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Research Article

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In Silico Approaches to Study the Anti Cancer Potential of Bioactive Compounds of Apium leptophyllum Pers by Molecular Docking

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Abstract: The Indian traditional health care system has suggested the presence of bioactive compounds in herbs used for the treatment of cancer. Natural medicinal plants have been used as therapeutics since the Vedic era. In-Silico studies have demonstrated to be an important tool that facilitates the use of the structural diversity of the natural products and designing new drugs for various diseases. Isolation studies by GC-MS analysis revealed that the ethanolic seed extract of *Apium leptophyllum* Pers contain natural bioactive compounds such as Thymol, Alpha –Terpineol and 9,12- Octadecadienoyl chloride(Z-Z-). These three active compounds are found in higher concentration in the ethanolic extract of *Apium leptophyllum* Pers seeds. The isolated active compounds were subjected to docking studies using Glide module (Schrodinger). Research was performed to find out the potential molecular targets for these selected compounds. The effectiveness of In-silico approach was carried out by performing docking of known specific phenolic mono terpenoids such as Thymol inhibitors against their respective selected macromolecules of cancer cell receptor. The present study was carried out to identify potential inhibitors for Bruton's tyrosine kinase and checkpoint kinase 2. The docking studies revealed that the some essential active compounds such as Thymol, Alpha -Terpineol, and 9, 12- Octadecadienoyl chloride(Z-Z-) isolated by GC-MS analysis have potent anticancer activity against cancer cell. The study will further pave the way in designing other potent drugs and drug analogs. The novel molecular entities have the potential as leads which certainly aid in designing anti-cancer molecules in short span of time.

Keywords: *Apium leptophyllum* Pers, Bio active compounds, Molecular Docking, Bruton's tyrosine kinase, Checkpoint kinase 2, Anti-cancer.

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1. INTRODUCTION

Cancer is the most deadly disease that causes the serious health issues, mortalities, morbidities and physical disabilities around the world. It is characterized by uncontrolled cell proliferation with the potential to invade or other parts of the body. Natural medicinal plant extracts and active compounds derived from plants have played a crucial role in the development of novel anticancer drugs. Recent treatment is basically directed on tumor by chemotherapeutic agent that can effectively remove the tumor but cause a lot of side effects. Therefore to find out the effective bioactive compounds from herbal plants with the target on genes arresting cancer cell division with less side effects is very much essential. Recent days the advancement in research and isolation of bioactive compounds from natural herbal plants by GC-MS analysis technique has helped in identifying novel drugs with anticancer activity. Different methods applied for the treatment of tumor includes radiation therapy, chemotherapy and surgery, used either alone or in combination[1]. These type of treatments are mainly followed for cancer therapy based on the severity of tumor. It has good effect for cancer cell but it leads to lot of side effects in our body .Vincristine and Vinblastine from *Catharan-thus roseus,* Paclitaxel from *Taxus brevifolia*, and Topotecan and Irinotecan from *Camptotheca acuminate* are the best example of naturally derived anticancer compounds.[2,3] Typical chemotherapy treatment destroys platelets and WBC along with tumor cells by damaging their immune system. It was also proved that the cancer patients taking natural medicines during \radiation and chemotherapy revealed lesser side effects. In recent days the utilization of traditional medicines is gradually increased in health care system, due to fewer side effects. Natural herbal medicine has more potent anticancer activity for the treatment of several types of cancer Natural bioactive compounds have been isolated and purified by various techniques for significant anticancer activity against target cancer cell. The target of the tumor was observed and was made to interact with bioactive compounds from medicinal plant by using in-silico approaches. *Apium leptophyllum* (Pers) .F.Muell, ex Benth belongs to the family Apiaceae (Umbellifereae). It is a green, branching herb with tap root arrangements [4]. Seed extract of *Apium leptopyllum* Pers has anti-inflammatory, antiseptic, antispasmodic, analgesic and diuretic properties[5]. The seed extract of *Apium leptophyllum* oil revealed potent antifungal activity against *Candida albicans*. The essential oil consists of thymoquinol, carvacrol and methyl esters of thymol, used as carminative.[6] In-Vitro computational methods were committed to evaluate the anticancer activity of herbal drugs. These methods have been used for drug designing aspects for various types of cancer[7,8]. Bruton's tyrosine kinase is an intracellular non receptor kinase that belongs to the TEC-family tyrosine kinases jointly with bone marrow-expressed kinase (BMX), redundant-resting lymphocyte kinase (RLK), and IL-2 inducible T-Cell kinase (ITK). All these proteins play a vital role in the intracellular signaling of both B and T lymphocytes. Currently a clinical research report have shown that BTK is found in certain cancer subtypes and in other relevant cells that are granting to the cancer microenvironment such as macrophages, dendritic cells, endothelial cells and myeloid derived suppressor cells[9]. Checkpoint kinase 2 is a serine/threonine kinase that engaged in a series of signaling networks important for protecting genomic integrity and reacting to DNA damage. Checkpoint kinase 2 inhibitors have currently interacted with sensitizing cancer cells to new DNA-damaging agents used in the treatment of tumor. Selective Checkpoint kinase 2 inhibitors may reduce p53-mediated apoptosis in normal tissues, thereby helping to reduce adverse effects from radiation and chemotherapy. Thus relatively few selective inhibitors of Chk2 have been demonstrated and none have yet progressed into clinical trials. So these two drug target proteins for the treatment of tumor.[10] The aim of the present study is to evaluate anti proliferative and cytotoxic effects of bioactive compounds of selected medicinal plant Apium leptophyllum Pers through molecular docking method by using target molecule such as Check point kinase -2 and Bruton's tyrosine kinase.

