**Supplementary Material**

**Molecular docking**

Molecular docking analyses were performed to study the possible binding modes of α-terpineol, β-eudesmol, eucalyptol, isohomogenol, isosafrole, and linalool with CYP1A2([Sansen et al., 2007](#_ENREF_8)), CYP51([Hargrove et al., 2017](#_ENREF_3)), CYP2C9\*2([Parikh et al., 2020](#_ENREF_5)), and CYP134A1 (7OW9) as potential inhibitors. AutoDock (v 4.2.1) and AutoDock Vina (v 1.0.2)([Trott and Olson 2010](#_ENREF_12)) were used for all dockings. The three-dimensional coordinates of all structures were optimized using MOPAC2016([Stewart 2007](#_ENREF_10)) using the PM6-D3H4 semi-empirical method([Stewart 2007](#_ENREF_11), Řezáč and Hobza 2012). The ligand files were prepared using the AutoDockTools package([Sanner 1999](#_ENREF_7)). The Mulliken partial atomic charges of each ligand were determined using the PM6-D3H4 semi-empirical method; this approach introduces dispersion and hydrogen-bonded corrections to the PM6 method. The crystal structures of CYP1A2 (PDB Code: 2HI4), CYP51 (PDB Code: 5FSA), CYP2C9\*2 (PDB Code: 6VLT), and CYP134A1 (PDB Code: 7OW9), were downloaded from the Protein Data Bank([Berman et al., 2000](#_ENREF_1)). CYP1A2, CYP51, CYP2C9\*2, and CYP134A1 were treated with Schrödinger's Protein Preparation Wizard([Sastry et al., 2013](#_ENREF_9)); polar hydrogen atoms were added; nonpolar hydrogen atoms were merged; and charges were assigned. Docking was treated as rigid and conducted using the empirical free energy function and the Lamarckian Genetic Algorithm provided by AutoDock Vina([Morris et al., 2009](#_ENREF_4)). The grid map dimensions were 22.5 Å × 22.5 Å × 22.5 Å. The center coordinates for binding pocket were 6.30, 21.27, and 21.35 for CYP1A2; 194.87, -4.53, and 36.29 for CYP51; 35.05, 42.07, and -4.10 for CYP134A1; and -18.05, -4.67, and -18.45 for CYP2C9\*2. All other parameters were set as the default defined by AutoDock Vina. Dockings were repeated 20 times, with space search exhaustiveness set to 100. The best interaction binding energy (kcal·mol-1) was selected for evaluation. Discovery Studio([BIOVIA 2017](#_ENREF_2)) 3.1 (Accelrys, CA) molecular graphics system was used for 2D and 3D representation of docking results.

**Molecular Docking Analysis**

The results of molecular docking analysis are presented in Figure S1. Molecular docking experiments showed more favorable interactions with CYP1A2, with an average binding energy of -7.2 kcal·mol−1, compared to CYP51, CYP2C9\*2, and CYP134A, with average binding energies of respectively -7.0, -6.7, and -4.5 kcal·mol−1.



**Figure S1**. Heat map of intermolecular docking energy values (kcal·mol-1) of *α*-terpineol, *β*-eudesmol, eucalyptol, isohomogenol, isosafrole, and linalool.

**Table S1.** Active pockets on essential oils in CYP1A2.

|  |  |
| --- | --- |
| **Compound** | **Interacting amino acids in the binding pocket** |
| CYP1A2 |
| **α-Terpineol** | Phe256, Phe260, Phe226, Phe125, Ile117 |
| **β-Eudesmol** | Phe260, Phe226, Phe227, Ile117, Gly316, Phe125, Ala317, Leu497, Val227 |
| **Eucalyptol** | Leu382, Leu497, Phe125, Phe226, Ala317, Heme group, Ile386 |
| **Isohomogenol** | Leu497, Val227, Ala317, Thr223, Phe226, Gly316 |
| **Isosafrole** | Phe260, Phe256, Phe226, Gly316, Ala317, Leu497 |
| **Linalool** | Phe256, Phe226, Ala317, Phe260, Asp313, Phe125, Ile117 |

To describe the binding and interaction of ligands with CYP1A2, AutoDock Vina was used for exploring how the ligand binds the respective protein. The best structural information was considered for analyses shown in Figure S1 and Table S1. Figure S2 shows the functionally interacting residues and the mode of ligand binding to the CYP1A2 site. Our molecular docking results revealed the involvement of Phe256, Phe260, Phe226, Phe125, and Phe227 residues in favoring the binding of LP\_EO, as they present conducive aromatic binding interactions with essential oils. These interactions form an aromatic pocket that contributes to the binding of these compounds. Mutational screening of these residues in subsequent studies is expected to be very effective. Several types of interactions were observed between LP\_EO and CYP1A2, such as π-stacking, hydrophobic and hydrophilic interactions, hydrogen bonding, and van der Waal interactions, in addition to steric interactions, indicating the affinity of LP\_EO to CYP1A2. The binding modes of α-terpineol, β-rudesmol, eucalyptol, isohomogenol, isosafrole, and linalool to the CYP1A2 binding site are shown in Figure S2. α-Terpineol shows aromatic and van der Waals interactions with Phe256, Phe260, Phe226, Phe125, and Ile117 residues. β-Eudesmol shows aromatic and van der Waals interactions with Phe260, Phe226, Phe227, Ile117, Gly316, Phe125, Ala317, Leu497, and Val227. Eucalyptol, shows aromatic and van der Waals interactions with Leu382, Leu497, Phe125, Phe226, Ala317, and Ile386, highlighting aromatic interaction with the Heme group. Isohomogenol and isosafrole present similar aromatic and van der Waals interactions with Phe260, Phe256, Phe226, Gly316, Ala317, Leu497, Val227, and Thr223. Linalool presents hydrogen bonding between its hydroxyl group and Asp313 and van der Waals and aromatics interactions with Phe256, Phe226, Ala317, Phe260, Phe125, and Ile117.



**Figure S2**. Docking for (A) α-terpineol; (B) β-Eudesmol; (C) eucalyptol; (D) isohomogenol; (E) isosafrole, and (F) linalool from LP\_EO binding to CYP1A2. The surrounding amino acid residues within 3Å of the binding pocket of CYP1A2 are shown.

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