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Article

Hydrocortisone Impairs the Activity of Antimicrobial Drugs against Clinical Isolates of *Staphylococcus aureus*

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Abstract: The clinical use of antimicrobials has increased the chances of cure and life expectancy. However, indiscriminate use and/or incorrect prescription have aggravated the worrying scenario of bacterial resistance. In antimicrobial therapies, the combined use of corticosteroids aims to modulate the inflammatory process triggered by the infection and prevent adverse reactions from antimicrobials such as nephrotoxicity. Several combinations are available as topical formulations, and they are commonly prescribed in the same device for intravenous administration in hospitals. Notwithstanding eventual benefits, the safety of these combinations remains poorly investigated. The aim of the present study was to conduct *in vitro* tests to assess the interference of hydrocortisone on the antimicrobial activity of some drugs against clinical isolates of *Staphylococcus aureus* and to provide insights into the chemical nature of such interactions. Tests of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were performed with and without the addition of hydrocortisone (HYDRO). Chemoinformatics data on predicted NMR, GC-MS and FTIR spectra of the drugs to obtain chemical data that could support a more detailed analysis of potential interaction. HYDRO elevated MIC and MBC of oxacillin, and abrogated the activity of gentamicin and chloramphenicol, suggesting that these combinations may pose a risk to clinical treatments. More studies should be carried out in animal models to confirm these effects *in vivo*.

Keywords: hydrocortisone; interaction; antimicrobials; *Staphylococcus aureus*

1. Introduction

Bacteria can undergo changes in their genome to adapt to the environment in which they find themselves for reasons that include the scarcity of nutrients and exposure to bacteriostatic or bactericidal compounds [1]. With the increased indiscriminate use of antimicrobials, a growing picture of bacterial resistance is observed, and resistant strains can spread the genes associated with resistance mechanisms to others, even those of different genera. The situation is considered a threat to public health worldwide [1,2]. Combinations of more than one type of antimicrobial are common for clinical treatments, especially given the risk of bacterial resistance. In this context, combinations of antimicrobials with corticosteroids are mostly used to control the inflammatory process associated with the infection, and to prevent eventual critical adverse reactions of the antimicrobials such as chondrotoxicity, nephrotoxicity, retinopathy, ototoxicity, cytokine-mediated neurotoxic effects and anaphylaxis [3]. However, investigations on the safety and efficacy of these combinations are still scarce.

Staphylococcus aureus is a Gram-positive and facultative anaerobic species part of the human microbiota, but it can present a pathogenic profile and cause infections such as meningitis, endocarditis and on the skin and soft tissues, with growing resistance to antimicrobials [4]. Patients in critical state due to *S. aureus* infections are often treated using combinations of antimicrobials and corticosteroids, and it seems to be an effective strategy for the treatment of infectious diseases [5–8]. However, previous research provided evidence that dexamethasone, a highly used corticosteroid, can decrease the activity of different antimicrobials against bacterial pathogens, suggesting that the combination offers risk of treatment failures [6,7]. In view of the above, there is a need to evaluate the effects of other relevant combinations, considering the risks of harm to patients' health. The aim of the present study was to conduct *in vitro* tests on possible interferences of hydrocortisone (HYDRO) on antimicrobials used in the treatment of *S. aureus* infections.

2. Materials and Methods

2.1. Preparation of the Drugs

The antimicrobials (Figure 1) used were gentamicin, chloramphenicol and oxacillin (Sigma-Aldrich, St. Louis, MO, USA). Stock solutions of 4 mg/mL were prepared by dilution in sterile water. HYDRO (Sigma) was prepared at a concentration of 1 mg/mL also in sterile water.