2. MATERIALS AND METHODS

2.1 Protein Preparation

Energy minimization of the resulting protein was accomplished by using Maestro 9.0.111 protein preparation wizard[11]. The energy minimization was performed at the default cut off RMSD value of 0.30 Å using OPLS 2001 force field[12]. The possible conformation of the refined protein was obtained using procheck analysis visualized with the aid of Ramachandran plot by checking the dihedral Phi and Psi angles of amino acid residues.

2.2 Active Site

Identification and characterization of binding site is the key step in structure based drug design [13]. The active site region of the protein is identified by Castp [14]. This server analytically furnishes the area and the volume at the probable active site of each pocket to envisage the binding site.

2.3 Receptor Grid Generation

The scoring grid was generated using a box size of 30 ˚A ×30 ˚A ×30 ˚A and centered on the centroid within a box of dimension 27 ˚A ×16 ˚A ×46 ˚A that encloses the entire groove near the active site to fit the ligands[15].

2.4 Docking

Docking studies a promising tool for identifying active lead compounds which has created a pipeline of drug discovery in most pharmaceutical companies[16]. Glide module has been used for all the docking protocol[17]. The ligands were processed with the Lig Prep program to assign the suitable protonation states at physiological pH= 7.2±0.2. Conformer formation was performed with the ConfGen torsional sampling and Ligand docking used OPLS_2005 force field. The van der Wals radii were scaled using a default scaling factor of 0.80 and default partial cutoff charge of 0.15 to decrease the penalties. There are there modes to screen the compound such as by HTVS, SP and XP in Glide modeule.[18].

3 RESULTS

Table 1. Binding interactions between Check point kinase-2 with hits compounds_9,12-Octadecadienoyl chloride(Z-Z)

Compounds name	Glide score (kcal/mol)	Glide energy (kcal/mol)	Binding residues	H-bond distances
9,12- Octadecadienoyl chloride(Z-Z-)	-4.2	-25.56	ASP 368 N-H..OO	2.56

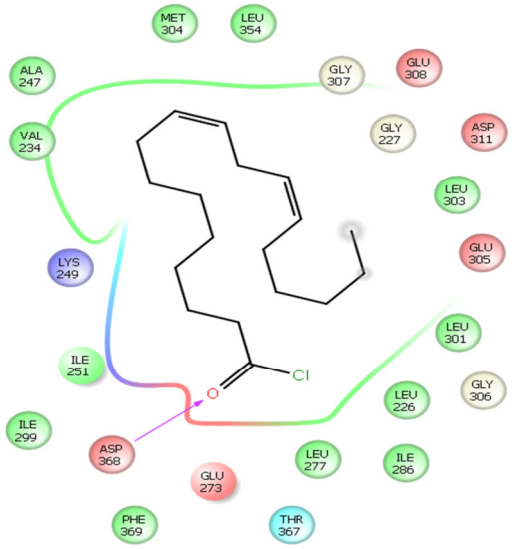

Fig 1. Ligand compound 9,12- Octadecadienoyl chloride(Z-Z-) interact with Check point kinase 2

