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A machine learning–assisted analysis of essential oil constituents targeting *Salmonella* Typhimurium

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ABSTRACT:
Some essential oils (EOs) have exhibited high efficacy against *Salmonella* Typhimurium, suggesting that specific molecular structures within their constituents could inform the development of alternative antimicrobial agents, potentially addressing the rise of antibiotic resistance in this bacterium. Through feature permutation analysis on a dataset of 171 EO samples encompassing 682 molecular substructures, we identified ten key predictors of antibacterial activity against *S.* Typhimurium. These predictors were used to train a logistic regression-based machine learning model. Hydroxyl-substituted benzene rings characteristic of phenolic compounds - such as carvacrol, thymol and eugenol - emerged as strong predictors of antibacterial activity. In contrast, non-aromatic bicyclic structures present in monoterpenoids like alpha-pinene, beta-pinene and delta-3-carene were associated with a lack of efficacy against *Salmonella*. The molecular features identified align with existing research on the antimicrobial properties of phenolic compounds, thereby validating the use of machine learning approaches in guiding the discovery of naturally occurring antimicrobial agents.

Keywords: antibacterial activity, Morgan fingerprints, phenols, classification, logistic regression, substituted benzene compounds

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INTRODUCTION

Non-typhoidal Salmonella (NTS) infections, including those caused by *Salmonella enterica* serovar Typhimurium, result in approximately 93.8 million gastroenteritis cases and 155,000 deaths globally each year (Gong *et al.* 2022). The rise of antibiotic resistance in *S.* Typhimurium is driving research into alternative prevention and treatment methods (Wang *et al.* 2022). Plants have evolved sophisticated defence mechanisms against bacterial infections, including physical barriers and the production of secondary metabolites which repel or destroy harmful organisms (Freeman & Beattie 2008). These compounds have been extensively studied. From 2005 to 2024, there was a 13% average annual increase in published research on the antimicrobial activity (AA) of essential oils (EO) (Fig. 1). Advanced computational methods have enabled new insights from this growing body of research.

Yabuuchi *et al.* (2023) demonstrated the effectiveness of machine learning (ML) algorithms in identifying bioactive compounds in EOs effective against *Staphylococcus aureus*. The study identified several active compounds, including perillyl alcohol, daphnoretin, and xanthohumol. Similarly, Artini *et al.* (2018) used a ML model to predict EO efficacy in disrupting the biofilms of

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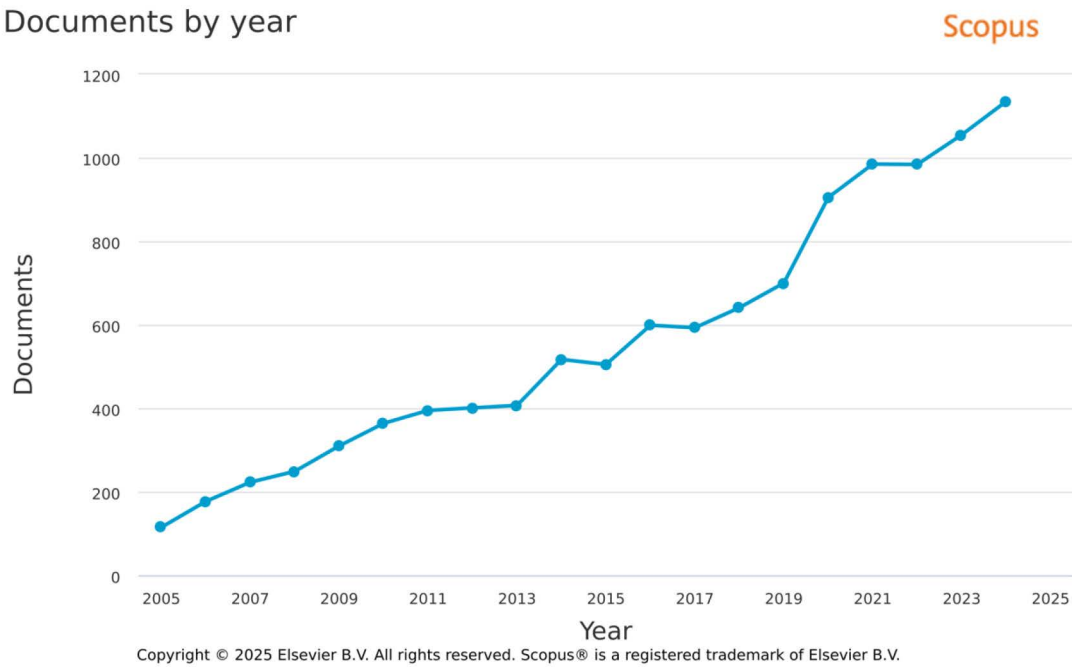


Fig. 1. The publication trend from 2005 to 2024 for scientific articles focusing on the antimicrobial activity of essential oils, based on data retrieved from Scopus using "essential oils" and "antimicrobial activity" as the keywords. Accessed in January 2025.

