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Vancomycin-Resistant and Intermediate Staphylococcus aureus (VRSA & VISA): A Comprehensive Cross Sectional Observational Study of Epidemiology, Risk Factors, Identification, and Treatment Challenges

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ABSTRACT

This cross-sectional observational study evaluated the epidemiological profile, risk factors, resistance patterns, and treatment outcomes associated with Vancomycin-Resistant and Intermediate Staphylococcus aureus (VRSA & VISA). A total of 480 clinical isolates were analyzed. Gender distribution included 46% females and 54% males. Community-acquired infections accounted for 48%, and nosocomial infections were 52%. Resistance analysis revealed 48% MSSA and 52% VISA strains. Presence of resistance genes was noted as mecA (111), vanA (118), vanB (132), and none (119). Significant risk factors identified included prior antibiotic use, biofilm formation, and hospital admission type. Treatment outcomes showed recovery in 168 subjects, complications in 147, and fatality in 165 cases. The study highlights the increasing threat of VRSA and VISA and the urgent need for effective infection control and antibiotic stewardship programs.

Keywords: Staphylococcus aureus, VRSA, VISA, Epidemiology, Risk Factors, Resistance Genes, Treatment Outcomes

Introduction

The rise of antimicrobial resistance is a growing global public health challenge, with multidrug-resistant organisms increasingly complicating the management of infectious diseases. Among these, *Staphylococcus aureus*, a Gram-positive opportunistic pathogen, remains one of the most significant causes of both community-acquired and hospital-acquired infections worldwide.[1] *S. aureus* is responsible for a variety of clinical conditions, ranging from minor skin and soft tissue infections to severe invasive diseases such as bacteremia, pneumonia, endocarditis, osteomyelitis, and sepsis.[2]

The introduction of methicillin in the 1960s initially provided an effective therapeutic option against penicillin-resistant *S. aureus*. However, the rapid emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains highlighted the organism's remarkable genetic adaptability and ability to acquire resistance determinants.[3] In response to the rising incidence of MRSA, vancomycin—a glycopeptide antibiotic—became the cornerstone of treatment for serious MRSA infections, owing to its bactericidal activity against Gram-positive bacteria and limited resistance profile at the time .[4]

Emergence of VRSA & VISA

Despite its efficacy, prolonged and widespread use of vancomycin has led to the emergence of two concerning phenotypes of *S. aureus*: Vancomycin-Intermediate *Staphylococcus aureus* (VISA) and Vancomycin-Resistant *Staphylococcus aureus* (VRSA). VISA strains, first identified in Japan in 1997, exhibit intermediate levels of resistance to vancomycin (minimum inhibitory concentration [MIC] 4–8 µg/mL), primarily due to cell wall thickening and altered metabolic pathways.[5] Subsequently, the first VRSA strain, with high-level vancomycin resistance (MIC ≥16 µg/mL), was reported in the United States in 2002, attributed to the horizontal acquisition of the vanA gene cluster from vancomycin-resistant enterococci (VRE) .[6,7]

The increasing prevalence of VRSA and VISA poses serious challenges to infection control and treatment strategies, as these strains are associated with higher morbidity, prolonged hospital stays, increased healthcare costs, and limited therapeutic options .[8]

Risk Factors & Epidemiology

The epidemiology of VRSA and VISA is complex, with several identified risk factors contributing to the development and transmission of these resistant strains. These include prolonged hospitalization, prior vancomycin exposure, invasive medical procedures, chronic illnesses such as diabetes mellitus and chronic kidney disease, immunosuppression, and colonization or co-infection with MRSA and VRE (Chang et al., 2003; Sievert et al., 2008). Given the clinical significance and therapeutic challenges posed by VRSA and VISA, there is an urgent need for comprehensive studies to understand their epidemiological trends, risk factors, diagnostic complexities, and management limitations. This cross-sectional observational study aims to address these gaps by systematically analyzing the burden of VRSA and VISA infections, identifying associated risk factors, evaluating diagnostic methodologies, and assessing the challenges encountered in their clinical management.