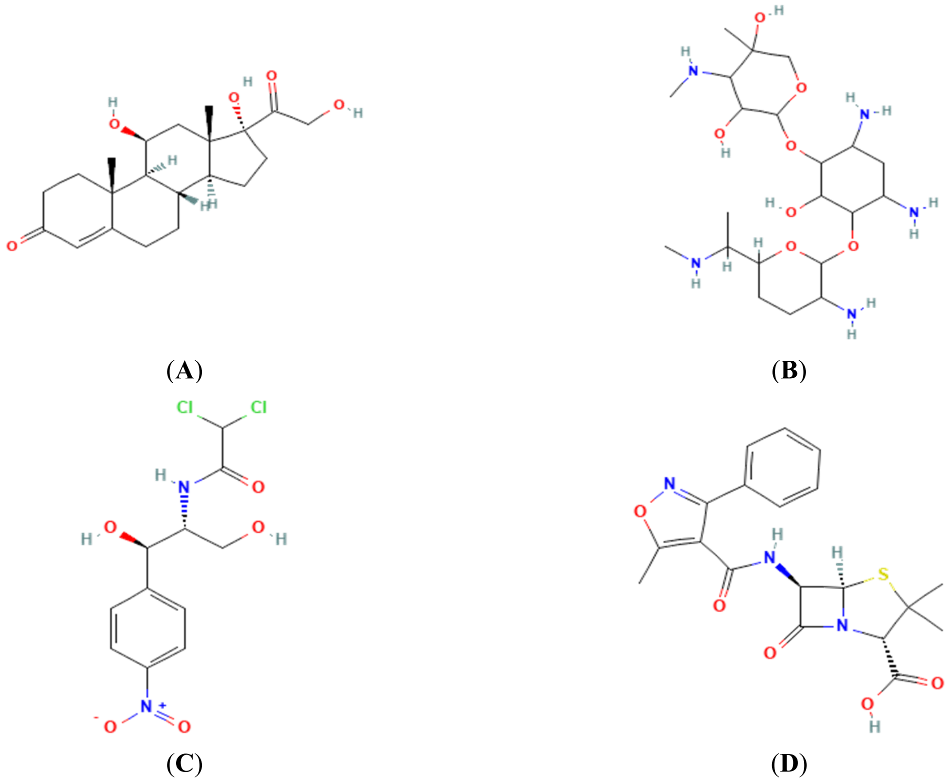

Figure 1. Drugs tested in this study. (**A**): HYDRO; (**B**): gentamicin; (**C**): chloramphenicol; (**D**): oxacillin. Structures were retrieved from PubChem.

2.2. Preparation of Microorganisms

The microorganisms used in the study were from the collection of the Microbiology Laboratory at UNIVALE. For antimicrobial activity tests, the broth microdilution methodology was used with flat bottom 96-well untreated polystyrene plates. The microbial inoculum was prepared in Mueller-Hinton broth, at a cell concentration of 1 on the McFarland turbidity scale (~3×10^8 CFU/mL). The optical density was adjusted by spectrophotometric readings (absorbance of 1.0 at 600 nm). A total of 10 isolates were used, and they had their identity confirmed using VITEK 2 system (version R04.02, BioMérieux SA, Marcy-l'Étoile, France) with Gram-positive identification cards, following the manufacturer's instructions.

2.3. Minimum Inhibitory Concentration (MIC)

MIC assay was conducted as previously described [7]. Each well containing the diluted drug received 100 µL of the standardized bacterial suspension, and thus, the bacterial suspension had its concentration reduced to 0.5 on the MacFarland scale, and the drug concentration was reduced by half reaching 1000 to 7.8 µg/mL. The plates were incubated at 35 ± 2 °C overnight. On the following day, resazurin (0.1 g/L) staining was used. Plates remained in a dark spot for 10 min at 35 ± 2 °C. The result was interpreted as follows: the lowest concentration in the wells where the blue-colored resazurin became pink (resofurin) was considered the MIC. This experiment was conducted in triplicate.

2.4. Minimal Bactericidal Concentration (MBC)

MBC assay was performed as described [7], with slight modifications. Spots were made with 10 µL of the content of each well of MIC assay plates on Mueller-Hinton agar plates. A negative control consisting of the drug in Mueller-Hinton broth was used. After the formation of the spots, the plates were incubated at 35 ± 2 °C overnight. After incubation, the plates were visualized to verify the growth of colonies. The concentration of the extract in which there was no bacterial growth was considered the MBC. This experiment was conducted in triplicate.

2.5. HYDRO Interference Test

The interference of HYDRO on the antimicrobial activity of the drugs that were tested was evaluated as follows: the entire MIC and MBC protocols were repeated with the addition of 50 µL of a 1 mg/mL solution of HYDRO (Sigma Aldrich, St. Louis, MO, USA). In the process of obtaining the results, comparisons were made with drugs without the addition of HYDRO. This experiment was conducted in triplicate.