Pseudomonas aeruginosa, identifying estragole and phellandral as the key components for inhibition, while d-limonene and pulegone were linked to biofilm production. A recent study by (Barros de Menezes *et al.* 2022) showed the use of ML to identify bioactive EO compounds from Cuban plants with potential anti-protozoan properties.

Certain EOs are particularly effective against *S.* Typhimurium (Fitsiou *et al.* 2018; Ebani *et al.* 2019; Lin *et al.* 2021). Key components, such as cinnamaldehyde and eugenol, have been shown through laboratory testing to contribute to EO efficacy (Purkait *et al.* 2020). However, there is limited data on which structural characteristics of EO constituents contribute to their effectiveness against *S.* Typhimurium. This is mainly due to the challenges of extracting, concentrating and testing the individual compounds present in EOs. To address this gap, we trained a logistic regression ML model to identify common molecular substructures in EOs with AA against *S.* Typhimurium (Morgan 1965).

Despite the fact that numerous EOs exhibit strong antimicrobial effects in labs, their hydrophobic nature reduces effectiveness in real-world food environments, especially with fats (Hyldgaard *et al.* 2012). Factors such as pH, temperature and contamination levels also affect their potency. This study identifies specific molecular substructures linked to the enhanced AA of EOs against *S.* Typhimurium, guiding future food preservation formulations. Our approach merges cheminformatics with machine learning, thus offering a new method to analyse decades of archived data. This novel strategy not only confirms existing findings, but also reveals fresh leads in the search for new antimicrobial agents inspired by the potent natural antimicrobials found in EOs, emphasising the role of local flora in drug discovery.

This study aimed to identify the structural configurations of EO components correlated with AA, excluding concentration effects.

MATERIALS AND METHODS

Acquiring data on the chemical composition and antimicrobial activity of essential oils. The computations were performed using Python 3.9 (https://www.python.org/) on Jupyter Notebook (version 6.5.6). The chemical composition data for the EOs was obtained from an open-access database (https://essentialoils.org/). The plant species considered were selected based on existing literature, representing common sources of EOs with botanical and pharmacological relevance. A literature review identified 87 EO samples with significant AA against *S.* Typhimurium, either through IC50 values below 100 µg/mL or effectiveness in disc diffusion assays with 1 µg of EO or less. The remaining 84 samples showed little or no activity or were not reported. EOs can contain over 100 distinct compounds, many of which are present in trace amounts, increasing computational load and hindering meaningful insights. Thus, only those compounds with a quantitative significance above 10% were analysed. The dataset, including references to the corresponding studies, is available on Zenodo (https://doi.org/10.5281/zenodo.12684760).

Acquiring Morgan molecular fingerprints. The chemical names were converted into SMILES strings (Simplified Molecular Input Line Entry System) (Weininger 1988). In this study, several open-access databases were used to obtain SMILES notations of EO compounds (Gaulton *et al.* 2012; Hastings *et al.* 2016; Kim *et al.* 2023). Morgan fingerprints represent molecules as binary vectors, indicating the presence or absence of molecular features (Morgan 1965). SMILES strings were converted into 2048-bit binary vectors with a radius of two using the RDKit library (Linstrom & Mallard 2001; Landrum 2024). A radius of two includes each atom's immediate neighbours and their adjacent atoms. Columns of zeros, indicating absent substructures, were removed to reduce dimensionality. The final dataset comprised 171 EO samples and 682 molecular descriptors, with a target column indicating AA against *S.* Typhimurium.