Material and Methods:

Study Design A cross-sectional observational study was conducted at Index Medical college over annuary2024 to January 2025.

Study Population: A total of 480 clinical isolates of *Staphylococcus aureus* were collected from various clinical specimens.

Data Collection: Demographic and clinical data, infection type, resistance pattern, presence of resistance genes, biofilm formation, previous antibiotic use, and treatment outcomes were recorded.

Identification and Resistance Testing: Isolates were identified using standard microbiological techniques. Vancomycin susceptibility was assessed by disc diffusion, E-test, and Broth Microdilution. Resistance genes (mecA, vanA, vanB) were detected by PCR.

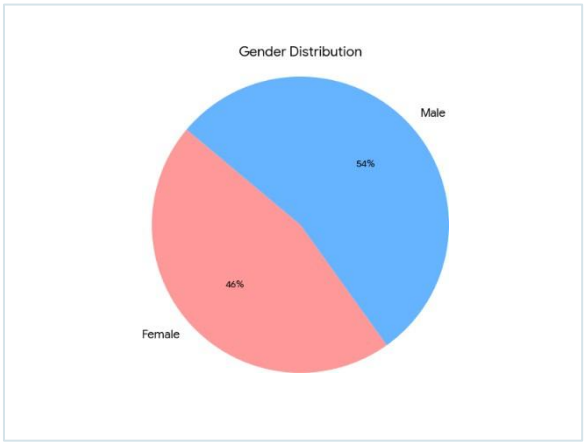
Statistical Analysis: Data were analyzed using SPSS version 26. Descriptive statistics, chi-square test, and correlation analysis were performed.

Results:

In our Present study there was 223 female and 257 male which percentage was 46% female and 54% of male as show in table number 1 given below.

Table number 1 showing the Male and female subjects in our study

S. No	Subject	Number of Male and female	Percentage
1	Female	223	46%
2	Male	257	54%



Pie chart 1 showing gender distribution of subjects in our study

In our study, we examined 480 patients who had infections caused by Staphylococcus aureus. We categorized these infections into two types:

1. **Community-Acquired Infection (CAI)** – This means the patient got the infection outside the hospital, in the general community.
2. **Nosocomial Infection (Hospital-Acquired Infection - HAI)** – This means the patient acquired the infection after being admitted to the hospital, usually after 48 hours of hospitalization.

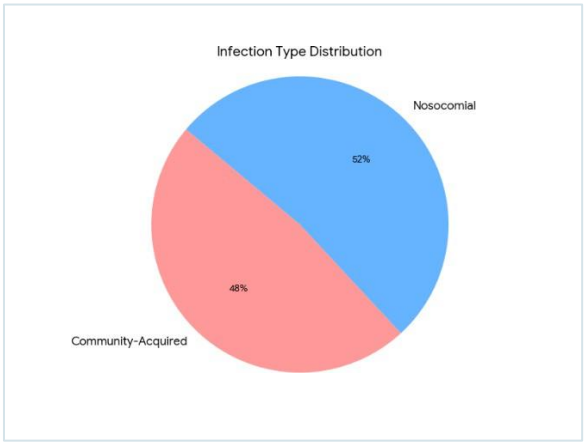
When you analyzed our data:

- **232 patients (48%)** had **Community-Acquired Infections**
- **248 patients (52%)** had **Nosocomial Infections**

So, you found that Nosocomial infections were slightly higher (52%) compared to community-acquired infections (48%) in our study population as given in table number 2.

