



Acute, synergistic and antagonistic effects of some aromatic compounds and essential oils on *Planococcus citri* by machine learning and feature selection approaches

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Abstract

The individual and combined acute toxic effects of D-limonene, menthol, aromatic compounds, and essential oils from *Salvia rosmarinus* Spenn., *Mentha spicata* L., and *Salvia sclarea* L. were evaluated against *Planococcus citri* (Risso) (Hemiptera: Pseudococcidae). Based on a comparison of lethal concentrations, menthol (LC₅₀: 0.39 g/L) and *M. spicata* L. (LC₅₀: 1.45 g/L) showed the highest efficacy, whereas D-limonene (LC₅₀: 14.67 g/L) demonstrated the lowest. The volatile oil ingredients were identified using GC–MS/FID (Gas Chromatograph–Mass Spectrometer/Flame Ionization Detector). To predict acute and synergistic effects, the performance of several supervised machine learning algorithms was assessed using K-fold cross-validation. Among the models tested, Random Forest Regression yielded the best predictive performance. Feature selection algorithms indicated that D-limonene, menthol, alpha-pinene, carvone, 1,8-cineole, and sabinene were the primary contributors to acute toxicity. Analysis of the combination index (CI), t-distributed stochastic neighbor embedding (t-SNE), and heat maps revealed that mixtures of essential oils and aromatic compounds exhibited both synergistic and antagonistic interactions. Notably, structurally similar molecules such as limonene and its cis- and trans-isomers, α-pinene and camphene, camphor and 1,8-cineole, and borneol and isoborneol were predicted to exert predominantly synergistic effects. Machine learning and traditional methods reveal that the synergistic effects of complex essential oil mixtures on *P. citri* remains insufficiently understood. Aromatic compounds and essential oils show diverse biological activities against *P. citri* and may serve as viable alternatives to synthetic pesticides in pest management strategies. Furthermore, machine learning and deep learning may offer more rapid predictions and insights into toxicity profiles.

Keywords *Planococcus citri* · Aromatic compounds · Essential oils · Machine learning · Acute toxicity

Introduction

Mealybugs are widely recognized as one of the most economically important pest groups in agricultural systems worldwide. The citrus mealybug, *Planococcus citri* (Risso) (Hemiptera: Pseudococcidae), is a major pest of citrus and cause economically important losses in other crops.

Although native to Asia, this species has spread to many regions including the Americas, Europe, and Oceania (CABI 1999). Chemical insecticides is the most commonly used method for managing mealybug populations, and compounds such as insect growth regulators, carbamates, neonicotinoids, and organophosphates are frequently applied for their control (Ulusoy et al., 2022). However, the intensive use of chemical insecticides has raised several ecological and management concerns. Repeated pesticide applications can disrupt natural enemy populations, lead to pesticide residues in agricultural products, and contribute to the development of resistance in pest populations. Indeed, resistance to several commonly used insecticides has been reported in *P. citri* populations (Mendel et al. 1999; Mruthunjayawamy et al. 2019). These challenges highlight the need for alternative pest management strategies and the development

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of novel insecticidal agents with different modes of action (Saddiq et al. 2014; Sparks and Nauen 2015).

Given the increasing global temperatures, environmental pollution, and prevalent patterns of insecticide usage, there is a vital requirement to support pest control precautions with eco-friendly frameworks, such as carbon footprint reduction, residue management, and the European Green Deal, which aims to reduce pesticide use by 50% by 2030 (Anonymous 2020). Consequently, there is a pressing demand to develop environmentally friendly agents with novel and diverse modes of action. Over the past decade, there has been a marked increase in interest in naturally derived bioactive compounds, considered viable alternatives to synthetic pesticides within integrated pest management (IPM) programmes. The low persistence of plant-based pesticides has further enhanced research in this field. Their eco-friendly nature and compatibility with IPM strategies as well as their classification under the “Generally Regarded As Safe” (GRAS) status have brought plant-derived pesticides to the forefront of sustainable pest control efforts (Alpkent et al. 2024). Recent studies have demonstrated that essential oil constituents can exhibit significant insecticidal activity against a wide range of agricultural pests, further supporting their potential as environmentally compatible pest management tools (Beniaicha et al. 2025; Usseglio et al. 2025). Essential oils are chemical cocktails composed of dozens of volatile secondary metabolites, often possessing biological activities resulting from synergistic or antagonistic interactions between their components (Isman 2020). These complex interactions make it difficult to determine which individual compounds or combinations of compounds are primarily responsible for the observed biological activity using traditional toxicological approaches (Pavela and Benelli 2021). Recent studies integrating chemical characterization and computational approaches have demonstrated that combining GC–MS profiling with *in silico* analyses can provide deeper insights into the biological activity of essential oil constituents and their interactions with insect target proteins (Lebbal 2026). Recent advances in data science and chemoinformatics have made it possible to use machine learning (ML) algorithms to analyze multidimensional chemical datasets and identify key bioactive compounds contributing to biological activity. Machine learning models are finding increasing application in natural product research, including predicting essential oil composition, biological activity, and structure–activity relationships (Cui et al. 2024; Adamczyk 2025). Recent reviews also emphasize that ML-based analytical frameworks are increasingly used to predict bioactive compound profiles and optimize essential oil applications across agricultural and biotechnological systems (Beniaicha et al. 2025). This provides researchers with powerful strategies for uncovering hidden patterns in complex chemical compositions that are difficult

to interpret with traditional statistical approaches and for identifying the key components responsible for biological activity (Chen et al. 2018; Zhou et al. 2019; Uzun and Saltan, 2024). Despite the growing body of literature on the insecticidal properties of essential oils, the specific compounds responsible for toxicity and their potential synergistic or antagonistic interactions remain poorly resolved, particularly when complex mixtures are evaluated using conventional analytical approaches (Hummelbrunner and Isman 2001; Pavela 2008; Koul et al. 2013). Furthermore, only a limited number of studies have attempted to integrate biological assays with chemoinformatics and machine learning techniques to identify the key drivers of insecticidal activity within essential oil mixtures. Therefore, a systematic framework combining chemical profiling, bioassays, and machine learning-based feature selection may provide new insights into the mechanisms underlying essential oil toxicity and facilitate the identification of key bioactive compounds.