Machine Learning. Due to the dataset's small size (<200 observations), a regularised logistic regression model was chosen to avoid overfitting (Araújo *et al.* 2023; Dudek *et al.* 2024). An L1 penalty with SAGA solver, with a regularisation parameter (C) set to 1.75 was used. The calibration curve was used to fine-tune C, targeting a slope close to 1 (accurate predictions) and an intercept close to 0 (unbiased predictions). Following Eertink *et al.* (2022), repeated stratified cross-validation (5 folds, 100 repeats) was employed to assess model performance with metrics such as accuracy, ROC AUC, sensitivity, specificity, precision, NPV, MCC and F1 score. Bootstrapping (1000 iterations) was applied to estimate coefficient stability and feature importance, as shown in Table 1 and Figs. 2–5. Molecular substructures were visualised using the Chem package from RDKit (Landrum 2024).

Table 1. Train and test metrics of the final logistic regression model.

Dataset	Accuracy	Sensitivity	Specificity	PPV	NPV	F1 Score	MCC	ROC AUC
Train	0.84	0.87	0.82	0.83	0.86	0.85	0.69	0.91
Test	0.81	0.83	0.80	0.81	0.82	0.82	0.63	0.88

RESULTS AND DISCUSSION

Application of Machine Learning Algorithms. Features with permutation importance scores below 0.01 were removed to reduce overfitting, leaving ten key features. The regularisation parameter C was set to 1.75, achieving a calibration slope of 1.03 and an intercept of -0.004, indicating minimal bias and accurate predictions. An accuracy of 0.81 was achieved, with sensitivity and specificity values of 0.82 and 0.79, demonstrating balanced classification (Table 1). The dataset was compiled from different studies conducted under varying conditions, introducing variability. Additionally, a known limitation in generating Morgan fingerprints is the occurrence of collisions, where different atomic environments produce the same hash value, introducing uncertainties into the model (Riniker & Landrum 2013). Nevertheless, the results are consistent with similar studies. For example, Barros de Menezes *et al.* (2022) reported accuracies of 0.84 and 0.71 using self-organising maps and a random forest classifier for predicting the antiprotozoal activity of Eos.

Feature impact analysis. Partial dependence plots (PDPs) (Fig. 4) provided insights into the influence of each molecular feature on the model's predictions. Features like bit 1607 and bit 549 had the strongest positive and negative impacts, respectively, indicated by steep slopes. Feature 1607, found in carvacrol, eugenol and thymol, denotes a hydroxyl group on a benzene ring. Feature 549, found in alpha-pinene, beta-pinene, and delta-3-carene, represents part of a bicyclic molecule (Tables 2 and 3).

Predictors of high antimicrobial potency. By bootstrapping over 1000 iterations, we estimated the mean coefficients and their variability (Fig. 5). The hydroxyl group attached to a benzene ring exhibited the highest positive contribution with minimal variability (Table 2). The model's selection of this feature as the most predictive of high AA can be explained by the fact that the outer membrane of Gram-negative bacteria contains lipopolysaccharides (LPS) which act as a barrier to polar substances. The hydrophobicity of the benzene ring can aid in disrupting lipid bilayers, facilitating membrane in-