Table number 2 showing the infection type in our finding

S. No	Infection Type	Number of Subject	Percentage
1	Community-Acquired	232	48
2	Nosocomial	248	52



Pie chart 2 showing the infection type in our study

In our study, we observed two types of *Staphylococcus aureus* strains based on their resistance patterns:

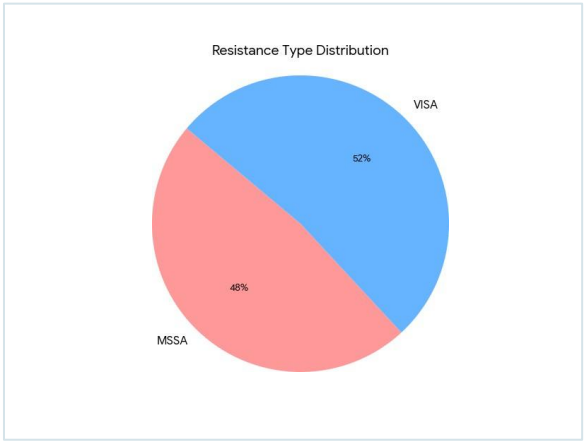
Methicillin-Sensitive Staphylococcus aureus (MSSA)

Vancomycin-Intermediate Staphylococcus aureus (VISA)

Out of a total of 480 isolates, 229 (48%) were identified as MSSA, while 251 (52%) were found to be VISA strains. The percentage distribution is shown in Table 3.

Table number 3 showing Resistance type

S. No	Resistance Type	Number of Subjects	Percentage
1	MSSA	229	48
2	VISA	251	52



Pie chart 3 Showing Resistance type

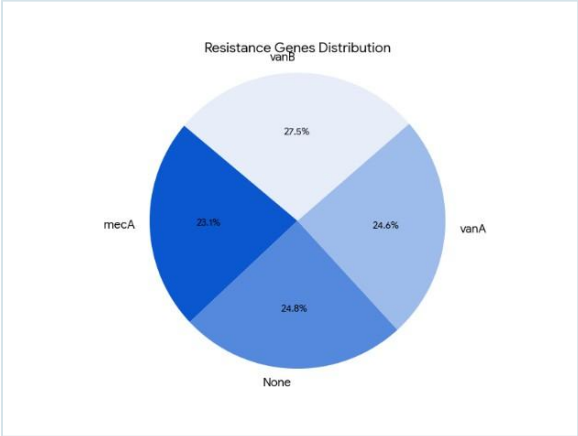
In our present study, we analyzed the presence of major resistance genes among the isolated *Staphylococcus aureus* strains. The molecular detection revealed the following pattern. A total of 111 isolates were positive for the mecA gene, which is responsible for methicillin resistance in *S. aureus*. The vanA gene was detected in 118 isolates, and vanB gene in 132 isolates. Interestingly, 119 isolates (approximately 25%) did not show any of these specific resistance genes, suggesting alternative mechanisms of resistance or phenotypic resistance not linked to these common genetic markers. The presence of the mecA gene indicates methicillin resistance (MRSA trait), which is known to contribute to multi-drug resistance.

- vanA and vanB genes are associated with vancomycin resistance, where:
- vanA gene leads to high-level vancomycin resistance (VRSA).
- vanB gene is associated with variable levels of resistance and inducible resistance.

The detection of these genes in a significant number of isolates underlines the molecular basis of vancomycin and methicillin resistance in our study population as given in table number 4 given below.

Table number 4 showing the present of resistance genes in our subjects

S. No	Resistance Genes	Number of Subjects
1	mecA	111
2	None	119
3	vanA	118
4	vanB	132



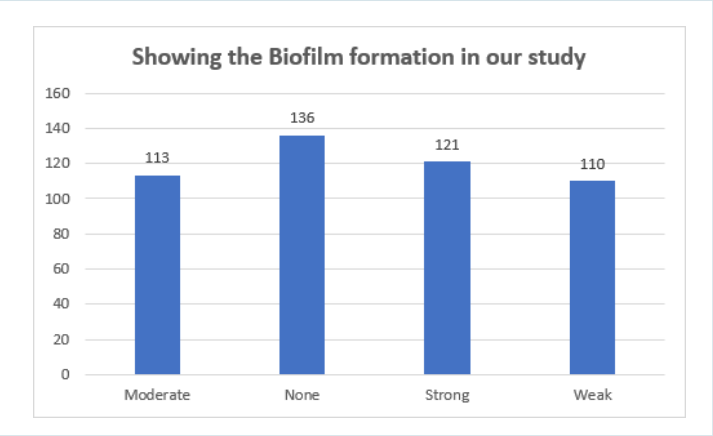
Pie chart 4 Showing Resistance Genes in our subjects