2.6. Chemoinformatics

Spectral data of predicted nuclear magnetic resonance (NMR), Fourier transform infrared spectroscopy (FTIR) and gas chromatography coupled to mass spectrometry (GC-MS) of the tested drugs were obtained from PubChem, Human Metabolome Database, Spectral Database for Organic Compounds, and SpectraBase. NMR data are from ^{13}C analyses, GC-MS data are of positive mode and non-derivatized molecules, and FTIR data are of KBr disk-based analyses. Oxacillin FTIR data was described by Coşkun et al. [9]. All data is freely available at the mentioned databases and paper and under Creative Commons Attribution 4.0 International (CC-BY-4.0) license. We explored ChemMine tools to determine Tanimoto similarity scores for each combination tested *in vitro*. We used *.SDF extension files from *PubChem* of 3D configuration of the molecules to calculate the scores.

3. Results

3.1. In Vitro Experiments

The antimicrobial susceptibility assays indicated interference of HYDRO on the activity of the tested antibiotics against clinical isolates of *S. aureus*. In the absence of HYDRO, gentamicin, chloramphenicol, and oxacillin exhibited inhibitory and bactericidal effects consistent with expected susceptibility profiles for clinical isolates. However, the addition of HYDRO to the assay system significantly altered these outcomes, with effects varying according to the antimicrobial class and, in the case of oxacillin, the individual isolate. As summarized in Table 1, the antimicrobial activity of gentamicin and chloramphenicol was completely abrogated in the presence of HYDRO. Under these conditions, no inhibitory effect was observed within the tested concentration range, precluding the determination of MIC and MBC values, which were therefore classified as undetectable. This antagonistic effect was consistently observed across all isolates evaluated, suggesting a drug-specific interaction. Importantly, HYDRO alone did not display antimicrobial activity against the tested strains (data not shown), confirming that the observed effects resulted from interference with antibiotic activity rather than intrinsic bacteriostatic or bactericidal properties of the corticosteroid.

In contrast, the interaction between HYDRO and oxacillin exhibited marked heterogeneity among isolates. While oxacillin maintained partial activity against several strains when combined with HYDRO, elevated MIC and MBC values were observed overall (Table 1), reflecting a reduction in antimicrobial efficacy. Notably, three isolates (3, 7, and 8) demonstrated complete loss of oxacillin activity in the presence of HYDRO, whereas the remaining isolates retained susceptibility at higher concentrations. This variability suggests that isolate-specific factors may influence the extent of hydrocortisone-mediated interference. Strain-specific variability can influence the susceptibility and interactions results observed in this study, particularly regarding the heterogeneous response to oxacillin. Clinical bacterial isolates differ in cell wall composition, expression of drug-target proteins and stress responses.

Table 1. Antimicrobial activity of drugs combined or not to HYDRO.

Parameter	GEN	GEN + HYD	CHLO	CHLO + HYD	OXA	OXA+HYD
MIC	250 µg/mL	Ø	500 µg/mL	Ø	781 µg/mL	625 µg/mL ***
MBC	$x > 1$ mg/mL	Ø	$x > 1$ mg/mL	Ø	1562 µg/mL	500 µg/mL

MIC: Minimum Inhibitory Concentration; MBC Minimum Bactericidal Concentration; Ø: abrogated antimicrobial activity; GEN: Gentamicin; CHLO: Chloramphenicol; OXA: Oxacillin; +HYD: associated with HYDRO. *** Isolates 3, 7 and 8: Oxacillin activity has been completely abrogated.

3.2. Chemoinformatics Analysis

To explore whether physicochemical similarities among the tested compounds could contribute to the observed antagonistic effects, predicted chemoinformatics analyses were conducted (Figures 2–4). Comparative evaluation of predicted ^{13}C NMR spectra demonstrated overlapping chemical shift regions among HYDRO (Figure 2, Supplementary Figure S1), gentamicin, chloramphenicol, and oxacillin, particularly within the δ60–80 ppm and δ120–140 ppm ranges (Figure 2). Similarly, predicted FTIR spectra revealed broad overlapping absorption bands between 1700 and 3000 cm^{-1} across all compounds (Figure 3, Supplementary Figure S2), suggesting shared functional group features. Analysis of predicted GC-MS chromatograms further indicated the presence of common low-molecular-weight fragments (<100 Da) among the drugs (Figure 4, Supplementary Figure S3). Despite these spectral overlaps, quantitative similarity analyses using ChemMine tools yielded low Tanimoto atom pair and maximum common substructure coefficients for all HYDRO–antimicrobial pairs (Figure 5). These indicate limited structural similarity at a molecular level, suggesting that the observed antagonistic effects are unlikely to be driven solely by direct structural congruence. Instead, the data support the involvement of more complex interactions within the aqueous assay system that impair antimicrobial activity.

