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Original Article

Antibacterial and Anti-quorum Sensing Activities of *Erianthemum dregei`s* Leaf Extract and Molecular Docking

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ABSTRACT

Background: The increasing incidence of multi-drug resistance among pathogens has propelled researchers to search for novel antimicrobial and anti-quorum sensing agents characterised by different mechanisms and high potency. **Objective:** The study aimed at investigating the antibacterial and anti-quorum sensing properties of compounds from *Erianthemum dregei* and their molecular interactions with the target proteins. **Methods:** The methanolic leaf extract from *E. dregei* was evaluated for its chemical composition and antibacterial activity using gas chromatography-mass spectrophotometry (GC-MS) and micro-dilution method, respectively. The inhibition of violacein production in *Chromobacterium violaceum* (ATCC 07) was assayed as anti-quorum sensing activity using micro-dilution method. The molecular docking of the GC-MS ligands and penicillin-binding protein 2x (PDP2) and CviR was executed using AutoDock Vina. **Results:** The two volatile compounds namely phytol (93.58%) and 3-tetradecyn-1-ol (6.42%) were shown by GC-MS. The extract exhibited antibacterial activity against the selected bacterial strains with minimum inhibitory concentration (MIC) values ranging from 1.56 to 3.125 mg/mL. The maximum inhibition of violacein production of 53.93% was observed at 1.56 mg/mL. Both compounds had docking scores of more than -6.0 kcal/mol against the target proteins**. Conclusion:** The results revealed that the extract is a potential source of antibacterial and anti-quorum sensing compounds and thus can have pharmacological applicability.
Key words: *Erianthemum dregei,* Antibacterial activity, Anti-quorum sensing activity, Molecular docking.

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INTRODUCTION

The constant emergence of drug resistance pathogens poses a threat to human health.[1] Drug resistance compromises the treatment of infections as it makes it difficult to effectively treat even the commonly known microbial infections. Drug-resistant pathogens results in significantly high morbidity and mortality rates worldwide, especially in developing countries.[2] Drug-resistant occurs when pathogens develop resistance mechanisms such as enzymatic inactivation of the drugs, modification of the target sites and extrusion by efflux pump when exposed to antimicrobial agents.[3] The drug-resistant traits are greatly influenced by the misuse of antimicrobials that exert selective pressure among pathogens.[4] Thus, the need to identify efficacious compounds and to use alternative treatment strategies such as anti-quorum sensing activity are paramount.

Quorum sensing (QS) is the ability of microorganisms to use signal molecules called autoinducers, as a means of communication.[5] Autoinducers are categorised into three classes namely: the acylated homoserine lactones (AHLs), used by the Gram-negative bacteria; the peptide signals, used by the Gram-positive bacteria; and the autoinducer-2, used by both the Gram-negative and Gram-positive bacteria.[6] In Gram-negative bacteria, genes involved in AHL-based QS systems are luxI-like and luxR-like genes. The luxI-like gene codes the enzymes responsible for the production of AHL, whereas luxR-like regulates the transcription of specific genes such as virulent genes.[7] QS regulates microbial gene expression, production of antibiotics and pigments such as violacein from *Chromobacterium violaceum* strains and aspects that contribute to microbial pathogenicity.[8] Since QS affects virulence factors that control bacterial pathogenicity, QS inhibition is considered a promising approach to antimicrobial therapy to combat the challenge of drug resistance.[9]

QS inhibitors interfere with this cell-to-cell communication and target microbial virulence without stopping their growth, thus averting the development of antimicrobial resistance as it does not induce selective or survival pressure.[10] QS inhibitors have been previously identified in some medicinal plants.[11] Plants produce a repertoire of bioactive compounds that can be categorised into three main groups namely: (a) phenolics, (b) terpenes, and (b) nitrogen-containing compounds.[12] These compounds generally exert anti-QS effect by: (1) inhibiting the synthesis of the signalling molecules, (2) degrading the signalling molecules and (3) binding to the LuxR signal receptors.[13] The variations in the structures result in the differences in the inhibitory activity.