In this context, combining biological assays with chemical profiling and computational analysis represents a promising strategy for investigating the insecticidal activity of complex plant-derived mixtures. Therefore, the present study aimed to investigate the acute, synergistic, and antagonistic effects of selected aromatic compounds and essential oils against *Planococcus citri* using an integrative framework combining bioassays, GC–MS chemical characterization, machine learning modelling, and chemoinformatics-based molecular similarity analysis. This study aims to identify the key compounds driving insecticidal activity and to clarify the relationship between essential oil composition and biological efficacy, thereby providing a data-driven framework for the discovery and optimisation of botanical insecticides.

Materials and methods

The test material menthol (CAS No: 1490–04–6), with a purity of 96%, was purchased from Sigma-Aldrich. Essential oils of *D-limonene*, *Salvia rosmarinus* Spenn., *Mentha spicata* L., and *Salvia sclarea* L. were obtained by the company Biomesi R&D (Technopark of Çukurova University) through cold pressing and distillation methods. The essential oil components were identified using a Gas Chromatograph–Mass Spectrometer/Flame Ionisation Detector (GC–MS/FID) system. In the preparation of the essential oil mixtures used as test materials, Tween 20, 40, and 60 were employed as emulsifiers.

Collection and rearing of *Planococcus citri*

The primary insect material, *Planococcus citri*, was obtained from the Biological Control Research Institute Directorate in Adana, Türkiye, where it had previously been identified

and reared. The mealybugs were cultured in the climate chambers of the Biological Control Laboratory (ESBIO-CONTROL) at the Department of Plant Protection, Faculty of Agriculture, Eskişehir Osmangazi University. The mealybugs were maintained on fresh potato sprouts in trays and containers under controlled conditions of 26 ± 2 °C, 65% relative humidity, and a 16:8 h light:dark photoperiod in climate chambers.

Gas chromatography-based chemical profiling of essential oils

Essential oil composition: The essential oil composition of samples was analyzed by gas chromatography (Agilent 7890A) coupled by flame ionization detector and mass spectrometry (Agilent 5975C) using capillary column (HP Innowax Capillary; 60.0 m \times 0.25 mm \times 0.25 μ m). Essential oils were diluted in a 1:50 ratio with hexane. GC-MS/FID analysis was carried out at split mode of 40:1. Injection volume and temperature were adjusted as 1 μ L and 250 °C, respectively. Helium was the carrier gas at a constant flow rate of 0.8 mL/min. The oven temperature was programmed as follows: 60 °C for 10 min, increased at 4 °C/min to 220 °C, and held at 220 °C for 10 min. MS spectra were monitored between 35 to 450 amu and the ionization mode used was electronic impact at 70 eV. The relative percentage of the components was calculated from GC-FID peak areas, and components were identified by Wiley 7 and Oil Adams Libraries (Uysal Bayar and Çınar, 2020).

Insecticide bioassay trials

Bioassay trials were established with modifications to the methodologies described by IRAC (2021) and Prabhaker et al. (2012). In these assays, adult female individuals of *P. citri* were used. Except for the control group, a minimum of four replicates and six different concentrations were tested for each insecticide dose. The essential oils were diluted to the following concentrations and used in the bioassay experiments: D-limonene (0.5, 1, 2, 3, 4, 6, 10, 18, and 36%), menthol (0.02, 0.04, 0.08, 0.1, 0.25, 0.5, 1, and 2%), *Salvia rosmarinus* Spenn. (0.1, 0.25, 0.4, 4, 7, and 14%), *Mentha spicata* L. (0.1, 0.25, 0.4, 0.5, 1, 2, and 4%), and *Salvia sclarea* L. (0.5, 1, 2, 4, 7, and 14%). Tween 20, Tween 40, and Tween 60 were used as emulsifiers to facilitate the dispersion of the essential oils in water. Distilled water was used for the control treatment. For each replicate, at least 20 adult females were carefully transferred using a fine-tipped sable brush into empty Petri dishes (30 mm in diameter) with aeration holes. Insecticide solutions of varying concentrations were applied using a Spray Tower delivering 2 ml (equivalent to 1.89 ± 0.25 mg cm⁻²) per dish at a pressure of 101.3 kPa. Following application, the Petri dishes were

allowed to dry for 30 min before being placed into climate chambers. Mortality assessments were conducted 72 h post-treatment. Trials in which the mortality rate in control dishes exceeded 15% were deemed invalid and repeated.

The assessment of the synergistic effects of essential oil mixtures

To determine the antagonistic and synergistic effects of essential oil mixtures on *Planococcus citri*, various combinations of essential oils were prepared at different ratios. The bioassays were conducted using five-component mixtures, formulated in varying proportions based on their LC₁₅ concentrations (as presented in Table 4). The Combination Index (CI) was calculated according to the method proposed by Chou (2006), wherein a CI value of less than 1.0 indicates synergistic interaction, a CI equal to 1.0 denotes an additive effect, and a CI greater than 1.0 signifies antagonistic interaction. This index enabled a quantitative assessment of the interactions between essential oils and was calculated using CompuSyn software version 1.0.1.

