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Bioinformatics analysis of the fungal volatile and non-volatile compounds effects on ethylene and salicylic acid biosynthesis in ISR and SAR mechanisms

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A B S T R A C T

Objective: This study used in silico methods to explore the physicochemical properties, pharmacokinetic profiles, and molecular interactions of certain fungal-derived compounds with important enzymes in the ethylene and salicylic acid biosynthesis pathways. These enzymes include ACC Synthase (ACS), ACC Oxidase (ACO), Isochorismate Synthase (ICS), and Phenylalanine Ammonia-Lyase (PAL), all known to be involved in plant defense mechanisms triggered by bioactive secondary metabolites produced by Plant Growth-Promoting Fungi (PGPFs).

Methods: Volatile and non-volatile PGPF compounds were obtained from PubChem. SwissADME calculated physicochemical properties, while PlantCyc mapped the ethylene and salicylic acid pathways. Avogadro optimized 3D structures for docking using AutoDock-4.2.6, and PyMOL/AutoDockTools analyzed binding energies and interactions. PDBsum evaluated the effects of the compounds on ISR/SAR-related gene expression and stress responses.

Results: Physicochemical analysis showed that bioactive compounds from Plant Growth-Promoting Fungi have a variety of molecular properties. β-caryophyllene, farnesol, and lovastatin were found to be highly lipophilic (XLogP > 4), indicating good membrane permeability, while hydrophilic compounds like glutathione displayed increased solubility in water. Pharmacokinetic evaluation supported these findings, with most compounds showing minimal inhibition of cytochrome P450, indicating safety. Molecular docking simulations revealed that verrucarin A had the strongest binding affinity to ACC Oxidase (−7.06 kcal/mol) and Phenylalanine Ammonia-Lyase (−8.52 kcal/mol), while abscisic acid showed strong interactions with ACC Synthase (−6.52 kcal/mol) and Isochorismate Synthase (−8.5 kcal/mol). Pathway simulations identified ACC Synthase, ACC Oxidase, Isochorismate Synthase, and Phenylalanine Ammonia-Lyase as key regulatory points in the biosynthesis of ethylene and salicylic acid.

Conclusion: These findings show that compounds derived from PGPF can alter plant defense pathways through precise enzyme interactions, establishing a biochemical basis for sustainable agricultural practices.

Keywords: ACC Synthase, ACC Oxidase, Isochorismate Synthase, Phenylalanine Ammonia-Lyase, Volatile Organic Compounds

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Introduction

Plant growth-promoting fungi (PGPFs) are essential for enhancing plant growth and improving resistance to various stresses. These fungi influence plant development by producing secondary metabolites like volatile organic compounds (VOCs) and non-volatile compounds. VOCs, such as alcohols, ketones, and terpenes, impact cellular signaling pathways and boost plant defense systems to help plants cope with environmental pressures. On the other hand, non-volatile compounds like enzymes and phytohormones activate defense genes and trigger biosynthetic pathways like ethylene and salicylic acid, promoting systemic resistance (ISR) and systemic acquired resistance (SAR) in plants (1, 2).

The ISR mechanism, through modulation of jasmonic acid and ethylene signaling pathways, increases a plant's ability to tolerate biotic and abiotic stresses. On the other hand, the SAR mechanism, which is dependent on salicylic acid regulation, provides long-term systemic defense and targets a wide range of pathogens. These two mechanisms work synergistically, creating a complex network of signaling interactions within the plant (3).

Recent advances in bioinformatics have brought forth new tools for identifying key genes and proteins linked to ISR and SAR mechanisms. These tools empower researchers to carry out more precise molecular analyses of plant resistance mechanisms and provide creative strategies for crop breeding and stress management. For example, fungi *like Trichoderma* boost plant resistance to soilborne diseases by producing volatile compounds (4).

Volatile compounds, especially those that assist in regulating the expression of defense genes, have become a major focus in recent research. Compounds like 2,3-butanediol and isobutyl acetate are among the substances that significantly improve plant resistance to biotic stress (5). Furthermore, non-volatile compounds, including enzymes and specific proteins, contribute to plant defense by influencing growth and regulatory pathways (6).

The biosynthetic pathways of ethylene and salicylic acid are crucial in how plants respond to environmental stress and defend themselves. Ethylene is essential for regulating growth and responding to biotic stresses by controlling the expression of defense genes to help plants fight pathogens. On the other hand, salicylic acid plays a significant role in the systemic acquired resistance (SAR) mechanism, boosting overall resistance and aiding in the formation of defense memory. This memory enables plants to better defend themselves upon subsequent exposure to stressors (7).

The practical applications of these findings in sustainable agriculture and plant breeding are vast. Bioinformatics tools provide the ability to identify and assess growth-promoting fungi that can be used in managing biotic stressors (8). These fungi have the potential to reduce the use of chemical pesticides and enhance agricultural productivity. For example, fungi that produce volatile compounds, such as *Fusarium* and *Penicillium*, are emerging as promising candidates in plant disease management (9).

This paper aims to explore the bioinformatics impact of volatile and non-volatile compounds produced by plant growth-promoting fungi on the biosynthetic pathways of ethylene and salicylic acid. It also investigates their role in triggering ISR and SAR mechanisms. The results of this study may offer innovative strategies for leveraging growth-promoting fungi in sustainable agriculture, enhancing plant disease management, and increasing crop yields.

Materials and Methods

Collection and Identification of Volatile and Non-Volatile Compounds

The volatile and non-volatile chemical compounds produced by Plant Growth-Promoting Fungi (PGPFs) were gathered from reliable biochemical databases like PubChem. These compounds consist of secondary metabolites that are crucial for inducing systemic resistance (ISR) and systemic

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acquired resistance (SAR). The structural properties of these compounds were extracted in SDF format for bioinformatics analyses (10, 11).

Analysis of Physicochemical Properties of Chemical Compounds

The SwissADME online server, accessible at http://www.swissadme.ch, was utilized to assess the physicochemical properties of the chemical compounds. This tool automatically computes various features like molecular weight, melting point, LogP, LogS, and membrane permeability potential. These evaluations aimed to ascertain the compounds' capacity to impact signaling pathways in plants (12).

Simulation of Ethylene and Salicylic Acid Biosynthetic Pathways

The PlantCyc database was used to simulate the biosynthetic pathways of ethylene and salicylic acid. These pathways include enzymes and proteins responsible for producing ethylene and salicylic acid, which play a vital role in ISR and SAR phenomena. Recent studies have shown that these pathways are effective in improving plant resistance to environmental stresses like drought and pathogens (13, 14).

Modeling and Optimization of 3D Structures of Compounds

The Avogadro software was used to optimize the three-dimensional structures of both volatile and non-volatile chemical compounds. These structures were then prepared for molecular docking with target proteins, focusing on those involved in the biosynthetic pathways of ethylene and salicylic acid. Structural optimization improves the accuracy of following simulations (14).

