Molecular docking of various bioactive compounds from essential oil of *Trachyaspermum ammi* against the fungal enzyme Candidapepsin-1

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**ABSTRACT**

The bioactive compounds from essential oil of *Trachyaspermum ammi* using gas chromatography–mass spectrometry and their inhibition potential against the enzyme Candidapepsin-1 were studied. The research work focuses on the molecular simulation of bioactive compounds against the enzyme that acts as a potential drug target and support the drug discovery process. Candidapepsin-1 has been reported to be the cause for biofilm formation, superficial skin infections, and oral infections. Fifteen active compounds and their interactions with Candidapepsin-1 were studied in this research work. The compounds satisfied Lipinski’s rule of five in order to be used as an oral drug. ADMET properties of the compounds used to determine pharmacodynamic and pharmacokinetic properties which were reported in the study. The compounds were docked against the enzyme with the help of AutoDock 4.2.6 software. Ligustilide has the lowest free binding energy of −5.75 kcal/mol against the Candidapepsin-1 with three hydrogen bond interactions at Ile 223, Tyr 225, and Thr 222 at the active site of the enzyme followed by cedrane with −5.20 kcal/mol. The hydrogen bond interactions, Vander Waals interactions, and two-dimensional and three-dimensional interactions were studied.

**INTRODUCTION**

*Trachyaspermum ammi* often known as Ajwain or carom seeds or bishop’s weed is a plant seed that are widespread across diverse areas of India and are cultivated predominantly in north-western states of India like Gujarat and Rajasthan, Madhya Pradesh and in other countries like Afghanistan, Bangladesh, Egypt, Iran, and Iraq. *Trachyaspermum ammi* belongs to the family of Apioaceae, dicot and possess high medicinal properties. *Trachyaspermum ammi* is used by the people traditionally as it possesses several properties to cure diverse liver, lungs, and stomach disorders. *Trachyaspermum ammi* is commonly used as an herbal medicine by the people. The seed also possesses carminative and antispasmodic properties which make it an effective remedy for various disorders, such as indigestion, abdominal pain, piles, amenorrhea, bronchial inflammation, asthma, hepatoprotective agent, and chronic diarrhea (Bairwa et al., 2012). Research has shown the significant antibacterial properties of *T. ammi* against a wide variety of bacteria, such as *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Shigella flexneri*, and *Salmonella typhi* (Kaur and Arora, 2009). Multiple drug resistant fungal strains, such as *Candida albicans*, *Candida krusei*, *Candida tropicalis*, and *Candida glabrata*, were also inhibited by *T. ammi* (Khan et al., 2010). Volatile oils of *T. ammi* has the potential to for antifungal properties against *C. albicans* and *Aspergillus* species (Ishwar and Singh, 2000). The plant and its seeds contain several phytochemicals and essential oils, such as thymol, g-Terpine, isobomylisobutyrate, o-Cymene, p-Cymene, a-Pinene, sipleine, verbene, ionone myrcene, thymyl acetate, etc. (Dhaiwal et al., 2017). Thymol is the major constituent of *T. ammi* seeds. *Trachyaspermum ammi* contains 50% of thymol. Thymol is an essential oil obtained from the seeds of *T. ammi* and finds applications in toothpaste and perfume industries (Joshi, 2000).

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Phytochemical analysis

*Trachyspermum ammi* contains diverse phytochemicals. Carbohydrates make the predominant principal composition (38.6%), fats (18.1%), proteins (15.4%), flavone and saponins (7%). Ajwain also contains trace elements of calcium, nicotinic acid, and iron (Pruthi and Jiwan Singh, 1998). Thymol (36%–60%) is the major proportion of ajwain fruits essential oils (Ishikawa et al., 2001). Other principal oils in *T. ammi* are carvone (46%), dillapiole, and limonene. Non-thymol (thymene) fractions are γ-terpinene, dipentene, α-terpenene, α-pinene, β-pinene, para-cymene, α-3-carene, and carvacrol. Ethanolic extracts of ajwain fruits yields hydrosopic saponins. Characteristic yellow colored flavone isolated from ajwain fruits possesses 6-O-β-glucopyranosyloxythymol, oleoresin, and volatile oils (Garg and Kumar, 1998).

