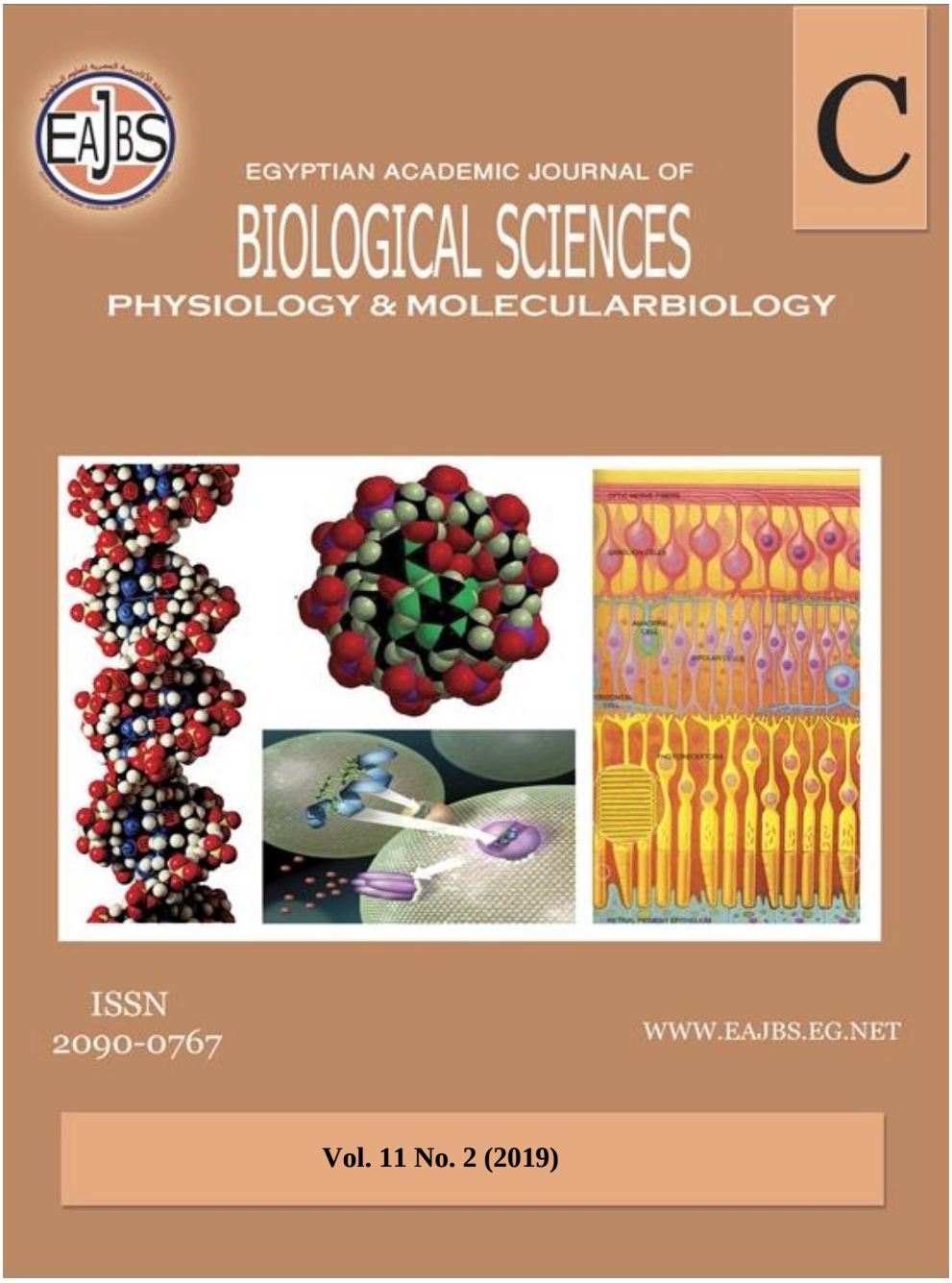


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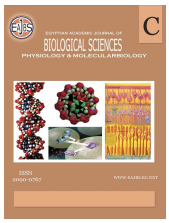