Molecular Docking of Compounds with Target Proteins

Molecular docking simulations were performed with AutoDock-4.2.6 software to predict how chemical compounds interact with proteins in the ethylene and salicylic acid biosynthetic pathways. The software uses genetic algorithms to analyze the compounds' conformations and interactions with proteins. The aim of these simulations was to model how the compounds influence gene expression and enzymes related to ISR and SAR (15).

Analysis of Docking Results and Interaction Evaluation

The docking results were analyzed using PyMOL and AutoDockTools to identify and analyze contact points and interactions between the ligands and proteins. Binding energies and interaction stabilities were calculated for each compound to select the ones with the highest potential to induce immune responses (16).

Analysis of Compound Effects on ISR and SAR Pathways

After conducting docking simulations, we analyzed how chemical compounds affected the ISR and SAR pathways. We utilized databases like PDBsum to study these pathways and evaluate any alterations in gene expression associated with these processes. Our assessments covered the compounds' influence on ethylene and salicylic acid production, as well as their role in regulating plant immune responses to different stressors (15).

Results

Physicochemical Characterization of Selected Bioactive Compounds

A thorough physicochemical analysis was performed to assess the structural and functional characteristics of specific volatile and non-volatile secondary metabolites obtained from Plant Growth-Promoting Fungi (PGPFs). These active compounds, sourced from the PubChem database, were identified based on essential molecular descriptors such as molecular formula, molecular weight, hydrogen bond donor and acceptor counts, lipophilicity (XLogP), water solubility, predicted

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toxicity, SMILES notation, and IUPAC name. Furthermore, three-dimensional conformers were optimized using Avogadro software to aid in subsequent molecular docking simulations.

Compounds such as β-caryophyllene, farnesol, and lovastatin, with high lipophilicity (XLogP > 4), show enhanced membrane permeability and potential intracellular bioactivity. On the other hand, highly hydrophilic compounds like glutathione and glucan may have limited passive diffusion but exhibit high systemic distribution in aqueous cellular environments. Differences in hydrogen bonding capacity, as seen in donor and acceptor counts, influence interaction potentials with protein targets. These features are crucial for molecular recognition and complex stabilization during ligand-protein interactions, especially in ethylene and salicylic acid biosynthesis pathways. Additionally, compounds with high aqueous solubility, such as 2,3-butanediol, citric acid, and acetoin, may have increased systemic mobility within plant tissues. In silico toxicity predictions suggest that the majority of compounds analyzed are non-toxic, supporting their application in sustainable biocontrol strategies. As has been emphasized (17) that both lipophilicity and hydrogen bonding profiles significantly contribute to the functional bioavailability and target-binding efficacy of antifungal secondary metabolites. Moreover, it has been demonstrated (18) the importance of physicochemical compatibility for stable molecular interactions between plant-derived metabolites and key defense-related enzymes. These findings collectively support the use of PGPF-derived compounds as promising regulators of plant defense signaling, establishing a strong biochemical basis for their incorporation into bio-based agricultural systems.

Pharmacokinetic Properties of Selected Bioactive Compounds

A pharmacokinetic evaluation was conducted for bioactive compounds derived from plant growth-promoting fungi (PGPFs, in addition to analyzing their basic physicochemical characteristics. The data for this assessment were obtained using the computational platform SwissADME (http://www.swissadme.ch), which is a reliable tool for predicting the drug-like behavior and pharmacokinetic properties of small molecules.

The study analyzed key parameters, including lipophilicity (Log Po/w – iLogP), water solubility (Log S based on the ESOL model), pharmacokinetic class, skin permeability (Log Kp), and the inhibitory potential against cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), as shown in Table 1.

The iLogP values showed that compounds like β-caryophyllene, farnesol, and lovastatin had high lipophilicity, indicating good membrane permeability and effective intracellular targeting. On the other hand, glutathione and glucan, with lower Log P values and greater hydrophilicity, displayed increased solubility and widespread distribution within cells, even though they had lower permeability.

The ESOL model predicted water solubility, categorizing compounds into different levels ranging from "low soluble" to "highly soluble." For example, compounds like acetoin and citric acid showed high solubility, allowing them to move effectively within plant tissues and quickly start their biological activity. While the Log Kp index is commonly used in pharmaceutical settings, it also offers useful information on compounds' ability to pass through cell membranes. Compounds with higher Log Kp values usually demonstrate better membrane penetration capabilities.

A notable finding from this study was the ability to predict cytochrome P450 enzyme inhibition potential using the chosen compounds. The majority of compounds did not show significant inhibitory effects, indicating little impact on plant metabolic pathways and a high level of biosafety. Nevertheless, lovastatin demonstrated moderate inhibition potential against CYP3A4, prompting the need for additional research.

These findings suggest that a balanced interplay between lipophilicity, solubility, and metabolic safety is critical in determining the biological

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effectiveness of bioactive compounds. As emphasized by Jha et al. (18) and Kaliaperumal et al. (17), compatibility in physicochemical and pharmacokinetic profiles is fundamental for efficient ligand–protein interactions and the successful application of such compounds in biotechnological systems.

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Table 1: Pharmacokinetic Properties, Solubility, Lipophilicity, and CYP450 Enzyme Inhibition Potential of Selected Bioactive Compounds Produced by Plant Growth-Promoting Fungi (PGPFs)

Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
2,3-Butanediol	262	-0.09	0.25	Highly soluble	No	No	No	No	No	-7.5
β-Caryophyllene	5281515	4.24	-3.87	Soluble	No	Yes	Yes	No	No	-4.44
Methyl Salicylate	4133	1.66	-2.66	Soluble	No	No	No	No	No	-5.42
Hexanoic Acid	8892	1.47	-1.51	Very soluble	No	No	No	No	No	-5.65
Acetoin	179	0.05	-0.13	Very soluble	No	No	No	No	No	-7.05
6-Pentyl-α-pyrone	33960	2.59	-2.89	Soluble	Yes	No	No	No	No	-5.16
Phenylacetaldehyde	998	1.73	-2.07	Soluble	Yes	No	No	No	No	-5.77
Benzyl Alcohol	244	1.41	-1.69	Very soluble	Yes	No	No	No	No	-6.18
Eucalyptol	2758	2.67	-2.52	Soluble	No	No	No	No	No	-5.3
α-Pinene	6654	3.44	-3.51	Soluble	No	No	Yes	No	No	-3.95

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Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Limonene	440917	3.37	-3.5	Soluble	No	No	Yes	No	No	-3.89
Terpinolene	11463	3.4	-3.5	Soluble	No	No	Yes	No	No	-3.96
1-Octanol	957	2.44	-2.14	Soluble	No	No	No	No	No	-4.96
2-Hexenal	5281168	1.5	-1.21	Very soluble	No	No	No	No	No	-5.82
Geraniol	637566	2.74	-2.78	Soluble	No	No	No	No	No	-4.71
Farnesol	445070	-	-	-	-	-	-	-	-	-
Isoprene	6557	1.83	-1.72	Very soluble	No	No	No	No	No	-5
Camphor	2537	2.37	-2.16	Soluble	No	No	No	No	No	-5.67
Linalool	6549	2.66	-2.4	Soluble	No	No	No	No	No	-5.13
Benzoic Acid	243	1.44	-2.2	Soluble	No	No	No	No	No	-5.72
Ferulic Acid	445858	1.36	-2.11	Soluble	No	No	No	No	No	-6.41