Figure –1 shows the interaction between the ligand and the protein and the bonds, bonds distance involved between them.The compound 9,12- Octadecadienoyl chloride(Z-Z-) binding with active site residues of ASP 368 amino acid of target Check point kinase -2.It has possessed Glide score – 4.2 and Glide energy –25.56 based on the interaction between ligand and target molecule

Table 2: .Binding interactions between target -Check point kinase-2 with hits compounds_Thymol

Compounds name	Glide score (kcal/mol)	Glide energy (kcal/mol)	Binding residues	H-bond distances
Thymol	-5.8	-50.21	MET 304 N-H…O	2.72

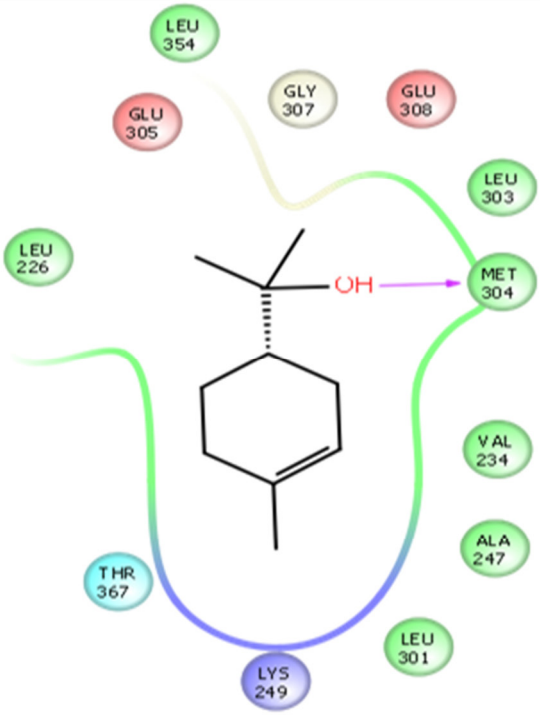

Fig 2: Ligand compound Thymol with Checkpoint kinase 2

Figure –2 shows the interaction between the ligand and the protein and the bonds, bonds distance involved between them. The compound Thymol binding with active site residues of MET 304 amino acid of target Check point kinase 2.It has possessed Glide score – 5.8 and Glide energy – 50.21 based on the interaction between ligand and target molecule.

Table 3. Binding interactions between target - Bruton's tyrosine kinase with hits compounds - Alpha –Terpineol

Compounds name	Glide score (kcal/mol)	Glide energy (kcal/mol)	Binding residues	H-bond distances
Alpha -Terpineol	-6.3	-22.21	MET 477 N-H…O	2.34

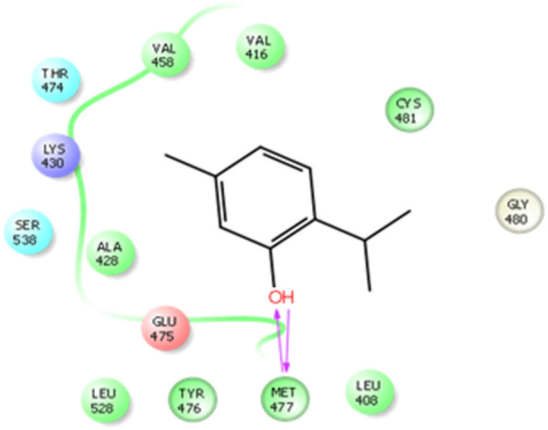

Fig 3. Ligand compound Alpha -Terpineol with Bruton's tyrosine kinase

Figure –3 shows the interaction between the ligand and the protein and the bonds, bonds distance involved between them. The compound Alpha-Terpineol binding with active site residues of MET 477 amino acid of target Bruton's tyrosine kinase.It has possessed Glide score – 6.3 and Glide energy – 22.21 based on the interaction between ligand and target molecule.