# *In-Silico* Study of Olive's (*Olea europaea L)* Bioactive Compounds as Anti-Cancer Agents

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**ABSTRACT**

Recent studies suggest that Olives bioactive compounds are very important and mainly associated with cancer fight. They can suppress tumor growth through the direct interaction with several important proteins which are directly associated with tumor associated pathways such as P53, P16, P21, BCL2, BAX, MDM2, MMP2 and MMP9 proteins. The main aim of the present work is to perform a docking analysis of the Olives bioactive compounds with tumor-associated proteins. To do that, we first retrieved all the known structures of Olive bioactive compounds using different available online databases. Next, we analyzed these structures using Molegro Virtual Docker (MVD-2010, 4.2.0) software. Further, we narrowed four important compounds (namely, Deacetoxyoleuropein aglycone, Hydroxytyrosol, Tyrosol and Erlotinib) of Olive bioactive compounds that showed very distinguished properties. The ADME properties of these four compounds were predicted based on Lipinski's rule of five. The active sites of the very widely known tumor-associated proteins (P53, P16, P21, BCL2, BAX, MDM2, MMP2 and MMP9) were explored using MVD software. Finally, the active sites of these proteins were docked with the above mentioned four compounds. Based on the docking study, it was concluded that Deacetoxyoleuropein Anglican showed strong inhibition with EGFR, VEGFR1 and VEGFR2.

## INTRODUCTION

Cancer is a very complex disease. It involves the uncontrolled division of normal cells. Further, these abnormal cells transfer from one place to another through the blood and lymph to invade other tissues, leading to the development of the most devastating stage and the cause of death in cancer – metastasis (Ahmad et al., 2018; T. Hussain et al., 2018; Mohd Saeed et al., 2018). Cancer is found to be one of the major causes of death all over the world. Several studies reported that the major cause of cancer is in our modern lifestyles. These lifestyle choices include excessive alcohol consumption, smoking, lack of exercise, poor diet, hormones etc.

(Anand et al., 2008; Ji et al., 2010). Depending on the lifestyle, cancer can originate at any site in the body including breast, ovary, prostate, mouth and lungs. Several methods used to treat cancer such as surgery, chemotherapy, radiation therapy and immunotherapy. The most commonly used method among all these chemotherapies is to treat metastatic cancer using cytotoxic drugs (Adnan et al., 2017; Li-Weber, 2009). However, chemotherapy often has shown to generate side effects by affecting not only the cell viability of tumor but also normal cells (Mangal, Sagar, Singh, Raghava, & Agarwal, 2012). Presently, various anticancer compounds derived from plants (Harvey, 2008). Plants have a long history of the use in the treatment of cancer providing some of the currently used effective anticancer agents such as vinblastine, cisplatin, teniposide, mechlorethamine, procarbazine, prednisone, vincristine, etoposide, paclitaxel, bleomycin, and taxanes (Browder et al., 2000). However, these compounds were found to be ineffective as cancer cells are resistant to some of them (Kausar et al.; Wang & Sun, 2010). Therefore, the recent focus is shifted towards the identification of novel natural compounds that can suppress the cancer cell growth or able to enhance the cancer cell death reducing chemo-resistance caused during chemotherapy (Barbaro et al., 2014). In search of a novel source of the traditional medicine, we found olive as a source of medicinal plant, which is reported and used worldwide for the treatment of various diseases (A, 2011; Barbaro et al., 2014; M. S. Hussain et al., 2012). Olive belongs to the family Oleaceae, popularly known as Black Olive, Common Olive or Green Olive and popularly known as Zeytoon in Arabic. Species of its genus are spread throughout the tropical and temperate regions of the world. For humans, the most important species is by far the olive (*Olea europaea L.*), native to the Mediterranean region, Africa, Southwest Asia and the Himalayas. Various parts of olive are used to treat different diseases and work as neuroprotective active, antibacterial, anti-inflammatory, anti-allergic, anti-hepatitis, cardiac arrhythmia and anti-cancer in folk medicine (Alenazi FSH, Comparative Analysis of Effects of Herbal Drugs and Analgesics on Chronic Kidney Disease Pattern in Ha'il, Saudi Arabia; Barbaro et al., 2014; Martinez-Gonzalez et al., 2015). These activities are mainly attributed to the presence of polyphenols, oleuropein, Hydroxytyrosol, caffeic acid etc., in the members of this family. Hence, the present work is undertaken to evaluate the anticancer activity of olive's *(Olea europaea)* bioactive compounds using *In-silico* experimental models.