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Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Glutathione	124886	-2.36	1.82	Highly soluble	No	No	No	No	No	-11.37
Oxalic Acid	971	-0.79	-0.17	Very soluble	No	No	No	No	No	-7.03
Succinic Acid	1110	-0.3	0	Very soluble	No	No	No	No	No	-7.44
Fumaric Acid	444972	-0.35	-0.21	Very soluble	No	No	No	No	No	-7.25
Malonic Acid	867	-0.65	0.16	Highly soluble	No	No	No	No	No	-7.51
Citric Acid	311	-1.51	0.38	Highly soluble	No	No	No	No	No	-8.69
Gallic Acid	370	0.21	-1.64	Very soluble	No	No	No	No	Yes	-6.84
Protocatechuic Acid	72	0.65	-1.86	Very soluble	No	No	No	No	Yes	-6.42
Coumaric Acid	637542	1.26	-2.02	Soluble	No	No	No	No	No	-6.26

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Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Pyrocatechol	289	0.97	-1.63	Very soluble	No	No	No	No	Yes	-6.35
Anthranilic Acid	227	0.72	-1.83	Very soluble	No	No	No	No	No	-6.28
Quinic Acid	6508	-1.69	0.53	Highly soluble	No	No	No	No	No	-9.15
Shikimic Acid	8742	-1.1	0.23	Highly soluble	No	No	No	No	No	-8.58
Aspartic Acid	5960	-2.04	1.98	Highly soluble	No	No	No	No	No	-9.87
Glutamic Acid	33032	-1.68	1.84	Highly soluble	No	No	No	No	No	-9.82
Fusaric Acid	3442	1.75	-2.66	Soluble	No	No	No	No	No	-5.55
Kojic Acid	3840	-0.16	-0.7	Very soluble	No	No	No	No	No	-7.62
Fusarin C	6435894	2.17	-3.75	Soluble	No	No	Yes	No	No	-6.8

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Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Lovastatin	53232	3.88	-4.57	Moderately soluble	No	No	Yes	No	Yes	-5.74
Patulin	4696	0	-0.17	Very soluble	No	No	No	No	No	-7.94
Gliotoxin	6223	-0.19	-1.34	Very soluble	No	No	No	No	No	-8.8
Verrucarin A	6326658	-	-	-	-	-	-	-	-	-
Indole-3-acetic acid	802	1.51	-2.19	Soluble	No	No	No	No	No	-6.37
2,5-Dimethylpyrazine	31252	0.99	-1.46	Very soluble	No	No	No	No	No	-6.51
Cyclopropyl carbinol	75644	0.67	-0.4	Very soluble	No	No	No	No	No	-6.53
Salicylic Acid	338	1.24	-2.5	Soluble	No	No	No	No	No	-5.54
Glucan (β-glucan)	439262	-5.79	1.83	Highly soluble	No	No	No	No	No	-14.26

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Name	Accession code	Lipo-philicity	Water solubility		Pharmacokinetics					
		Log Po/w (iLogP)	Log S (ESOL)	Class a	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
Ethylene	6325	1	-0.77	Very soluble	No	No	No	No	No	-5.62
Aminocyclopropane-1-carboxylate (ACC)	535	-1.18	1.35	Highly soluble	No	No	No	No	No	-8.89
Salicylaldoxime	135408751	1.32	-2.44	Soluble	No	No	No	No	No	-5.59
Abscisic Acid	5280896	-	-	-	-	-	-	-	-	-
Camalexin	636970	2.77	-3.48	Soluble	Yes	No	No	No	Yes	-5.58
Pterostilbene	5281727	3.31	-4.01	Moderately soluble	Yes	Yes	Yes	Yes	No	-5.18

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Simulation of Ethylene and Salicylic Acid Biosynthesis Pathways

The biosynthetic pathways of ethylene and salicylic acid were simulated using the PlantCyc databases. These databases were chosen for their thorough and well-organized data on enzymes, proteins, and metabolites related to plant metabolic processes. The main goal of this simulation was to pinpoint important regulatory points and examine the molecular interactions in these pathways. This analysis aimed to shed light on their involvement in activating Induced Systemic Resistance (ISR) and Systemic Acquired Resistance (SAR) mechanisms.

Ethylene Biosynthesis Pathway

The ethylene biosynthesis pathway (Figure 1) begins with the precursor **S-**Adenosyl Methionine (SAM), which is transformed into 1-Aminocyclopropane-1-Carboxylic Acid (ACC) by the enzyme ACC Synthase (ACS) (Figure 2). In the final **stage,** ACC Oxidase (ACO) (Figure 2) converts ACC into ethylene, the ultimate bioactive product. This pathway plays a crucial role in regulating ethylene production, which is vital for both plant defense responses and developmental processes. Ethylene serves as a key signaling molecule involved in inducing plant resistance to various stresses, such as pathogen attacks (biotic stresses), drought, and salinity (abiotic stresses) (19). The results indicated that ACS and ACO enzymes act as major control points in this pathway. An increase in ACS activity leads to elevated accumulation of ACC, which in turn significantly enhances ethylene production rates.