Table 4: Binding interactions between target - Bruton's tyrosine kinase with hits compounds - Thymol

Compounds name	Glide score (kcal/mol)	Glide energy (kcal/mol)	Binding residues	H-bond distances
Thymol	-4.1	-20.56	LEU 408 N-H…O	2.70

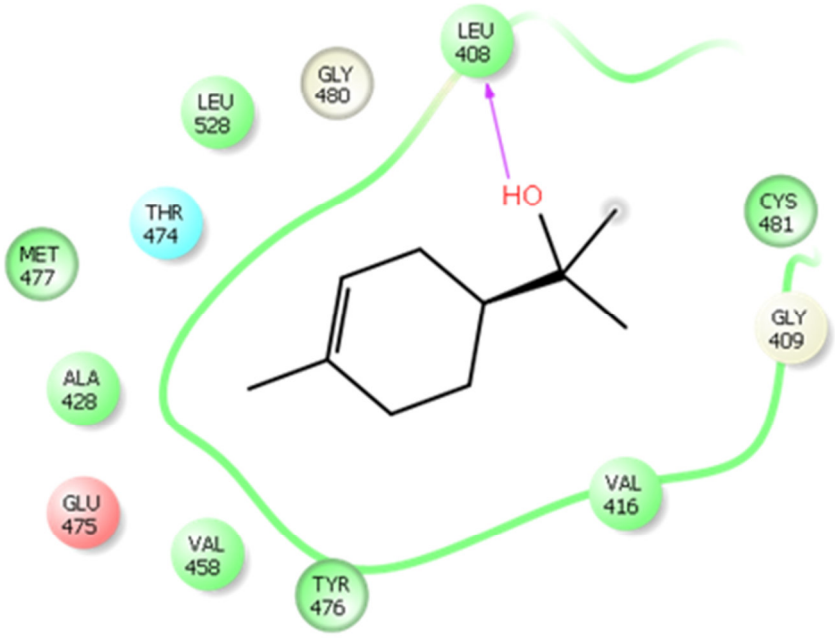

Fig 4. Ligand compound Thymol with Bruton's tyrosine kinase

Figure –4 shows the interaction between the ligand and the protein and the bonds, bonds distance involved between them. The compound Thymol binding with active site residues of LEU 408 amino acid of target Bruton's tyrosine kinase.It has possessed Glide score - 4.1 and Glide energy -20.56 based on the interaction between ligand and target molecule.

Table 5: Binding interactions between target - Bruton's tyrosine kinase with hits compounds - 9,12-Octadecadienoyl chloride(Z-Z-)

Compounds name	Glide score (kcal/mol)	Glide energy (kcal/mol)	Binding residues	H-bond distances
9,12- Octadecadienoyl chloride(Z-Z-)	-3.4	-20.34	ASP 539 N-H…O	2.62

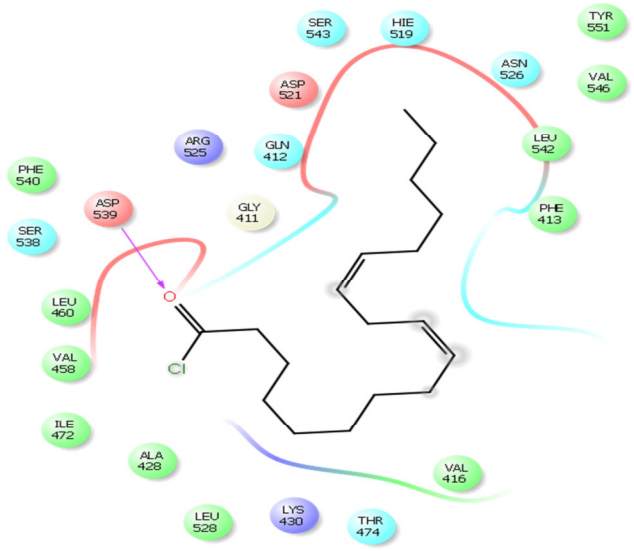

Fig 5. Ligand compound 9,12- Octadecadienoyl chloride(Z-Z-) with Bruton's tyrosine kinase

Figure –5 shows the interaction between the ligand and the protein and the bonds, bonds distance involved between them. The compound 9,12- Octadecadienoyl chloride(Z-Z -) binding with active site residues of amino acid ASP 539 of target Bruton's tyrosine kinase.It has possessed Glide score – 3.4 and Glide energy -20.34 based on the interaction between ligand and target molecule.