## MATERIALS AND METHODS

### 1. Preparation of Ligands:

The structures of olive compounds, which are currently available as anticancer drug molecules, were extracted from the PubChem database (http://puBChEm. ncbi. nlm. nih.goc/) and Zinc Database (http://zinc. docking.org/). The inhibitors (anticancer drug) were converted to the .pdb format and optimized using default settings in Molegro Virtual Docker (MVD-2010,4.2.0). The missing bond orders, charges, bonds, and hybridization states of the extracted ligands were assigned with the help of MVD software.

### 2. Preparation of Receptor:

The X-ray crystal coordinates of proteins were retrieved from the protein data bank. Since these proteins have their crystal structure in a state that represents the pharmacological target for the development of new drugs to cure any diseases, these PDBs were selected for modeling studies. It is well known that PDB files often have poor or missing assignments of explicit hydrogen, and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization, and charges were assigned using the MVD (Saeed et

al., 2013; M. Saeed et al., 2018; Shahid SMA, 2018). The potential binding sites of receptors were calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active site cleft. The water molecules were also taken into consideration, and the replaceable water molecules were given a score of 0.50.

**3 Molecular Docking Study with MVD:**

We used MVD software due to its better docking accuracy than other software such as Glide, GOLD, Surflex, and FlexX2. MVD software is based on a differential evolution algorithm, i.e. MolDock. MolDock Score energy, $E_{score}$, is defined by two terms (Baig et al., 2019; Saeed et al., 2013) (1), (a) $E_{inter}$ which is ligand-receptor interaction energy and (b) $E_{intra}$ is the internal energy of the ligand. $E_{inter}$ is calculated according to (2):

$$E_{score} = E_{inter} + E_{intra} \quad (1)$$

$$E_{inter} = \sum_{i=ligand} \sum_{j=protein} [E_{PLP}(r_{ij}) + 332.0 \frac{q_i q_j}{4r^2_{ij}}] \quad (2)$$

The $E_{ELP}$ term is known as piecthe ewise linear potential that uses two different parameters, one for the estimate of the steric term (van der Waals) between atoms and another for the potential for hydrogen bonds. It further describes the electrostatic interactions between charged atoms. $E_{intra}$ is calculated according to (3).

$$E_{intra} = \sum_{i=ligand} \sum_{j=protein} [E_{PLP}(r_{ij})] + \sum_{flexible\ bond} A[1 - \cos(m\Theta - \Theta_0)] + E_{clash} \quad (3)$$

The first term in (3) calculates the summation of the energies involving pairs of atoms of the ligand, except those associated with two bonds. The second term represents the torsional energy, where *h* is the torsional angle of the bond. The average of the torsional energy bond contributions is taken when several torsions found. $E_{clash}$ , assigns a penalty of 1,000 kcal/mol if the distance between two heavy atoms (more than two bonds apart) is smaller than 2.0 $A^0$, ignoring infeasible ligand conformations.

MVD is an automated docking software with fast processing. The preparation of selected ligands and proteins were done using default parameters, which automatically adds the missing hydrogen atoms. The software has a module to create a surface over the receptor molecule and to give a possible binding site for its activity. The active site region of receptor proteins was chosen for docking. It gives ten conformations for each ligand and returns five outputs with MoleDockScore and other thermodynamically calculated values. The MoleDockScore is an anonymous value on which we have to suggest the best-docked ligand with its conformation. It also provides hydrogen bond information together with other thermodynamic values, which suggest the formation of a stable complex between ligand and receptor molecule.

**4. Parameters for Docking Search Algorithms:**

**4.1. MolDock Optimizer:**

In MVD, selected parameters were used for the guided differential evolution algorithm: number of runs =10 by checking constrain poses to cavity option), population size=50, maximum interactions =2000, cross over rate=0.9,and scaling factor=0.5.Ao variance-based termination scheme was selected rather than the root mean square deviation(RMSD).To ensure the most suitable binding mode in the binding cavity, Pose clustering was employed, which lead to multiple binding modes.

