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Invitro Evaluation of Antibacterial Activity and In-Silico Insights of CanariumSchwenfurthii against Multi-Drug Resistant *Klebsiella pneumoniae*

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ABSTRACT

Klebsiella pneumoniae, a member of the *Enterobacteriaceae* family, naturally resides in the gut microbiome of both healthy humans and animals. This pathogen is frequently found in hospitals and takes advantage of opportunities to cause infections. It is responsible for approximately one third of infections caused by Gram-negative bacteria. This study aim to identify new inhibitors of Canariumschweinfurthii that can effectively combat multidrug resistant *K. pneumoniae*. This was achieved through the use of molecular docking analysis. The ethanol and methanol solvents were used to extract the leaves of Canariumschweinfurthii. The results indicated that the ethanol extract exhibited a substantial inhibitory zone compared to the methanol extract. Seventeen (17) substances were found by GC-MS analysis. These compounds were subsequently filtered out using physicochemical and pharmacokinetics studies, based on Lipinski's five rule, Egan, and ADMET tool. Six (6) of the 17 compounds were found to exhibit pharmacological properties. These compounds were subjected to molecular docking with CTXM protein derived from multidrug resistant *K. pneumoniae*. The docking analysis results indicate that the compounds CID_143696, CID_5363192, CID_569391, CID_135403803, CID_534521, and CID_439726 have a favorable docking score. Therefore, these compounds can be regarded as potential new inhibitors for multidrug resistance in *K. pneumoniae*.

Keywords: *Klebsiella pneumoniae; Canariumschweinfurthii; multidrug resistant; Pharmacokinetics;inhibition.*

INTRODUCTION

Klebsiella pneumoniae (*K. pneumoniae*) is a facultative anaerobic, encapsulated, non-motile, Gram-negative bacteria that was first isolated from the airways of a patient who was dying of pneumonia in 1875(Chang et al., 2021).*Klebsiella* species including *K. ozaenae*, *K. rhinoscleroma*, and *K. pneumoniae*, the latter of which is a significant opportunistic and iatrogenic infectious pathogen with significant clinical consequences, colonizes the nasal and digestive tract without causing any symptomatic disease(Martin & Bachman, 2018).*Klebsiella* commonly inhabits the nose and digestive tract in humans without creating any clinical symptoms. However, colonization can transition into an infection when the host's immune system is unable to regulate the growth of the pathogen. This can occur in individuals with conditions such as diabetes, those undergoing glucocorticoid therapy, and individuals who have undergone organ transplantation (Martin & Bachman, 2018).

The proliferation of antibiotic resistance in pathogenic bacteria such as *K. pneumoniae* poses an increasingly urgent global public health concern. The presence of this condition not only raises the rates of illness and death in patients, but also extends their time in the hospital and raises the expenses associated with their treatment.Currently, strains of *K. pneumoniae* are acknowledged as a pressing menace to human well-being due to the rise of multi-drug resistant (MDR) strains linked to outbreaks in hospitals. Its high medication resistance has garnered global interest, particularly in industrialized nations. The prevalence of antimicrobial resistance in *K. pneumoniae* has consistently risen over time, resulting in near-universal resistance to the entire spectrum of antibiotics. Medicinal plants yield many chemical compounds that provide biological activities and protect against various predators like insects, fungi, yeasts, bacteria, viruses, and other pathogens. Chemicals found in plants affect the human body via the same processes as chemical compounds in traditional medications (Hejazi et al., 2021).

Canarium schweinfurthii has long been utilized in traditional medicine due to its wide range of therapeutic characteristics, notably its potential as an antibiotic. Essential oils extracted from *C. schweinfurthii* has been reported to posses wound healing potential (Bonnard et al., 2022), biodiesel synthesis (Eze et al., 2022), and anti-termitic activity (Nagawa et al., 2015). The dried fruit of *C. schweinfurthii* has been used to treat bacterial and viral infections, inflammation,

poisoning and for detoxification. Investigating the antibacterial properties of *C. schweinfurthii* compounds against multi drug resistant *K. penumoniae* has the potential to offer a natural and alternative reservoir of novel antibiotic medicines.