Pharmacological and medicinal activities of *Trachyspermum ammi* (ajwain)

*Trachyspermum ammi* (Ajwain) has a characteristic aromatic and pungent smell. Often, the seeds are used as spices in recipes, perfume industry, and food preservatives. In Ayurveda, ajwain is used to heal stomach- and liver-related disorders. A fraction of crushed fruits of ajwain are used to cure colonic pains. Dry and hot fomentations of fruit extracts are applied externally onto the chest to relieve asthma- and lung-related disorders. Ajwain seeds have shown potential to have anti-inflammatory property, antifungal (Saednia et al., 2005), antibacterial, antifilarial (Mathew et al., 2008), digestive stimulant, antiplasmodic, broncho-dilating, galactogogic (Kaur, 1998), detoxification of toxins G1 (AFG 1) (Velazhahan et al., 2010), diuretic (Ahsan et al., 1990), antihelminthic, hypolipidemic (Kumari and Prameela, 2005), antihypertensive, antihyperglycemic, hypolipidemic (Dai et al., 2008), diuretic (Dhaiwal et al., 2008). This enzyme is similar in structure and function with the enzyme Candidapepsin-1. The gene responsible for this enzyme is SAP1 and is located on the chromosome 6 of the organism. The Candidapepsin-1 is a proteolytic virulent enzyme from the endophytic polymorphic fungal species *C. albicans* and is responsible for superficial Candida infections like oral and skin infections in immunocompromised individuals (Correia et al., 2010; Meenambiga et al., 2018; Staib et al., 2000). The enzyme invades and adheres to the host tissue by digesting the host cell membrane and small molecules to acquire nutrition. The enzyme digests the cell host cell membrane to inhibit the attack from the host immune system (Naglik et al., 2003). The enzyme attacks the oxygen carrier molecule hemoglobin through its proteolytic activity and releases various antimicrobial hemocidins to combat against various microbes of the same niche (Schaller et al., 2001). The enzyme is very stable and active at pH 5.0 (Aoki et al., 2011). This enzyme is similar in structure and function with its isoenzyme Candidapepsin-5. There are 10 subclasses of acidic hydrolases in the Sap family from Candidapepsin-1 to 10. The structural investigation discloses the highly conserved overall secondary structure of Candidapepsin-1 enzyme (Borelli et al., 2008). However, Candidapepsin-1, Candidapepsin-2, and Candidapepsin-3 differ from Candidapepsin-5 in two aspects, namely, the net overall electrostatic charge and structural conformation of its entrance toward the active site of the enzyme (Borelli et al., 2008). The active site of the enzyme holds a net negative electrostatic charge due to the presence of basic amino acids. The enzyme contains two chains A and B with 391 amino acid residues and molecular weight of 41.6 KDa. The active site is located between the positions at Asp82 and Asp267 of the enzyme. The entry toward the active site of the enzyme is wider. Figure 1 denotes the three-dimensional structure of the Candidapepsin-1 enzyme. The most predominant inhibitor of the enzyme is Pepstatin A. Hence, molecular docking of the enzyme with bioactive plant secondary metabolites supports the existing drug development process as molecular chemical interactions can be comprehensively studied.

MATERIALS AND METHODS

Bioactive compounds obtained from gas chromatography–mass spectrometry (GC–MS) analysis of *Trachyspermum ammi* essential oils

The bioactive compounds from essential oils of *T. ammi* were obtained from the conventional hydrodistillation process using Dean–Stark apparatus (Dhaiwal et al., 2017; Javed et al., 2012). The essential oils were analyzed using GC–MS (Dhaiwal et al., 2017).

The information about the bioactive compounds, such as IUPAC name, structure, and chemical formula, were retrieved from PubChem database (Table 1). The bioactive compounds mentioned in Table 1 were used for molecular docking against the enzyme Candidapepsin-1. Lipinski properties and ADMET properties of the compounds were studied.