**5 Parameters for scoring functions (MolDock score)**

The ignore-distant-atoms option was used to ignore atoms far away from the binding site. Additionally, hydrogen bond directionality was said to check whether hydrogen bonding between potential donors and acceptors can occur. The binding site on the protein was defined as extending in X, Y & Z directions around the selected cavity with a radius of 25 Angstroms.

## RESULTS AND DISCUSSION

### 1 Predicted ADME properties

We analysed 10 physically relevant properties of bioactive compounds from *Olea europaea L.*(Table 3) , among which were molecular weight, H-bond donors, H-bond acceptors and Log P (octanol/water). Lipinski's rule of 5 is a thumb to evaluate drug-likeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it an orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including its ADME. However, the rule does not predict if a compound is pharmacologically active. In this study, all the showed allowed values for the properties analysed and exhibited drug-like characteristics based on Lipinski's rule-of-five. There are four compounds of *Olea europaea L.* namely Deacetoxyoleuropein aglycone, Hydroxytyrosol, Tyrosol and Erlotinib are found to be more effective than others. The chemical structure of the Olives bioactive compounds is shown in figure 1.

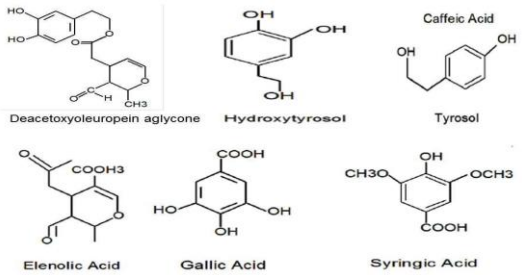



**Fig. 1.** Chemical structure of important bioactive compounds in olive/olive oil

### 2 Prediction of Binding Mode:

The docking results concluded that in angiogenesis, Deacetoxyoleuropein aglycone showed strong inhibition with EGFR, VEGFR1 and VEGFR2 that have MVD score of (-101.53, -82.84 and -78.46), respectively followed by hydroxytyrosol (-82.42, -48.56, -67.25) and Tyrosol (-78.46,-49.57, -65.52) (Table 1) and their docking view is shown in figure 2.Furthermore, these ligands were docked for the active site of various important proteins such as P53, P16, P21, BCL2, BAX, MDM2, MMP2 and MMP9 as shown in figure 2. Corresponding MVD scores are tabulated in tables 2 and 3 which is in the range of -59.02 to -103.61.

We also plot a Ligplot to show protein-ligand interactions as shown in figure 3 with ADME studies of *Olea europaea L.* Compounds and their Physical representation in table 4. In Ligplot, there are two types of interactions are shown which is based on the contacts between protein and ligand namely hydrogen bonds contact and hydrophobic contacts. In this plot, the hydrogen bonds contacts are shown by dashed lines between the atoms, while hydrophobic contacts are shown by an arc with spokes which radiate towards the ligand atoms as shown in figure 3.

**Table 1:** Docking studies of ligands with bioactive compounds in olive/olive oil

| Ligand | Protein | Residues making hydrophobic Contacts |
|---|---|---|
| Deacetoxyoleuropein aglycone | EGFR | Asn175,Leu760, leu704 and Ala763 |
| Axitinib | VEGFR-1 | Lys745, Val786, Leu747, Asp751, and Glu762 |
| Deacetoxyoleuropein aglycone | VGFR2 | Asn756,Asp858,Glu857 and Leu747 |
| Erlotinib | P16 | Arg776,Cys775,Gln791 |
| Erlotinib | P53 | Asn900, Leu901, Glu917, Cys919Asp857 |
| Hydroxytyrosol | P21 | Asp1046, Cys1045, Val899, and Glu917 |
| Erlotinib | BCL2 | Ala859, Lys861, and Val909 |
| Erlotinib | BAX | Cys 912, Lys861, Asp1040 and Leu1029 |
| Erlotinib | MDM2 | Lue844, Thr790Met793, and Gly796 |
| Erlotinib | MMP2 | Gly893, His894, Leu 899 |
| Nutlin | MMP9 | Leu890, Gly893, Glu885, and Asn900 |