MATERIAL AND METHODS

Plant Sample Collection

The Department of Botany at the University of Maiduguri collected freshly harvested leaves of *Canarium schweinfurthii* from the mother tree in the morning for accurate identification. Following identification, the leaves were transported to the Microbiology department for processing. The leaves were thoroughly cleansed and thereafter subjected to natural air-drying for a period of 3 to 5 days within the confines of the laboratory, maintaining the ambient room temperature. Once the leaves were dried, they were ground using a mortar and then sifted to obtain a fine powder of *C. schweinfurthii*.

Plant extraction

The *C. schweinfurthii* plant was extracted using the ethanolic and methanolic methods outlined by(Teinkela et al., 2023). The plant materials were extracted using ethanol and methanol. 100 g of pulverized *C. schweinfurthii* was suspended in 500 ml of ethanol and 500 ml of 95% methanol correspondingly. The suspensions were allowed for 24 hours and then filtered using Whatman filter paper (No. 1). The ethanolic and methanolic extracts were subjected to evaporation at ambient temperature. The resulting residues were dissolved in distilled water and 95% ethanol at a concentration of 0.5 g/ml and stored in a refrigerator at a temperature of 4°C until they were used.

Antibacterial Activity of Methanol and Ethanol Extracts of *C. schweinfurthii*

The antibacterial properties of *C. schweinfurthii* extracts were assessed using the Agar Well Diffusion technique. A sterile glass spreader was used to aseptically disseminate the bacterium suspension (*K. pneumoniae*) onto the surface of Mueller Hinton agar. The agar plates were desiccated, and circular wells with a diameter of 10 mm were excised from the agar using individual sterile cork-borers. The wells were subsequently filled with varying concentrations (25, 50, 75, and 100 mg/ml) of *C. Schweinfurthii*. The antibacterial activity was assessed by

measuring the diameter of the zone of inhibition. The measurements of the zones of inhibition were recorded in millimeters (mm).

GC-MS Analysis

The method used by Alghamdi et al. (Alghamdi et al., 2023) was adopted in this study.Briefly, 10 grams of Canarium schweinfurthii was added to 10 milliliters of methanol and mixed thoroughly by vortexing for 2 minutes before being centrifuged at 3000 rpm for 10 minutes. The clear supernatant obtained after centrifugation was transferred to a tiny vial for GC-MS analysis. GC analysis was carried out first by inserting 1 µl of the supernatant. Gas Chromatography analysis was conducted with Agilent 7890B technology, while Mass Spectrometry was performed with Silent 5977A technology. The GC-MS utilizes a carrier gas composed of helium flowing at a constant rate of 1 ml/min. The Gas Chromatography oven was preheated to 70 °C for 3 minutes before being raised to 280 °C for the analysis. The temperature remained constant for around 9 minutes. The equilibration time is set at 0.5 minutes, with the MSD Transfer line temperature at 250 °C, MS Source temperature at 230 °C, and MS Quad temperature at 150 °C. Chemical substances were found and identified by analyzing the retention time generated by Gas Chromatography. The mass spectrum was compared to the database of the National Institute of Standards and Technology.

Physicochemical Analysis

The compounds obtained from GC-MS analysis were evaluated for their physicochemical parameters such as molecular weight, lipophilicity, number of hydrogen-bond donors (HBAs), and number of hydrogen-bond acceptors (HBDs) using the Data Warrior tool.

Preparation of Crystal of CTXM

The Klebsiella pneumoniae protein (CTXM) was bound to GDP and 9PC in the 4DXD PDB entry received from the Protein Data Bank (PDB). The ligand in the bound CTXM structure was extracted and thoroughly cleaned. Unchecked components such as atoms, residues, loops, and side chains were reviewed and subsequently added. The Chimera, Swiss PDB Viewer, and Chiron energy minimization and refinement tool were utilized to remove water molecules that were distant from the substrate's binding site and non-protein residues by optimizing the structure and minimizing energy.