Erianthemum dregei is a medicinal plant belonging to Loranthaceae family. It is widely distributed in the northern part of KwaZulu-Natal, South Africa.[14] *E. dregei* has been used to treat sexually transmitted diseases, snake bites and stomach ailments.[15] However, according to our knowledge, there are no scientific studies confirming the medicinal properties of this plant.

The aim of this work was to assess the antibacterial and anti-quorum sensing properties of *E. dregei`s* leaf extract using standard methods. The chemical profiling of the extract was performed using gas chromatography-mass spectrometry (GC-MS)

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analysis. Lastly, the molecular interaction of the GC-MS identified ligands with the target receptor protein was investigated by AutoDock-Vina.

MATERIALS AND METHODS

Plant collection and extraction

The leaves of *E. dregei* were collected from their natural habitat in Manguzi, KwaZulu-Natal Province, South Africa (28 °45 ′S31 °54 ′E) and transported to the University of Zululand, South Africa. The plant specimen was identified by Dr Ntuli in the Department of Botany, University of Zululand using standard herbarium materials and taxonomic keys. The voucher specimen of *E. dregei*-NNM01 was deposited in the University of Zululand Herbarium [ZULU]. The leaves were then washed, dried at room temperature and milled to a fine powder. The ground material (20 g) was subjected to extraction using 200 mL of methanol (technical grade, Merck) in 500 mL Erlenmeyer flask. The flask was left on a mechanical shaker at 130 rpm for 48 hours at room temperature. Thereafter, the extract was filtered using Whatman No.1 filter paper before being transferred into pre-weighed glass container. The methanol was evaporated under a stream of air in a fume-hood at room temperature.

Phytochemical analysis

The preliminary screening of the classes of phytochemicals (alkaloids, flavonoids, glycosides, saponins, steroids, tannins and terpenoids) in the extract was done using standard methods.[16] The phytochemistry evaluation of the volatile compounds in the methanol extract was done using gas chromatography-mass spectrophotometry (GC-MS). The GC oven temperature was initially adjusted to 40 °C for 3 minutes and subsequently raised by 5 °C per minute to 220 °C. The injector temperature was set at 250 °C. Helium gas was used as a carrier gas with a constant flow rate of 1.0 mL per minute and split ratio of 10:1. The MS system had an ion source temperature of 250 °C and an electron ionization system of 70 eV. The compounds were analysed based on the retention indexes and mass spectra were compared with those from the libraries.[17]

Standard laboratory bacterial strains

The standard laboratory strains of *S. aureus* [American Type Culture Collection (ATCC) 25923], *K. pneumoniae* (ATCC 4352) and *C. viocelaceum* (ATCC 107) were obtained from the Department of Biochemistry and Microbiology Laboratory, University of Zululand. They were resuscitated on nutrient broth (NB) and incubated at 37 °C, overnight. Thereafter, the McFarland standard was used to standardise the inoculum density to 1×10^6 CFU/mL using spectrophotometer (Spectroquant-Pharo 100).

Minimum inhibitory concentration (MIC)

The Minimum inhibitory concentration (MIC) of the extract was evaluated against the selected bacterial strains using broth dilution method. Mueller-Hinton broth (50 µL) was added to each well in the 96 micros well plate followed by addition of 50 µL of 100 mg/mL of the extract in the first row. Serial dilution was performed to vary the concentrations. About 50 µL of the fresh bacterial cultures was separately pipetted into the wells. Ciprofloxacin was used as a positive control while 5% DMSO as a negative control. Thereafter, the plate was sealed and incubated at 37 °C for 24 hours. P-Iodonitrotetrazolium violet (40 µL; 0.2 mg/mL) was poured into all wells as a cell viability indicator. The plate was then incubated at 37 °C for 15 minutes. The lowest concentration that inhibited the bacterial growth of the tested strains was considered as the MIC.[18]