Enzyme target preparation

The enzyme Candidapepsin-1 (PDB Id: 2qzw) was used as the drug target in this research work with resolution 2.05 Å and the method of incorporation was done using X-ray diffraction. The

Figure 1. Three-dimensional structure of Candidapepsin-1 (PDB Id: 2qzw) with chain A and B.
Table 1. Bioactive compounds from essential oil of *T. ammi* analyzed through GC-MS analysis reported by Dhaiwal *et al.* (2017).

| S. no | Compound   | IUPAC name                                                                                       | Structure | Chemical formula |
|-------|------------|-------------------------------------------------------------------------------------------------|-----------|-----------------|
| 1     | Cedrane    | (1S,2R,5S,7S,8R)-2,6,6,8-tetramethyltricyclo [5.3.1.0(1,5)] undecane                          | ![Structure](structure_cedrane.png) | C_{15}H_{26}   |
| 2     | Cineole    | 1,8-Epoxy-p-menthane                                                                           | ![Structure](structure_cineole.png)     | C_{10}H_{18}O  |
| 3     | m-Cymene   | 1-methyl-3-prop-1-en-2-yl benzene                                                              | ![Structure](structure_m-cymene.png)    | C_{10}H_{14}    |
| 4     | Davanol    | 2-[(25,5R)-5-ethenyl-5-methyloxolan-2-yl]-6-methylhept-5-en-3-ol                                | ![Structure](structure_davanol.png)     | C_{15}H_{26}O_{2} |
| 5     | Dillapiole | 4,5-dimethoxy-6-prop-2-enyl-1,3-benzodioxole                                                   | ![Structure](structure_dillapiole.png)  | C_{11}H_{14}O_{3} |
| 6     | Foeniculin | 1-(3-methylbut-2-enoxy)-4-[(E)-prop-1-enyl] benzene                                              | ![Structure](structure_foeniculin.png)  | C_{14}H_{18}O   |
| 7     | Ligustilide| (3Z)-3-Butylidene-4,5-dihydro-2-benzofuran-1-one                                               | ![Structure](structure_ligustilide.png) | C_{12}H_{14}O_{2} |
| 8     | Methyl palmitate | Methyl hexadecanoate                                                                 | ![Structure](structure_methyl_palmitate.png) | C_{17}H_{34}O_{2} |
| 9     | o-Cymene   | 1-methyl-2-propan-2-ylbenzene                                                                 | ![Structure](structure_o-cymene.png)    | C_{10}H_{14}    |
| 10    | p-Cymene   | 1-methyl-4-propan-2-ylbenzene                                                                  | ![Structure](structure_p-cymene.png)    | C_{10}H_{14}    |
| 11    | Phellandrene| 2-methyl-5-propan-2-ylicyclohexa-1,3-diene                                                      | ![Structure](structure_phellandrene.png) | C_{16}H_{26}    |
| 12    | Tetradecanal| Tetradecanal                                                                                  | ![Structure](structure_tetradecanal.png) | C_{16}H_{30}O   |
| 13    | Thujanol   | 4-methyl-1-propan-2-ylcyclo [3.1.0] hexan-3-ol                                                 | ![Structure](structure_thuwanol.png)    | C_{16}H_{16}O   |
| 14    | Thymol     | 5-methyl-2-propan-2-ylphenol                                                                   | ![Structure](structure_thymol.png)      | C_{16}H_{16}O   |
| 15    | Totarol    | (4bS,8aS)-4b,8,8-trimethyl-1-propan-2-yl-5,6,7,8a,9,10-hexahydrophenanthren-2-ol               | ![Structure](structure_totarol.png)      | C_{20}H_{30}O   |
Molecular weight

The molecular weight of thymol is 154 Da, whereas the molecular weight of cedrane is 270 Da.

ADMET properties of bioactive compounds from essential oil

Prediction of absorption, distribution, metabolism, and excretion properties of the compounds were done using the freely available SwissADME software package (Kramer et al., 2017). This was performed to enhance the success of drug discovery and development process.

