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Original Article

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Exploring *in-silico* antimicrobial potential of *Cymbopogon citratus* phytochemicals in the treatment of drug-resistant *Escherichia coli* using molecular docking and ADMET screening

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*Correspondence to: orija.funmbi@bowen.edu.ng; 08136046292; ORCID: <https://orcid.org/0009-0002-9397-9467>**Abstract:**

Background: Antimicrobial resistance (AMR) poses a serious global health threat, particularly by to multidrug-resistant *Escherichia coli*, which reduces the efficacy of conventional antibiotics. Medicinal plants such as *Cymbopogon citratus* have gained attention as potential alternative antimicrobial sources. This study evaluated the *in-silico* antimicrobial potential of *C. citratus* phytochemicals against drug-resistant *E. coli*.

Methodology: The chemical structures of bioactive compounds of *C. citratus* were identified from the literature and retrieved from PubChem. Molecular docking was conducted using AutoDock Vina against three *E. coli* protein targets (1JL2, 8EY4, and 8XZU). QSAR modeling was performed using the genetic function approximation method. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties were predicted using ADMETlab 3.0 to assess pharmacokinetics and toxicity.

Results: Ligand 16,17-dimethoxyviolanthrone of *C. citratus* demonstrated the strongest binding affinity, particularly against 8XZU (−9.7 kcal/mol) *E. coli* protein, indicating stable protein–ligand interactions. However, ADMET analysis revealed high lipophilicity, poor solubility, strong plasma protein binding, CYP enzyme inhibition potential, and predicted hepatotoxicity and cardiotoxicity risks.

Conclusion: *Cymbopogon citratus* contains promising bioactive compounds with potential anti-*E. coli* activity, but structural optimization and experimental validation are necessary to address pharmacokinetic and safety concerns before therapeutic application.

Keywords: Antimicrobial resistance, *Cymbopogon citratus*, drug-resistant *Escherichia coli*, molecular docking, ADMET screening, QSAR modeling.

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Exploration *in silico* du potentiel antimicrobien des composés phytochimiques de *Cymbopogon citratus* dans le traitement d'*Escherichia coli* résistant aux médicaments par amarrage moléculaire et criblage ADMET

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Contexte: La résistance aux antimicrobiens (RAM) constitue une grave menace pour la santé mondiale, notamment en raison de l'émergence d'*Escherichia coli* multirésistant, qui réduit l'efficacité des antibiotiques conventionnels. Les plantes médicinales telles que *Cymbopogon citratus* suscitent un intérêt croissant en tant que sources antimicrobiennes alternatives potentielles. Cette étude a évalué *in silico* le potentiel antimicrobien des composés phytochimiques de *C. citratus* contre *E. coli* résistants aux antibiotiques.

Méthodologie: Les structures chimiques des composés bioactifs de *C. citratus* ont été identifiées dans la littérature et extraites de PubChem. Un amarrage moléculaire a été réalisé à l'aide d'AutoDock Vina contre trois protéines cibles d'*E. coli* (1JL2, 8EY4 et 8XZU). Une modélisation QSAR a été effectuée par la méthode d'approximation de la fonction génétique. Les propriétés d'absorption, de distribution, de métabolisme, d'excrétion

et de toxicité (ADMET) ont été prédites à l'aide d'ADMETlab 3.0 afin d'évaluer la pharmacocinétique et la toxicité. **Résultats:** Le ligand 16,17-diméthoxyviolanthrone de *C. citratus* a démontré la plus forte affinité de liaison, en particulier contre la protéine 8XZU d'*E. coli* (−9,7 kcal/mol), indiquant des interactions protéine-ligand stables. Cependant, l'analyse ADMET a révélé une lipophilie élevée, une faible solubilité, une forte liaison aux protéines plasmatiques, un potentiel d'inhibition des enzymes CYP et des risques prédits d'hépatotoxicité et de cardiotoxicité. **Conclusion:** *Cymbopogon citratus* contient des composés bioactifs prometteurs présentant une activité anti-*E. coli* potentielle, mais une optimisation structurale et une validation expérimentale sont nécessaires pour répondre aux préoccupations pharmacocinétiques et de sécurité avant toute application thérapeutique.

Mots-clés: Résistance aux antimicrobiens, *Cymbopogon citratus*, *Escherichia coli* résistante aux médicaments, amarrage moléculaire, criblage ADMET, modélisation QSAR.