Minimum bactericidal concentration (MBC)

Bactericidal effect of the extract was assessed on nutrient agar (NA). The wells that demonstrated no visible bacterial growth during MIC evaluation were streaked on NA plates. Thereafter, the agar plates were incubated at 37 °C, overnight. The lowest concentration to kill the selected strains was considered as MBC.[19]

Anti-quorum sensing activity

Inoculum preparation

C. violaceum (ATCC 07) was resuscitated on Lysogeny broth (LB) and incubated at 37 °C, overnight. The fresh culture was then adjusted to the inoculum density of 1×10^6 CFU/mL using a spectrophotometer (Spectroquant-Pharo 100).

Inhibition of quorum sensing potential

The effect of the extract on inhibition of violacein production by the biosensor bacterial strain- *C. violaceum* (ATCC 107). The strain was cultured aerobically in LB at 30 °C with varying sub-MIC concentrations of the extract (< MIC). *C. violaceum* that was untreated with the extract served as the control. About 2 mL of an overnight culture was centrifuged at 12000 rpm for 15 minutes to precipitate the insoluble violacein. The supernatant was discarded and the pellet was evenly re-suspended in 200 µL of methanol (technical grade, Merck). The solution was centrifuged at 12000 rpm for 15 minutes to remove the cells. Thereafter, 100 µL of the supernatant was transferred to a 96 micro-well plate and the optical density (OD) was read at 585 nm using a UV-Vis spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan). Violacein inhibition was expressed as inhibition percentage measured by the formula: % inhibition = untreated control $OD_{585\ nm}$ - test $OD_{585\ nm}$ / untreated control $OD_{585\ nm}$ x 100.[20]

Molecular docking simulations

Computer-based molecular docking method was employed in order to understand the molecular interactions involved during the inhibition of bacterial growth and violacein production based on the binding scores and types of bonds formed by the GC-MS identified compounds and ciprofloxacin with the receptor proteins. Penicillin-binding protein 2x (PDP2) is a membrane-associated enzyme essential for cell growth as it is associated with peptidoglycan biosynthesis.[21] CviR is a regulatory protein that triggers transcription of *vioABCD* operon which is responsible for violacein production in *C. violaceum*.[22] The three-dimensional structures of PDP2 and CviR were retrieved from Protein Data Bank (PDB ID: 1QMF and 3QP1, respectively). Then proteins were optimized by deleting water molecules, heteroatoms and other ligands prior to addition of polar hydrogens using Discovery Studio tool.[23] Thereafter, the chemical structures of the GC-MS identified compounds were procured from PubChem online database and energy minimized using UCSF Chimera.[24] AutoDock Vina was then used to execute molecular docking study of the prepared ligands and target proteins and the best docked conformations were selected based on their binding scores.[25] Discovery Studio visualizer was employed in visualization and analysis of the docked complexes.

Statistical analysis

Experiments were all done in triplicate and data was expressed as mean ± standard deviation. The statistical analyses were performed by one-way analysis of variance and considered to be significantly different at $p < 0.05$.

RESULTS AND DISCUSSION

Phytochemical analysis

The pharmaceutical importance of medicinal plants lies in their chemical composition. A qualitative phytochemical evaluation of the *E. dregei*`s was investigated using well established methods. The phytochemicals; alkaloids, flavonoids, glycosides, saponins, steroids,

tannins and terpenoids were analysed and the results are displayed in Table 1. The extract demonstrated the presence of all the tested classes of phytochemicals. The bioactivity of plant extracts was attributed to phytochemical constituents.[26]

GC-MS identified compounds

The GC-MS chromatogram displayed the presence of 3, 7, 11, 15-tetramethyl-hexadecen-1-ol also known as phytol (93.58%) and 3-tetradecyn-1-ol (6.42%) (Table 2). Phytol is a diterpene that is recognised for its antimicrobial activity.[27] 3-Tetradecyn-1-ol is an alcoholic compound which is also reported to have antibacterial property.[28] These compounds were assumed to have contributed to the observed bioactivity of the extract.