Molecular docking studies using the AutoDock 4.2.6 software

Molecular docking was performed using the 15 bioactive compounds depicted in Table 1. The bioactive compounds were docked against the Candidapepsin-1 enzyme using the comprehensive bioinformatics tool AutoDock 4.2.6 software. The AutoDock 4.2.6 is relied on the principle of Lamarckian genetic algorithm and is the most reliable automated tool used by the researchers to understand the protein-ligand interactions and protein-protein interactions (Meenambiga et al., 2015). The ligand-protein structure-based drug design was performed using this software. AutoDock 4.2.6 is dependent on two techniques, namely, the Rapid-grid based estimation and systematic search of torsional freedom for the ligand-protein molecular docking (Meenambiga et al., 2015).

Grid parameters

Default grid size of 20 Å was set. Total grid points per map were 64,000. Grid spacing was 0.375 Å (default). The center grid box sizes were x center: −16.302, y center: −23.34, and −16.245, respectively.

Table 2. Lipinski properties of bioactive compounds from essential oil of T. ammi.

| S. no | Compound name         | Molecular weight (<500 Da) | Log P (<5.6) | H-bond donor (<5) | H-bond acceptor (<10) | Molar refractivity (<40-130) |
|-------|-----------------------|----------------------------|--------------|-------------------|------------------------|-----------------------------|
| 1     | Cedrane               | 206                        | 4.49         | 0                 | 0                      | 64.60                       |
| 2     | Cineole               | 154                        | 2.74         | 0                 | 1                      | 45.52                       |
| 3     | m-Cymene              | 132                        | 3.02         | 0                 | 0                      | 45.84                       |
| 4     | Davanol               | 238                        | 3.46         | 1                 | 2                      | 71.92                       |
| 5     | Dillapiole            | 222                        | 2.16         | 0                 | 4                      | 59.56                       |
| 6     | Foeniculin            | 202                        | 4.06         | 0                 | 1                      | 66.07                       |
| 7     | Ligustilide           | 190                        | 2.87         | 0                 | 2                      | 54.48                       |
| 8     | Methyl palmitate      | 270                        | 5.60         | 0                 | 2                      | 82.32                       |
| 9     | o-Cymene              | 134                        | 3.11         | 0                 | 0                      | 45.26                       |
| 10    | p-Cymene              | 134                        | 3.11         | 0                 | 0                      | 45.26                       |
| 11    | Phellandrene          | 136                        | 3.16         | 0                 | 0                      | 45.84                       |
| 12    | Tetradecanal          | 212                        | 4.88         | 0                 | 1                      | 67.14                       |
| 13    | Thujanol              | 154                        | 2.04         | 1                 | 1                      | 45.16                       |
| 14    | Thymol                | 150                        | 2.82         | 1                 | 1                      | 46.93                       |
| 15    | Totarol               | 286                        | 5.54         | 1                 | 1                      | 88.99                       |

Discovery studio 3.1 - visualizer

Discovery studio 3.1 is a visualizer programed and developed by the Accelrys. This software is free of cost, provides comprehensive information, and is the most often used by the scientific community to view the ligand-receptor interactions. The software provides us with the necessary information about the interactions of small and large molecules taking part in the interaction. The software deals with various aspects of molecular docking, such as macromolecule engineering, ligand-receptor interactions, pharmacophore modeling, antibody modeling & optimization simulations, macromolecule design, and protein-protein interactions (Almagro et al., 2011; Luu et al., 2011; Sutter et al., 2011). The two-dimensional and three-dimensional interactions images displayed in this study were developed through this software.

RESULTS AND DISCUSSION

The following are the bioactive compounds obtained from the GC-MS analysis of essential oil from the seeds of Trachyspermum ammi: (1) cedrane, (2) cineole, (3) m-cymene, (4) davanol, (5) dillapiole, (6) foeniculin, (7) ligustilide, (8) methyl palmitate, (9) o-cymene, (10) p-cymene, (11) phellandrene, (12) tetradecanal, (13) thujanol, (14) thymol, and (15) totarol. These bioactive compounds were reported by Dhaiwal et al. (2017). Although the bioactive compounds were found to be an effective antioxidant, there were no reports available for the potential of T. ammi against the virulence of fungal enzyme, namely, Candidapepsin-1.