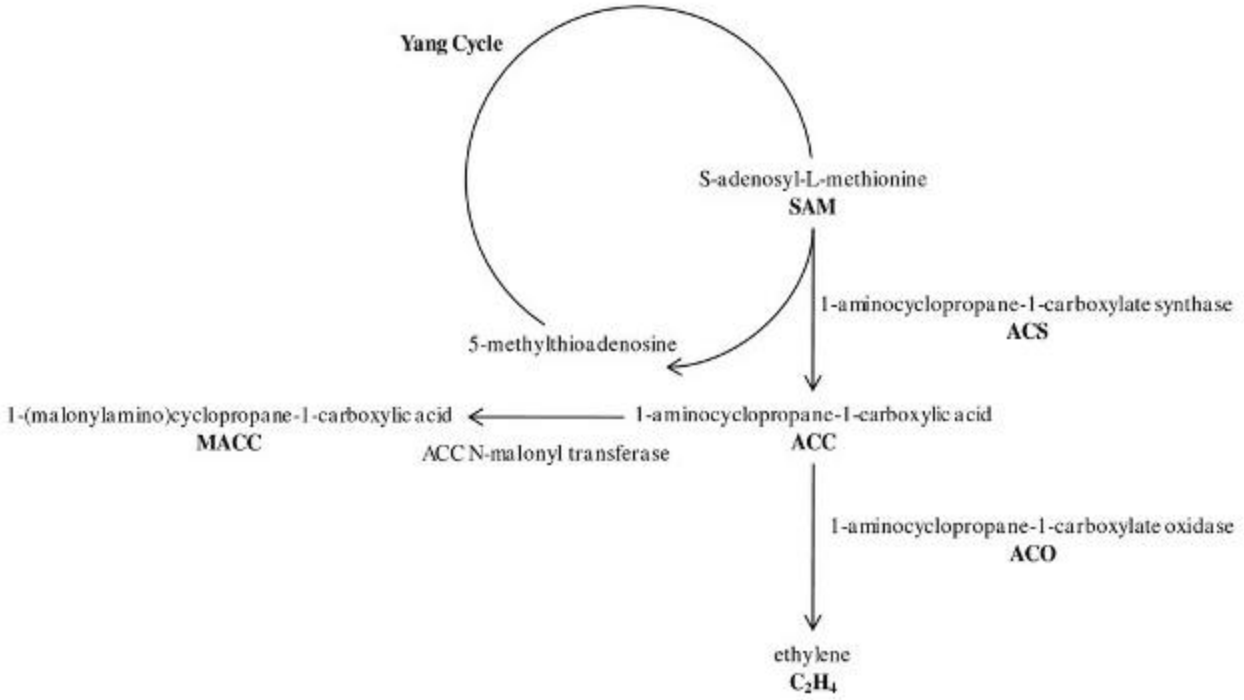

Figure 1: Ethylene biosynthesis follows a well-defined metabolic pathway. The process begins when S-adenosyl-L-methionine (SAM) is converted into 1-aminocyclopropane-1-carboxylic acid (ACC), a reaction catalyzed by the enzyme ACC synthase (ACS). Subsequently, ACC can undergo one of two possible transformations: it can be malonylated by ACC N-malonyltransferase to form 1-(malonylamino)cyclopropane-1-carboxylic acid (MACC), or it can be oxidized by ACC oxidase (ACO) to produce ethylene, the final product of this pathway (19). This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0),

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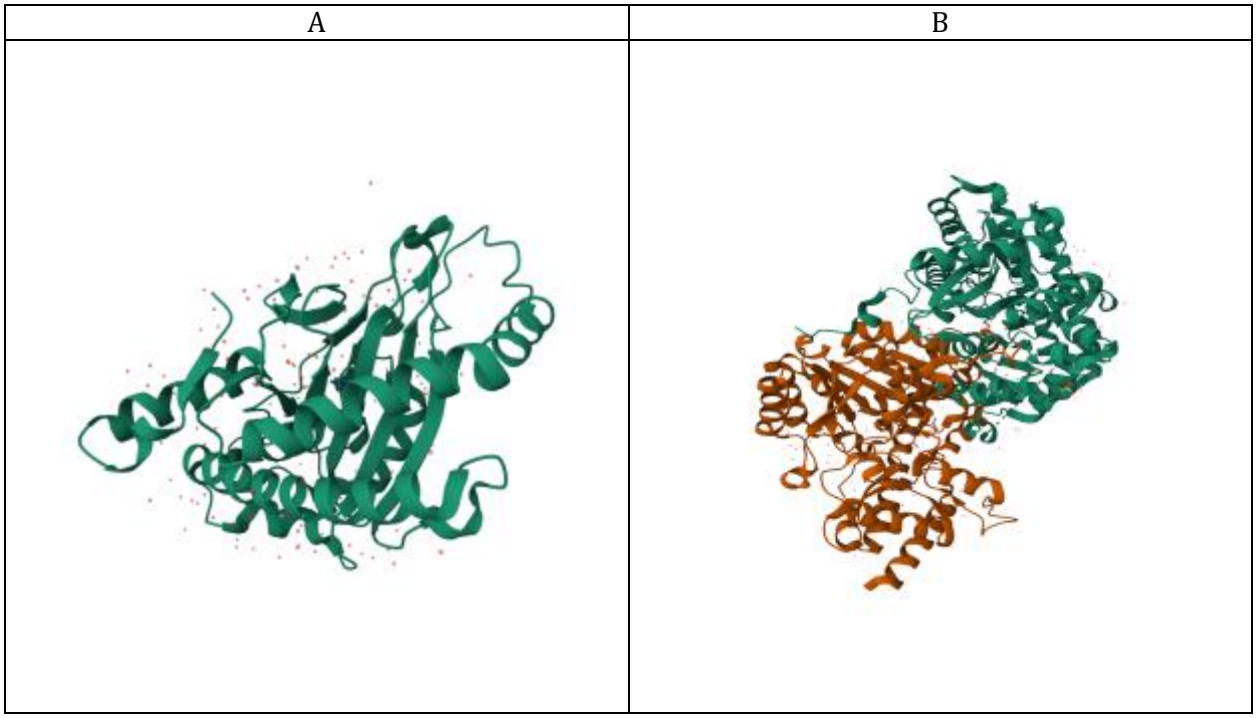

Figure 2. Three-dimensional structures of ACC Oxidase (A) and ACC Synthase (B) involved in the ethylene biosynthesis pathway

Salicylic Acid Biosynthesis Pathway

The biosynthetic pathway of salicylic acid (SA) (Figure 3) involves two main branches. In the phenylpropanoid pathway, the enzyme Phenylalanine Ammonia-Lyase (PAL) catalyzes (Figure 4) the conversion of phenylalanine to cinnamic acid, which then becomes salicylic acid. Higher PAL activity in this pathway is strongly linked to increased SA accumulation. On the other hand, in the isochorismate pathway, Isochorismate Synthase (ICS) (Figure 4) is the key enzyme that converts isochorismate into salicylic acid. Salicylic acid plays a crucial role in regulating genes related to Systemic Acquired Resistance (SAR) and acts as a primary signaling molecule in plant responses to biotic stress. Similarly, in the isochorismate branch, ICS activity serves as the main regulatory point.