**Table 2: Docking studies between Ligands and proteins involved in Angiogenesis with their binding affinities.**

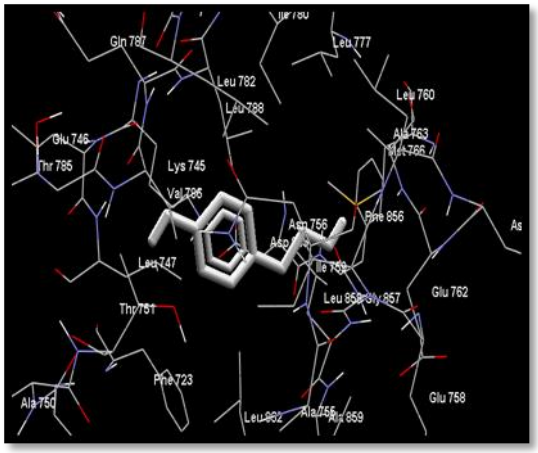
| Sl. No. | Ligands | Mol. Wt. g/mol | Log p | EGFR | | VEGFR-1 | | VEGFR-2 | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity |
| 1. | Deacetoxyoleuropein aglycone | 364.35 | 0.8 | -101.53 | -20.19 | -44.23 | -17.41 | -113.87 | -18.82 |
| 2. | Hydroxytyrosol | 154.1 | 0.52 | -82.42 | -19.27 | -48.56 | -18.02 | -67.25 | -17.56 |
| 3. | Tyrosol | 138.1 | 1.00 | -78.46 | -20.47 | -49.57 | -18.51 | -65.52 | -21.31 |
| 4. | Erlotinib | 393.4 | 2.80 | -150.9 | -34.27 | -104.29 | -34.18 | -160.01 | -34.38 |
| 5. | Gifitinib | 446.9 | 4.1 | -129.02 | -43.37 | - | - | - | - |
| 6. | Axitinib | 386.4 | 3.98 | - | - | -123.37 | -31.11 | -157.17 | -30.73 |
| 7. | Eriodictyol | 288.2 | 2 | | | -60.67 | -19.74 | -117.93 | -26.37 |

**Table 3: Docking studies between Ligands and proteins involved in Apoptosis with their binding affinities.**

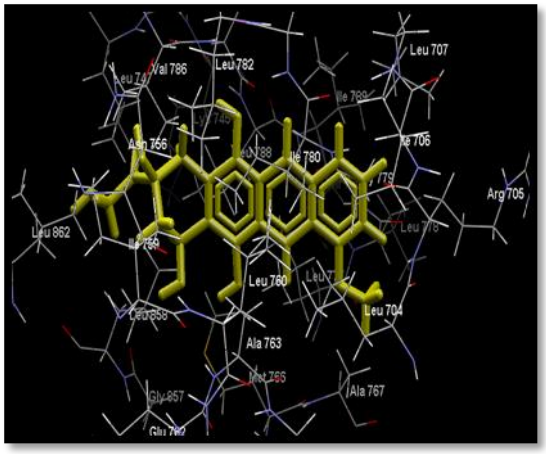
| Sl. No. | Ligands | P16 | | P53 | | P21 | | BCL2 | | BAX | | MDM2 | | MMP2 | | MMP9 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity | Mol doc score | Affinity |
| 1. | Deacetoxyoleuropein aglycone | -52.03 | -16.07 | -72.42 | -20.14 | -79.56 | -19.03 | -38.96 | -18.81 | -63.26 | -21.92 | -103.61 | -20.46 | -59.02 | -20.42 | -89.54 | -18.61 |
| 2. | Hydroxytyrosol | -60.34 | -18.40 | -61.67 | -16.12 | -82.33 | -22.46 | -63.69 | -17.24 | -69.05 | -17.30 | -67.32 | -18.35 | -59.35 | -20.44 | -70.09 | -19.57 |
| 3. | Tyrosol | -66.13 | -22.60 | -71.47 | -22.24 | -77.18 | -22.07 | -63.90 | -18.21 | -71.77 | -20.73 | -68.04 | -19.49 | -82.63 | -21.75 | -71.37 | -22.02 |
| 4. | Erlotinib | -119.69 | -36.76 | -126.04 | -37.47 | -98.53 | -18.60 | -148.0 | -32.87 | -109.86 | -33.83 | -139.52 | -35.93 | -116.72 | -34.74 | -147.34 | -36.25 |
| 5. | Nutlin | -117.58 | -33.86 | -105.88 | -37.79 | -146.35 | -30.77 | -115.85 | -30.41 | -87.81 | -34.40 | -128.15 | -31.80 | -125.14 | -31.43 | -163.00 | -33.62 |