The constant increase in antimicrobial resistance to most aliphatic drugs necessitate an intense search for compounds with potent antibacterial effect. In the present study, the antibacterial activity of the methanolic *E. dregei*`s leaf extract was evaluated against four common pathogenic bacteria, including a Gram-positive bacterium (*Staphylococcus aureus* (ATCC 25925)) and two Gram-negative bacteria (*K. pneumoniae* (ATCC 4352) and *C. viocelaceum* (ATCC 07)) and the results are summarized in Table 3. The MIC values for the extract varied from 0.78 to 3.13 mg/mL. *S. aureus* (ATCC 25925) as the most sensitive strain with the MIC value of 0.78 mg/mL whereas the other bacterial strains displayed the MIC value of 3.125 mg/ml. Thus, it was observed that the activity of the extract was profound against the Gram-positive strain with a noteworthy activity (MIC value less than 1 mg/mL) than the Gram-negative strains. Thus, the differences in the bioactivity of the extract against the classes of bacterial strains was associated with the differences in the cell walls of the strains. Gram-negatives in comparison to Gram-positive bacteria, have phospholipid membranes with structural lipopolysaccharide components that enable their cell wall impermeability to some antimicrobial agents.[29] Parvez *et al.*[30] observed similar results whereby the extract`s antibacterial activity was more profound against the Gram-positive than Gram-negative strains. The observed antibacterial activity of the *E. dregei*`s leaf extract was attributed to the synergistic effects of the different antibacterial compounds within the extract.

Table 1: The qualitative phytochemical analysis of *Erianthemum dregei*.

Phytochemicals	Presence of phytochemicals
Alkaloids	+
Flavonoids	+
Glycosides	+
Saponins	+
Steroids	+
Tannins	+
Terpernoids	+

Key: + denotes presence and – denotes absence

Table 2: Volatile constituents of the extract.

Number of compounds	Compounds	Area (%)
1	Phytol	6.42
2	3-Tetradecyn-1-ol	93.58

Table 3: MIC AND MBC values of the extract against the selected bacterial strains.

Bacteria	Extract		Ciprofloxacin	
	MIC (mg/mL)	MBC (mg/mL)	MIC (µg/mL)	MBC (µg/mL)
S. aureus (ATCC 25925)	0.78	> 50	0.2	0.3
K. pneumoniae (ATCC 4352)	1.56	> 50	0.13	1.56
C. viocelaceum (ATCC 107)	3.13	> 50	0.39	0.78

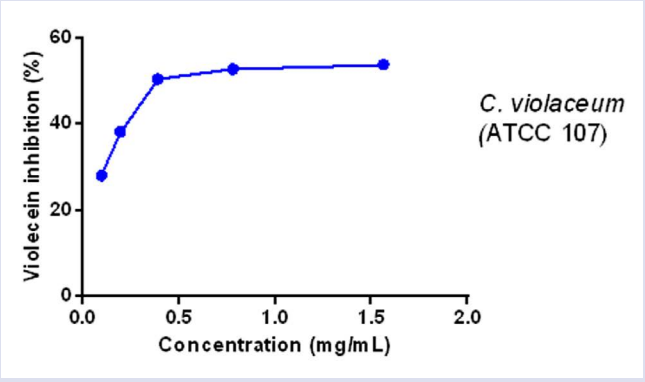

Figure 1: Anti-quorum sensing activity of the extract.