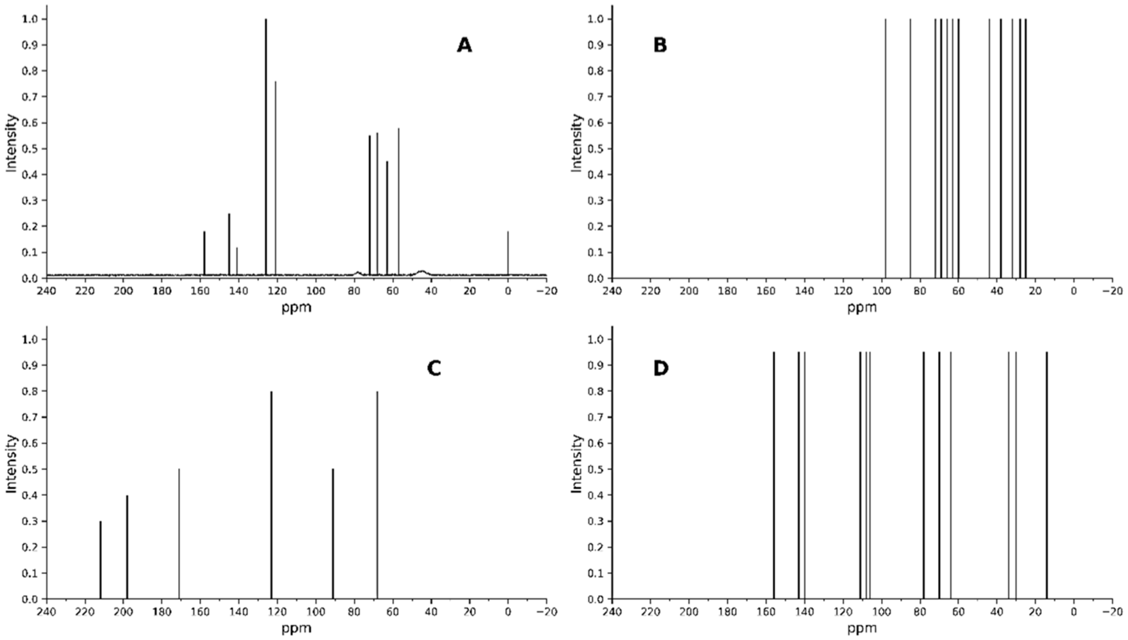

Figure 2. Predicted ^{13}C NMR spectra of chloramphenicol (**A**), gentamicin (**B**), oxacillin (**C**), and HYDRO (**D**). Overlapping regions in the δ60–80 and δ120–140 ppm ranges indicate the presence of similar carbon environments among molecules, suggesting shared functional features without implying direct molecular congruence.