Introduction:

According to the World Health Organization (WHO), antimicrobial resistance (AMR) is a global concern for all countries because it has a high cost for both health systems and national economies overall. The increase of AMR is caused by human activities, misuse, overuse, and incomplete use of antibiotics to treat, prevent, or control microbial infections in humans, animals, and plants (1). The WHO has emphasized the urgency of this crisis by identifying several priority pathogens that exhibit resistance to multiple antibiotic classes (2). These include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*, all of which are linked to high morbidity and mortality rates. Their ability to withstand conventional therapies underscores the pressing need for alternative and complementary antimicrobial agents capable of targeting MDR strains effectively.

Escherichia coli, a common cause of urinary tract infection mostly in females, has developed resistance to one of the commonly used antibiotics (fluoroquinolone). Patients who have infections caused by drug-resistant bacteria are at a very high risk of worse clinical outcomes or possibly death. Treatment of drug-resistant bacteria lead to increased healthcare cost (1). Worldwide, multidrug-resistant *E. coli* complicate treatment outcomes, and the burden is especially severe in low-and-middle-income countries, including Nigeria, where inappropriate antibiotic use and weak infection control practices contribute to high resistance rates. Reports from Nigeria highlight widespread resistance of bacteria to β -lactams, fluoroquinolones, and cephalosporins, further aggravating the clinical and public health burden of skin and soft tissue infections (SSTIs) (3).

The emergence and rapid spread of multidrug-resistant *E. coli* pose a significant global health challenge, limiting the effectiveness of conventional antibiotics and contributing to increased morbidity, mortality, and healthcare costs (4,5). As resistance rates escalate, there is an urgent need to identify alter-

native, safe, and affordable antimicrobial agents.

Medicinal plants have become a major focus of research due to their rich diversity of bioactive compounds and their long history of use in traditional medicine (6). Plant-derived phytochemicals, including alkaloids, flavonoids, terpenoids, and phenolics, have demonstrated antibacterial activity against MDR bacteria through a variety of mechanisms, such as disrupting bacterial cell walls and modulating resistance pathways (7,8). Furthermore, several studies have shown that medicinal plant extracts can enhance the efficacy of conventional antibiotics when used in combination, indicating their potential role in integrated antimicrobial strategies (8).

Cymbopogon citratus (lemongrass) is an aromatic plant widely used in culinary, cosmetic, and ethnomedicinal applications. Previous studies have demonstrated that its essential oils and extracts contain bioactive constituents such as citral, geraniol, limonene, and myrcene, which exhibit antimicrobial, anti-inflammatory, and antioxidant properties (4). These phytochemicals are known to exert antimicrobial effects through mechanisms such as disruption of microbial cell membranes, inhibition of enzymatic activity, and interference with quorum sensing pathways (4). However, despite these promising attributes, there are limited scientific data specifically evaluating its effectiveness against MDR bacterial strains, which represent one of the most critical threats to current antimicrobial therapies (5). This gap highlights the need for targeted investigations assessing its activity against MDR pathogens.

Laboratory experimental studies have shown that *C. citratus* extracts and essential oil have antibacterial properties due to the presence of citral in the essential oil, making it a strong antibacterial against several bacteria including *S. aureus*, *Bacillus subtilis*, *P. aeruginosa*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Neisseria gonorrhoeae*, *Clostridium perfringens*, *Pseudomonas fluorescens*, *Acinetobacter baumannii*, *Aeromonas veronii* bio-group *sober*, *Enterobacter faecalis*, *K. pneumo-*

niae, *Salmonella enterica* subsp *enterica* serotype *typhimurium*, *Serratia marcescens*, *Proteus mirabilis*, *Shigella flexneri*, and *Salmonella* Typhi (9).

In-silico analysis refers to the utilization of computer-based tools to investigate biological or chemical interactions, as opposed to traditional laboratory experiments. This approach plays a critical role in modern drug discovery by enabling the identification, screening, and rational design of potential drug candidates through computational techniques (10, 11). Research indicates that drug development is significantly enhanced by *in-silico* investigations because these methodologies allow rapid virtual screening, molecular modeling, and prediction of therapeutic potential prior to experimental validation. In antimicrobial research, computational strategies such as molecular docking provide valuable insights into ligand-target interactions, thereby supporting the evaluation of the antimicrobial potential of *C. citratus* against resistant pathogens (11).

Furthermore, *in-silico* methods facilitate toxicity and pharmacokinetic prediction through absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis, which helps forecast drug-likeness, bioavailability, and possible off-target effects (5,10). By identifying potentially harmful effects early in the development process, these computational tools significantly reduce time, laboratory workload, and financial costs. The integration of molecular docking and ADMET prediction into antimicrobial research therefore enhances drug quality and increases the probability of success fully harnessing the bioactive compounds of *C. citratus* for innovative therapeutic strategies against antimicrobial resistance (AMR).