Molecular docking of ligands against the active site of the enzyme will elucidate the interactions between them. This will pave way for discovery of novel phytomedicines in the field of drug discovery and development.

The compounds from the GC-MS analysis satisfied the Lipinski’s rule of five. This rule comprises of five sub rules, namely, (1) molecular weight (<500), (2) log P (<+5.6), (3) Number of hydrogen donors (<5), (4) Number of hydrogen
The in silico analysis through molecular docking revealed the importance of structure-based drug design strategy toward the development for novel drugs against the inhibition of potential drug target. The virulent enzyme responsible for superficial skin infections like candidiasis and biofilm formation is Candidapepsin-1 (Korting et al., 1998). The enzyme’s active site was docked with several bioactive compounds from T. ammi. The binding energy for each bioactive compound against the Candidapepsin-1 enzyme, interaction of hydrogen bonds, Vander Waals interactions, and essential details were listed in Table 3. Ligustilide has the lowest binding energy of ~5.75 kcal/mol and has three hydrogen bond interactions with amino acids Ile 223, Tyr 225, and Thr 222 at the active site. Lower the binding energy, greater is the binding efficiency. Greater the hydrogen bonds between the enzyme and ligand determines the strength of binding (Kortemme et al., 2003). The two-dimensional and three-dimensional molecular modeling techniques are useful tools for understanding the binding mode of the compounds. It can be observed that the binding efficiency of the compounds is not only dependent on the lipophilicity but also on the hydrogen bond interaction and ionic interaction. The compounds with higher binding efficiency are naturally present in the essential oil of T. ammi.

Table 3. Molecular docking result analysis of bioactive compounds from essential oil of T. ammi against Candidapepsin-1 (PDB Id: 2qzw) enzyme.