Anti-quorum sensing activity

Plant-based compounds are reported to offset gene expression responsible for virulence and pathogenesis by hindering QS and other related activities.[31] Thus, the anti-QS activity of the *E. dregei*`s extract was assessed on its ability to inhibit violacein production in *C. violaceum* strains and the results are displayed in Figure 1. The extract revealed moderate activity against *C. violaceum* (ATCC 107) with the maximum inhibition of violacein production at 53.93 mg/mL. The extract demonstrated moderate (violacein inhibition > 40%) inhibitory effect against violacein production. This means that the extract has potential to disrupt cell to cell communication system, consequently leading to attenuation of bacterial virulence.[32] The violacein inhibition was attributed the synergistic action of the identified volatile compounds and classes of phytochemicals. In conclusion, the extract has potential to inhibit virulence factor production without inhibiting bacterial growth and this can alleviate selection pressure on microbial communities, resulting in the reduction of antimicrobial resistance.[33] Jovanović *et al.*[34] also observed similar results whereby the plant extracts displayed anti-QS against *C. violaceum*.

Molecular docking

Antibacterial activity mechanism

AutoDock Vina was used to simulate the interaction of the GC-MS identified ligands and ciprofloxacin against the antibacterial target protein, penicillin-binding protein 2x (ID 1QMF), which is common among bacterial strains. The molecular structures of both of ligands showed moderate interaction with PBP2 with the docking score of -5.6 and -5.0 kcal/mol against phytol and 3-tetradecyn-1-ol, respectively (Table 4). The lower values indicate very decent fitness of the ligands in the binding pocket of the receptor showing that ligands have established good interaction with receptor. Moreover, the free energy scores suggest that phytol has more binding affinity for PBP2 than 3-tetradecyn-1-ol. However, the positive control-ciproflaxaxin demontrated better binding affinity than the test ligands with the free energy score of -7.0 kcal/mol. Nevertheless, it can be concluded that both test ligands (phytol and 3-tetradecyn-1-ol) are involved in inhibition of cell wall synthesis as they revealed moderate binding capacity with PBP2, which is involved in peptidoglycan biosynthesis of the cell wall in bacterial strains.[35]

The binding of ligands to receptors are governed by the concept of chemical bonding. Intermolecular interactions play a vital role in the binding chemistry between the ligands and the receptors.[36] To analyse the types of interactions formed between the ligands and PBP2, the desirable poses were visualized by discovery studio. The amino acids, LYS A:219 and ASP A:221 of the active site of PBP2 interacted with phytol through H-bond (Table 4, Figure 2 and 3). On the other hand, LYS A:218 and LYS A:219 interacted with 3-tetradecyn-1-ol by H-bond