This study aims to identify the major chemical constituents of *C. citratus* through an exhaustive search of established online databases and to determine the binding affinities and interaction profiles of these compounds against specific *E. coli* protein targets. It seeks to assess the pharmacokinetic properties of the top-performing phytochemicals using computational tools, in order to distinguish potential lead compounds that exhibit both strong binding potency and favorable safety and metabolic profiles. Ultimately, the study evaluates the overall suitability of these bioactive constituents for further development as effective antimicrobial agents.

Materials and method:

Study design:

This study employed an *in-silico* re-

search design to investigate the antimicrobial potential of *C. citratus* against drug-resistant *E. coli*. Molecular docking techniques were applied to predict the binding affinity and interaction patterns between the bioactive compounds of *C. citratus* and selected *E. coli* target proteins. The methodology includes ligand selection and preparation, *E. coli* protein target preparation, molecular docking, interaction analysis, and ADMET screening. Furthermore, ADMET screening was conducted to assess the drug-likeness and safety profile of the identified compounds.

Identification of bioactive compounds of *C. citratus* from databases:

The phytochemical constituents of *C. citratus* were identified through a comprehensive literature review and validated phytochemical databases (PubMed). The chemical structures of selected bioactive compounds were obtained in SDF format from a publicly accessible chemical database (PubChem). These compounds were selected based on their reported antimicrobial activity and structural relevance.

QSAR modeling:

Molecular parameters were derived from the optimized compounds and subsequently used in the development of a valid and reliable quantitative structure-activity relationship (QSAR) model. The calculated molecular parameters functioned as independent variables, while the experimental inhibitory concentration (IC₅₀) values were designated as the dependent variable. The development of the QSAR model was conducted using the Genetic Function Approximation (GFA) method, as implemented in Materials Studio software (15). The resulting Multiple Linear Regression-GFA (MLR-GFA) model was articulated in the following equation: Predicted IC₅₀ = $\alpha + \beta_1X_1 + \beta_2X_2 + \dots + \beta_nX_n$ where α denotes the regression constant, $X_1, X_2, \dots, X_n$ represent the molecular parameters, and $\beta_1, \beta_2, \dots, \beta_n$ are the respective regression coefficients.

Molecular docking:

Protein targets associated with antimicrobial resistance and bacterial survival in *E. coli* were identified through literature review and sourced from the RCSB Protein Data Bank (PDB). Only proteins with co-crystallized structures resolved by X-ray diffraction at 1.5–2.5 Å were included to ensure high structural fidelity. Proteins from other organisms or lacking crystallographic data were excluded. The three-dimensional structures of ligands were retrieved from PubChem in SDF format, converted to PDB using Open Babel in PyRx workspace, and energy minimization was done to achieve

stable conformations before conversion to PDBQT for docking. Protein preparation involved removing water molecules, co-crystallized ligands, and heteroatoms, followed by the addition of polar hydrogens and conversion to PDBQT format using AutoDock tools.

Docking was performed using AutoDock Vina in the PyRx workspace. Grid box parameters were set for each target protein: 1JL2 (X: 35.95 Å, Y: 46.97 Å, Z: 44.26 Å; center X: 11.46 Å, Y: 3.20 Å, Z: 24.33 Å), 8XZU (X: 59.15 Å, Y: 53.33 Å, Z: 50.31 Å; center X: -8.72 Å, Y: -16.60 Å, Z: -7.49 Å), and 8EY4 (X: 38.54 Å, Y: 33.95 Å, Z: 45.87 Å; center X: 12.26 Å, Y: 9.97 Å, Z: 16.59 Å). Ligand orientations were scored based on forcefield calculations; the top binder was identified. Docked complexes were visualized in BIOVIA Discovery Studio 2025 (Dassault Systèmes, Vélizy-Villacoublay, France), generating 2D and 3D representations of molecular interactions to evaluate binding profiles.

ADMET screening:

The ADMET properties of the selected compounds were assessed using online prediction tools, specifically ADMETlab 3.0. The parameters evaluated included oral bioavailability, permeability across the blood-brain barrier, interactions with cytochrome P450, and toxicity. Drug-likeness was determined based on molecular weight, the number of hydrogen-bond donors and acceptors, and lipophilicity (LogP). ADMETlab 3.0 employs canonical SMILES inputs to deliver highly accurate predictions of

physicochemical profiles, pharmacokinetics and toxicity. By utilizing comprehensive databases, the platform evaluates essential metrics, including drug-likeness, bioavailability, and therapeutic potential, for one or more query compounds.