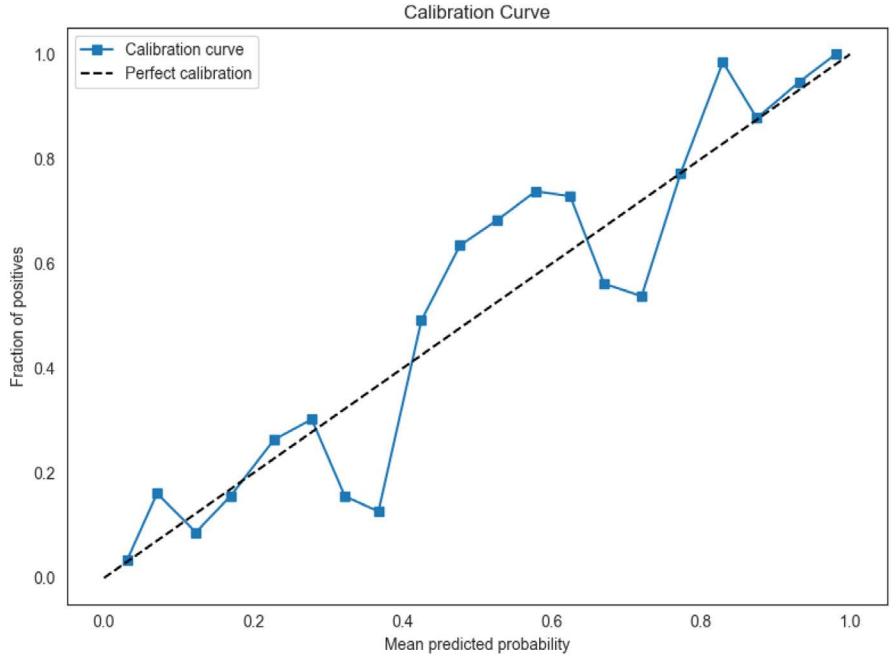


Fig. 2. A calibration curve comparing predicted probabilities to true outcomes. The dashed line represents perfect calibration, while the blue line shows model performance across 20 bins of predicted probabilities. Calibration slope: 1.0324; calibration intercept: -0.0041.

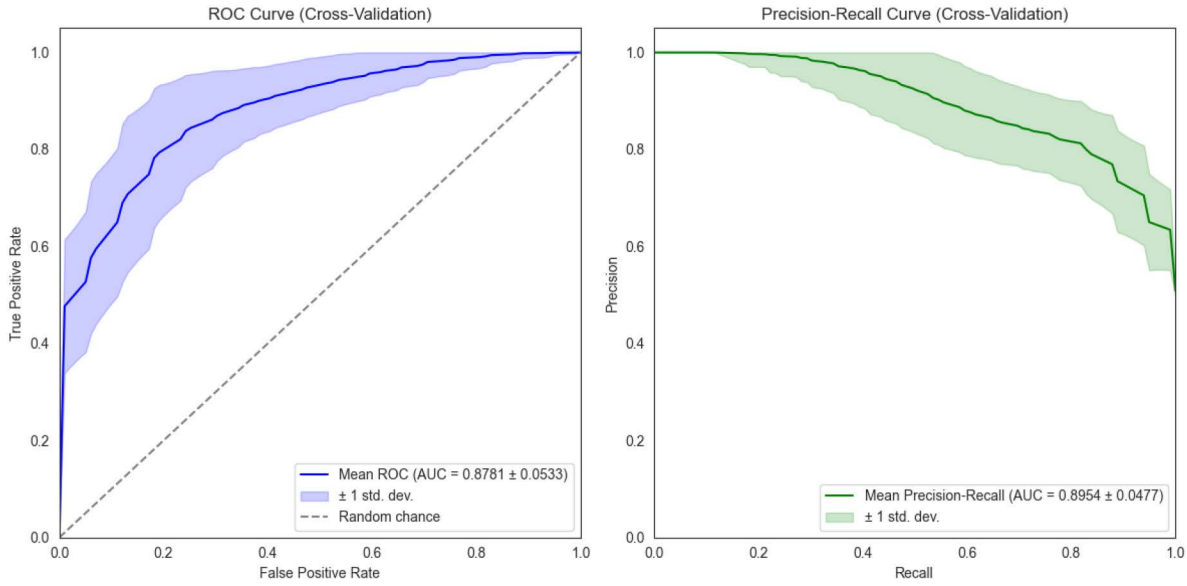


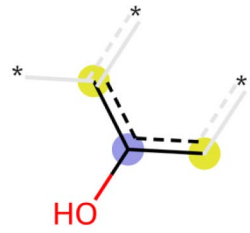
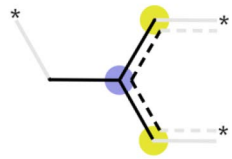
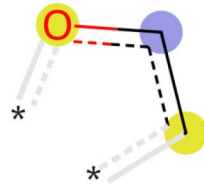
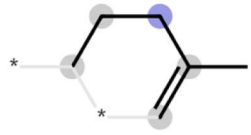
Fig. 3. ROC and Precision-Recall curves generated using repeated stratified k-fold cross-validation over 500 models. The ROC curve on the left demonstrates the model's ability to distinguish between classes with a mean AUC of 0.8781 (±0.0533). The shaded region indicates the variability of the true positive rate (± 1 standard deviation). The Precision-Recall curve on the right highlights the model's precision in predicting the positive class, showing a mean AUC of 0.8954 (±0.0477), with the shaded areas representing the precision variability.

teraction and penetration (Li *et al.* 2017). Compounds with a balance of hydrophobicity and polarity are more effective at targeting bacterial cells. Once inside, these compounds form hydrogen bonds and interact with microbial proteins, disrupting their function (Dhakal *et al.* 2023; Liang *et al.* 2023; Sun & Shahrajabian 2023).