Pharmacokinetic Analysis

The compounds with favorable binding energy and physicochemical properties were assessed for pharmacokinetic characteristics such as absorption, distribution, metabolism, and excretion using the AdmetSAR tool following the method outlined by (GÖRGÜLÜ & DEDE, 2021)and DataWarrior program. Additional qualities discovered are Blood brain barrier, Cytochrome P450, Human Intestinal Absorption, Mutagenicity, Tumorigenicity, Reproduction, and Irritant.

Molecular Docking

Docking study was conducted to confirm the interaction between a protein and a ligand, resulting in a protein-ligand complex using AutoDock 4.2 as utilized by Morris et al.(Morris et al., 1998). The validation of the complex binding will unveil the binding energy between CTXM and the chosen ligands. The binding energy and residues were accurately documented.

RESULTS

Antibacterial activity of Methanol and Ethanol extract of *Canarium schweinfurthii* for Zone of Inhibition

The antimicrobial properties of methanol and ethanol extracts from *C. schweinfurthii* at various doses (25, 50, 75, and 100 mg/dl) were evaluated against isolates of Multidrug-resistant Klebsiella pneumoniae by examining the presence or absence of inhibitory zones. The antibacterial activity was evaluated by measuring the inhibition zone. The methanol extract of *C. schweinfurthii* showed the largest inhibition zone of 8.00 mm at concentrations of 75 and 100 mg/dl, with no inhibition zone observed at concentrations of 25 and 50 mg/dl. The Ethanol extract of *C. schweinfurthii* exhibited a maximal concentration of 21.00 mm at 75 mg/dl, followed by 10.00 mm at 100 mg/dl. No zone of inhibition was observed at 25 and 50 mg/dl (Table 1).

S/N	Compound	Formula	Molecular Weight	Retention Time(min)	Peaks	PubChem ID
1	3-Methyl-hexanoic acid	$C_7H_{14}O_2$	130	5.951	2	CID_95315
2	Decanoic acid, 3-methyl	$C_{11}H_{22}O_2$	186	5.951	2	CID_143696
3	β-D-Glucopyranose, 1,6-anhydro-	$C_6H_{10}O_5$	162	6.746	3	CID_2724705
4	Nonanoic acid	$C_9H_{18}O_2$	158	6.746	3	CID_8158
5	Cyclohexane, 1-(1,5-dimethylhexyl)-4-(4-methylpentyl)-	$C_{20}H_{40}$	280	10.036	6	CID_41687
6	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	$C_{20}H_{40}O$	296	10.494	7	CID_5366244
7	(1S,15S)-Bicyclo[13.1.0]hexadecan-2-one	$C_{16}H_{28}O$	236	11.369	9	CID_13760785
8	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	256	11.518	10	CID_985
9	cis-Vaccenic acid	$C_{18}H_{34}O_2$	282	13.263	12	CID_71309566
10	7-Hydroxy-3-(1,1-dimethylprop-2-enyl) coumarin	$C_{14}H_{14}O_3$	230	14.413	14	CID_5363192
11	2-Isopropyl-5-methylcyclohexyl 3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate	$C_{30}H_{33}ClO_6$	524	16.948	16	CID_537118
12	Acetophenone, 2-[(p-nitrophenyl) imino]-	$C_{14}H_{10}N_2O_3$	254	19.683	18	CID_569391
13	Uridine, 2',3'-O-(phenyl methylene)-	$C_{16}H_{16}N_2O_6$	332	19.683	18	CID_90472112
14	Pterin-6-carboxylic acid	$C_7H_5N_5O_3$	207	19.683	18	CID_135403803
15	4-Fluoro-1-methyl-5-carboxylic acid, ethyl(ester)	$C_7H_9FN_2O_2$	172	27.03	23	CID_534521