3-D Conformation of Molecular Docking of Active Compounds of Apium leptophyllum Pers

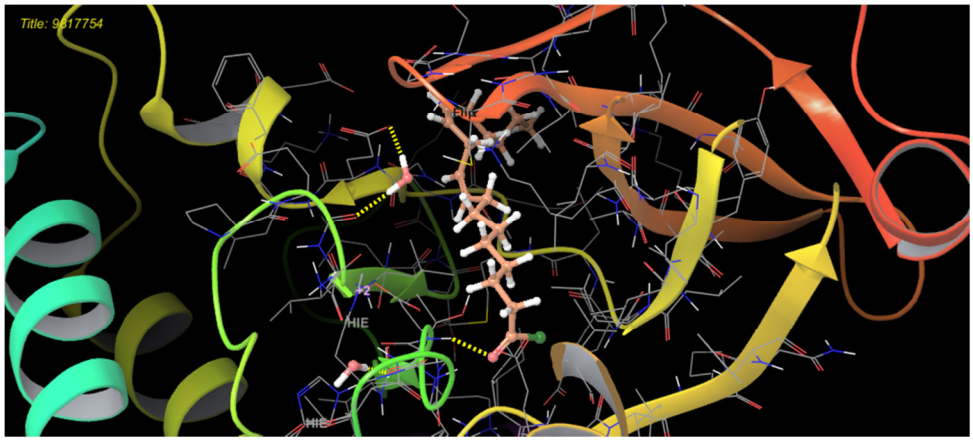

Fig 6. Ligand compound 9,12- Octadecadienoyl chloride(Z-Z-) interact with checkpoint kinase 2

