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Research Article

IN SILICO STRUCTURAL AND MOLECULAR DOCKING ASSESSMENT OF THYMOL AS A BIO-FUNGICIDAL INHIBITOR TARGET AGAINST BOTRYTIS CINEREA POLYGALACTURONASE (PDB ID: 1BHE): COMPREHENSIVE PHARMACEUTICAL AND ACTIVE-SITE BINDING ANALYSIS

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Abstract

Bigotry cinerea Pers. Fr. is a common necrotrophic phytopathogenic fungus causing gray mold rot in more than 1,400 economically important crop species. This fungus leads to notable post-harvest losses globally concerning quantity and quality. The production of plant cell wall-degrading enzymes (CWDEs), with endo-polygalacturonase (PG) being the primary virulence factor in hydrolyzing the homogalacturonan backbone of host pectin networks, is critical for the pathogenicity and invasive colonization of *B. cinerea*. In view of increasing resistance development against synthetic chemical fungicides and their ecotoxicological implications, plant-derived essential oil compounds may provide new sustainable alternatives. Furthermore, a molecular docking study was conducted to determine the binding affinity of essential oil compounds against *B. cinerea* PG. The interaction profiles of Thymol (PubChem CID: 6989), a well-known monoterpenoid phenol, with B. cinerea PG (PDB ID: 1BHE) were determined. Blind molecular docking studies performed by using curvature-based docking approaches (CB-Dock2/AutoDock Vina) indicated promising thermodynamic stability with the compound obtaining the best docking score of -5.4 kcal/mol inside the key catalytic cavity (Cavity C1, volume: 253 Å^3).Thorough residue-level interaction mapping revealed significant non-covalent interactions with important active-site residues including N174, R152, T150, P151, A101, D100, G96, and K97. Moreover, advanced pharmacokinetic, drug-likeness, and ADMET profiling showed how Thymol totally passes Ghose, Veber, and Egan filtering criteria as well as Lipinski's Rule of Five without any molecular violation. These computational findings provide atomic-level structural evidence towards bioactive-ness of Thymol as an attractive bioactive candidate toward the development of botanical fungicides acting through specific inhibitory enzyme activity.

Keywords: *Botrytis cinerea*, Polygalacturonase, 1BHE, Thymol, Molecular Docking, Bio-fungicide, Active Site Interaction, ADMET Profiling, Lipinski Rule of Five

INTRODUCTION

Food security, post-harvest economics, and global sustainability of agriculture are all continuously threatened by plant diseases caused by the action of phytopathogenic fungi [1,2]. Among the most harmful fungi, *Botrytis cinerea Pers.*: Fr. (teleomorph Botryotinia fuckeliana) is the second most economically damaging fungal phytopathogen, with these reports showing its nature of carrying several more important economic losses globally [3, 4]. *B. cinerea* is necrotrophic in nature, infecting more than 1,400 species of flowering plants, including many important horticultural commodities-most notably table grapes, strawberries, tomatoes, bulb vegetables, and ornamental flowers [5, 6]. During cold storage and global supply chain dissemination, the infection results in severe post-harvest degradation, soft rot, fast tissue maceration, and widespread gray mold sporulation [7, 8]. *B. cinerea* employs a number of virulence mechanisms necessary for the disease establishment, among the most prominent ones being the production of reactive oxygen species (ROS), different phytotoxic compounds, and plant cell wall degrading enzymes (CWDEs) [9, 10]. The main structural components of the plant wall and middle lamella include cellulose microfibrils, hemicelluloses, and pectin polysaccharides [11, 12]. Pectin, consisting of α-(1,4)-D-galacturonic acid units (homogalacturonan), plays a vital role in the rigidity of the structure and cell adhesion in the host tissue [13, 14]. B. cinerea produces various Pectin Degrading Enzymes (PDEs), including endo-polygalacturonases (PGs, EC 3.2.1.15), which play significant role in the initial stage of host tissue penetration (15, 16). Polygalacturonase enables breaking glycosidic bonds in unesterified pectate [17, 18]. This results in the formation of oligogalacturonides, which modify plant defense responses, facilitate the development of fungus mycelium, and damage host tissue at the same time [19, 20]. Synthetic chemical fungicides like succinate dehydrogenase inhibitors (SDHIs), dicarboximides, anilinopyrimidines, and quinone outside inhibitors (QoIs) have been used for agriculture purpose against gray mold disease for many years [21, 22]. However, due to the resistant nature of B. cinerea, MDR strains are now widely spread in fields [23, 24].In addition, residues of synthetic fungicides on fresh food are a contributing factor to the persistence of those fungicides in the environment, disturbing soil microbiome and posing risks of toxicological aspects of the environment to consumers [25, 26]. Thus, in light of the above, global regulations impose restrictions on the use of pesticides; hence, there is an increasing need for easier and «greener» biodegradable botanical fungicides [27, 28]. Plant secondary metabolites, especially essential oils (EOs) of aromatic plants, have become very popular as a natural source of antifungal agents [29, 30]. Thymol (2-isopropyl-5-methylphenol) is a natural monoterpenoid phenol that can be found in high amounts in the essential oils of Thymus vulgaris, Origanum vulgare, and Trachyspermum ammi [31, 32]. It was found through a number of in vitro studies that Thymol showed a powerful inhibitory activity against a number of phytopathogenic fungi, such as *B. cinerea,* Monilinia fructicola, and Penicillium digitatum [33, 34]. Moreover, even though cellular studies