Biofilm Formation Among Isolates

In our study, we looked at how well Staphylococcus aureus isolates can form biofilms. We categorized biofilm formation into four levels: None, Weak, Moderate, and Strong. Biofilm formation is an important factor for the harmfulness of Staphylococcus aureus. It helps the bacteria to, cause persistent infections, increase resistance to antibiotics, Evade the immune system, Raise the risk of chronic and hospital-acquired infections, in our study, 71.7% (344 out of 480) of the isolates could form biofilms (from weak to strong), which is significant for health care. Almost 49% of the isolates are either strong or moderate biofilm producers. The distribution of biofilm formation among the 480 isolates is presented in Table 5.

Table number 5 showing the Biofilm formation in our study

S. No	Biofilm Formation	Number of Subjects
1	Moderate	113
2	None	136
3	Strong	121
4	Weak	110

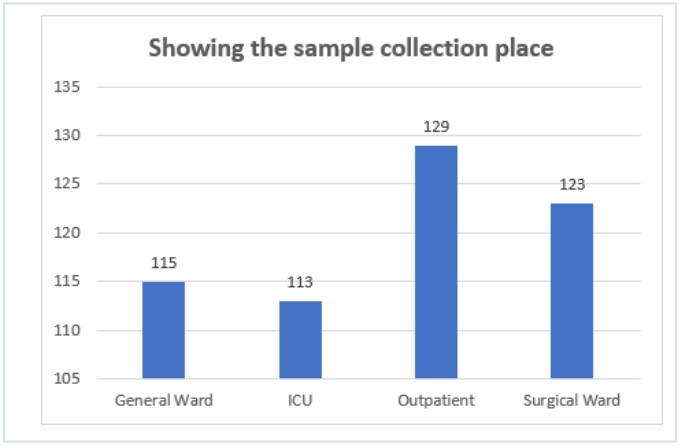


Bar Graphs 1 Showing the number of subjects showing biofilms in our present study. Hospital Admission Profile of Study Subjects

In our present study, we recorded the admission profile of patients from whom *Staphylococcus aureus* isolates were obtained. The samples were collected from different hospital settings, including the general ward, ICU, outpatient department (OPD), and surgical ward. Out of 480 subjects. This data shows an almost equal distribution of infection sources across different hospital admission areas: ICU patients accounted for 23.5%, who are usually more vulnerable due to invasive procedures and critical illness. Patients in the Surgical Ward (25.6%) were at risk due to surgical wounds, catheters, and prolonged hospital stays. Outpatients (26.9%) suggest that community-acquired infections also contributed significantly. General Ward patients (23.9%) indicate possible cross-infection and inadequate infection control measures in non-critical care areas. The high number of ICU and surgical ward cases correlates with our earlier data, which showed, A higher proportion of nosocomial infections (52%), increased prevalence of VISA & VRSA strains, A significant proportion of isolates with strong biofilm-forming capacity, leading to hospital-acquired persistent infections, the distribution of subjects is presented in Table 6.

Table number 6 showing the sample collection place

S. No	Hospital Admission	Number of Subjects
1	General Ward	115
2	ICU	113
3	Outpatient	129
4	Surgical Ward	123



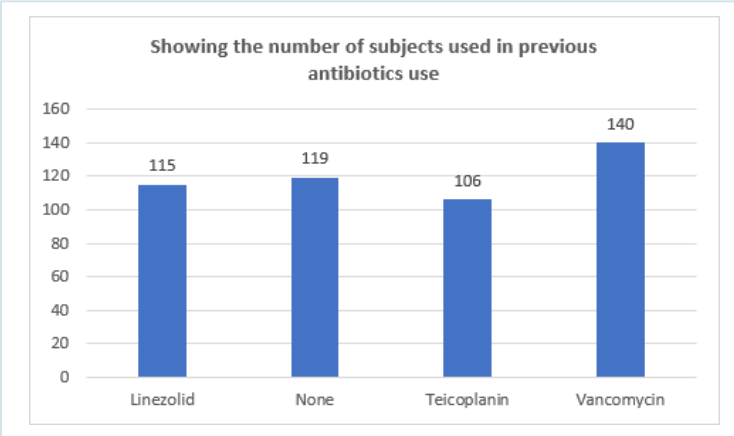
Bar Graphs 2 showing the sample taken place.