Results

Molecular docking results:

The molecular docking analysis of *C. citratus* offers an in-depth examination of the interactions between its phytochemicals and three specific protein structures of *E. coli*. Each table delineates a unique target, elucidating which compounds exhibit the greatest potential for bacterial inhibition. The analysis of the docking simulations indicates that Ligand 16,17-Dimethoxyviolanthrone is the most effective constituent from the lemon grass extract, demonstrating a binding affinity of -9.2 kcal/mol toward the *E. coli* 1JL2 protein (Table 1, Fig 1).

This high energy score signifies a notably stable protein-ligand complex, significantly surpassing other competitive compounds such as Ligand 11-Nor-9-carboxy-delta9-tetrahydrocannabinol and Ligand Gossypol which displayed affinities of -7.2 and -6.9 kcal/mol, respectively. Although Ligands Butylated hydroxytoluene and Tymazoline exhibited more moderate interactions, with affinities ranging from -5.8 to -5.5 kcal/mol, the comprehensive data underscore Ligand 16,17-Dimethoxyviolanthrone as the foremost candidate for inhibiting this particular bacterial target (Table 1).

Table 1: Binding Results of *Cymbopogon citratus* phytochemical with 1JL2_ *Escherichia coli* protein target

S/N	Ligands	Binding affinity	rmsd/ub	rmsd/lb
1	1JL2_ <i>E. coli</i> _Cannabinor_uff_E=980.84	-6.2	0	0
2	1JL2_ <i>E. coli</i> _Butylated hydroxytoluene_uff_E=304.14	-5.8	0	0
3	1JL2_ <i>E. coli</i> _Dronabinol_uff_E=235.27	-6.4	0	0
4	1JL2_ <i>E. coli</i> _Dexanabinol_uff_E=339.23	-6.4	0	0
5	1JL2_ <i>E. coli</i> _11-Nor-9-carboxy-delta9-tetrahydrocannabinol_uff_E=323.17	-7.2	0	0
6	1JL2_ <i>E. coli</i> _16,17-Dimethoxyviolanthrone_uff_E=779.90	-9.2	0	0
7	1JL2_ <i>E. coli</i> _Tymazoline_uff_E=283.52	-5.5	0	0
8	1JL2_ <i>E. coli</i> _Gossypol_uff_E=866.62	-6.9	0	0
9	1JL2_ <i>E. coli</i> _2-amino-4-phenyl-4Hpyrano(3,2-H)quinoline-3-carbonitrile_uff_E=241.32	-6.8	0	0
10	1JL2_ <i>E. coli</i> _2-((1S,6S)-3-Methyl-6-(Prop-1-En-2-Yl)Cyclohex-2-Enyl)-5-Pentylbenzene-1,3-Diol_uff_E=215.14	-6.2	0	0

1JL2: Crystal structure of TCEO RNase H-a chimera combining the folding core from *Thermus thermophilus* RNase H and the remaining region of *Escherichia coli* RNase H (12); msd: root mean square deviation; ub: upper bound; lb: lower bound

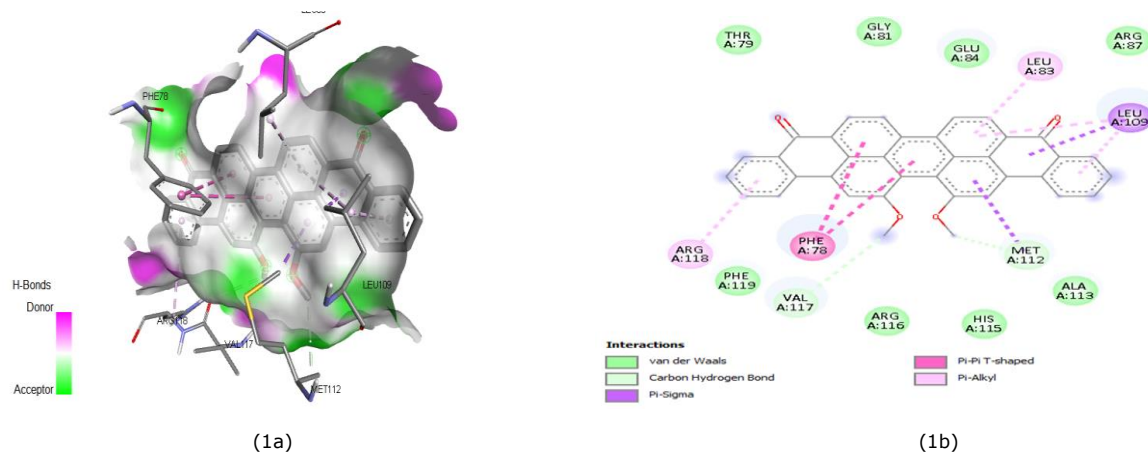


Fig 1: (a) 3D and (b) 2D binding interaction of 16, 17- dimethoxyviolanthrone with 1JL2 of *Escherichia coli*