**Table 4: ADME studies of *Olea europaea L.* Compounds and their Physical representation.**

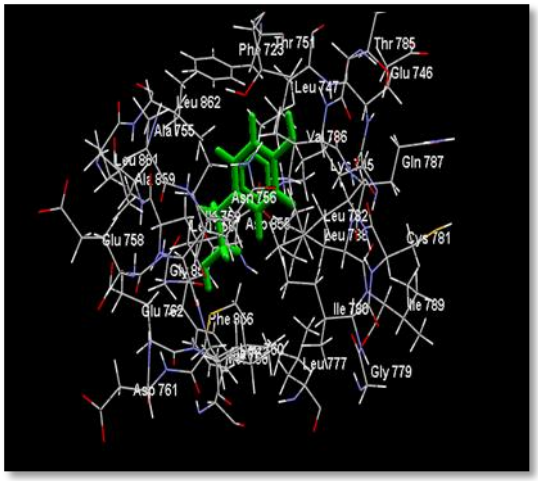
| S.NO | Ligands | pH range | xlogP | Apolar desolvation (kcal/mol) | Polar desolvation (kcal/mol) | H-bond donors | H-bond acceptors | Mol. Wt. | Net charge | tPSA(Å²) | Rotatable bonds |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Deacetoxyoleuropein aglycone | - | - | - | - | - | - | | - | - | - |
| 2. | Hydroxytyrosol | Reference (pH 7) | 0.52 | -2.34 | -7.58 | 3 | 3 | 154.165 | 0 | 61 | 2 |
| 3. | Tyrosol | Reference (pH 7) | 1.00 | -0.27 | -4.99 | 2 | 2 | 138.166 | 0 | 40 | 2 |
| 4. | Erlotinib | Reference (pH 7) | 2.80 | 9.59 | -15.77 | 1 | 7 | 393.443 | 0 | 75 | 10 |
| 5. | Gifitinib | - | - | - | - | - | - | | - | - | - |
| 6. | Axitinib | Reference (pH 7) | 3.98 | 8.98 | -14.29 | 2 | 5 | 386.48 | 0 | 71 | 5 |



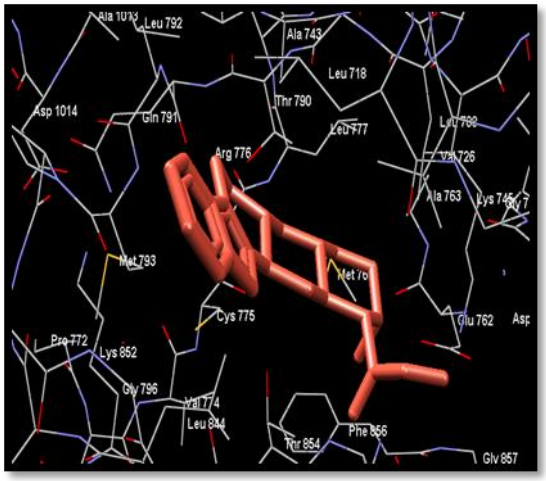

1.Docking between **EGFR** and **Deacetoxyoleuropein aglycone**(Asn175, Leu760, leu704, and Ala763)



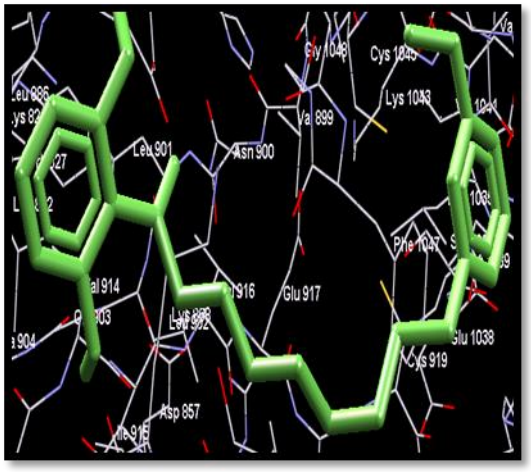

2.Docking between **VEGFR-1** and **axitinib** (Lys745, Val786, Leu747, Asp751, and Glu762)