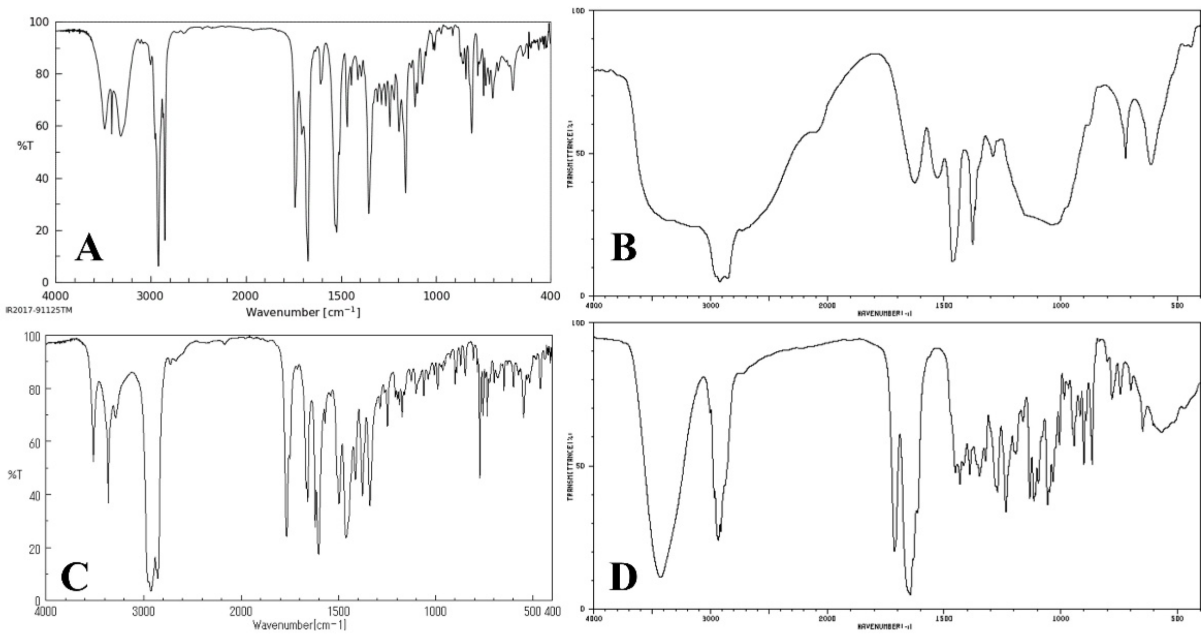

Figure 3. Predicted FTIR spectra of chloramphenicol (**A**), gentamicin (**B**), oxacillin (**C**), and HYDRO (**D**). The spectra illustrate broad absorption patterns associated with common functional groups, particularly at 1700–3000 cm^{-1} region. The overlapping bands suggest similarities in functional group composition across compounds.

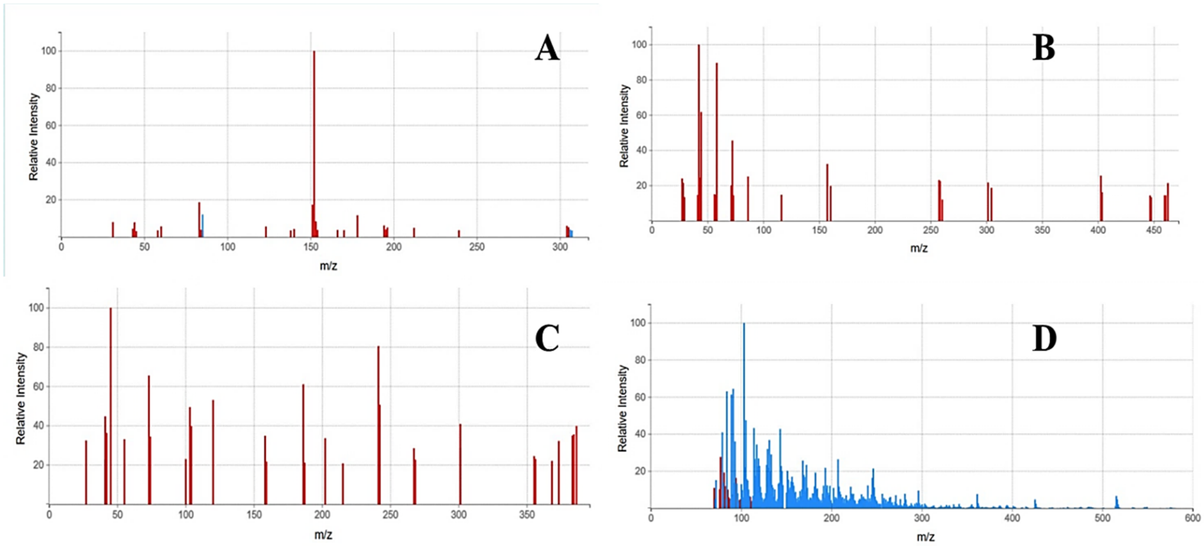

Figure 4. Predicted GC-MS chromatograms of chloramphenicol (**A**), gentamicin (**B**), oxacillin (**C**) and HYDRO (**D**), obtained from non-derivatized molecules analyzed in positive ion mode. The presence of low-molecular-weight fragment ions shared among the compounds indicates partial overlap in fragmentation behavior. Blue fragments observed in HYDRO chromatogram (**D**) correspond to ions that could not be properly identified.