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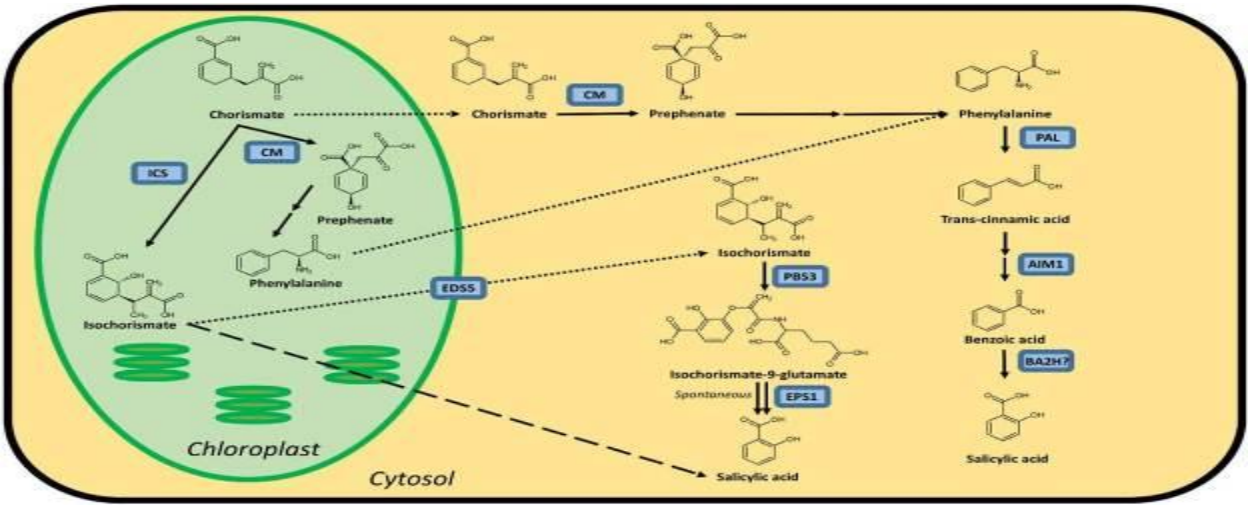

Figure 3: Biosynthetic Pathways of SA in Plants**.** Solid lines represent enzymatic conversions, while dotted lines indicate transport processes from the chloroplast to the cytosol. A dashed line denotes an alternative, yet uncharacterized biosynthetic route, and a question mark signifies an unidentified protein. The subcellular localization of the steps preceding phenylalanine remains uncertain—they may occur in the chloroplast, cytosol, or both, given the presence of chloroplastic and cytosolic chorismate mutases (CMs) (20). This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0),

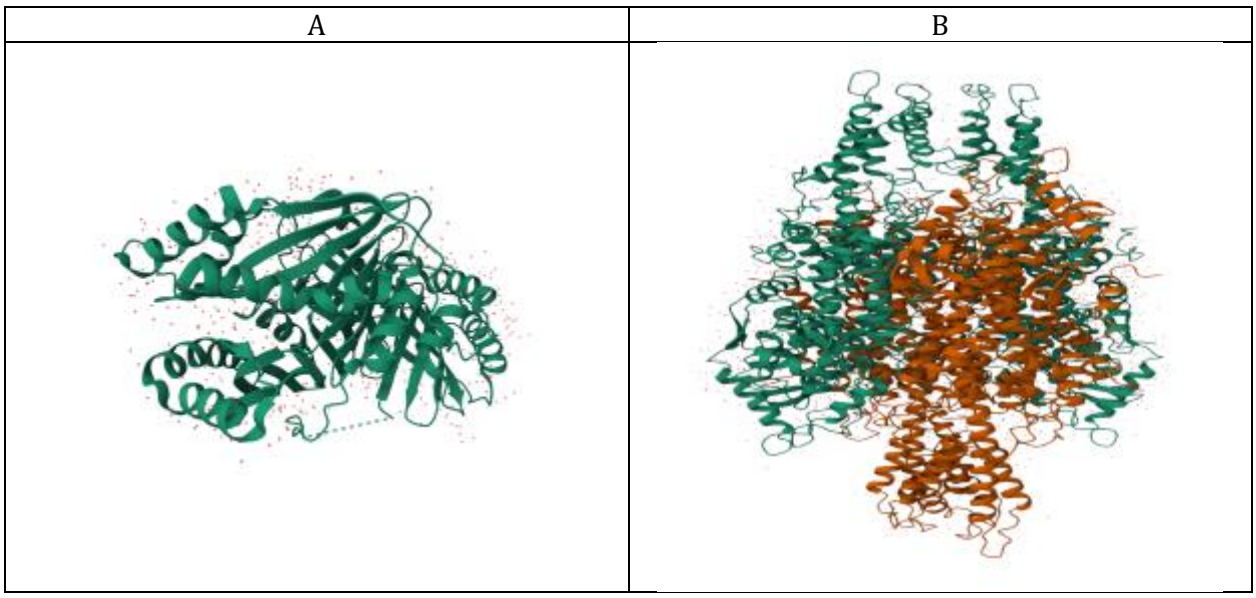

Figure 4: Three-dimensional structures of Isochorismate Synthase (ICS) (A) and Phenylalanine Ammonia-Lyase (PAL) (B) involved in the salicylic acid biosynthesis pathway

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The Role of Biosynthetic Pathways in Inducing ISR and SAR

The results showed that both the ethylene and salicylic acid biosynthesis pathways are vital in inducing Induced Systemic Resistance (ISR) and Systemic Acquired Resistance (SAR). In ISR, ethylene serves as the main signaling molecule, triggering defense responses that rely on microbe-plant interactions. On the other hand, in SAR, salicylic acid facilitates long-distance signaling to boost resistance against biotic stresses. Previous studies have proven that increasing the activity of key enzymes like ACC Synthase (ACS) and Phenylalanine Ammonia-Lyase (PAL) can boost the production of ethylene and salicylic acid, thereby enhancing plant resistance to pathogenic organisms (21). This simulation provides valuable insights into the regulatory nodes of ethylene and salicylic acid biosynthesis pathways, which can serve as a foundation for the development of biotechnological strategies aimed at improving crop resistance (22, 23).

Molecular Docking Analysis of Bioactive Compounds with ACC Oxidase (ACO)

A molecular docking simulation was conducted to evaluate the molecular interaction potential of selected bioactive compounds with ACC Oxidase (ACO), a key regulatory enzyme in the ethylene biosynthesis pathway. The simulation utilized the optimized 3D structures of ligands and the target protein. The results of the docking analysis, presented in Figure 5, include data on binding energy (kcal/mol) and inhibition constant (Ki) values for each compound. The binding energy values indicate the strength and stability of the ligand-protein complexes. Among the compounds examined, Verrucarin A displayed the lowest binding energy (-7.06 kcal/mol), signifying the strongest interaction with the active site of ACO. This compound also demonstrated one of the lowest inhibition constants (Ki), suggesting higher binding affinity and potential inhibitory effectiveness compared to the other ligands. Lower Ki values typically correspond to stronger binding, increasing the likelihood of effectively interfering with enzymatic activity. This suggests that such compounds could regulate ethylene production by directly interacting with ACC Oxidase and influencing its catalytic performance. These results align with prior studies underscoring the importance of ligand affinity in impacting ethylene signaling pathways (17, 18). Overall, the docking results suggest that certain bioactive metabolites derived from PGPFs may serve as potent modulators of ethylene biosynthesis by targeting ACO. Such interactions provide a promising biotechnological basis for manipulating ethylene-mediated defense responses in plants.