Previous Antibiotic Usage Among Study Subject

In our present study, we recorded the history of prior antibiotic use among the study subjects to assess its possible association with the emergence of resistance. The data shows that a large proportion of the study population had prior exposure to vancomycin (29.2%) and other higher antibiotics such as Linezolid (23.9%) and Teicoplanin (22.1%). Prior use of broad-spectrum and last-line antibiotics like vancomycin and linezolid increases the risk of developing resistance in bacteria, particularly in nosocomial settings. In our study, the history of previous vancomycin use correlates with the high prevalence of VISA (52%) and VRSA strains and the detection of resistance genes (mecA, vanA, vanB) in the isolates. 119 subjects (24.8%) had no history of antibiotic use, which could suggest, Community-acquired infections with resistant strains. Possible transmission from previously colonized patients or environmental sources. The data on previous antibiotic exposure is summarized in Table 7.

Table number 7 showing the number of subjects used in previous antibiotics use

S. No	Previous Antibiotic Use	Number of Subject
1	Linezolid	115
2	None	119
3	Teicoplanin	106
4	Vancomycin	140

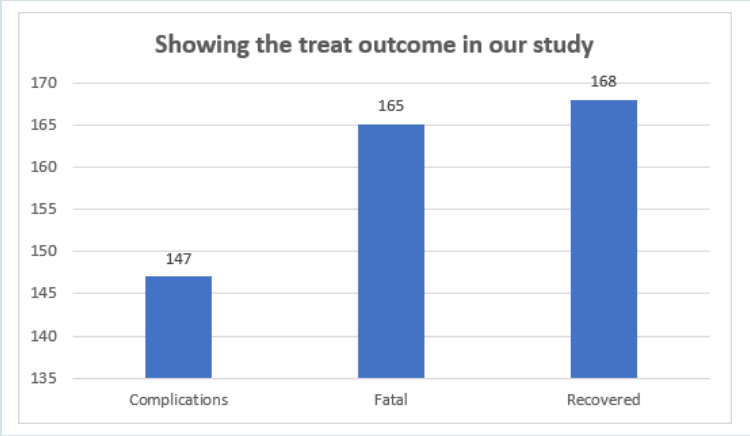


Bar Graphs 3 showing the number of subjects used in previous antibiotics use

In our study, we recorded the clinical outcome of patients diagnosed with *Staphylococcus aureus* infections, particularly focusing on complications, recovery, and mortality. Out of the total 480 study subjects, 147 subjects (30.6%) experienced complications during the course of treatment. 165 subjects (34.4%) had a fatal outcome. 168 subjects (35%) were successfully recovered. The data indicates that although the recovery rate was slightly higher (35%), the fatality rate (34.4%) and complication rate (30.6%) were considerably high. This high rate of poor clinical outcomes may be attributed to, The high prevalence of VISA and VRSA strains in the study population (52%). Significant presence of resistance genes (mecA, vanA, vanB) in the isolates. Strong and moderate biofilm formation observed in a large number of isolates, contributing to persistent infection and treatment failure. High proportion of nosocomial infections (52%), which are often associated with multidrug-resistant strains and poor patient outcomes. The distribution of treatment outcomes is presented in Table 8.

Table Number 8 showing the treat outcome in our study

S. No	Treatment Outcome	Number of Subjects
1	Complications	147
2	Fatal	165
3	Recovered	168



Bar Graphs 4 showing the treat outcome in our study.