| S. no | Compound name | Binding Energy Kcal/mol | No of Vander Waal's interaction | No. of hydrogen bonds | Hydrogen bond interaction | Total polar and non-polar bonding |
|-------|----------------|-------------------------|---------------------------------|-----------------------|--------------------------|---------------------------------|
| 1.    | Cedrane        | −5.20                   | GLY 220, ASP 86, THR 221, GLY 85, ASP 218, SER 35, GLY 34, LEU 216, ILE 223, ASP 32, ILE 123, ILE 30, TYR 84. | 0                      | 0                        | GLY 220, ASP 86, THR 221, GLY 85, ASP 218, SER 35, GLY 34, LEU 216, ILE 223, ASP 32, ILE 123, ILE 30, TYR 84. |
| 2.    | Cineole        | −4.20                   | ILE 123, ILE 30, ASP 86, SER 35, TYR 84, GLY 85, GLY 34, ASP 218, ASP 32, GLY 220. | 0                      | 0                        | ILE 123, ILE 30, ASP 86, SER 35, TYR 84, GLY 85, GLY 34, ASP 218, ASP 32, GLY 220. |
| 3.    | p-Cymene       | −3.58                   | ASP 32, GLY 34, SER 35, ASP 86, LEU 216, ASP 218, GLY 220, ILE 123, ASP 86, TYR 84. | 0                      | 0                        | ASP 32, GLY 34, SER 35, ASP 86, LEU 216, ASP 218, GLY 220, ILE 123, ASP 86, TYR 84. |
| 4.    | Davanol        | −2.94                   | THR 78, GLY 135, PHE 80, LEU 94, ALA 134, ALA 133, TYR 81, PRO 79. | 0                      | 0                        | THR 78, GLY 135, PHE 80, LEU 94, ALA 134, ALA 133, TYR 81, PRO 79. |
| 5.    | Dillapiole     | −3.91                   | GLY 220, ASP 86, THR 225, THR 221, VAL 12, SER 13, ILE 30, ASP 32, ILE 123. | 1                      | THR 222                  | THR 222. |
| 6.    | Foeniculin     | −4.36                   | VAL 12, GLY 220, THR 222, THR 221, THR 225, GLY 85, ILE 305, ASP 86, ILE 30, SER 13. | 0                      | 0                        | VAL 12, GLY 220, THR 222, THR 221, THR 225, GLY 85, ILE 305, ASP 86, ILE 30, SER 13. |
| 7.    | Ligustilide    | −5.75                   | ILE 305, THR 221, VAL 12, ILE 30, SER 13, GLY 220, ASP 86. | 3                      | ILE 223, THR 225, THR 222 | ILE 305, THR 221, VAL 12, ILE 30, SER 13, GLY 220, ASP 86. |
| 8.    | Methyl         | +0.92                   | LEU 76, THR 78, PRO 79, PHE 80, TYR 81, TYR 81, ALA 133, GLY 135. | 0                      | 0                        | LEU 76, THR 78, PRO 79, PHE 80, TYR 81, TYR 81, ALA 133, GLY 135. |
| 9.    | o-Cymene       | −3.62                   | GLY 220, ASP 86, THR 221, ASP 218, GLY 34, SER 35, ILE 123, TYR 84, ASP 32, ILE 30. | 0                      | 0                        | GLY 220, ASP 86, THR 221, ASP 218, GLY 34, SER 35, ILE 123, TYR 84, ASP 32, ILE 30. |
| 10.   | p-Cymene       | −3.65                   | ASP 86, THR 221, ILE 305, ASP 218, THR 84, GLY 44, GLY 220, ASP 32, ILE 30, ILE 123. | 0                      | 0                        | ASP 86, THR 221, ILE 305, ASP 218, THR 84, GLY 44, GLY 220, ASP 32, ILE 30, ILE 123. |
| 11.   | Phellandrene   | −3.97                   | ILE 123, GLY 220, ASP 32, TYR 84, THR 221, ASP 218, ASP 86. | 0                      | 0                        | ILE 123, GLY 220, ASP 32, TYR 84, THR 221, ASP 218, ASP 86. |
| 12.   | Tetradecanal   | −3.17                   | THR 221, THR 225, ASP 86, TYR 84, ASP 32, ILE 123, ILE 30, GLY 220, SER 13, VAL 12. | 1                      | THR 222                  | THR 221, THR 225, ASP 86, TYR 84, ASP 32, ILE 123, ILE 30, GLY 220, SER 13, VAL 12. |
| 13.   | Thujanol       | −4.14                   | ASP 86, THR 84, SER 35, GLY 85, GLY 34, THR 221, ASP 218, ILE 305, ILE 30, ILE 123, ASP 32, GLY 220. | 0                      | 0                        | ASP 86, THR 84, SER 35, GLY 85, GLY 34, THR 221, ASP 218, ILE 305, ILE 30, ILE 123, ASP 32, GLY 220. |
| 14.   | Thymol         | −0.05                   | GLY 220, ASP 218, THR 221, GLY 85, ASP 86, ILE 305, GLY 34, SER 35, TYR 84, ILE 30, ILE 123. | 1                      | ASP 32                   | ASP 218. |
| 15.   | Totarol        | −0.87                   | VAL 12, SER 13, TYR 84, ILE 123, ILE 30, SER 35, ASP 86, GLY 220, THR 221, THR 222. | 1                      | ASP 32                   | VAL 12, SER 13, TYR 84, ILE 123, ILE 30, SER 35, ASP 86, GLY 220, THR 221, THR 222. |
Figure 2. Two-dimensional and three-dimensional residual interactions map of ligustilide against the active site of Candidapepsin-1.

Figure 3. Two-dimensional and three-dimensional residual interactions map of cedrane against the active site of Candidapepsin-1.

Figure 4. Two-dimensional and three-dimensional residual interactions map of totarol against the active site of Candidapepsin-1.
Figure 5. Two-dimensional and three-dimensional residual interactions map of foeniculin against the active site of Candidapepsin-1.

Figure 6. Two-dimensional and three-dimensional residual interactions map of cineole against the active site of Candidapepsin-1.

Figure 7. Two-dimensional and three-dimensional residual interactions map of thujianol against the active site of Candidapepsin-1.
Figure 8. Two-dimensional and three-dimensional residual interactions map of thymol against the active site of Candidapepsin-1.

Figure 9. Two-dimensional and three-dimensional residual interactions map of Pepstatin A against the active site of Candidapepsin-1.