Data analysis

Dose-response probit analyses in the bioassay experiments were performed using the Polo-Plus software programme (Leora Software, Berkeley, CA, USA). The LC₅₀ values were calculated individually for each essential oil. Machine learning algorithms were implemented using Python, employing the Scikit-learn (Sklearn) library as the primary tool for computational modelling.

Compounds acute toxicity prediction model using ensemble strategy

In this study, the dataset used for machine learning consisted of the chemical composition profiles of the tested essential oils and the corresponding mortality rates obtained from the bioassay experiments. Each sample represented an essential oil treatment characterized by the relative abundance (%) of its major chemical constituents determined by GC-MS/FID analysis. These component ratios were used as independent variables (X). The dependent variable (Y) corresponded to the observed mortality rate of *Planococcus citri* following exposure to the essential oil treatments. Therefore, the machine learning models were trained to capture the relationship between essential oil composition and insecticidal activity rather than individual compound concentrations in artificially designed mixtures. To find out the relationship between the primary (independent) variables and the outcome (dependent) variables in the study, and to optimise model performance, ten distinct supervised machine learning algorithms were applied. For this purpose, the performance

of the following supervised learning models was evaluated: Multiple Linear Regression (MLR), Random Forest Regression (RFR), Gradient Boosting Regression, Extreme Gradient Boosting Regression (XGBRegression), Decision Tree Regression (DTR), AdaBoost Regression (ABR), Support Vector Machine Regression (SVR), Least Absolute Shrinkage and Selection Operator Regression (Lasso), and Ridge Regression (Gambella et al. 2021).

K-fold cross validation

In this study, K-fold cross-validation, a hyperparameter tuning approach commonly used in machine learning (ML), was applied. Through this method, the most optimised ML algorithms were tested to reveal the effects of essential oil components responsible for mortality rates and synergistic interactions. Hyperparameter tuning via K-fold cross-validation is a technique applied to evaluate a model's generalisability and performance on unseen data sets (Burman 1989). Compared to conventional ML applications, this approach helps to prevent overfitting between training and testing datasets by partitioning the dataset into k equally sized, non-overlapping subsets. Each subset is used in turn as a validation or test set, while the remaining $k-1$ subsets serve as the training data, and the average model performance is computed (Cawley Talbot, 2010; Fushiki 2011; Jung 2018).

Similarity screening

To evaluate the structural similarity of the molecules comprising the essential oils and to perform dimensionality reduction, the RDKit cheminformatics toolkit was applied (Landrum 2013). The SMILES (Simplified Molecular Input Line Entry System) strings of each molecule were converted into Morgan fingerprints. Molecular similarities were then quantified using the Tanimoto coefficient. Additionally, t -Distributed Stochastic Neighbour Embedding (t-SNE) was applied to project the fingerprint data into a two-dimensional space, thereby facilitating the visualisation of molecular clusters and patterns. The similarity matrix was rendered as a heatmap, with each cell representing the Tanimoto

coefficient between pairs of molecules (Babicki et al. 2016; Wilkinson & Friendly, 2009).

Model evaluation parameters

To assess the performance of the various predictive modelling approaches (machine learning) employed in this study, the following statistical metrics were utilised: Mean Squared Error (MSE), Mean Absolute Error (MAE), and Root Mean Squared Error (RMSE) (Piñeiro et al. 2008).

Feature selection

Feature selection involves identifying the optimal subset of variables that exert the most significant influence on the predicted outcomes. This subset can be used to enhance model performance and reduce computational time (Saeys et al., 2008). For this purpose, the Random Forest Regression (RFR), algorithm identified as the best-performing ML model, was utilised to rank the importance of features in relation to their contribution to acute toxic effects (Dhal and Azad 2022).

Results

The acute toxicological effects of essential oils on *Planococcus citri* were examined, revealing that menthol exhibited the highest efficacy (LC_{50} : 0.39 g/L), whereas limonene demonstrated the lowest lethality (LC_{50} : 14.67 g/L) (Table 1). Analysis of the essential oil components via GC-MS data indicated that in *Salvia rosmarinus* Spenn., α -pinene (28%), camphor (22%), 1,8-cineole (21%), and limonene (20%) were the predominant constituents. In *Mentha spicata* L., limonene (54%) and carvone (27%) were most abundant, whereas *Salvia sclarea* L. contained higher concentrations of α -pinene (13%), camphor (13%), and 1,8-cineole (24%) (Table 2).

Across all three essential oils (*Salvia rosmarinus* Spenn., *Mentha spicata* L., and *Salvia sclarea* L.), α -pinene, 1,8-cineole, and limonene consistently emerged as major common components in substantial quantities (Table 2).