In the examination of the 8EY4 protein target, Ligand 16,17-Dimethoxyviolanthrone consistently exhibited superior inhibitory potential, demonstrating a high binding affinity of -9.1 kcal/mol (Table 2, Fig 2). This sustained performance is further supported by the notable results of Ligand 11-Nor-9-carboxy-delta 9-tetrahydrocannabinol and Ligand Lenabasum which achieved affinities of -7.9 kcal/mol and -7.7 kcal/mol, respectively.

Conversely, this particular target also recorded the lowest affinity observed in the study, with Ligand 10346 attaining only -5.0 kcal/mol. This finding suggests that the binding pocket of 8EY4 may possess a more restrictive geometry or a chemical environment that is less compatible with certain phytochemical structures in comparison to other proteins analyzed (Table 2).

Table 2: Binding Results of *Cymbopogon citratus* phytochemicals with 8EY4_ *Escherichia coli* protein target

S/N	Ligands	Binding affinity	rmsd/ub	rmsd/lb
1	8EY4_ <i>E. coli</i> _Cannabinor_uff_E=980.84	-6.3	0	0
2	8EY4_ <i>E. coli</i> _Butylated hydroxytoluene_uff_E=304.14	-5	0	0
3	8EY4_ <i>E. coli</i> _Dronabinol_uff_E=235.27	-6	0	0
4	8EY4_ <i>E. coli</i> _Dexanabinol_uff_E=339.23	-7	0	0
5	8EY4_ <i>E. coli</i> _11-Nor-9-carboxy-delta9-tetrahydrocannabinol_uff_E=323.17	-7.9	0	0
6	8EY4_ <i>E. coli</i> _16,17-Dimethoxyviolanthrone_uff_E=779.90	-9.1	0	0
7	8EY4_ <i>E. coli</i> _Tymazoline_uff_E=283.52	-6	0	0
8	8EY4_ <i>E. coli</i> _Lenabasum_uff_E=328.21	-7.7	0	0
9	8EY4_ <i>E. coli</i> _Bromothymol Blue_uff_E=891.42	-6.5	0	0
10	8EY4_ <i>E. coli</i> _6-Nitrosothymol_uff_E=112.46	-5.5	0	0

8EY4: Contact-dependent growth inhibition toxin-immunity protein complex from *Escherichia coli* O32:H37 (13); msd: root mean square deviation; ub: upper bound; lb: lower bound

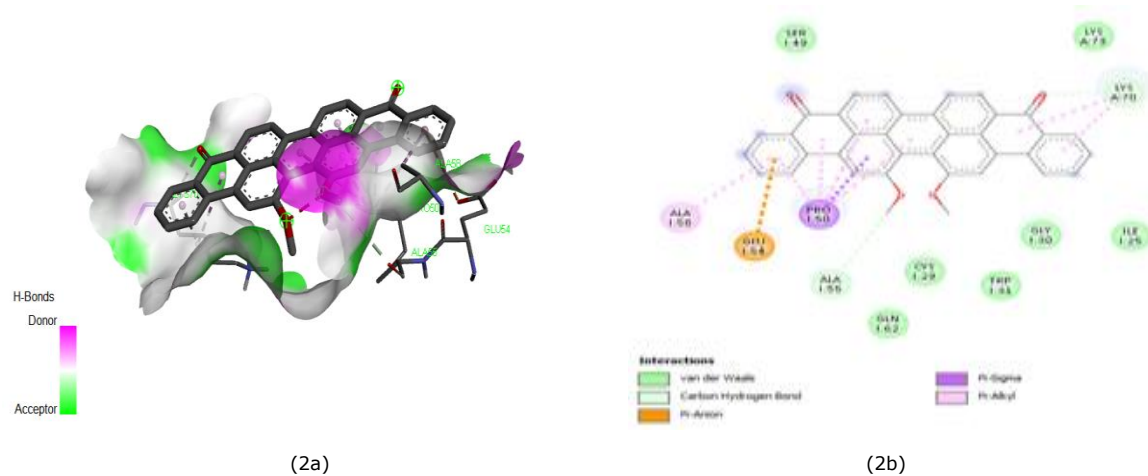
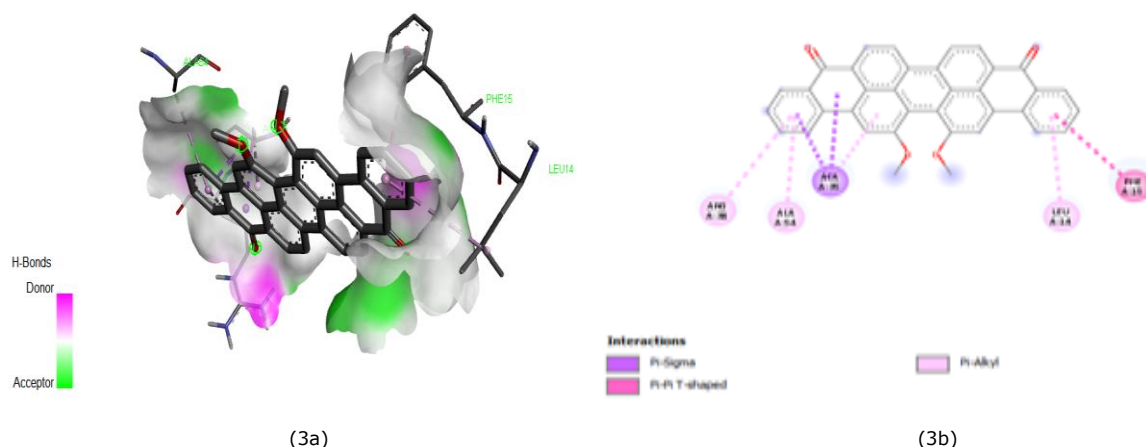