Satureja thymbra L. and *Thymus zygis* L. exhibited high concentrations of thymol (66% and 51.65%, respectively), while *Origanum syriacum* L. and *Origanum onites* L. contained substantial carvacrol (88.3% and 75%). Both compounds confer AA via a hydroxyl-substituted benzene ring (Gören *et al.* 2004; Peñalver *et al.* 2005; Mohamad *et al.* 2021). *Pimenta dioica* (L.) Merr. was the richest in eugenol (87%), with AA attributed to its functional substituents on the benzene ring. *Mimusops elengi* L. demonstrated notable 2-phenylethanol content (37.8%), with ethyl alcohol attached to a benzene ring. *Tamarindus indica* L. showed high furfural levels (72.4%), with the furan ring's oxygen potentially contributing to the activity against *S.* Typhimurium. *Mentha* × *citrata* Ehrh., containing 66.2% linalyl acetate, was similarly reported as a potent inhibitor of *S.* Typhimurium. (Verma *et al.* 2016). The ester moiety in linalyl acetate increases lipophilicity, enhancing membrane penetration and thereby improving antimicrobial potency compared to its parent alcohol (linalool) (Dorman & Deans 2000). Collectively, these plants show considerable promise as sources of bioactive antimicrobial compounds (Escalona-Arranz *et al.* 2010; Gündüz *et al.* 2010; Almuzaini 2023). Table 2 combined with the initial database (http://essentialoils.org/db) enable filtering for EOs rich in antimicrobial compounds linked in this study with high AA against *S.* Thyphimurium, supporting further research and formulation development.

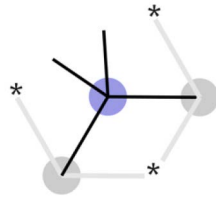
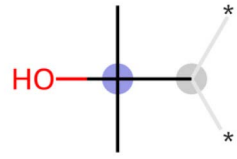
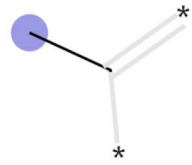
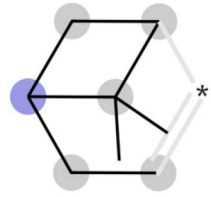
Predictors of low antimicrobial potency. Among the features predicting low AA were bicyclic structures and long hydrocarbon chains in fatty acids (Table 3). Large hydrocarbon chains in long-chain fatty acids may struggle to penetrate the outer membrane of Gram-negative bacteria. In contrast, short- and medium-chain fatty acids (SCFAs and MCFAs) penetrate more effectively due to their smaller size and higher solubility, integrating into the lipid bilayer and disrupting membrane integrity (López-Colom *et al.* 2019). *Catharanthus roseus* (L.) G. Don. exhibited the highest hexadecanoic acid content (64.9%), whereas *Osmanthus fragrans* (Thunb.) Lour. was the richest in linolenic acid

Table 2. Molecular substructures linked by the logistic regression model with high antimicrobial activity against *Salmonella* Typhimurium

SMILES	Fragment	Drawing	Bit	Chemicals	Previous studies
cc(c)O	hydroxyl group attached to a benzene ring		1607	carvacrol, eugenol, thymol	(Helander *et al.* 1998; Rota *et al.* 2004; Trevisan *et al.* 2018)
cc(c)C	a functional group attached to a benzene ring		1754	2-phenylethanol, eugenol, eugenyl acetate	(Dorman & Deans 2000; Bakkali *et al.* 2008; Ulanowska & Olas 2021)
cco	part of a furan ring		787	furfural	(Youssef *et al.* 2006; Chai *et al.* 2013)
C=Cc	part of a cycloalkene		835	(e)-anethole, bicyclogermacrene, ethyl cinnamate, germacrene d, limonene, alpha-terpineol, alpha-terpinyl acetate, beta-bisabolene, beta-caryophyllene	(Burt 2004; Hyldgaard *et al.* 2012; Fink 2023)
COC(C)=O	acetate ester		75	linalyl acetate, alpha-terpinyl acetate	(Dorman & Deans 2000; Burt 2004)

* The central atom is marked in blue, indicating the specific atom to which the bit refers. Aromatic atoms are highlighted in yellow, and aliphatic atoms are in grey

Table 3. Molecular substructures linked by the logistic regression model with low antimicrobial activity against *Salmonella* Typhimurium