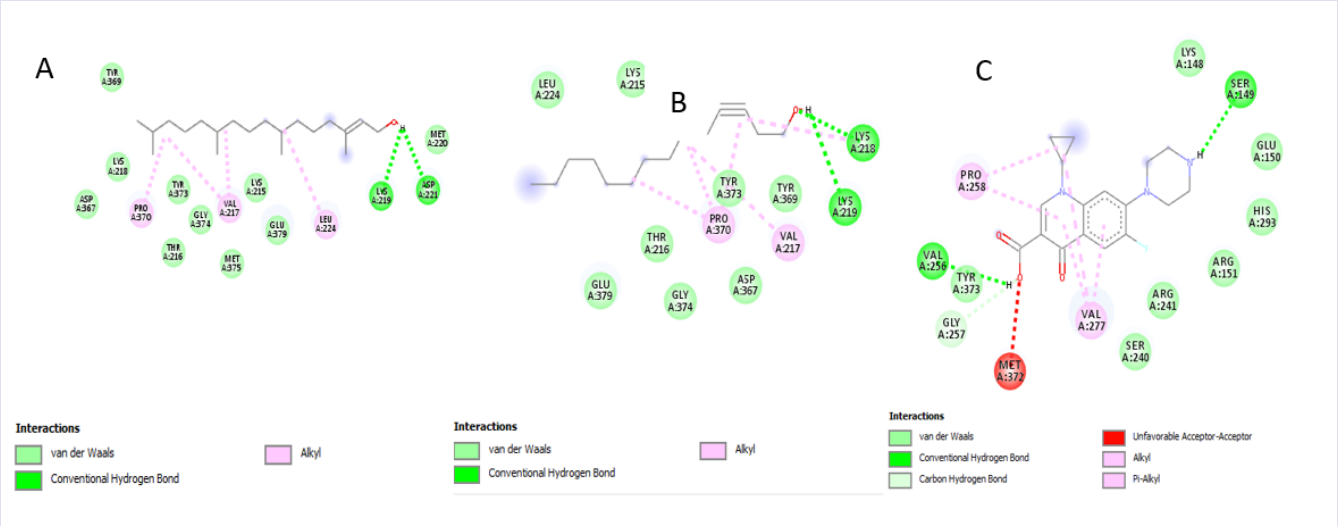

Figure 2: The 2D structures of the interactions between the ligands and PBP2: A phytol- PBP2, B 3-tetradecyn-1-ol-PBP2 and C ciprofloxacin-PBP2.

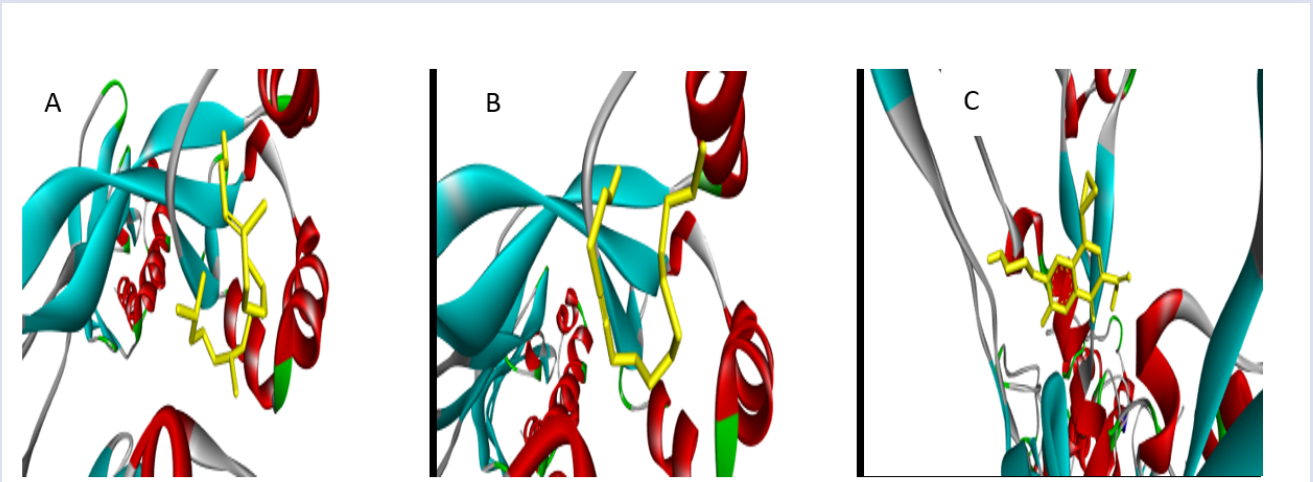

Figure 3: The 3D structures of the ligands (yellow) docked with PBP2. A phytol-PBP2, B 3-tetradecyn-1-ol-PBP2 and C ciprofloxacin-PBP2.