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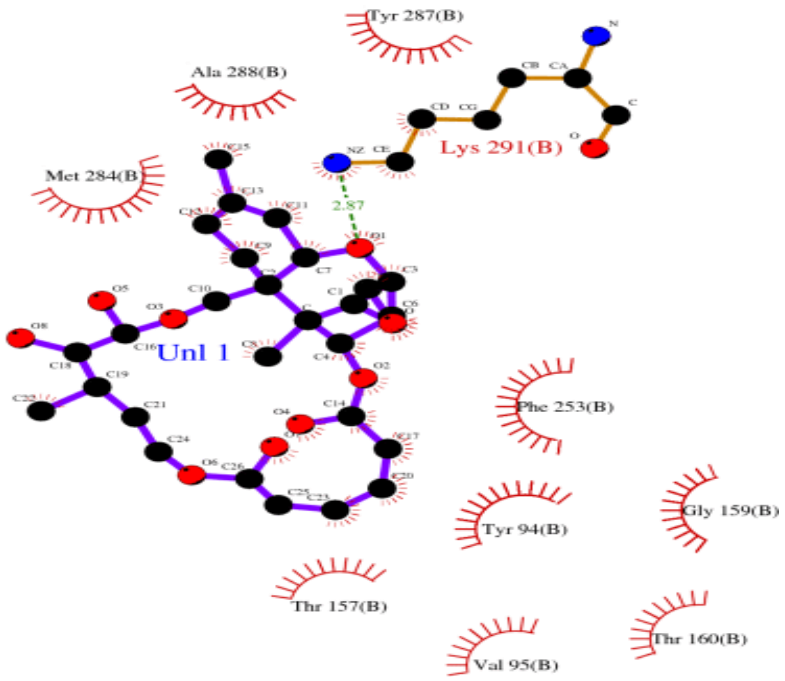

Figure 5: Docked conformation of Verrucarin A at the active site of ACC Oxidase (ACO) illustrating ligand–protein interactions

Molecular Docking Analysis of Bioactive Compounds with ACC Synthase (ACS)

Molecular docking simulations were conducted to explore the potential interactions between specific bioactive compounds and ACC Synthase (ACS), a crucial enzyme in the ethylene biosynthesis pathway. The simulations utilized optimized 3D structures of ligands and the ACS protein. The docking results, featured in Figure 6, include the binding energy values (kcal/mol) and inhibition constants (Ki) for each compound. Notably, Abscisic Acid demonstrated the lowest binding energy (-6.52 kcal/mol) among the compounds tested, indicating a more robust interaction with the ACS active site compared to other ligands. Moreover, this compound exhibited one of the lowest Ki values, suggesting a stronger binding affinity and the potential for inhibiting ACS activity.

Stronger binding between ligands and proteins, shown by more negative binding energy and lower Ki values, suggests that these compounds might affect the ethylene biosynthesis process by disrupting ACS catalytic activity. While abscisic acid is not a direct product of the ethylene pathway, its significant interaction with ACS could indicate communication between the ethylene and abscisic acid signaling pathways, as previous studies have proposed (17, 18). Overall, these results highlight abscisic acid as a potentially significant regulator of ethylene biosynthesis through its interaction with ACS, offering a new perspective on the integration of hormonal signaling in plant defense mechanisms.

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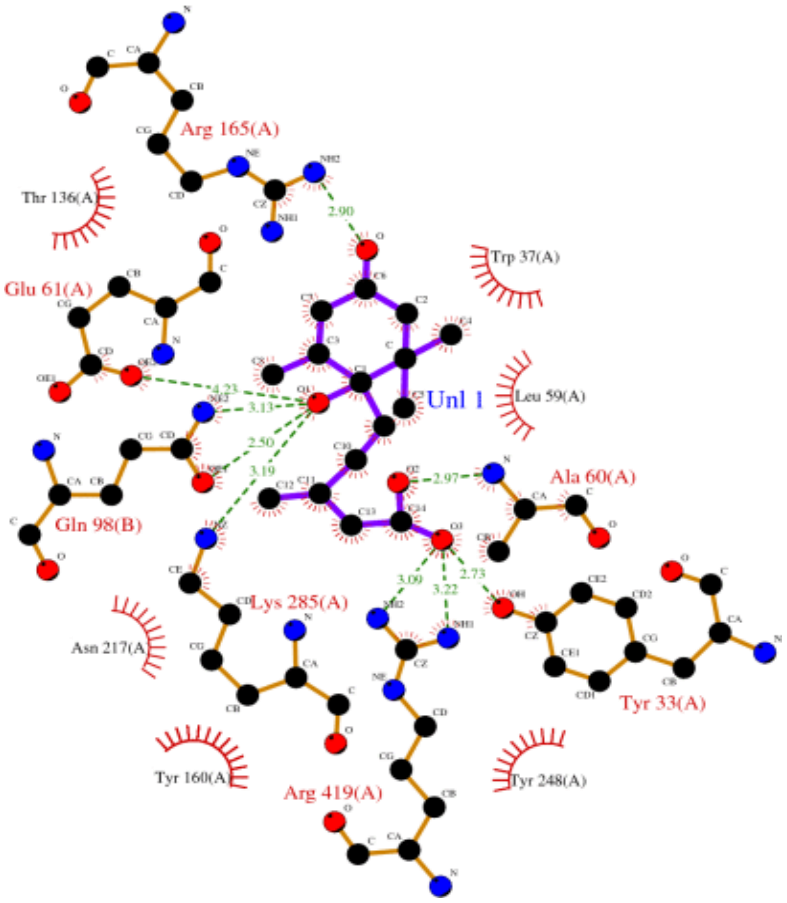

Figure 6: Docked conformation of Abscisic Acid at the active site of ACC Synthase (ACS) illustrating ligand–protein interaction

Molecular Docking Analysis of Bioactive Compounds with Isochorismate Synthase (ICS)

Molecular docking simulations were conducted to assess the interactions between certain bioactive compounds and Isochorismate Synthase (ICS), a key enzyme in the salicylic acid biosynthesis pathway. The study utilized the optimized 3D structures of ligands and the ICS protein. The results of the docking process, outlined in Figure 7, include the binding energy (in kcal/mol) and inhibition constant (Ki) values for each compound. Notably, Abscisic Acid demonstrated the lowest binding energy (-8.5 kcal/mol) among the tested ligands, indicating a robust and stable interaction with ICS's active site. Additionally, this compound exhibited a significantly low inhibition constant, pointing towards a strong binding affinity and potential inhibitory effect on ICS's enzymatic activity. These robust interactions suggest that Abscisic Acid, despite not being a direct part of the salicylic acid biosynthesis pathway, may have a regulatory function through cross-pathway interactions, potentially impacting the SAR signaling cascade. These findings align with prior research emphasizing the connection between salicylic acid and abscisic acid signaling networks, particularly under stressful conditions (17, 18). The docking results provide further evidence that abscisic acid may act as a modulator of salicylic acid synthesis by interacting with ICS, revealing new perspectives for integrated hormonal regulation in plant defense mechanisms