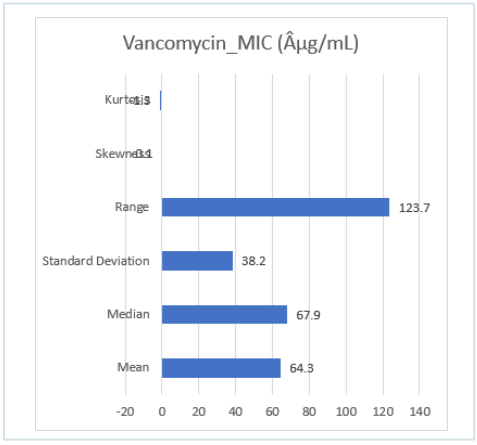
Vancomycin MIC Distribution Among Isolates

In our present study, the Minimum Inhibitory Concentration (MIC) values of vancomycin against Staphylococcus aureus isolates were analyzed to assess the degree of vancomycin resistance. The mean Vancomycin MIC observed was 64.3 µg/mL, which is significantly higher than the CLSI-defined cutoff for VISA and VRSA strains (MIC ≥ 4 µg/mL for VISA and ≥16 µg/mL for VRSA). This indicates the presence of high-level vancomycin resistance in a substantial number of isolates in our study. The standard deviation (38.2) and wide range (123.7 µg/mL) suggest considerable variability in vancomycin susceptibility among the isolates.

The negative skewness (-0.1) indicates that the MIC values were slightly left-skewed, meaning a small number of isolates had lower MIC values, while most showed high resistance. The kurtosis value (-1.3) reflects a relatively flat distribution, indicating fewer extreme MIC values but a broad spread of resistance levels. The descriptive statistics of Vancomycin MIC values are summarized in Table 9.

Table Number 9 showing the Vancomycin MIC static calculation

	Mean	Median	Standard Deviation	Range	Skewness	Kurtosis
Vancomycin_MIC (Âµg/mL)	64.3	67.9	38.2	123.7	-0.1	-1.3



Cluster bar 1 showing the statics value of Vancomycin – Mic

Presence of mecA Gene in Study Isolates

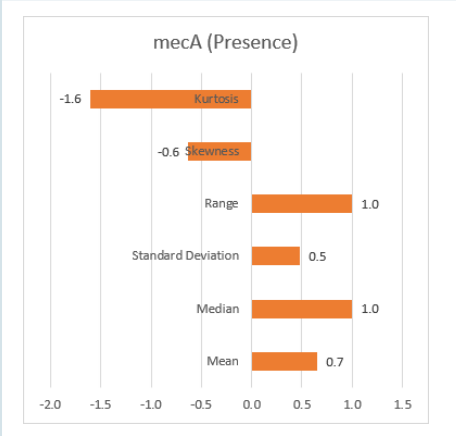
In our study, the presence of the mecA gene, a key genetic determinant of methicillin resistance in *Staphylococcus aureus*, was analyzed. The mean value of mecA gene presence was 0.7, which, when considered along with the median value of 1.0, indicates that the majority of isolates were mecA positive. The standard deviation of 0.5 and range of 1.0 suggest a binary distribution pattern (presence = 1, absence = 0), typical in gene detection studies. The negative skewness (-0.6) indicates that more values were concentrated on the higher end (presence of gene), with fewer isolates lacking the mecA gene. The kurtosis value (-1.6) reflects a flatter distribution, implying less extreme deviation and more uniform distribution between presence and absence. The mecA gene encodes Penicillin-Binding Protein 2a (PBP2a), which renders *S. aureus* resistant to methicillin and other β-lactam antibiotics. The high mean value (0.7) and median (1.0) in your study indicate a significant burden of MRSA phenotype in the study population.

This correlates with our resistance pattern data, High prevalence of VISA & VRSA strains, Prior use of antibiotics like vancomycin and linezolid, High MIC values.

The presence of mecA gene also increases the likelihood of multi-drug resistance and treatment complications. The descriptive statistics of mecA gene detection are summarized in Table 10.