Figure 10. Docked conformation of ligustilide against the active site of Candidapepsin-1.

Figure 11. Docked conformation of Pepstatin A against the active site of Candidapepsin-1.
dimensional interactions of the ligustilide with the enzyme are depicted in Figure 2. Cedrane with the binding energy of $-5.20$ kcal/mol occupies the next spot in the ranking Figure 3. Totarol ($-5.91$ kcal/mol) follows up the order. The binding energies of bioactive compounds docked were compared with the binding energy of the reference ligand (Pepstatin A) (Fig. 9) against the enzyme with the same grid parameters. The binding energy of reference inhibitor ligand was found to be $+2.77$ kcal/mol, which is lower when compared to the binding energies of bioactive compounds from \textit{T. ammi} (Fig. 11). The binding of bioactive compounds inhibits the activity of enzyme resulting in the neutralization the enzymes virulence (Hube et al., 1997). Ligustilide isolated from essential oil of Umbelliferae family has immense antifungal properties against several species of fungi, thus restricting the fungal growth and proliferations (Lee et al., 2008). Essential oils from \textit{T. ammi} at different temperatures and pressures through minimum inhibitory concentration (MIC) studies against a variety of \textit{Candida} species were studied by Rath and Mohapatra (2015). The MIC values for essential oil from \textit{T. ammi} was $31.25$ µl/ml for \textit{C. albicans}, and $62.50$ µl/ml for \textit{Candida glabratra}, and $125$ µl/ml for \textit{Candida parapsilosis}, respectively (Rath and Mohapatra, 2015). This proves that the essential bioactive compounds from the oil has antifungal potential and can be used in therapeutic applications. Also, upon increasing the temperature and pressure had an augmented therapeutic inhibition potential of the essential oil against \textit{Candida} infection (Pattnaik et al., 1995). Fungal hyphae are an important measure for the fungal growth and virulence. The development of the hyphae is inhibited by thymol, hence disturbing the cell membrane

### Table 4. Absorption properties of various bioactive compounds.

| S. No | Compound   | Water solubility (log mol/l) | CACO permeability (Log Pabb in $10^{-6}$ cm/Sec) | GI absorption (%) | Skin permeability (Log Kp) | P-glycoprotein substrate | P-glycoprotein I inhibitor | P-glycoprotein II inhibitor |
|-------|------------|-----------------------------|-----------------------------------------------|-------------------|---------------------------|--------------------------|--------------------------|-----------------------------|
| 1     | Cedrane    | $-6.06$                     | $1.38$                                         | $94.42$           | $-2.12$                   | No                       | No                       | No                          |
| 2     | Cineole    | $-2.77$                     | $1.51$                                         | $96.26$           | $-2.13$                   | Yes                      | No                       | No                          |
| 3     | m-Cymene   | $-4.10$                     | $1.53$                                         | $93.65$           | $-1.21$                   | No                       | No                       | No                          |
| 4     | Davanol    | $-3.24$                     | $1.64$                                         | $93.41$           | $-2.29$                   | No                       | No                       | No                          |
| 5     | Dillapiol  | $-2.44$                     | $1.83$                                         | $95.10$           | $-2.45$                   | No                       | No                       | No                          |
| 6     | Foeniculin | $-4.65$                     | $1.80$                                         | $95.04$           | $-1.30$                   | No                       | No                       | No                          |
| 7     | Ligustilide| $-3.09$                     | $1.62$                                         | $96.30$           | $-2.22$                   | No                       | No                       | No                          |
| 8     | Methyl palmitate | $-6.93$             | $1.60$                                         | $92.33$           | $-2.60$                   | No                       | No                       | No                          |
| 9     | o-Cymene   | $-4.11$                     | $1.53$                                         | $93.88$           | $-1.18$                   | No                       | No                       | No                          |
| 10    | p-Cymene   | $-4.08$                     | $1.53$                                         | $93.54$           | $-1.19$                   | No                       | No                       | No                          |
| 11    | Phellandrene | $-3.85$                  | $1.41$                                         | $96.55$           | $-1.51$                   | No                       | No                       | No                          |
| 12    | Tetradecanal | $-6.49$                | $1.48$                                         | $93.02$           | $-2.07$                   | No                       | No                       | No                          |
| 13    | Thujanol   | $-2.51$                     | $1.50$                                         | $94.78$           | $-2.13$                   | No                       | No                       | No                          |
| 14    | Thymol     | $-2.79$                     | $1.61$                                         | $90.84$           | $-1.62$                   | No                       | No                       | No                          |
| 15    | Totarol    | $-5.91$                     | $1.56$                                         | $92.77$           | $-2.65$                   | No                       | No                       | Yes                         |