SMILES	Fragment	Drawing	Bit	Chemicals	Previous studies
CC(C)(C)C	branched alkyl side chain attached to a bicyclic structure		549	alpha-pinene, beta-pinene, delta-3-carene	(Soković *et al.* 2010)
CC(C)(C)O	hydroxyl group bonded to a tertiary carbon		1604	alpha-terpineol	(Fink 2023)
CCCCC	portion of a hydrocarbon chain		1143	hexadecanoic acid, linolenic acid	(López-Colom *et al.* 2019)
CC	part of an unsaturated carbonyl		1017	(e)-beta-ocimene, carvone, citronellal, citronellol, eugenyl acetate, geranial, geraniol, geranyl acetate, limonene, linalool, linalyl acetate, myrcene, alpha-farnesene, alpha-terpinyl acetate, beta-bisabolene, beta-elemene	(Helander *et al.* 1998; Burt 2004)
CCC1CCC1(C)C	part of a bicyclic structure		1969	alpha-pinene	(Soković *et al.* 2010)

* The central atom is marked in blue, indicating the specific atom to which the bit refers. Aromatic atoms are highlighted in yellow, and aliphatic atoms are in grey

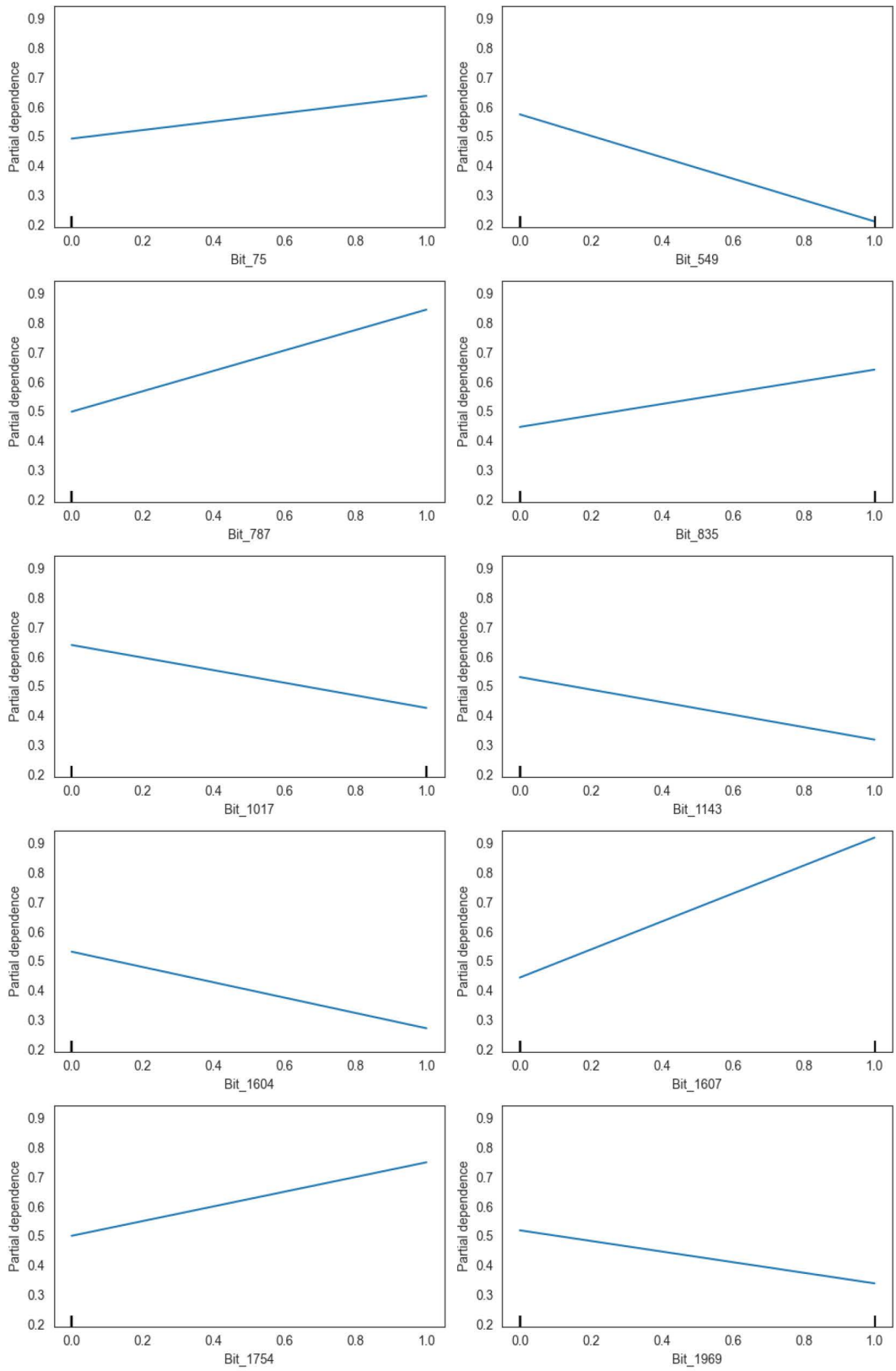