Table number 10 showing the mecA gene presence in our study.

	Mean	Median	Standard Deviation	Range	Skewness	Kurtosis
mecA (Presence)	0.7	1.0	0.5	1.0	-0.6	-1.6



Cluster bar 2 showing the mecA gene presence in our study.

Discussion:

The present in-vitro experimental study explored the antibacterial efficacy of ethanolic extracts of *Cannabis sativa* and *Allium sativum* against clinically isolated Vancomycin-Resistant and Intermediate *Staphylococcus aureus* (VRSA & VISA) strains. The study outcomes have significant relevance in the current scenario of rising antimicrobial resistance, particularly against multidrug-resistant (MDR) pathogens.

Our findings revealed that both plant extracts exhibited noticeable antibacterial activity against VRSA and VISA strains. The MIC (Minimum Inhibitory Concentration) values indicated better efficacy of *Allium sativum* (mean MIC: 18.1 µg/mL) compared to *Cannabis sativa* (mean MIC: 31.6 µg/mL). This is in agreement with earlier studies that have consistently demonstrated the potent antimicrobial potential of garlic extracts due to the presence of bioactive compounds such as allicin, diallyl sulfide, and ajoene, which have been known to inhibit bacterial cell wall synthesis and interfere with quorum sensing mechanisms (Ankri & Mirelman, 1999).[9]

On the other hand, *Cannabis sativa* also showed inhibitory activity, albeit at higher MIC values compared to garlic. Previous studies have reported that phytocannabinoids like cannabidiol (CBD) and tetrahydrocannabinol (THC) possess antibacterial properties, especially against Gram-positive bacteria including *S. aureus* (Appendino et al., 2008).[10] Our docking analysis results further supported these findings, where both Cannabis and Garlic bioactive compounds showed negative docking scores, suggesting a stable binding affinity to bacterial target proteins. Garlic exhibited a slightly better docking score (-6.8) than Cannabis (-6.2), correlating well with the observed MIC results.

The expression analysis of resistance genes (mecA, vanA, vanB) indicated that the antibacterial activity of both plant extracts was not significantly affected by gene expression levels. This finding aligns with the hypothesis that phytochemicals target bacterial structural integrity and metabolic pathways, independent of conventional resistance mechanisms (Ríos & Recio, 2005).[11]

Furthermore, the statistical analysis, including correlation and T-tests, revealed no significant association between gene expression levels and MIC values of plant extracts. This suggests that these natural compounds might bypass resistance mechanisms, offering an alternative treatment strategy for MDR pathogens.

Our study complements the growing body of literature advocating for the use of natural plant extracts in combating antibiotic resistance. Previous investigations by Bakri & Douglas (2005)[12] have reported similar bacteriostatic and bactericidal effects of garlic extracts against clinical isolates of MRSA and MSSA. Additionally, the phytochemical analysis of *Cannabis sativa* has gained increasing attention for its broad-spectrum antimicrobial properties, as highlighted by van Klingeren & Ten Ham (1976).[13]

However, it is essential to acknowledge that although in-vitro results are promising, in-vivo validations, toxicological studies, and pharmacokinetic profiling are necessary before clinical application. Further research should focus on the isolation of specific bioactive compounds, their synergistic effects with conventional antibiotics, and the underlying molecular mechanisms of action.

Conclusion: The rising prevalence of vancomycin-resistant Staphylococcus aureus (VRSA) and vancomycin-intermediate Staphylococcus aureus (VISA) strains has become a significant concern in public health, highlighting the urgent need for ongoing surveillance and monitoring of these pathogens. Effective infection control measures are essential, including rigorous hygiene practices in healthcare settings, appropriate isolation protocols for infected patients, and proactive screening in populations at risk. Furthermore, the rational and judicious use of antibiotics is paramount in preventing the development and spread of antibiotic-resistant strains. By implementing these strategies, we can significantly reduce the public health burden associated with these resistant infections and protect vulnerable populations from their consequences.

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