Fig 2: (a) 3D and (b) 2D binding interaction of 16, 17- dimethoxyviolanthrone with 8EY4 of *Escherichia coli*

Table 3: Binding Results of *Cymbopogon citratus* phytochemicals with 8XZU_*Escherichia coli* protein target

S/N	Ligands	Binding affinity	rmsd/ub	rmsd/lb
1	8XZU_ <i>E. coli</i> _Cannabinor_uff_E=980.84	-7.9	0	0
2	8XZU_ <i>E. coli</i> _16,17-Dimethoxyviolanthrone_uff_E=779.90	-9.7	0	0
3	8XZU_ <i>E. coli</i> _Dronabinol_uff_E=235.27	-6.9	0	0
4	8XZU_ <i>E. coli</i> _Dexanabinol_uff_E=339.23	-7.4	0	0
5	8XZU_ <i>E. coli</i> _Butylated hydroxytoluene_uff_E=304.14	-6.5	0	0
6	8XZU_ <i>E. coli</i> _Imlunestrant_uff_E=859.08	-7.9	0	0
7	8XZU_ <i>E. coli</i> _11-Nor-9-carboxy-delta9-tetrahydrocannabinol_uff_E=323.17	-7	0	0
8	8XZU_ <i>E. coli</i> _o-Thymotic acid_uff_E=158.94	-5.3	0	0
9	8XZU_ <i>E. coli</i> _Thymol Iodide_uff_E=472.35	-7	0	0
10	8XZU_ <i>E. coli</i> _10-Isobutyryloxy-8,9-epoxythymol isobutyrate_uff_E=1624.85	-6.2	0	0

8XZU: Crystal structure of N-terminal deletion mutant of Staphylococcal atypical two-cysteine thiol peroxidase complexed with substrate analog (14); msd: root mean square deviation; ub: upper bound; lb: lower bound

Fig 3: (a) 3D and (b) 2D binding Interaction of 16, 17- dimethoxyviolanthrone with 8XZU of *Escherichia coli*

The interactions with the 8XZU protein suggest that it is the most receptive target among the three proteins examined, as demonstrated by Ligand 16,17-Dimethoxyviolanthrone achieving a peak binding affinity of -9.7 kcal/mol (Table 3, Fig 3). This protein exhibits a significant binding capacity with several other ligands, with Ligands Cannabinor and Imlunestrant both achieving a commendable binding score of -7.9 kcal/mol. Additionally, mid-range ligands such as Dexanabinol and Thymol Iodide displayed stronger binding affinities of -7.4 kcal/mol and -7.0 kcal/mol, respectively, compared to their counterparts in prior assessments. This finding positions 8XZU as a primary site for potential antimicrobial action, attributable to its highly compatible binding pocket (Table 3).