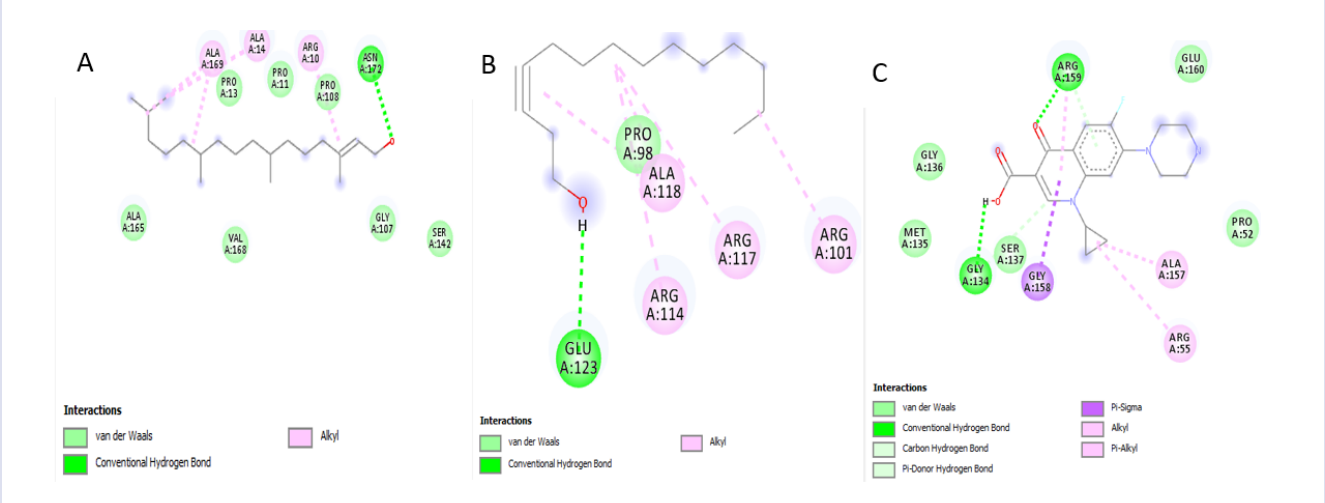

Figure 4: The 2D structures of docked complexes. A phytol-CviR, B 3-tetradecyn-1-ol-CviR and C ciprofloxacin-CviR.

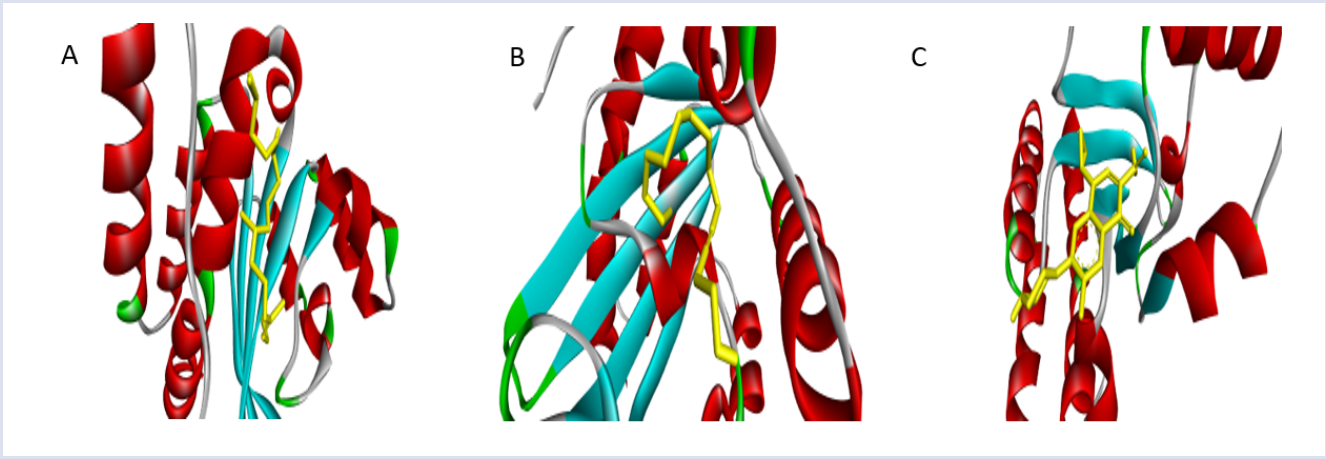

Figure 5: The 3D structures of docked ligands (yellow) inside the binding pocket of CviR. A phytol-CviR, B 3-tetradecyn-1-ol-CviR and C ciprofloxacin-CviR.