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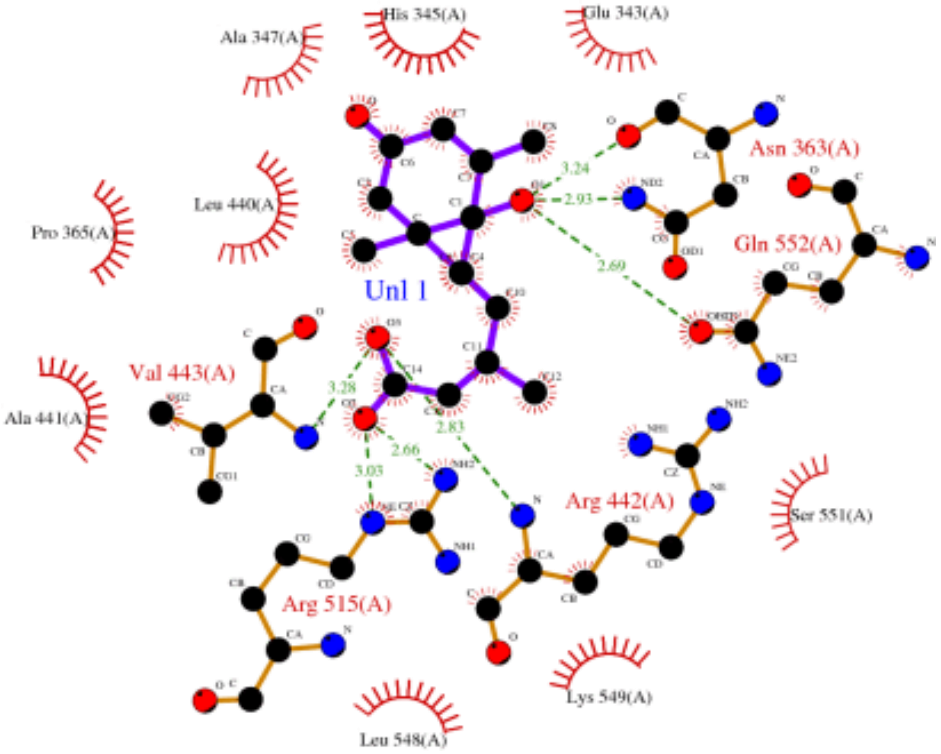

Figure 7: Docked conformation of Abscisic Acid at the active site of Isochorismate Synthase (ICS) illustrating ligand–protein interaction

Molecular Docking Analysis of Bioactive Compounds with Phenylalanine Ammonia-Lyase (PAL)

Molecular docking simulations were conducted to explore the interaction potential between specific bioactive compounds and Phenylalanine Ammonia-Lyase (PAL), a crucial enzyme in the phenylpropanoid branch of the salicylic acid biosynthesis pathway. The docking results, shown in Figure 8, provide binding energy values (kcal/mol) and inhibition constants (Ki) for each compound.

Among the tested ligands, Verrucarin A showed the lowest binding energy at -8.52 kcal/mol, signifying a stable and robust interaction with the PAL active site. This compound also displayed a notably low inhibition constant, indicating a high binding affinity and potential inhibitory effect on PAL activity. These strong molecular interactions suggest that Verrucarin A could influence the salicylic acid biosynthesis pathway by affecting PAL function, thereby impacting SAR-related signaling mechanisms. Past research has emphasized the significance of ligand affinity in modulating defense-related enzyme activity (17, 18).

These findings highlight the potential role of verrucarin A in modulating both the ethylene pathway (as observed through ACO docking) and salicylic acid signaling, showcasing its multifaceted involvement in regulating plant defense mechanisms.

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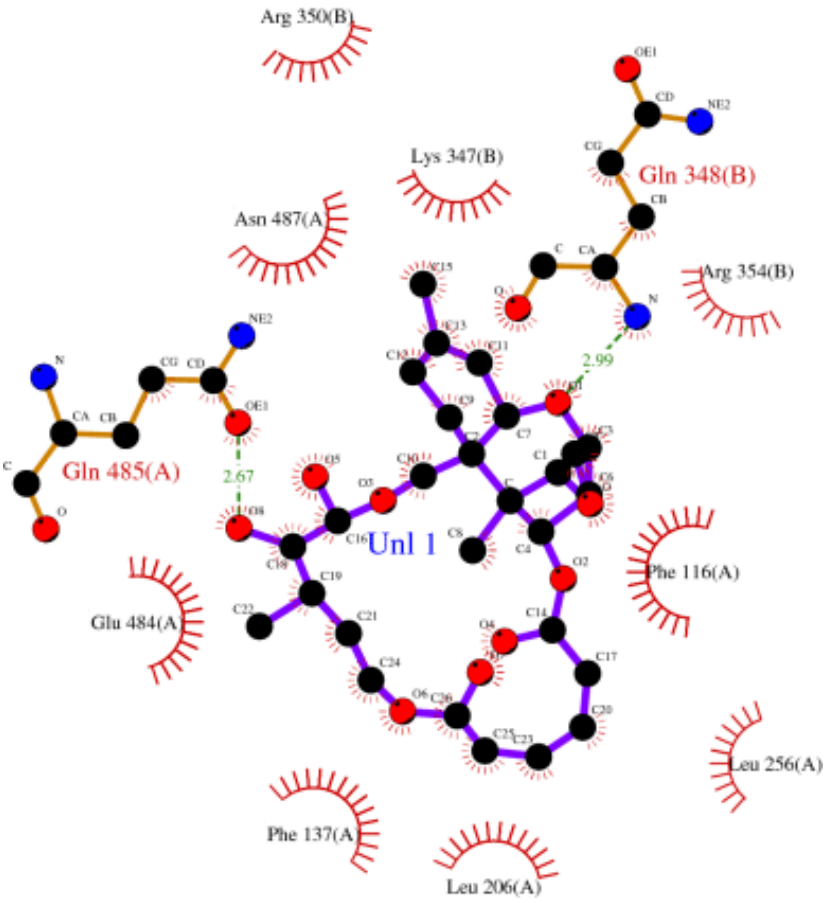

Figure 8: Docked conformation of Verrucarin A at the active site of Phenylalanine Ammonia-Lyase (PAL) illustrating ligand–protein interaction

Discussion

These molecular docking results provide additional evidence for the hypothesis that bioactive fungal metabolites can effectively influence plant hormonal signaling by targeting essential regulatory enzymes like ACC Oxidase (ACO). The noteworthy high binding affinity and low inhibition constant (Ki) values identified for Verrucarin A are particularly important, suggesting a robust interaction between the ligand and protein that may lead to changes in the catalytic activity of ACO and, in turn, affect ethylene production. Similar findings have been reported by Ayadi *et al*. (24) and Vincent *et al*. (25), who demonstrated that certain natural compounds with high docking scores against ethylene-related enzymes could enhance stress resilience in plants via controlled hormonal signaling.