Table 1 LC_{50} , LC_{90} (values of essential oils applications bioassays of *Planococcus citri*)

Essential oil	n ^a	Slope \pm SE ^b	LC_{50} (g/L) (0.95 CI ^c)	LC_{90} (g/L) (CI)	χ^2 (dF) ^d
<i>D-Limonene</i>	380	3.69 \pm 1.26	14.67 (6.11–19.94)	32.62 (23.74–39.10)	0.27(4)
<i>Menthol</i>	385	3.48 \pm 1.07	0.39 (0.20–0.55)	0.91 (0.63– 2.54)	0.19(3)
<i>Salvia rosmarinus</i> Spenn	400	1.70 \pm 0.54	3.20 (1.15–6.75)	17.17 (7.44–30.84)	0.73(3)
<i>Mentha spicata</i> L	360	2.12 \pm 0.69	1.45 (0.36–2.36)	5.84 (3.55–11.28)	1.21(4)
<i>Salvia sclarea</i> L	405	2.97 \pm 0.89	10.81 (5.45–16.31)	29.19 (18.86–41.83)	0.29(3)

^an: Total number of individuals, ^bSE: standard error, ^cCI: confidence interval, ^ddF: degrees of freedom

Table 2 GC–MS data of the components of the essential oils of *Salvia sclarea*, *Mentha spicata* L. and *Salvia rosmarinus* Spenn. respectively

Compounds	Salvia sclarea		Mentha spicata		Salvia rosmarinus Spenn	
	Retention Time	(%)	Retention Time	(%)	Retention Time	(%)
α -pinene	12.93	13.82	12.9	3.89	13.03	28.22
α -thujene	13.08	0.42	–	–	–	–
Camphene	14.86	4.98	–	–	14.85	6.60
β -pinene	16.79	5.39	16.7	0.91	16.67	3.24
β -myrcene	19.41	2.07	19.4	1.13	–	–
Limonene	21.27	2.17	21.33	54.00	8.38	20.82
1,8-Cineole	21.74	24.99	21.72	5.77	21.31	21.20
Gamma-terpinene	23.55	0.42	–	–	–	–
Cymene	24.81	1.48	24.82	1.01	23.89	2.29
β -thujone	32.50	3.73	–	–	–	–
Camphor	35.67	13.71	–	–	33.40	22.16
Linalool	35.88	0.43	–	–	–	–
Bornyl acetate	37.70	1.70	–	–	–	–
β -Caryophyllene	38.54	7.54	38.53	1.49	35.88	0.64
α -humulene	41.11	2.81	–	–	–	–
Borneol	41.78	1.80	–	–	38.66	1.35
α -Terpinene	–	–	20.33	0.92	–	–
Menthole	–	–	33.45	2.30	–	–
Menthol	–	–	39.49	1.57	–	–
Carvone	–	–	43.32	27.00	–	–
β -Terpineol	–	–	–	–	36.42	0.16
Isoborneol	–	–	–	–	37.69	0.53
α -Terpineol	–	–	–	–	38.44	2.09
Gamma-Terpineol	–	–	–	–	38.51	0.45
α -Ocimene	–	–	–	–	38.58	0.98
Caryophyllene oxide	–	–	–	–	46.78	0.37

Distinctively, camphor (22%) was notably abundant in *Salvia rosmarinus* Spenn., while carvone (27%) was predominantly found in *Mentha spicata* L. To reveal the similarity relationships among the molecules constituting the essential oils, a Tanimoto similarity index analysis was performed on 23 molecules using the RDKit Python library, widely applied in chemoinformatics (Fig. 1A). The similarity results were subsequently visualised in two dimensions using the dimensionality reduction technique t-Distributed Stochastic Neighbour Embedding (t-SNE) (Fig. 1B). The three common major components, α -pinene, 1,8-cineole, and limonene, were observed to show considerable molecular dissimilarity. Molecules such as limonene-cis/trans isomers, alpha-pinene-camphene, camphor-1,8-cineole, and borneol-isoborneol demonstrated closer similarity relationships. Borneol and isoborneol were identified as essentially identical molecules. Menthol was noted to be more distantly related to the other molecules in terms of similarity. Model performance for explaining acute toxic and synergistic effects was assessed using the K-fold cross-validation method (Fig. 2). Error metrics including Mean Squared Error (MSE), Root Mean Squared Error (RMSE), and Mean Absolute Error

(MAE) were applied to evaluate predictive accuracy, with model selection based on the principle of the lowest error values (Table 3). The Random Forest Regression (RFR) model was identified as the optimal predictive model for mortality estimation. Feature importance analysis via the RFR model revealed that limonene was the most influential molecule affecting mortality rates, followed by menthol, carvone, and α -pinene (Fig. 3). Figure 5 illustrates the mixture design, indicating that mixtures 5, 6, 7, and 8 exhibited synergistic effects ($CI < 1$), whereas the other mixtures displayed antagonistic effects ($CI > 1$) (Table 4).

Discussion

This study aims to apply phytochemicals as safer, more environmentally friendly, and more effective alternatives to conventional pesticides in the management of the citrus mealybug (*Planococcus citri*). The present study integrates bioassay experiments, GC–MS chemical profiling, machine learning modeling, and chemoinformatics-based similarity analysis to better understand the insecticidal potential of