### Table 5. Distribution properties of various bioactive compounds.

| S. no | Compound   | VDss (human) (Log L/kg) | Fraction unbound (human) (Fu) | BBB permeability (Log BB) | CNS permeability (Log PS) |
|-------|------------|------------------------|-------------------------------|--------------------------|---------------------------|
| 1     | Cedrane    | $0.67$                 | $0.10$                        | $0.84$                   | $-1.44$                   |
| 2     | Cineole    | $0.36$                 | $0.51$                        | $0.67$                   | $-2.55$                   |
| 3     | m-Cymene   | $0.72$                 | $0.15$                        | $0.47$                   | $-1.39$                   |
| 4     | Davanol    | $0.23$                 | $0.40$                        | $0.55$                   | $-2.84$                   |
| 5     | Dillapiol  | $0.03$                 | $0.20$                        | $0.22$                   | $-2.24$                   |
| 6     | Foeniculin | $0.68$                 | $0.11$                        | $0.62$                   | $-1.70$                   |
| 7     | Ligustilide| $0.30$                 | $0.42$                        | $0.56$                   | $-2.45$                   |
| 8     | Methyl palmitate | $0.23$            | $0.07$                        | $0.75$                   | $-1.68$                   |
| 9     | o-Cymene   | $0.74$                 | $0.16$                        | $0.48$                   | $-1.40$                   |
| 10    | p-Cymene   | $0.70$                 | $0.16$                        | $0.48$                   | $-1.39$                   |
| 11    | Phellandrene | $0.41$               | $0.43$                        | $0.76$                   | $-2.05$                   |
| 12    | Tetradecanal | $0.48$                | $0.15$                        | $0.78$                   | $-1.67$                   |
| 13    | Thujanol   | $0.35$                 | $0.47$                        | $0.66$                   | $-2.24$                   |
| 14    | Thymol     | $0.51$                 | $0.20$                        | $0.41$                   | $-1.66$                   |
| 15    | Totarol    | $1.16$                 | $0$                           | $0.55$                   | $-1.35$                   |
thereby affecting the enzymes responsible for cell wall synthesis (Braga et al., 2007). Figures 2–10 list the two-dimensional and three-dimensional interactions of bioactive compounds with low binding energies against Candidapepsin-1. ADMET profiles of the compounds were depicted in Tables 4–7. All the compounds have high rates of gastrointestinal absorption (Table 4). From Table 5, it is clear that none of the drug penetrates the blood-brain barrier since the logBB value of all the compounds is less than three. For a drug to cross the blood-brain barrier, the logBB value must be greater than three (Muehlbacher et al., 2011).

CONCLUSION

Trachyaspermum ammi is traditionally used in ayurvedic medicine due to its anti-inflammatory, antifungal, antibacterial, anticancer, and antiarthritic potential. The current study revealed the inhibition potential of bioactive compounds from essential oil of T. ammi against the virulent enzyme Candidapepsin-1 of C. albicans. The bioactive compound ligustilide has the lowest binding energy of −5.75 kcal/mol. This proves the antifungal activity of the T. ammi against the Candida biofilm formation, thereby inhibiting the virulence of the enzyme. The inhibition of the enzyme leads to novel discovery of plant-based therapeutic products. Computational molecular docking could be used as an effective supporting tool for the drug development process. Computational simulations also provide us with comprehensive results with high accuracy. Hence, their presence is necessary toward the development of drug discovery and development sector.
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CONFLICTS OF INTEREST

Authors declare that there are no conflicts of interest.

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