The Root Mean Square Deviation (RMSD) values across all three tables consistently measured at 0, thereby confirming that the data accurately reflects the optimal docking pose for each compound. A comparative analysis of the three targets reveals that while the ligands derived from *C. citratus* demonstrate general efficacy, their potency is particularly enhanced when directed towards the 8XZU protein, with

compound 16,17-Dimethoxyviolanthrone consistently identified as the leading candidate for further investigation.

Physicochemical and ADMET properties of the lead compound:

The physicochemical and ADMET properties of the lead compound, 16,17-dimethoxyviolanthrone, is presented in Table 4. The compound presents considerable challenges for oral drug delivery, attributed to its high lipophilicity (logP, with an optimal range of 0-3) and its extremely low solubility (logS of -11.965), which reflects poor aqueous solubility. Furthermore, it exhibits a low Quantitative Estimate of Drug-likeness (QED of 0.172), suggesting that it is deemed overly complex. It demonstrates optimal Caco-2 permeability, suggesting efficient translocation through tissue cells; however, it exhibits low bioavailability, indicating inadequate oral absorption attributable to first-pass metabolism. Furthermore, the high level of P-glycoprotein (P-gp) inhibition raises concerns regarding potential drug-drug interactions, as it may influence the efficacy of concomitantly administered medications.

Table 4: Physicochemical and ADMET properties of the lead compound (16,17- dimethoxyviolanthrone)

Compound	Properties					
16,17- dimethoxyviolanthrone	Physicochemical properties					
	Molecular weight	logP	logS	TPSA	nHA/nHD	QED
	516.14	7.573	-11.965	52.6	4.0/0.0	0.172
	Absorption					
	Caco-2 permeability	HIA	Pgp-inhibitor	Bioavailability		
	-4.726	0.045	0.992	0.935		
	Distribution					
	PPB	VDss	BBB penetration			
	98.805%	0.603 L/kg	0.252			
	Metabolism					
	CYP1A2 inhibitor	CYP3A4 substrate	CYP2C9 inhibitor			
	0.957	0.697	0.817			
	Excretion					
Plasma clearance	Half-life (T _{1/2})					
4.16	0.512					
Toxicity						
hERG blockers	Hepatotoxicity	Mutagenicity	Rat oral toxicity	Carcinogenicity		
0.983	0.988	0.106	0.237	0.826		

The assessment of Human Intestinal Absorption (HIA) indicates a low likelihood of suboptimal intestinal absorption, predicting a human intestinal absorption rate of 30% or greater for the compound. The compound has a notably high protein binding affinity, exceeding the optimal threshold of 90%. This observation suggests a potential low therapeutic index, as a reduced amount of free drug is accessible to reach the intended target due to the substantial proportion of the drug binding to plasma proteins. The volume of distribution at steady state (VDss) suggests a uniform distribution throughout the tissues. Furthermore, the compound's limited ability to penetrate the blood-brain barrier (BBB) implies a reduced distribution to the central nervous system, which may correlate with a diminished risk of central nervous system-related adverse effects.

16,17-dimethoxyviolanthrone demonstrated significant predicted inhibition of CYP 1A2 and CYP2C9, indicating a substantial risk of drug-drug interactions and a potential for reduced metabolism of other drugs that are processed by these enzymes. Furthermore, it is probable that the compound will be metabolized by CYP3A4, which is recognized as the predominant enzyme involved in drug metabolism within the liver. It showed a moderate plasma clearance rate and possesses a short half-life, suggesting that more frequent dosing may be necessary to sustain therapeutic levels. Finally, it presents notable safety concerns, sp-

ecifically regarding hepatotoxicity, cardiotoxicity, and carcinogenicity. This indicates that the compound is detrimental in its existing formulation.

Discussion:

Antimicrobial resistance is a significant issue in modern medicine, especially with the increase of multidrug-resistant *E. coli* infections, which has made many standard antibiotics less effective. The global health impacts of infections caused by MDR *E. coli* have been highlighted by various clinical studies that show widespread resistance and emphasize the urgent need to investigate alternative antibacterial agents (16).

In this study, *in-silico* methods, including molecular docking and ADMET prediction, were employed to assess selected phytochemicals from *C. citratus* for their potential to inhibit important *E. coli* resistance-related proteins. The docking results showed that 16,17-dimethoxyviolanthrone exhibited the strongest binding affinities for several target proteins, including the 8XZU protein, which might indicate a high degree of compatibility within the protein's active site. These findings are in agreement with broader research that suggests computational screening can effectively identify phytomolecules that have strong protein-ligand binding potential against drug-resistant bacterial targets (10).