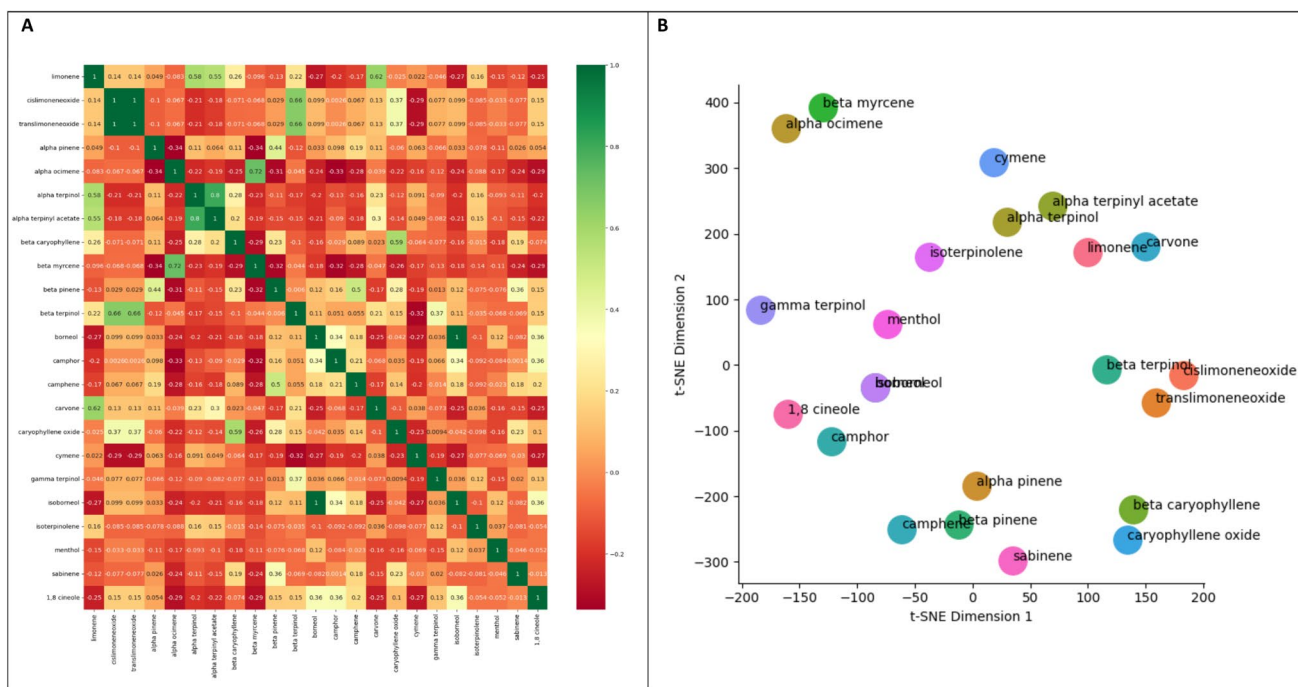


Fig. 1 Molecular clustering analysis. **A**, The SMILES strings of each molecule were converted to Morgan fingerprints using RDKit. Similarity between molecules was quantified using the Tanimoto coefficient. Similarity matrix was visualized as a heatmap, with each cell

displaying the Tanimoto coefficient. **B**, T-distributed stochastic neighbor embedding (t-SNE) was used to visualize fingerprint similarities in a scatter plot, where each dot represents a unique hit compound

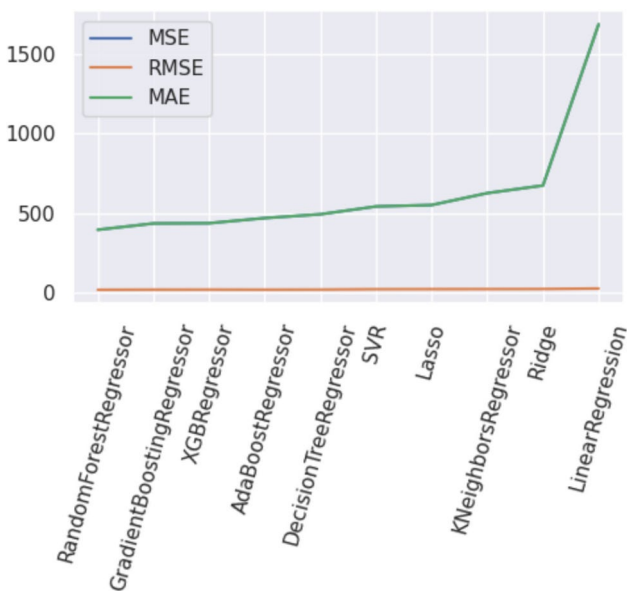


Fig. 2 Mortality efficiency prediction performance of different models with K-Fold cross-validation in essential oil compounds

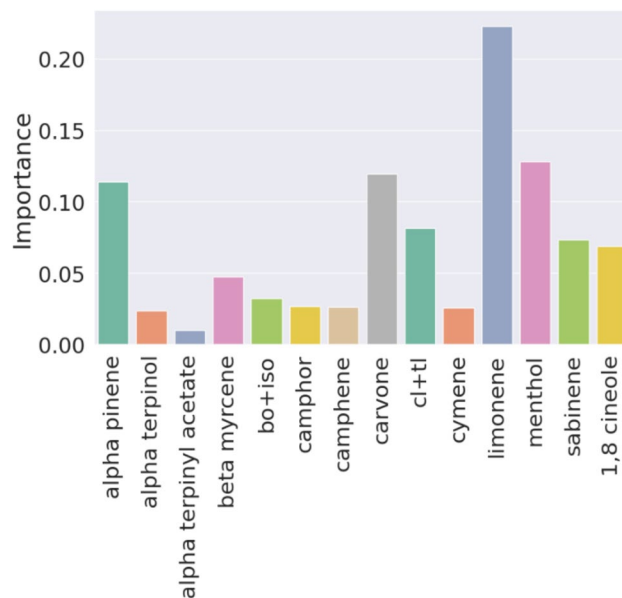


Fig. 3 Feature importance of essential oil compounds. Mortality efficiency were observed with Random Forest Regression

essential oils against *Planococcus citri*. Botanical insecticides often exhibit complex biological activity because essential oils are composed of multiple bioactive compounds that may act additively, synergistically, or antagonistically.