Fig. 4. Partial dependence plots (PDPs) showing the marginal effect of each feature on the prediction made by the logistic regression model. Each plot illustrates the relationship between the selected feature and the predicted probability of the target class, while accounting for the average effect of all other features in the model.

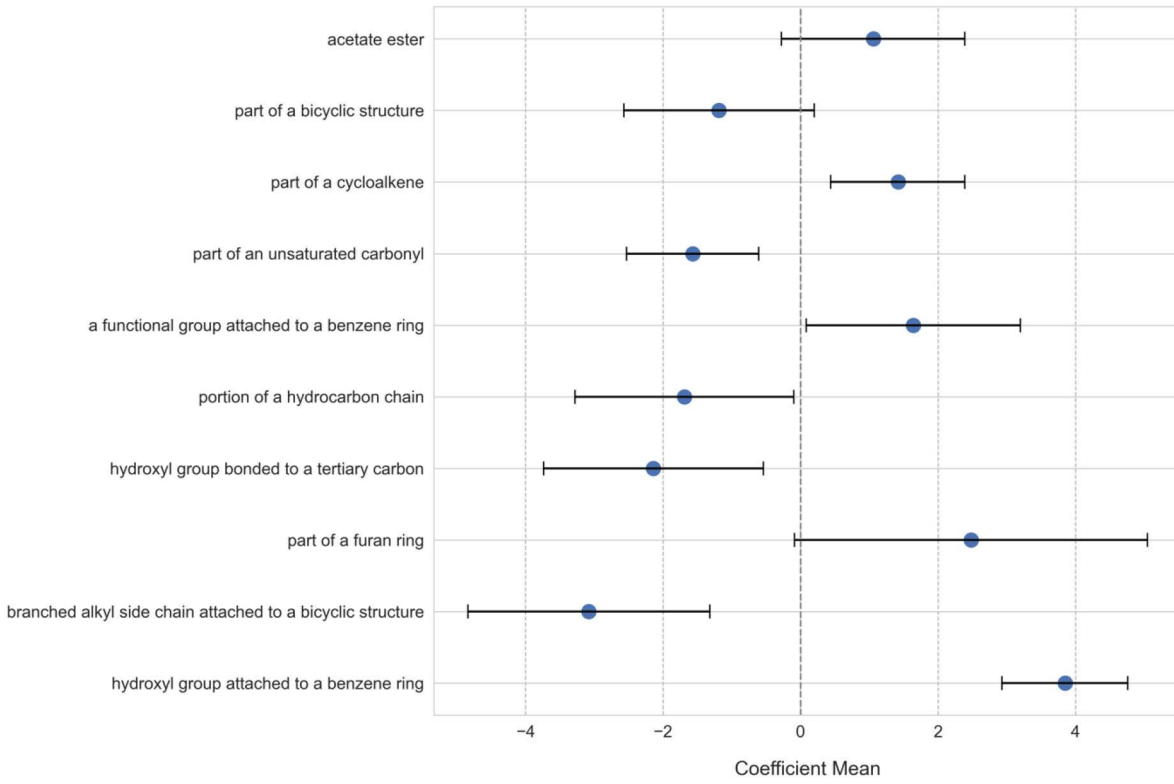


Fig. 5. Bootstrapped coefficient estimates for the features from the logistic regression model, with 95% confidence intervals. The mean coefficient (dots) represents the average effect of each feature, while the error bars indicate the uncertainty in these estimates based on 1000 bootstrap iterations. Features with coefficients further from zero have a stronger impact on the model's predictions.

(17.4%). The AA of their essential oils has not been documented. However, ethanol and methanol extracts from *C. roseus* have been reported to show moderate inhibitory effects against *S.* Typhimurium (Patil & Ghosh 2010).