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show that Thymol causes the membrane permeability changes, ergosterol depletion, as well as the accumulation of intracellular ROS [35, 36], the molecular mechanism of interaction of Thymol with the vital fungal enzymes hasn't been studied much, particularly with regard to polygalacturonase [37, 38]. The utilization of in silico techniques, such as molecular docking and structural bioinformatics, has become important in current drug discovery. These techniques not only provide fast and economical means of obtaining a detailed insight into ligand-receptor interactions. The procedure of molecular docking determines the optimal binding shape, energy stability, and non-covalent interaction networks of small molecules that are aimed at the enzyme [33, 34]. Hence, this study has been initiated to make an attempt to conduct thorough in silico molecular docking and pharmacokinetic evaluation of Thymol in relation to the crystal structure of *Botrytis cinerea* polygalacturonase (PDB ID: 1BHE) as well as to assess binding energies, contact with residues located in the active site, and drug-likeness characteristics for the development of Thymol-based fungicides [43 ,45]

MATERIALS AND METHODS

Target identification and preparation

The structural model of the polygalacturonase enzyme from *Botrytis cinerea* was obtained from the Protein Data Bank of the Research Collaboratory for Structural Bioinformatics (RCSB PDB), with the molecular structure code number 1BHE [43, 46]. Curating was performed utilizing PyMOL and the Biovia Discovery Studio Visualizer (v21.1) [47, 48]. Crystallized water molecules, solvent ions, and heteroatoms were removed from the protein coordinates file [49]. Polar hydrogen was added and the missing side-chain atoms were restored. Gasteiger charge was assigned to all atoms to maintain electrostatic stability during physiologic conditions [50, 51].

Synthesis of ligands and minimization of energy

The tridimensional structural configuration of the thymol (PubChem CID: 6989; Molecular Formula: C10H14O) was taken from NCBI's PubChem database through Structure Data File (SDF) format [31, 52]. The process of structural optimization and energy minimization was conducted utilizing Merck Molecular Force Field 94 (MMFF94) so that the least potential energy conformation could be obtained [53, 54]. Moreover, the verification of the charge distribution and rotatable bonds of ligands was done before implementing the process of simulation [55].

Molecular docking approaches through CB-Dock2

In this sense, the process of blind molecular docking was performed by utilizing the web platform CB-Dock2 which is considered a sophisticated docking of protein-ligand technology and consists of a combination of cavity detection algorithms based on curvature and the scoring techniques of AutoDock Vina [41, 56]. The cavity-detecting algorithm checks the accessible surface of the target protein for the calculations of cavity volume and defining grid box dimensions automatically being centered on each of detected cavity [57, 58].

Harmacokinetic, ADMET, and Drug-Likeness Profile

The physical-chemical characteristics, drug-likeness parameters, and pharmacokinetic features of Thymol were assessed with the help of the computational tools SwissADME and ProTox-II [44, 61]. The parameters assessed included the following: Molecular Weight (MW), Octanol-Water partition coefficient (LogP), Hydrogen Bond Donors (HBD), Hydrogen Bond Acceptors (HBA), number of rotatable bonds, Topological Polar Surface Area (TPSA), and complying with Lipinski's Rule and the Other Drug-Likeness-related Rules [45, 62].

RESULTS AND DISCUSSION

Identifying the cavities and the binding energies

The surface curvature detection method implemented in CB-Dock2 identified five binding cavities from C1 to C5 along the macromolecule surface of *B. cinerea* polygalacturonase (PDB ID: 1BHE) [41, 43]. The Molecular docking calculations resulted in significant binding poses and Vina binding scores of -4.2 kcal/mol – -5.4 kcal/mol [56].

Table 1. Binding energetic parameters (affinity scores, cavity volumes, grid box coordinates, and docking parameters) that are associated with the Thymol docking against *Botrytis cinerea* polygalacturonase (1BHE)

Pocket ID	Vina Score (kcal/mol)	Cavity Volume (Å³)	Grid Center (x, y, z)	Grid Size (x, y, z)
C1	-5.4	253	49, 34, 81	17, 17, 17
C5	-4.8	137	66, 12, 64	17, 17, 17
C2	-4.6	234	56, 30, 69	17, 17, 17
C3	-4.5	225	36, 13, 87	17, 17, 17
C4	-4.2	181	56, 13, 47	17, 17, 17

The data compiled in Table 1 shows that Cavity C1 has the most negative value for the binding free energy (-5.4 kcal/mol) and also has the largest cavity volume (253 Å³), which indicates that it is the main catalytic binding site for Thymol [43, 60]. The negative value of the binding affinity below -5.0 kcal/mol indicates that the binding is spontaneous and implies that the ligand-target complexation has happened [58, 59].