Traditional toxicological approaches generally evaluate the activity of whole extracts or individual compounds but often fail to identify which constituents contribute most strongly to biological effects. By combining GC–MS compositional

analysis with machine learning approaches, it becomes possible to quantitatively link chemical composition with biological outcomes such as insect mortality. In addition, chemoinformatics methods such as molecular fingerprints and Tanimoto similarity provide complementary insights into structural relationships among compounds that may influence their biological activity. Similar integrative approaches have recently been proposed as powerful tools for discovering bioactive natural products and understanding complex phytochemical interactions in botanical insecticides (Pavela, 2015; Pavela, 2016; Isman 2020). Accordingly, the toxicity and synergistic activities of certain plant-derived active compounds and their combinations against *P. citri* were investigated. Generally, the biological activities of plant essential oils (EOs) are attributed to the synergistic nature of their various active components, which can be applied individually or in mixtures for pest control (Anaya-Eugenio et al. 2016; Afshar et al. 2017; Pavela & Benelli 2021). Unlike previous EO efficacy studies on *P. citri*, this work specifically demonstrated the lethal effects of the pure active compounds menthol and D-limonene. Throughout the study, D-limonene exhibited acute toxicity against *P. citri* with an LC₅₀ value of 14.6 g/L (Table 1), while prior research reported a mortality rate of up to 70% at a 1% (10 g/L) limonene concentration (Hollingsworth 2005). Menthol was identified as the most potent molecule in this study, with an LC₅₀ of 0.39 g/L (Table 1). The pronounced lethality of menthol may be attributable to its low molecular weight, propensity to volatilize at ambient temperature, and the likelihood of rapid penetration into the insect's physiology. The *Mentha* genus (mint) is reported to contain natural compounds such as ketone monoterpenes, which induce mortality in insects and enhance the overall lethality of their constituent compounds (Khadem et al. 2022). Furthermore, molecules like menthol have been suggested to compete with octopamine, a neurophysiologically active compound in insects, potentially explaining rapid mortality even at low doses (Devrnja et al. 2022; Höld et al. 2000; Iqbal et al., 2022). Similar studies on mealybugs have documented the lethal activities of essential oils. The acute toxicity, repellent properties, and enzyme inhibitory effects of various plant-derived essential oils have been investigated across multiple mealybug species within the family Pseudococcidae. Specifically, the acute toxicity of *Eucalyptus lesouffii*, *Mentha pulegium*, *Thymus vulgaris*, and limonene against *P. citri* has been documented (Hollingsworth 2005; Attia et al. 2022; Cloyd et al. 2009; Khedhri et al. 2023). Moreover, Erdemir and Erler (2018) reported repellent effects of *Mentha piperita*, *Origanum onites*, and *Salvia rosmarinus* Spenn. against *P. citri*. Acute toxic effects of EOs have also been recorded in several other Pseudococcidae pests, including *Maconellicoccus hirsutus* (El-Ashram et al. 2020), *Phenacoccus solenopsis* (Ghada and Naglaa 2020; Abasse 2018),

Dysmicoccus brevipes (Martins et al. 2017), *Planococcus ficus* (Peschiutta et al. 2017), *Pseudococcus jackbeardsleyi* (Pumnuan and Insung 2016), and *Paracoccus marginatus* (Sifa et al. 2013). Additionally, acetylcholinesterase and glutathione S-transferase inhibitory effects of certain monoterpenoid mixtures (ocimene and β -myrcene) have been reported in *Planococcus lilacinus* (Arokiyaraj et al. 2022). However, individual assays and synergistic effect studies of EO mixtures involving *Salvia sclarea* L., *Mentha spicata* L., and *Salvia rosmarinus* Spenn. on *P. citri* remain limited. Considering the chemical composition (GC–MS analyses), acute toxicity, and mixture studies of all EOs employed in this research, α -pinene, 1,8-cineole, D-limonene, menthol, camphor, and carvone were identified as the major distributed compounds (Tables 1, 2; Fig. 4). Furthermore, feature importance ranking derived via Random Forest Regression (RFR) modelling ($R^2 = 0.50$) implicated D-limonene, menthol, α -pinene, carvone, 1,8-cineole, and sabinene as principal contributors to lethality (Fig. 3). This concurs with reports indicating the heightened mortality effects of these actives against various pests within the Pseudococcidae family (Prabhaker et al. 2012). Erdemir and Erler (2018) reported repellent effects of *Mentha piperita* rich in menthol (70.08%), *Origanum onites* rich in carvacrol (48.0%), and *Salvia rosmarinus* Spenn. containing 1,8-cineole (44.97%) and camphor (10.79%) against *P. citri*. Additionally, Attia et al. (2022) documented the acute toxicity of *Mentha pulegium*, characterized by a high menthone content (26.3%), while Khedhri et al. (2023) reported significant acute toxicity of *Eucalyptus lesouffii*, containing 67.9% 1,8-cineole, against *P. citri*. The Random Forest regression model identified several monoterpenoid compounds as major contributors to the observed mortality patterns. Monoterpenes such as limonene, menthol, camphor, and 1,8-cineole have been widely reported to exhibit neurotoxic effects against different insect taxa. For instance, limonene has demonstrated strong fumigant and contact toxicity against stored-product pests such as *Sitophilus zeamais* and *Tribolium castaneum*, where it has been associated with disruption of neural transmission and interference with octopaminergic signaling pathways (Enan 2001; Isman 2020; Iqbal et al., 2022). Similarly, 1,8-cineole has shown significant insecticidal activity against agricultural pests including *Spodoptera litura* and *Bemisia tabaci*, with studies suggesting that its toxicity may involve inhibition of acetylcholinesterase and increased permeability of insect cuticle tissues (Pavela, 2016; Regnault-Roger et al., 2012). Camphor has also been reported to exhibit fumigant toxicity against *Callosobruchus maculatus* and *Sitophilus oryzae*, where its mode of action has been linked to neurophysiological disruption and respiratory inhibition (Koul et al. 2008). In addition, menthol and structurally related monoterpenoids have demonstrated insecticidal effects against several hemipteran pests, including aphids