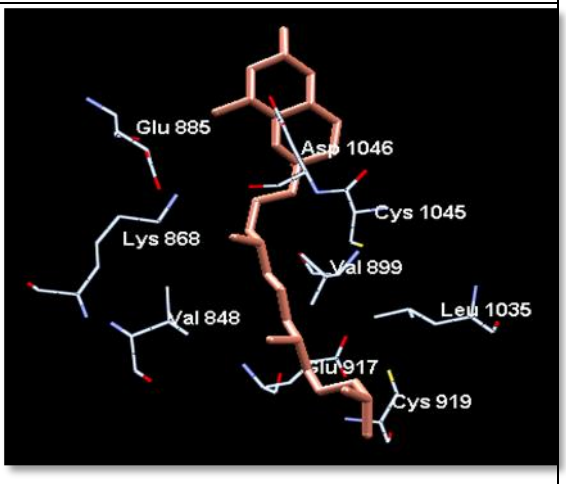

3.Docking between **VGFR2** and **Deacetoxyoleuropein Aglycone** (Asn756,Asp858,Glu857 and Leu747)



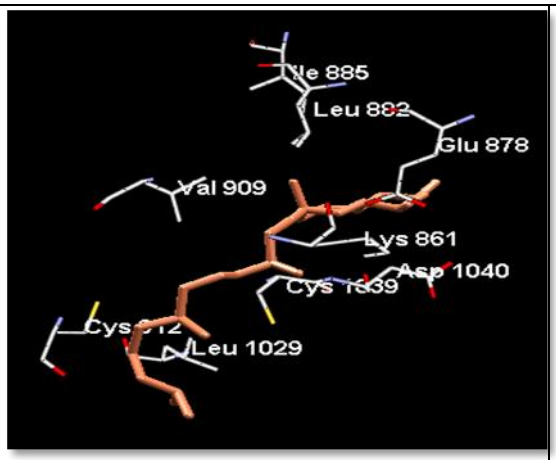

**4.**Docking between **P16** and **Erlotinib**(Arg776,Cys775,Gln791)



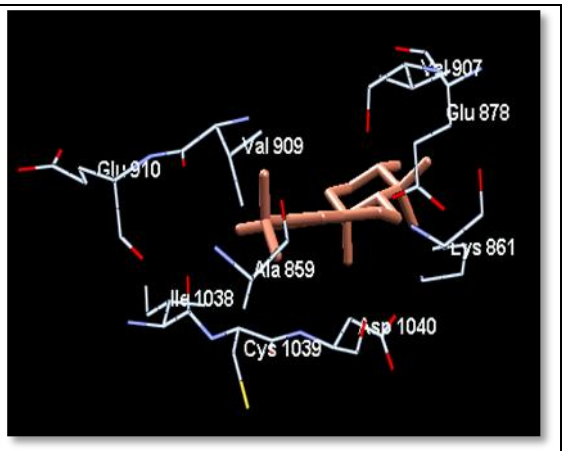

5. Docking between **P53** and **Erlotinib** (Asn900, Leu901, Glu917, Cys919Asp857)



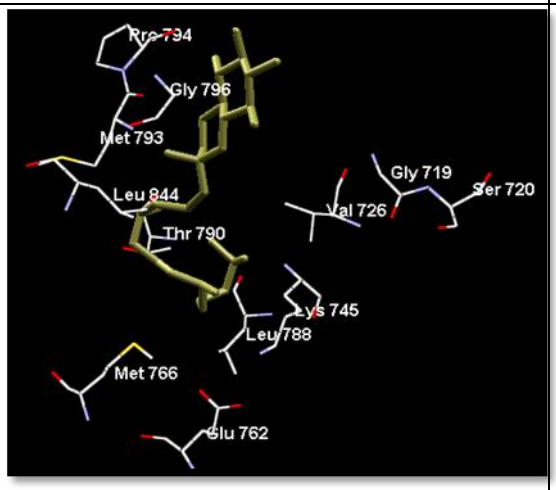

6. Docking between **P21** and **Hydroxytyrosol**(Asp1046, Cys1045, Val899 and Glu917)



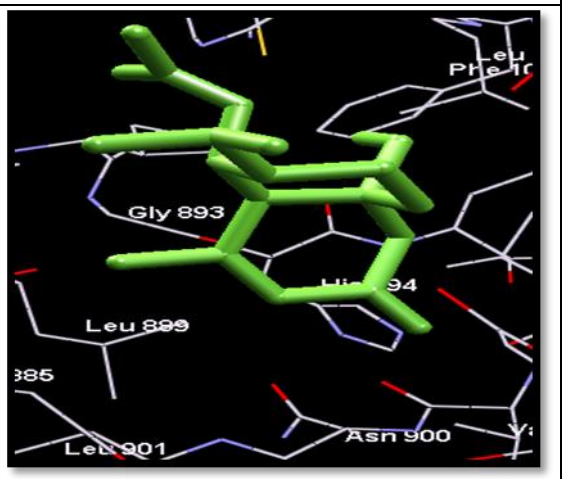

7. Docking between **BCL2** and **Erlotinib**(Ala859, Lys861 and Val909)



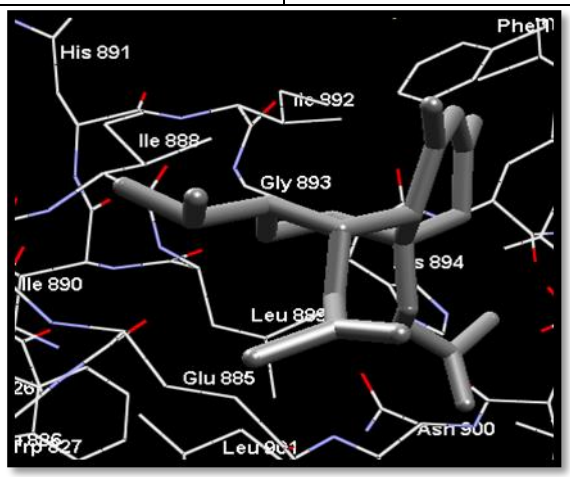

8.Docking between **BAX** and **Erlotinib**(Cys 912, Lys861, Asp1040 and Leu1029))