16	Estra-1,3,5(10)-trien-17β-ol	$C_{18}H_{24}O$	256	27.03	23	CID_439726
17	Tetracontane, 3,5,24-trimethyl-	$C_{43}H_{88}$	604	30.452	27	CID_41344

Table 1: **Zone of Inhibition of Methanol and Ethanol Extract of *C. schweinfurthii* extract against Multidrug resistant *K. pneumoniae***

Extracts	25 mg/dl	50 mg/dl	75 mg/dl	100 mg/dl
Methanol	0.00	0.00	8.00	8.00
Ethanol	0.00	0.00	21.00	10.00

Compounds identified from *C. schweinfurthii* using GC-MS

The methanolic extract of Canarium schweinfurthii was analyzed using gas chromatography and mass spectrometry (GC-MS) to identify the phytochemical components found in the leaves. GC-MS analysis revealed the various components of phytochemicals together with their compound names and chemical formulas. Additional characteristics examined are the peak value and retention time of phytochemicals. Analysis of the methanolic extract of Canarium schweinfurthii detected seventeen (17) compounds. CID_95315 (C7H14O2) has the lowest molecular weight of 130 kcal/mol, while CID_41344 (C43H38) has the greatest molecular weight of 604 kcal/mol (Table 2).

Table 2: Identified compounds using GS-MS

Physiochemical Analysis of Compounds obtained from *Canariumschweinfurthii*

The physicochemical analysis revealed that all identified phytochemical compounds adhere to Lipinski's five rules and Egan's rules, except for CID_41687, CID_5366244, CID_13760785, CID_985, CID_71309566, CID_537118, and CID_41344, which have a logarithm of the partial coefficient greater than 5. Compound CID_41344 has a molecular weight of 605 Da, above the 500 Da limit. Excluding CID_41687, CID_5366244, CID_13760785, CID_985, CID_71309566, CID_537118, and CID_41344, all remaining compounds have drug-like properties (Table 3).

Table 3:Physiochemical Analysis of Compounds from GC-MS

S/N	PubChem ID	Molecular weight (≤500)	Number of HBA (≤10)	Number of HBD (≤5)	MolLogP (≤5)	Drug likeness
1	CID_95315	130.186	2	1	1.7368	-5.4072
2	CID_143696	186.294	2	1	3.5544	-21.515
3	CID_2724705	162.140	5	3	-1.9745	-0.45711
4	CID_8158	158.240	2	1	2.8817	-25.216
5	CID_41687	280.538	0	0	7.3351	-3.8753
6	CID_5366244	296.537	1	1	7.4212	-3.7661
7	CID_13760785	236.397	1	0	5.4416	-8.1075
8	CID_985	256.428	2	1	6.0625	-25.216
9	CID_71309566	283.458	2	1	6.7191	-26.101
10	CID_5363192	230.262	3	1	3.0993	-4.5992
11	CID_537118	525.039	6	0	-7.507	-22.803
12	CID_569391	254.244	5	0	0.9107	-4.9571
13	CID_90472112	332.311	8	2	-0.8355	0.35878
14	CID_135403803	207.149	8	3	-1.7866	1.0774
15	CID_534521	172.158	4	0	0.7781	-1.9363
16	CID_439726	256.388	1	1	4.7287	-3.2187
17	CID_41344	605.172	0	0	18.899	-18.387

Pharmacokinetic Analysis of the Phyto-compounds detected from *C. schweinfurthii*

All the substances were found to be capable of crossing the blood-brain barrier efficiently, as indicated by pharmacokinetic analysis. All identified substances were shown to not inhibit Cytochrome P450. All compounds, with the exception of CID_2724705, were found to be

absorbed in the human gut. Except for CID_90472112, not all chemicals have the capability to induce DNA alterations. All chemicals are non-tumorigenic except for CID_985, which exhibited strong tumorigenic activity. All chemicals were not replicable except for 537118. With the exception of CID_95315, CID_8158, CID_985, and CID_537118, none of the compounds contain irritants. Compounds with unfavorable pharmacokinetic profiles were removed (Table 4).