Furthermore, ethylene biosynthesis and its regulation through ACC Oxidase are now widely acknowledged as key targets for enhancing plant tolerance to both abiotic and biotic stresses (26, 27). The ability of fungal-derived metabolites to interfere with or modulate such pathways not only reinforces their role as elicitors in Induced Systemic Resistance (ISR) but also opens up opportunities for the development of bioformulated plant protectants. Given the current shift toward sustainable agriculture, utilizing natural metabolites for the fine-tuning of stress-related pathways has garnered increasing interest in plant biotechnology (17, 18).

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The docking interactions observed between specific fungal compounds and ACO offer a valuable mechanistic foundation for considering their potential use in crop enhancement strategies. These findings underscore the importance of incorporating in silico tools in natural compound screening processes and support the promising potential of fungal metabolites as next-generation plant defense modulators.

The significant interaction observed in this study between abscisic acid (ABA) and ACC Synthase (ACS) implies an interesting cross-talk between the ABA and ethylene signaling pathways. While ABA is not directly involved in the ethylene biosynthesis pathway, past research has shown that ABA can impact ethylene production and signaling by affecting crucial biosynthetic enzymes like ACS (28, 29). The current docking results demonstrate that ABA has a high binding affinity and low inhibition constant towards ACS, suggesting its potential to indirectly regulate ethylene levels through protein-ligand interactions. Recent research widely acknowledges the antagonistic or synergistic roles of ABA and ethylene in plant stress responses. For instance, Naing et al. (30) demonstrated that ABA-responsive transcription factors can modulate ethylene-responsive genes under combined drought and salinity stress. These cross-regulatory mechanisms suggest that ABA might not only function on its own but also regulate ethylene biosynthesis or signaling components in particular physiological circumstances. The interaction of ABA with ACS, based on docking, supports a mechanistic model in which ABA could impact ethylene production at a molecular level. This adds a new layer of complexity to hormonal interactions in plant defense. These discoveries present new opportunities for investigating the crosstalk between ABA and ethylene as a targetable interface in plant biotechnology. This could be especially valuable in developing stress-resistant crop varieties through interventions based on natural compounds.

The docking simulation revealed a strong binding affinity of abscisic acid (ABA) to Isochorismate Synthase (ICS), providing valuable insights into the possible interaction between the salicylic acid (SA) and abscisic acid (ABA) signaling pathways. Although ABA is not directly involved in the SA biosynthesis pathway, past studies have indicated that ABA may impact SA-mediated defense responses through transcriptional and enzymatic regulation mechanisms (15, 31). The observed high binding interaction and low Ki value of ABA toward ICS suggest a possible inhibitory role that may affect the enzymatic flow toward SA production.

Recent studies have increasingly highlighted the antagonistic and synergistic interactions between ABA and SA during abiotic and biotic stress responses, emphasizing the role of hormonal cross-talk in integrated defense signaling (32, 33). For example, Xia et al. (34) reported that exogenous application of ABA can modulate SA-associated gene expression under oxidative stress, implying an indirect regulation route through shared metabolic pathways. The docking interaction observed in this study between ABA and ICS supports a potential molecular mechanism through which ABA could regulate SA biosynthesis. This sheds new light on hormonal cross-communication in plant immunity. These findings emphasize the broader importance of fungal-derived bioactive compounds in adjusting inter-pathway hormonal balance. They also offer valuable insights for developing biotechnological strategies that target hormones in stress-resistant crop systems.

The molecular docking analysis revealed that Verrucarin A has a strong binding affinity for Phenylalanine Ammonia-Lyase (PAL), suggesting its potential as a key regulator of the phenylpropanoid pathway linked to salicylic acid (SA) production. The notably low binding energy and inhibition constant (Ki) observed for Verrucarin A indicate a stable and energetically favorable interaction with the PAL active site. These results suggest that Verrucarin A could significantly impact PAL activity, thus influencing the initial stages of SA synthesis. Prior research has highlighted the crucial role of ligand-enzyme interactions in modulating the expression and function of essential defense-related enzymes, including PAL, which is a central player in systemic

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acquired resistance (SAR) signaling (35, 36). The cross-regulatory roles of bioactive metabolites, particularly fungal-derived compounds, have been highlighted as crucial components of multifaceted plant defense strategies. The concurrent interaction of Verrucarin A with both ACO and PAL, as demonstrated in this study, further strengthens its position as a dual-pathway modulator, capable of simultaneously influencing both ethylene and salicylic acid signaling pathways.

The multifunctional behavior of Verrucarin A highlights its value not just as a structural ligand with strong binding affinity, but also as a biologically active compound with promising potential for eco-friendly plant protection strategies. These findings are consistent with previous reports on how secondary metabolites play an integrative role in coordinating various defense signaling pathways (17, 18).

Conclusion

This study presents a comprehensive in silico framework for assessing the physicochemical, pharmacokinetic, and molecular interaction profiles of bioactive compounds derived from plant growth-promoting fungi (PGPFs), especially concerning plant defense signaling. The docking simulations revealed that certain fungal metabolites have a strong binding affinity with essential enzymes in ethylene and salicylic acid biosynthesis pathways - particularly ACC Oxidase (ACO), ACC Synthase (ACS), Isochorismate Synthase (ICS), and Phenylalanine Ammonia-Lyase (PAL). Verrucarin A and abscisic acid exhibited the most favorable binding energies and inhibition constants among the compounds studied, indicating their potential as dual modulators affecting both ISR and SAR pathways through direct molecular interactions. These results underscore the promising role of fungal secondary metabolites as natural inducers of defense responses, offering possibilities for bolstering crop resilience against biotic and abiotic stressors. Furthermore, by integrating computational analyses covering physicochemical and pharmacokinetic profiling via SwissADME, and biosynthetic pathway simulations using the PlantCyc database, this study facilitated the identification of critical regulatory points and molecular interaction mechanisms. It not only enhances comprehension of the crosstalk among hormonal signaling pathways but also establishes a robust scientific foundation for the advancement of sustainable and environmentally friendly biotechnological strategies in upcoming agricultural systems.

Abbreviations

ICS: Isochorismate synthase; CM: Chorismate mutase; PAL: Phenylalanine ammonia-lyase; AIM1: Abnormal inflorescence meristem 1; BA2H: Benzoic acid 2-hydroxylase; EDS5: Enhanced Disease Susceptibility 5; PBS3: AvrPphB Susceptible 3; EPS1: Enhanced Pseudomonas Susceptibility 1.

Authors' contribution statement

B. Fazeli-Nasab: Conceptualization, Supervision, Project administration, Software, Writing - Original Draft and Revision. Yeganeh Shafiei: Methodology, Software, Validation, Visualization, Writing-Original Draft. Ali Salehi Sardoei: Formal Analysis, Investigation, Resources, Data curation. B. Fazeli-Nasab: Software, Writing - Review and preparation of final version. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Data will be made available on request

Conflict of interest

The authors declare no competing interests.

Ethical Approval

Not applicable.

Funding Declaration

Not applicable.

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