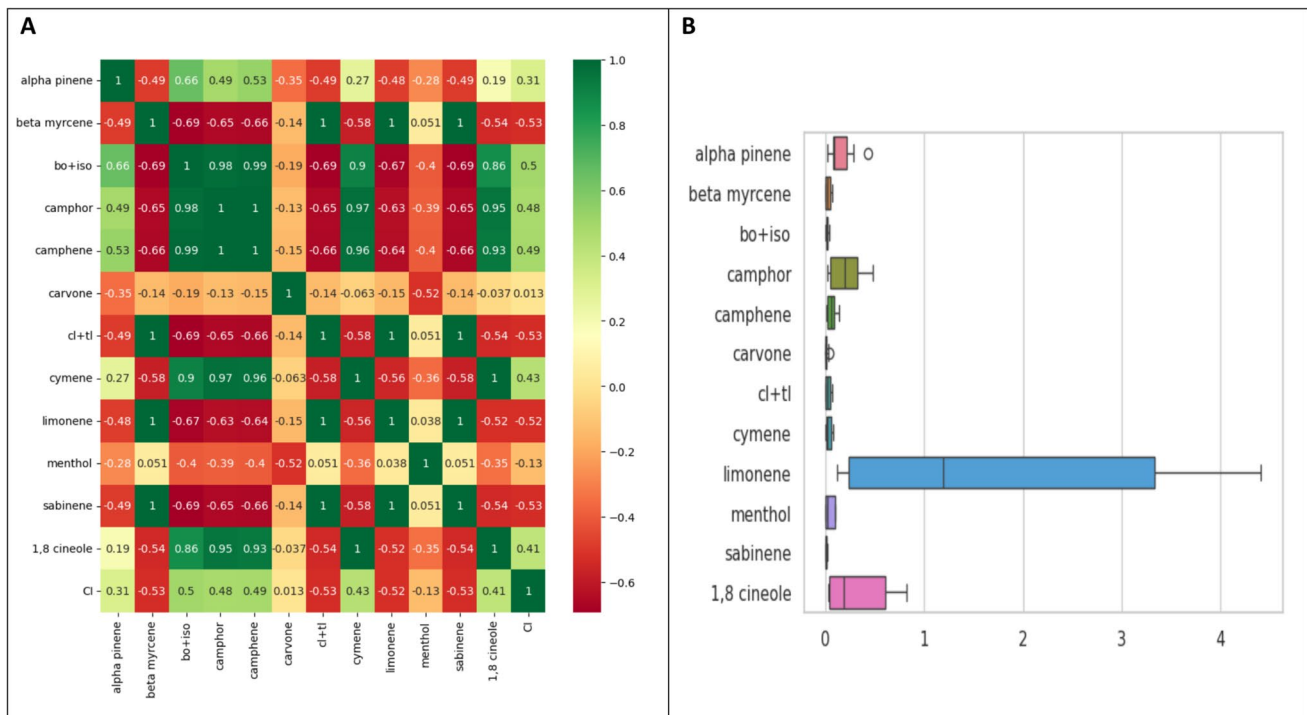


Fig. 4 A. Similarity matrix was visualized as a heatmap, EO molecules correlation with combination index B. Boxplot of essential oil some components distribution in mixtures

and whiteflies, possibly through modulation of GABA-gated chloride channels and other neuroreceptors involved in insect neurotransmission (Enan 2005; Pavela & Benelli 2016; Iqbal et al., 2022). The occurrence of these compounds as major constituents in the tested essential oils is therefore consistent with the high mortality observed in the bioassay experiments. Consequently, the feature importance results obtained from the Random Forest model provide a biologically meaningful interpretation of the toxicity data and suggest that these monoterpenoid constituents likely act as key toxic effect molecules contributing to the insecticidal activity against *Planococcus citri*. This present research used Random Forest algorithms and attained an R^2 value of 0.50. Previous studies have demonstrated superior predictive performance ($R^2 = 0.99$) using ensemble algorithms and varied implementations in agriculture (Gu et al. 2020; Fredj et al. 2021). Expanding the dataset could enhance algorithm training on more samples, thereby improving prediction accuracy (Mendes-Moreira et al. 2012; Chen et al. 2018). Moreover, deep learning approaches have recently garnered increasing attention, complementing traditional regression models (Upadhyay et al., 2025). Synergistic effects of the EO mixtures were predominantly observed (Combination Index, $CI < 1$) (Fig. 5). Nonetheless, the antagonistic-synergistic variability among mixtures may stem from the complex interaction of diverse molecules present in varying proportions within the EOs, as well as from physiological