The strong binding affinities observed in this study are seen as indicators of possible antimicrobial action *in-silico* (11). However, it is important to note that while molecular docking can predict favorable interactions, these results must be validated through experimental methods since computational binding scores do not fully encompass biological complexities. Additional experimental research supports the antimicrobial potential of *C. citratus* extracts. For example, a 2025 *in vitro* study indicated significant zones of inhibition against *E. coli* and other pathogens when lemongrass leaf extracts were used, thereby confirming the antibacterial properties suggested by the computational models (17). Another recent study found that essential oils from *C. citratus* showed disruptive activity against *E. coli* biofilms, which is an important mechanism for overcoming bacterial defenses and persistence (18). These experimental findings reinforce the idea that phytochemicals from lemongrass have substantial biological activity, justifying their exploration as antimicrobial agents.

Despite the promising anti-*E. coli* activity of *C. citratus* phytochemicals in this study, the ADMET predictions showed concerns related to pharmacokinetics and toxicity. The lead compound demonstrated high lipophilicity and poor solubility, indicated by high log P and low log S values, which might pose challenges for bioavailability. Additionally, the predicted risks of hepatotoxicity and cardiotoxicity from hERG (human ether-à-gogo-related gene) inhibition point toward potential safety issues. These predicted liabilities are consistent with findings from toxicological evaluations where lemongrass extracts exhibited mild hepatotoxic effects at higher doses, underscoring the necessity for careful dose exploration and safety profiling (17).

A promising direction noted in recent literature is the combination of phytochemicals with conventional antibiotics to achieve synergistic effects and diminish resistance development (19). This approach reflects a growing interest in combination therapies that can enhance antimicrobial effectiveness while potentially reducing the necessary doses of toxic compounds.

Conclusion:

This *in-silico* study identified 16,17-dimethoxyviolanthrone of *C. citratus* with strong docking performance, suggesting potential as a lead compound against drug-resistant *E. coli*. However, ADMET analysis highlighted significant pharmacokinetic and safety concerns,

including hepatotoxicity, cardiotoxicity, carcinogenicity, and possible drug-drug interactions. Overall, while *C. citratus* demonstrates promise as a source of novel antimicrobial agents, further structural modification and optimization are necessary to improve safety, metabolic stability, and therapeutic suitability before clinical development for antimicrobial-resistant infections.

To enhance the therapeutic potential of bioactive compounds, future research should prioritize structural modification and optimization. By concentrating on derivatives of lead compounds such as 16,17-dimethoxyviolanthrone, medicinal chemists can address identified risks, including hepatotoxicity and cardiotoxicity. This endeavor requires a careful balance of modifying the chemical scaffold to diminish adverse effects while simultaneously preserving or ideally enhancing the compound's antimicrobial efficacy against target pathogens.

Moreover, it is imperative to move beyond computational modeling to ensure clinical relevance. Although current *in silico* findings are encouraging, rigorous *in vitro* and *in vivo* experimental validation is essential as the subsequent step. Laboratory experiments and animal models will be crucial for confirming the actual antimicrobial effectiveness and physiological safety of these *C. citratus* phytochemicals when confronted with the complexities of living biological systems, particularly with respect to drug-resistant *E. coli*.

Additionally, addressing the safety profile and metabolic challenges identified during ADMET screening is of utmost importance. Specialized studies should examine the risks of drug-drug interactions associated with compounds that exhibit strong inhibition of enzymes such as CYP1A2 and CYP2C9. To mitigate these risks and compensate for short half-lives or specific clearance rates, subsequent research should investigate dosage and formulation strategies. The development of advanced drug delivery systems could be instrumental in maintaining therapeutic concentrations within the body and ensuring a stable metabolic profile.

Finally, the scope of research should be expanded to investigate the synergistic and broad-spectrum potential of these extracts. Testing these phytochemicals against a broader range of drug-resistant pathogens beyond *E. coli* will elucidate the full utility of lemongrass-derived compounds. Furthermore, exploring the synergy between different phytochemicals or their combinations with existing antibiotics could unveil innovative strategies for combating AMR and rejuvenating the current pharmaceutical arsenal.

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PD supervised the study; FO performed the *in-silico* analysis; and KP co-supervised the study.

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Authors declare no conflicts of interest.

Ethics statement and informed consent:

This study did not involve human participants, animal samples, or materials requiring ethical approval. As no human participant were involved, informed consent was not applicable.

Artificial Intelligence (AI) use disclosure:

Generative AI, Quillbot and Grammarly, were used in this study for rephrasing and spell checks. My bib was used to arrange the reference. Google Gemini was used to assist in the interpretation and clarification of results. The authors reviewed, edited, and validated all outputs to ensure accuracy and scientific integrity.

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