Pinus nigra J.F.Arnold (49%) and *Pinus pinaster* Aiton. (71%) exhibited high alpha-pinene content and previously demonstrated low AA against *S.* Typhimurium (Keeratirathawat *et al.* 2013). Oxygenated monoterpenoids, like carvacrol and thymol, show greater AA than bicyclic hydrocarbons like alpha- and beta-pinene (Soković *et al.* 2010). This is due to functional groups, such as phenolic hydroxyls, enhancing interaction with microbial targets (Guimarães *et al.* 2019). These groups also engage in hydrophobic interactions and π-π stacking with membrane components (Zhuang *et al.* 2019). Hydrocarbon monoterpenoids lack these reactive groups, leading to lower activity. The structural features and lipophilic-hydrophilic balance of oxygenated monoterpenoids enable effective membrane integration and intracellular target interaction, driving higher AA (Griffin *et al.* 2000; Soković *et al.* 2010). As can be seen from Tables 2 and 3, breaking down each compound into Morgan fingerprint bits revealed the overlapping of some substructures in both high- and low-activity groups. This overlap arises because molecules often contain both active and inactive substructures. For example, it is eugenyl acetate's phenolic core which drives its potency, not its CC segments.

Based on López-Colom *et al.* (2019) and our findings, a synthetic compound combining a medium-chain fatty acid tail from coconut oil with a hydroxyl-substituted benzene ring is proposed for further studies. This compound may effectively target a range of pathogens, including antibiotic-resistant *Salmonella*. Balancing hydrophilic and hydrophobic properties is key in antimicrobial design. Extending the alkyl chain (C7–C12) enhances lipophilicity and cell penetration, while adding halogens or functional groups

can improve hydrogen bonding with microbial targets. Optimising these modifications is crucial to ensure efficacy while addressing safety concerns such as cytotoxicity and environmental impacts.

CONCLUSION

By using a logistic regression model trained on Morgan fingerprints of EO compounds, we identified molecular substructures linked to high AA against *S.* Typhimurium, thus offering a data-driven perspective on the design of potential new antimicrobials. This study demonstrated that hydroxyl-substituted benzene rings, commonly found in phenolic compounds such as carvacrol, thymol and eugenol, are the most reliable predictors of AA against *S.* Typhimurium among EO constituents.

Integrating advanced computational methods with botanical research underscores the potential of local and regional plant chemical profiles to accelerate antimicrobial discovery. Our combined approach, merging cheminformatics, microbiology, machine learning and plant science illustrates the promise of computational phytochemistry for future breakthroughs.

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COMPREHENSIVE PLANT BIOLOGY

REZIME

Analiza sastojaka esencijalnog ulja koje cilja *Salmonella* Typhimurium podržana mašinskim učenjem

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Neka eterična ulja (EU) pokazuju visoku efikasnost protiv *Salmonella* Typhimurium, ukazujući na to da bi određene molekulske strukture u njihovim komponentama mogle biti korisne u razvoju alternativnih antimikrobnih agenasa, posebno za suzbijanje sve većeg problema rezistencije na antibiotike kod ove bakterije. Kroz analizu permutacije osobina (feature permutation) na skupu podataka od 171 uzorka eteričnog ulja, koji obuhvataju 682 molekulske podstrukture, identifikovali smo deset ključnih prediktora antibakterijske aktivnosti protiv *S.* Typhimurium. Ovi prediktori iskorišćeni su za obuku modela mašinskog učenja zasnovanog na logističkoj regresiji. Hidroksilne grupe benzenovog prstena, karakteristične za fenolna jedinjenja poput karvakrola, timola i eugenola, pokazale su se kao snažni prediktori antibakterijske aktivnosti. Nasuprot tome, nearomatične biciklične strukture prisutne u monoterpenoidima, kao što su alfa-pinen, beta-pinen i delta-3-karen, povezane su sa neefikasnošću protiv sojeva *Salmonella*. Identifikovane molekulske karakteristike u skladu su sa postojećim istraživanjima o antimikrobnim svojstvima fenolnih jedinjenja, što potvrđuje korisnost pristupa zasnovanih na mašinskom učenju u otkrivanju prirodnih antimikrobnih agenasa.

Ključne reči: antibakterijska aktivnost, Morgan fingerprints, fenoli, klasifikacija, logistička regresija, supstituisana benzenska jedinjenja