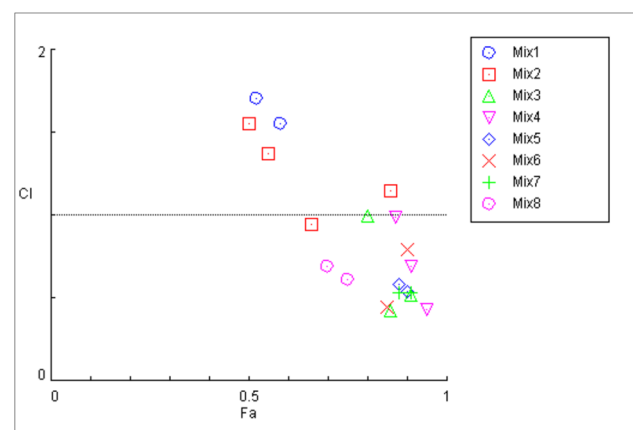


Fig. 5 Mixed essential oils Combination Index Plot

mechanisms in the target pest that are not yet fully understood. Examination of the correlation heatmap between molecules and CI values revealed that chemically similar molecules tend to cluster within the same correlation groups (Fig. 4A). Specifically, limonene-cis/trans isomers, α -pinene-camphene, camphor-1,8-cineole, and borneol-isoborneol pairs exhibited high Tanimoto similarity coefficients and proximity on the t-SNE scale, indicating strong chemical resemblance (Fig. 1A, B). These molecular similarities suggest that closely related compounds might exert

comparable synergistic or antagonistic effects (Zhang et al. 2025). Overall, isolated major components have been found to reflect the biophysical and biological properties of their parent essential oils with reasonable reliability (Ipek et al. 2005; Lebbal 2026), yet the spectrum of activity varies depending on whether the constituents act alone or in concert at different concentrations. Therefore, the synergistic functions of multiple molecules within an EO may account for observed discrepancies when compared to the effects of one or two isolated major components. Moreover, the activities of primary components may be modulated by minor components (Franzios et al. 1997; Santana-Rios et al. 2001; Hoet et al. 2006; Bakkali et al. 2008; Usseglio et al. 2025). In this context, examining the entire EO rather than select components provides more informative insights for biological applications, given the meaningful role of synergism. Considering the study findings along machine learning methodologies and conventional approaches, the potential synergistic effects of single or combined EO mixtures on *P. citri* mortality remain incompletely understood. This may be

due to the physiological influence of terpenes and their derivatives via the octopaminergic system. The data suggest that EOs possess the capacity to elevate intracellular cyclic adenosine monophosphate (cAMP) and calcium levels within neuronal cells. Furthermore, electrophysiological studies conducted on *Periplaneta americana* and related models have identified competitive binding and similarity between EO components and octopamine receptors (Devrnja et al. 2022; Höld et al. 2000; Stankiewicz et al. 2012; Shaaya and Rafaeli 2007). The findings of the present study confirm that aromatic compounds and essential oils exhibit diverse biological activities against *P. citri* and may serve as viable alternatives to synthetic pesticides in pest management. Moreover, it can be inferred that emerging methodologies such as machine learning and deep learning offer promising avenues for the rapid prediction and assessment of toxicity, thereby facilitating more efficient decision-making processes.

Conclusion

This study demonstrates the potential of plant-derived essential oils and their monoterpene components as effective, environmentally friendly alternatives to synthetic insecticides in the management of the citrus mealybug, *Planococcus citri*. Through an integrative framework combining GC–MS analysis, toxicity bioassays, machine learning modelling, and chemoinformatics-based similarity analysis, the present study provides a comprehensive evaluation of both the individual and combined effects of essential oil components. Among the tested compounds, menthol exhibited the highest toxicity ($LC_{50} = 0.39$ g/L), distinguishing it as a key bioactive compound with rapid and potent insecticidal activity. Mixture-based analyses further revealed that insecticidal efficacy is strongly dependent on interactions among components, with specific combinations producing pronounced

Table 3 Model performance error metrics in mortality efficiency

Model_Tested	KF_MSE	KF_RMSE	KF_MAE
RandomForestRegressor	394.6	16.6	394.6
GradientBoostingRegressor	434.4	17.5	434.4
XGBRegressor	435.8	17.8	435.8
AdaBoostRegressor	468.2	17.2	468.2
DecisionTreeRegressor	492	17.8	492.0
SVR	541.4	20.1	541.4
Lasso	550.5	20.6	550.5
KNeighborsRegressor	625.4	20.9	625.4
Ridge	673.2	21.5	673.2
LinearRegression	1688.3	24.7	1688.3

MSE; Mean squared error, RMSE; Root mean squared error, MAE; Mean absolute error

Table 4 Essential oil mixture design and combination index means

	Menthol	<i>Mentha spicata</i> L	<i>Salvia rosmarinus</i> Spenn	<i>Salvia sclarea</i> L	D-Limonen	CI Mean
Mixture 1	1	0	1	1	1	1.6
Mixture 2	1	1	1	1	0	1.3
Mixture 3	1	1	1	0	1	1.3
Mixture 4	1	0	0	1	1	0.7
Mixture 5	1	1	1	0	1	0.6
Mixture 6	1	0	1	0	1	0.6
Mixture 7	0	1	1	1	1	0.5
Mixture 8	0	1	0	1	1	0.7

CI: Combination Index

synergistic effects ($CI < 1$), particularly in Mixtures 5, 6, and 7 ($CI = 0.6–0.5$), while other combinations exhibited antagonistic effects. Machine learning models, particularly Random Forest regression, demonstrated superior predictive performance and enabled the identification of key compounds driving mortality responses, while dimensionality reduction techniques such as t-SNE and similarity-based analyses (Tanimoto coefficient) supported the relationship between molecular structure and biological activity. These findings provide a robust, data-driven framework for interpreting complex mixture effects and for the targeted screening and optimization of botanical insecticides. Overall, the integration of experimental toxicology with computational modelling represents a powerful and scalable strategy for decoding the complexity of essential oil mixtures and accelerating the development of novel bioinsecticides. In particular, synergistically active mixtures identified in this study highlight the importance of interaction-driven efficacy and offer promising candidates for formulation development aimed at reducing reliance on conventional synthetic insecticides. Further studies involving field trials and formulation optimization are recommended to transfer these findings into practical agricultural applications.

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Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate Not applicable.

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