Table 4: Free energy scores and H-bond interactions of the ligands with PBP2.

Compounds	Binding scores (kcal/mol)	H-bonds interaction residues
Phytol	-5.6	LYS A:219 and ASP A:221
3-Tetradecyn-1-ol	-5.0	LYS A:218 and LYS A:219
Ciprofloxacin	-7.0	VAL A:256 and SER A:149

Table 5: Free energy scores and H-bond interactions of the ligands with CviR.

Compounds	Binding scores (kcal/mol)	H-bonds interaction residues
Phytol	-4.2	ASN A:172
3-Tetradecyn-1-ol	-3.2	GLU A:123
Ciprofloxacin	-6.3	ARG A:159 and GLY A:134

(Table 3 and Fig). H-bonds are important in drug-target interactions as they are responsible for stabilisation of ligand-receptor protein complexes, consequently leading to inhibition bacterial growth.[37] The other types of bonds that were revealed by both ligands with PBP2 are alkyl and van der Waals bonds. Alkyl bond is a covalent bond. Covalent bonds are strong and hence ligands forming them often bind permanently to their target. Thus, it is expected that both ligands will strongly bind to PBP2 and result in cell suppression. VAL A:256 and SER A:149 formed H-bonding with the hydroxyl group of the ciprofloxacin. Carbon hydrogen, alkyl, pi-alkyl and van der Waals bonds were also formed between ciprofloxacin and PBP2.

Anti-quorum sensing mechanism

C. violaceum use CviR to regulate the production of violacein. QS inhibitors tend to bind to CviR, consequently interfering with the CviR-dependent quorum-sensing pathways.[38] Thus, the docking study was carried out in order to understand the interaction of the GC-MS identified ligands against the QS regulator protein-CviR and the results are shown in Table 5, Figure 4 and 5. Phytol exhibited the docking score of -4.2 kcal/mol. It formed hydrogen bond with the amino acid residue ASN A:172. The other revealed interactions are van der Waal and alkyl bonds. The 3-tetradecyn-1-ol had a docking score of -3.2 kcal/mol with CviR receptor and formed hydrogen bond with the amino acid residue GLU A:123. It also formed van der Waal and alkyl bonds. The binding scores of both test ligands were relatively higher than that of the positive control-ciprofloxacin. Thus, we concluded that the test GC-MS identified compounds exhibited lower affinity than ciprofloxacin with the QS receptor protein. As stated earlier, the effectiveness of the compounds is strongly dependent on the binding energy and the type of bonds formed with the receptors.[39] Thus, although the ligands have lower binding affinity than ciprofloxacin, they still have potential to interact with CviR, consequently inhibiting QS system. The results were similar to those obtained by other researchers.[40]

CONCLUSION

E. dregei extracts showed the presence of all tested classes of phytochemicals which are considered responsible for the plant`s bioactivity. The methanol extract exhibited moderate inhibitory effect against the growth of the selected bacterial strains and violacein production by *C. violaceum*. The computed binding scores suggested the GC-MS components to have potential to inhibit PBP2 and CviR with varying binding affinities, consequently leading to antibacterial and anti-quorum sensing activities. For future studies, *in vivo* studies are recommended.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest in this manuscript.

ABBREVIATIONS

E. dregei: *Erianthemum dregei*; ATCC: American Type Culture Collection; *S. aureus*: *Staphylococcus aureus*; *C. viocelaceum*: *Chromobacterium violaceum; K. pneumoniae*: *Klebsiella pneumoniae*; CFU: colony forming units; MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration; rpm: revolution per minute; µg/mL: microgram/milliliter; g: gram; mL: millimeter; °C: degree Celsius; µL: microliter; %: percent; GC-MS: gas chromatography-mass spectrometry; GC: gas chromatography; MS: mass spectrometry; INT: p-iodonitrotetrazolium violet.

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