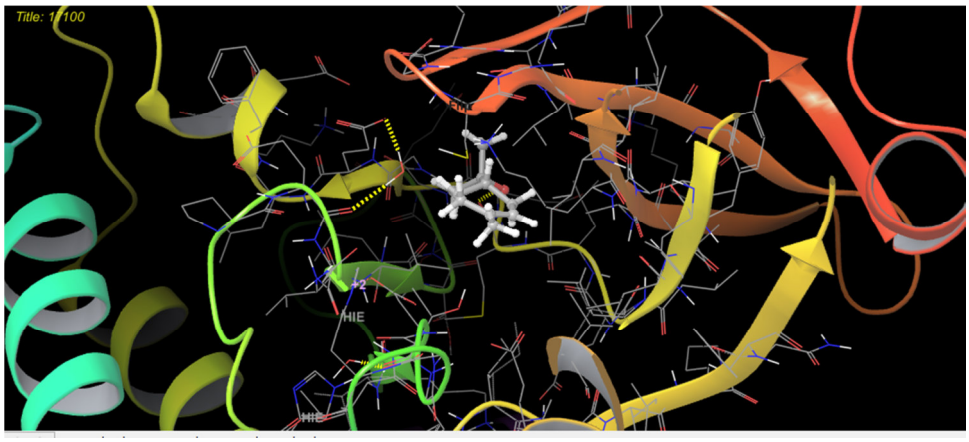

Fig 7. Ligand compound Thymol with checkpoint kinase 2

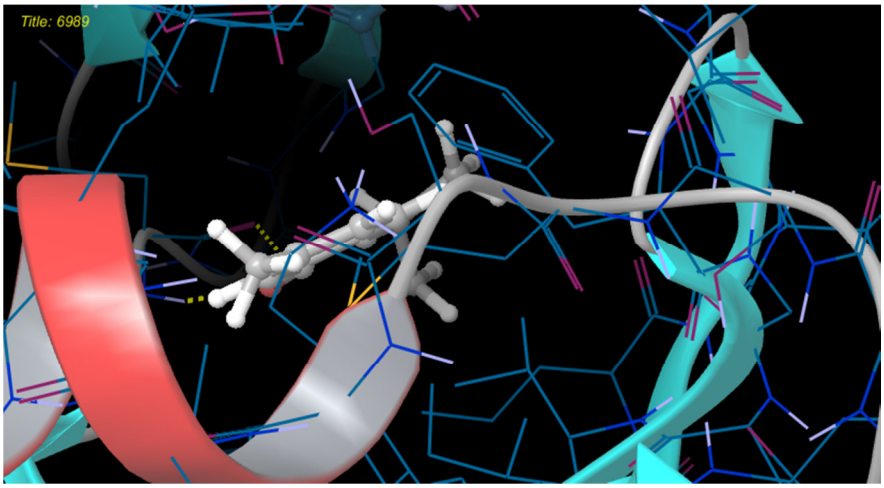

Fig 8. Ligand compound Alpha -Terpineol with Bruton's tyrosine kinase

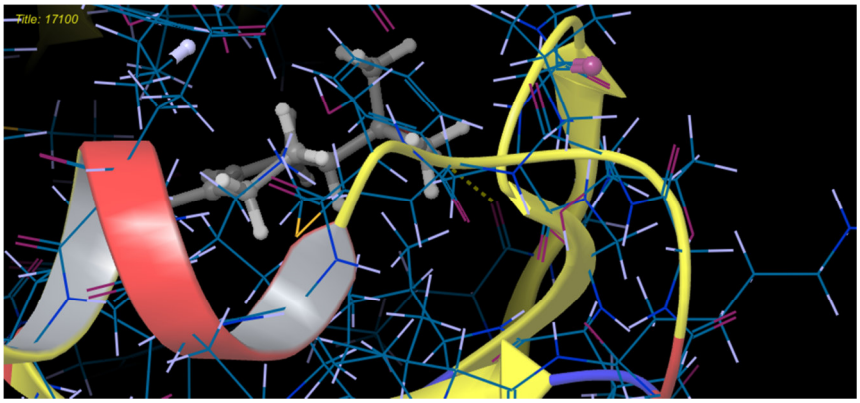

Fig 9. Ligand compound Thymol with Bruton's tyrosine kinase

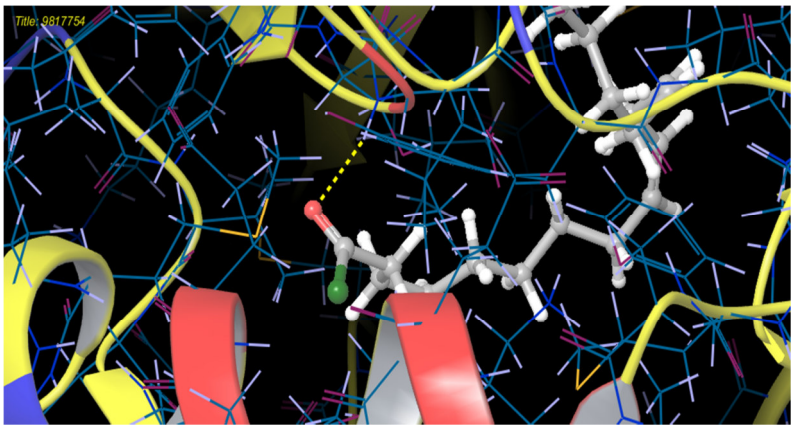

Fig 10. Ligand compound 9,12- Octadecadienoyl chloride(Z-Z-) with Bruton's tyrosine kinase