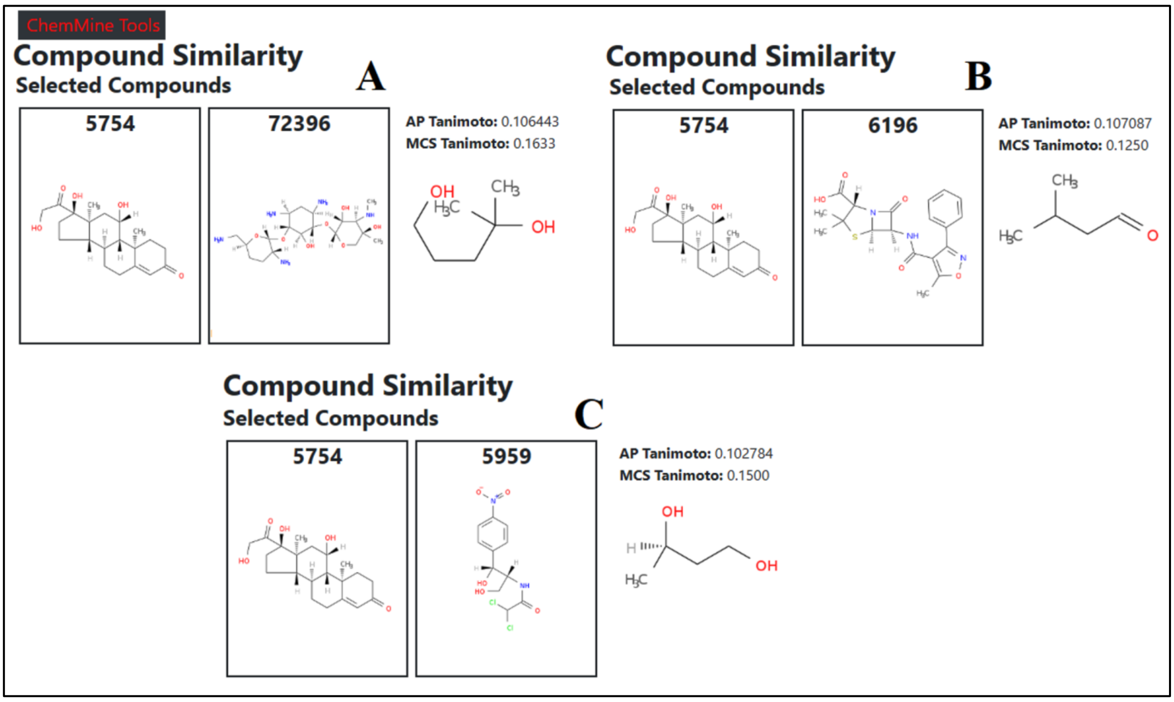

Figure 5. ChemMine similarity calculations for the interactions tested *in vitro* with HYDRO (5754): gentamicin (**A**, 72396), oxacillin (**B**, 6196), chloramphenicol (**C**, 5959). Tanimoto atom pair and maximum common substructure coefficients are shown for each drug pair. The low similarity values indicate limited shared molecular features.

4. Discussion

Studies evaluating interactions between corticosteroids and antimicrobial drugs remain limited, despite the widespread clinical use of these combinations in both systemic and topical formulations. In the present study, we demonstrate that HYDRO markedly interferes with the *in vitro* antimicrobial activity of gentamicin, chloramphenicol, and oxacillin against clinical isolates of *Staphylococcus aureus*. These findings expand previous observations describing negative interference of dexamethasone on antimicrobial efficacy and reinforce concerns regarding the indiscriminate use of corticosteroids with antibacterial therapies [6,7].

The complete abrogation of gentamicin and chloramphenicol activity observed in this study contrasts with several reports describing beneficial or neutral outcomes of corticosteroid–antimicrobial combinations in clinical or experimental settings [8,10−17]. This apparent discrepancy underscores the complexity of interpreting steroid–

antimicrobial interactions, which are influenced by formulation type, route of administration, drug concentrations, and the presence of host immune responses. *In vivo*, corticosteroids exert potent anti-inflammatory and immunomodulatory effects that may indirectly enhance clinical outcomes by mitigating tissue damage and excessive immune activation [10,11]. In contrast, the *in vitro* model employed in this study isolates direct drug-drug and drug-microorganism interactions, indicating antagonistic effects that may otherwise be masked in living systems.