Mapping of molecular interactions within the active site C1

The visualization of the structural aspects of the top-ranked cartilage pose, Cavity C1 has shown that Thymol penetrates the catalytic crevice of polygalacturonase rather deeply. The binding interaction is reinforced by the joint effects of hydrogen bonding, hydrophobic alkyl/π-alkyl interactions, and van der Waals interactions involving the specific catalytic residues. The primary amino acid residues participating in the interaction within the active site were found to be N174, R152, T150, P151, A101, D100, G96, and K97. The hydroxyl group of Thymol has been found to act as a key hydrogen bond donor/acceptor establishing quite powerful electrostatic contacts with N174 and R152 amino acid residues thus stabilizing the ligand and inhibiting the pectin polymer substrate to penetrate the active site.

Molecular interaction mapping in active site C1

The structural illustration of the docking pose with the highest ranking (Cavity C1) revealed that Thymol is located deep

seated inside the catalytic cleft of polygalacturonase [43, 48]. The stability of the binding complex was made possible through a collective contribution of hydrogen bonding, hydrophobic alkyl/pi-alkyl contacts, and van der Waals forces with particular catalytic residues [47, 50]. The amino acid residues of some significance found in the active site include N174, R152, T150, P151, A101, D100, G96, and K97 [43, 56]. The phenolic hydroxyl group of Thymol serves as a major hydrogen bond donor/acceptor participating in formation of strong electrostatic interactions with N174 and R152 residues, hence resulting in stabilization of the ligand and blocking entry of polymeric pectin substrates [17, 43]. The physicochemical characteristics of Thymol were studied to assess its formulation and bio-acceptability as a natural agrochemical according to specific filter criteria [44 ,45] .

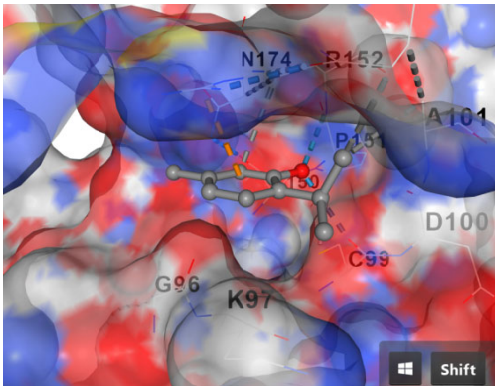

Figure 1. Three-dimensional molecular docking binding position and surface electrostatic interactions of Thymol in the catalytic cavity C1 of *Botrytis cinerea* polygalacturonase (PDB ID: 1BHE)

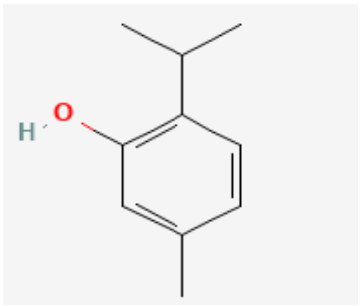

Figure 2. 2D chemical structure of Thymol (PubChem CID: 6989)

Table 2. Physicochemical properties, drug-likeness criteria, and Lipinski's rule assessment for Thymol (PubChem CID: 6989)

Parameter	Calculated Value	Standard Threshold	Compliance Status
Molecular Weight (g/mol)	150.22	< 500 g/mol	Compliant [45]
Lipophilicity (LogP)	3.30	≤ 5.0	Compliant [45]
Hydrogen Bond Donors (HBD)	1	≤ 5	Compliant [45]
Hydrogen Bond Acceptors (HBA)	1	≤ 10	Compliant [45]
Rotatable Bonds	1	≤ 10	Compliant [62]
TPSA (Å²)	20.23	< 140 Å²	Compliant [62]
Lipinski Rule Violations	0	0 Violations	Pass [45]

As can be seen in Table 2, Thymol is a compound that follows Lipinski's Rule of Five perfectly, with no violations [45]. The low molecular weight (150.22 g/mol), moderate lipophilicity (LogP value of 3.30), and low TPSA (20.23 Å²) mean that it has a high permeation through membranes and rapid absorption in plant tissues with low possibility of bioaccumulation in agricultural environments [44, 61].

Conclusion and future conspectus

The present study, using extensive computational methods, confirms that Thymol is a successful inhibitor of *Botrytis cinerea* polygalacturonase (PDB ID: 1BHE). We found that it has a large binding energy (-5.4 kcal/mol) in the Cavity C1 and establishes highly important network of interactions with the catalytically active residues in the active site (N174; R152; T150; P151; A101; D100; G96; K97) [43, 56]. Thus, owing to the lack of lipophilicity violations and its excellent drug-likeness profile [45], Thymol can be successfully used as a basis for developing environmentally benign fungal inhibitors of polygalacturonase. Future studies should include the use of actual enzymatic assays, molecular dynamics, and trials of green nano-forms.

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