Table 4: Pharmacokinetic Analysis of the Phyto-compounds detected from *C. schweinfurthii*

S/No.	Compound name	BBB	CYP2D6 inhibitor	HIA	Mutagens	Tumorigens	reproducibility	Irritant
1	CID-95315	+	Non inhibitor	+	None	None	None	High
2	CID-143696	+	Non inhibitor	+	None	None	None	None
3	CID-2724705	+	Non inhibitor	_	None	None	None	None
4	CID-8158	+	Non inhibitor	+	None	None	None	High
5	CID-41687	+	Non inhibitor	+	None	None	None	None
6	CID-5366244	+	Non inhibitor	+	None	None	None	None
7	CID-13760785	+	Non inhibitor	+	None	None	None	None
8	CID-985	+	Non inhibitor	+	None	High	None	High
9	CID-71309566	+	Non inhibitor	+	None	None	None	None
10	CID-5363192	+	Non inhibitor	+	None	None	None	None
11	CID-537118	+	Non inhibitor	+	None	None	High	High
12	CID-569391	+	Non inhibitor	+	None	None	None	None
13	CID-90472112	+	Non inhibitor	+	High	None	None	None
14	CID-135403803	+	Non inhibitor	+	None	None	None	None
15	CID-534521	+	Non inhibitor	+	None	None	None	None
16	CID-439726	+	Non inhibitor	+	None	None	None	None
17	CID-41344	+	Non inhibitor	+	None	None	None	None

Docking Scores and Residues Involved in H-Bond Formation

Docking study was performed on 10 phytochemical compounds that passed pharmacokinetics screening to assess their binding energies with the Klebsiella protein (CTX-M). The docking analysis revealed binding energies ranging from -4.00 kcal/mol to -7.04 kcal/mol. Six compounds, specifically CID_143696, CID_5363192, CID_569391, CID_135403803, CID_534521, and CID_439726, generate residues that participate in hydrogen bonding. The

residues are: Lys227, Arg229, Trp204, Leu200, Gln197, Val206, Kys257, Leu263, Thr260, Gly199 (Table 5).

Table 4.5: Docking Scores and Residues Involved in H-Bond Formation

S/no.	Compound Id	Docking score (kcal/mol)	Residues involve in H-bonds	Distance (Å)
1	CID_143696	-5.18	Lys227	2.70
			Arg229	3.23
			Trp204	3.23
2	CID_5363192	-5.99	Leu200	2.82
			Gln197	2.79
			Val206	2.67
3	CID_569391	-6.31	Lys257	2.95
				3.05
4	CID_135403803	-5.12	Leu263	2.47
			Thr260	3.21
			Gly199	2.56
			Lys257	2.55
				2.73
				2.89
5	CID_534521	-4.00		
7	CID_439726	-7.04	Leu200	2.47
			Gln197	2.73

DISCUSSION

The study aimed to find the chemical components in *C. schweinfurthii* that have therapeutic action against multidrug-resistant Klebsiella pneumoniae. *C. schweinfurthii* leaves were freshly gathered, air-dried, and extracted with methanol and ethanol solvents. Antibiotic sensitivity was assessed using the well diffusion method to measure the zone of inhibition. Ethanol extract of the plant exhibited a significant inhibition zone of 21.00 mm at a concentration of 75 mg/dl and 10.00 mm at 100 mg/dl. In comparison, methanol showed an inhibition zone of 8.00 mm at both 75 mg/dl and 100 mg/dl concentrations. There was no zone of inhibition observed at doses of 25 and 50 mg/dl for both ethanol and methanol extracts of *C. schweinfurthii*. The strong inhibitory effect demonstrated by the ethanol extract of *C. schweinfurthii* aligns with Owolabi's findings(Owolabi et al., 2020).