The heterogeneous response observed with oxacillin, where antimicrobial activity was completely abrogated in only a subset of isolates, highlights the role of strain-dependent factors in modulating hydrocortisone interference. Genetic variability among *S. aureus* isolates, including differences in cell wall architecture, penicillin-binding proteins, and stress response pathways, may contribute to differential susceptibility to combined treatments [4,5]. The absence of intrinsic antimicrobial activity of HYDRO against the tested isolates supports the hypothesis that the observed effects are not due to direct bacteriostatic or bactericidal properties but rather to interference with antibiotic action. Given that microorganisms lack classical molecular targets for corticosteroids, it is reasonable to hypothesize that physicochemical interactions between HYDRO and the antimicrobials may impair antibiotic availability, stability, or access to bacterial targets. This hypothesis is consistent with earlier reports suggesting that corticosteroids can influence antibiotic pharmacodynamics by altering drug distribution or interaction kinetics [13].

The chemoinformatics analyses conducted in this study provide limited but suggestive support for potential interactions at the molecular level. Predicted overlaps in NMR, FTIR, and GC-MS spectra indicate the presence of shared functional group features among the tested compounds. However, the Tanimoto similarity coefficients obtained from ChemMine analyses indicate that these interactions are unlikely to be driven by substantial structural similarity alone: Tanimoto atom pair coefficients calculated for hydrocortisone-antimicrobial pairs were consistently low, ranging from approximately 0.12 to 0.28, while maximum common substructure coefficients remained below 0.30 for all combinations (Figure 5). In cheminformatics, values below 0.40 are generally interpreted as indicating weak structural similarity, suggesting that the molecules share only small and chemically generic substructures rather than extensive common scaffolds [18,19]. Therefore, despite the presence of overlapping spectral regions in predicted NMR, FTIR, and GC-MS analyses, the low Tanimoto scores suggest that the tested compounds are structurally distinct at a molecular level. This discrepancy suggests that the antagonistic effects observed *in vitro* are unlikely to be driven by direct structural similarity or classical competitive interactions. Instead, they are more plausibly explained by indirect physicochemical phenomena, such as solvation effects, non-specific molecular aggregation, or altered diffusion behavior in the aqueous system [18–20], which may impair antimicrobial activity. This discrepancy highlights a well-recognized limitation of in silico similarity metrics, which do not always correlate with biological outcomes, particularly in complex aqueous systems where non-covalent interactions, solvation effects, and molecular aggregation may play critical roles [20].

An important consideration in interpreting the present findings is the use of a single hydrocortisone concentration (1 mg/mL) throughout the experiments. This concentration was selected to represent local levels that may be achieved in topical formulations, device-associated administration, or confined tissue compartments, rather than systemic plasma concentrations. In such settings, corticosteroids and antimicrobials can coexist at relatively high local concentrations for prolonged periods, increasing the likelihood of direct physicochemical interactions [7]. Nevertheless, we acknowledge that this concentration may exceed those typically observed in systemic circulation and may therefore favor non-specific effects, including alterations in drug solubility, molecular aggregation, or adsorption. As a result, the antagonistic effects observed here should be interpreted as evidence of potential interaction under high local exposure conditions, such as equipment for prolonged intravenous administration, rather than as a direct predictor of systemic clinical outcomes. Further studies employing dose-response designs and lower hydrocortisone concentrations are required to determine if similar interference with antimicrobial activity occurs across clinically relevant concentration ranges and to better define the translational relevance of these findings.

Despite these limitations, the present study provides compelling evidence that hydrocortisone can significantly impair the efficacy of clinically relevant antimicrobials against *S. aureus*. These findings raise important questions regarding the routine use of corticosteroid-antimicrobial combinations, particularly in settings where high local drug concentrations and prolonged exposure may favor direct drug-drug interactions.

5. Conclusions

HYDRO elevated the MIC and MBC of oxacillin and abrogated the activity of gentamicin and chloramphenicol. More studies should be carried out to evaluate the effects of this interaction on animal models, as the participation of the immune system of living beings, where there is a target for hydrocortisone, was not assessed. Despite the limitations associated with the number of microorganisms used and the number of tested drugs, the data presented here indicate that these combinations can impair clinical treatment of infectious bacterial diseases.

Supplementary Materials: The following supporting information can be downloaded at: https://media.sciltp.com/articles/others/2603250924182831/JIIM-25120169-SM.pdf. Figure S1. Predicted 13C NMR spectra of chloramphenicol, gentamicin, oxacillin, and HYDRO. Figure S2. Predicted FTIR spectra of chloramphenicol, gentamicin, oxacillin, and HYDRO. Figure S3. Predicted GC-MS chromatograms of chloramphenicol, gentamicin, oxacillin, and HYDRO.

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