4 DISCUSSION

Most of the medicinal plants were used in various traditional medicines for different ages. Although the essential ethnobotanical directed drug discovery efforts have been challenged due to their limited impact in the last two decades and unsatisfactory performance when compared to random screening approach, such approaches still play a vital role in drug discovery programs[19]. According to analysis on traditional medicine database, CDRUG was able to identify 5278 compound out of which 75% were similar to approved anticancer drugs (Tanimoto coefficient ≥ 0.70, MACCS fingerprint), and the top 346 compounds it identified were identical to compounds with proven anticancer potential on 60 cell lines [20]. Structural features are essential criteria in the assessment of drug-likeness. The combined presence of certain structures like heterocyclic rings (both aliphatic and aromatic), benzene ring, keto, alcohol, aliphatic amine, carboxyester groups and carboxamide may signal antineoplastic and other drug likenesses[21]. The Lipinski's rule of five is utilized to appraise the drug-likeliness of a compound to satisfy this rule in order to be administered orally. The Lipinski's rule of five is also used to assess the durability of a drug molecule[22]. Hence, this rule is essential for bioactive compounds to be considered as oral drug[23]. Molecular docking is an essential in silico technique, which predicts the mode of interaction between a small ligand and target protein molecule for an established binding site.[24] Binding energy informs us on the strength and how much affinity a compound binds to the pocket of a target protein . A compound with a lower binding energy is preferred as a possible drug candidate and vice versa[25,26] ·Molecular docking is considered as a highly efficient method for the identification of potential target, screening a potent drug and designing a novel drug by lead optimization.[27] The molecular docking technique to find potent small molecules against protein targets of Bruton's tyrosine kinase and checkpoint kinase 2. Various parameters such as Glide score, Glide energy and hydrogen bond interactions are used to assess the best conformation or binding site orientation to inactivate the target protein. Two main aspects were taken into account to assess the quality of docking methods: (i) Docking accuracy, which identifies the true binding mode of the ligand to the target protein, and (ii) Screening enrichment, which is a measurement of correlation between docking method and true binding ligands rather than random compound selection. Glide score denotes the binding interaction is an empirical scoring function that considers the energy contribution, the effects of the hydrophobicity as well as the hydrogen bonding and penalizes the steric clashes. The ligands Thymol, Alpha –Terpineol and 9,12- Octadecadienoyl chloride(Z-Z-) were specifically binding with the active site region of target proteins**.** The compound 9,12- Octadecadienoyl chloride(Z-Z-) binding with active site residues of ASP 368 amino acid and the compound Thymol binding with active site residues of MET 304 amino acid in Check point kinase 2. The compound Alpha -Terpineol binding with active site residues of MET 477 amino acid , the compound Thymol binding with active site residues of LEU 408 amino acid and the compound 9,12- Octadecadienoyl chloride(Z-Z-)binding with active site residues of ASP 539 amino acid in Bruton's tyrosine kinase. Three compounds such as Octadecadienoyl chloride(Z-Z-), Thymol and Alpha -Terpineol identified in ethanolic extract of tested drugs were subjected to docking studies. Check point kinase -2 and Bruton's tyrosine kinase are selected for the present study and docking analysis were carried out with the selected ligands found in Ethanolic extract of Apium leptophyllum Pers (EEAL), which was found to be highly effective against EAC cells. The isolated compounds Octadecadienoyl chloride(Z-Z-), Thymol and Alpha –Terpineol have been subjected to molecular docking process with target Check point kinase-2 and Bruton's tyrosine kinase to understand the anti-cancer activity of EAC cell .The Glide energy value of Thymol compound has better interaction of target Check point kinase -2 when compared to Octadecadienoyl chloride(Z-Z-).It has possessed high level of Glide energy -50.21 and Glide score -5.8 when compared to Octadecadienoyl chloride(Z-Z-). Alpha –Terpineol compound has significant interaction of target Bruton's tyrosine kinase when compared to Thymol and Octadecadienoyl chloride(Z-Z-). It has high Glide energy and Glide score such as -22.21 and -6.3 when compared to other two ligand active compounds.Thymol compound has good interaction of Bruton's tyrosine kinase target molecule followed by Octadecadienoyl chloride (Z-Z-).

5 CONCLUSION

The present study was carried out to identify potential inhibitors for Bruton's tyrosine kinase and checkpoint kinase 2. The docking studies was performed, which identified Thymol, Alpha -Terpineol,9,12- Octadecadienoyl chloride(Z-Z-) compounds proven to result in improved inhibition of cancer and active amino acid residues, which will be useful in designing other potent drugs and drug analogs. This study provides new insights into the identification of drugs in the in

vitro laboratory. The novel molecular entities have the potential as leads which certainly aid in designing anti-cancer molecules in short span of time. As whole results throw light for future development of more potent and drug like inhibitors for Bruton's tyrosine kinase and checkpoint kinase 2.

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7 AUTHOR CONTRIBUTION STATEMENT

Dr. J.Radhika conceived the presented idea motivating to investigate the research work and supervised the finding of this work. Both authors discussed the results and contributed to the final manuscript.

8 CONFLICT OF INTEREST

Conflict of interest declared none.

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