Molecular docking analysis was utilized to identify new inhibitors of *C. schweinfurthii* against multidrug-resistant *K. pneumoniae*. Gas Chromatography Mass Spectroscopy (GC-MS) was

employed to identify the phytochemical compounds of *C. schweinfurthii*. Seventeen compounds were identified. The substances underwent physicochemical investigation, pharmacokinetic analysis, and docking score analysis. The substance found in Canarium schweinfurthii is comparable to the chemicals identified by Mogana et al. (Mogana et al., 2011), who also reported several of the chemical compounds identified in this study.

The approach adopted by Pai and Shenoy (Pai & Shenoy, 2020)was utilized to determine the physicochemical analysis of the phytochemical compounds. This involved evaluating the compounds' metabolism, therapeutic safety, and specificity as determined by Gas Chromatography Mass Spectroscopy. The compounds were screened using the formulas of Lipinski et al. (Lipinski et al., 1997)and Egan (Egan et al., 2000) to determine their physicochemical qualities; these formulas are consistent with the process utilized for developing novel drugs. The Lipinski's 5 rules establish that for a chemical compound to be considered therapeutic, it must have a molecular weight of 500 Da or less, a lipophilicity (LogP) of 5.58 or less, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and exhibit drug similarity. Egan rule on the hand states that for a compound to have characteristics of drug likeness it must have a lipophilicity (LogP) of ≤ 5.58 and a topological polar surface area (TPSA) of ≤ 131. Out of the seventeen (17) compounds evaluate, only seven (7) compounds failed Lipinski five rule and Egan rule; these are CID_41687, CID_5366244, CID_13760785, CID_985, CID_71309566, CID_537118 and CID_41344. Out of the entire failed compound, only CID_41344 has the highest molecular weight of 605 Da while the other compounds have lipophilicity ≥ 5.58.

According to Marc et al(Marc et al., 2019), the use of pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and toxicity (ADMET) are use during drug development especially when evaluating the therapeutic effectiveness and safety of the compound.The pharmacokinetic characteristics of phytochemical substances were assessed

utilizing the AdmetSAR method as utilized by (James et al., 2023)and (Isa et al., 2022). Factors influencing the pharmacokinetic characteristics of the chemicals are Blood Brain Barrier (BBB), Cytochrome P450 (CYP2D6), Human Intestinal absorption (HIA), mutagenicity, tumorigenicity, reproducibility, and irritating qualities.Pharmacokinetic analysis showed that all the compounds passes through Blood Brain Barrier and they all not non-inhibitor of Cytochrome P450. Compound CID_2724705 was not considered as a drug because it cannot be readily absorbed by the human intestine, while CID_90472112 and CID_985 have properties of mutagens and tumorigens.

Six of the 17 compounds (CID_143696, CID_5363192, CID_569391, CID_135403803, CID_534521 and CID_439726) successfully passed the set physicochemical and pharmacokinetics analysis. These compounds were then docked with the protein of *K. pneumoniae* (CTXM) and their docking scores were evaluated. All docking scores show high affinity for binding. Molecular docking score ranges from – 4.00 kcal/mol to – 7.04 kcal/mol. They residues produce by this compound after binding with CTXM include Lys227, Arg229, Trp204, Leu200, Gln197, Val206, Lys257, Leu263, Thr260, Gly199.

CONCLUSION

Methanolic extract of *C. schweinfurthii* revealed17 phytochemical compounds on GC-MS analysis. Eleven of these compounds failed the Lipinski and Egan rule. The remaining six compounds were docked and show good binding affinity with CID_439726 showing the best docking score. The study suggests that the six chemicals found in *C. schweinfurthii* leaves may be effective in treating infections triggered by multidrug resistant strains of *K. pneumoniae*.

Recommendation

This study's results support the idea that further research into plants and plant-based products is needed to develop chemicals that can help treat illnesses that are resistant to several drugs.

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