9.Docking between **MDM2** and **Erlotini** (Lue844, Thr790Met793, and Gly796)




10.Docking between **MMP2** and **Erlotinib**(Gly893, His894, Leu 899)




11.Docking between **MMP9** and **Nutlin** (Leu890,Gly893, Glu885, and Asn900)

**Fig. 2:** Top pose for each ligand based on Moldock score and applying Lipinski's

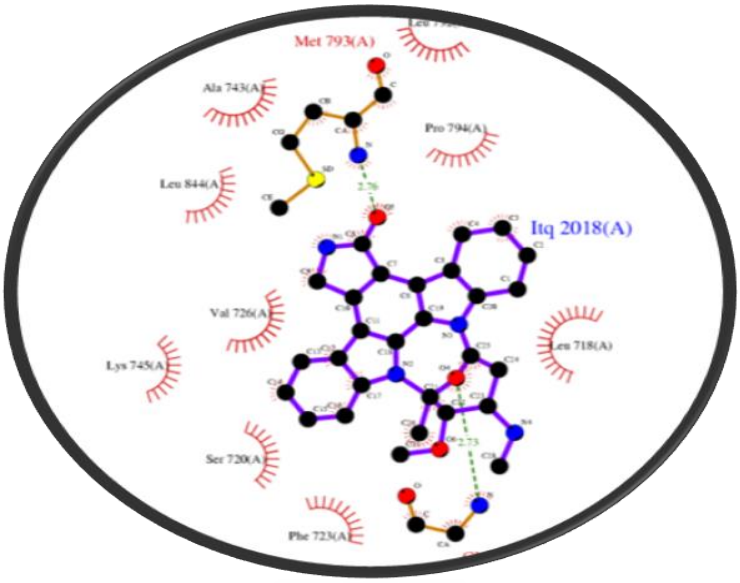



**Fig.3**: Ligplot diagram of Proteins with different ligand

**Conclusions**

In conclusion, docking results suggest that these olive bioactive compounds can play a very important and interesting role to control tumor-associated proteins. This study also predicts the therapeutic perspective of these compounds. Further, experimental validation is needed for the use of these compounds as a possible drug target.

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