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PROCEEDINGS ABSTRACT

In vitro pharmacodynamic modelling of the antibacterial effects of selected oral antidiabetic drugs against *Staphylococcus aureus* and *Escherichia coli*

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Type 2 diabetes mellitus (T2DM) represents a profound global health burden that is associated with a heightened susceptibility to localized and systemic bacterial infections. This enhanced risk profile is primarily driven by chronic hyperglycaemia-induced immune dysfunctions (including compromised neutrophil chemotaxis and impaired phagocytic activity), and managing infectious morbidities in diabetic patient cohorts remains a clinical challenge. Emerging evidence suggests that certain classes of oral antidiabetic drugs (OADs) possess pleiotropic, intrinsic antimicrobial properties extending beyond their primary role in glycaemic regulation. This study has aimed at rigorously assessing and comparatively quantifying the *in vitro* antibacterial efficacy of five structurally distinct OADs (namely, metformin, pioglitazone, gliclazide, vildagliptin, and dapagliflozin) against two major opportunistic human pathogens: *Staphylococcus aureus* and *Escherichia coli*. In an attempt to fully characterize these antibacterial profiles, a standardized *in vitro* methodological approach was employed. Antibacterial activity was quantitatively assessed utilizing a high throughput 96-well microdilution assay. Pathogen isolates were exposed to a calibrated, clinically relevant concentration gradient of the selected OADs, ranging from 0.125 to 8.0 mg/L, while bacterial proliferation was dynamically quantified by measuring the relative optical density at regular intervals. In order to translate empirical observations into robust quantitative metrics, the herein obtained concentration–effect datasets were subjected to advanced pharmacodynamic (PD) modelling. In fact, a sigmoidal maximum achievable inhibitory effect (E_{max}) model was applied so as to accurately estimate critical PD parameters, encompassing the half maximal inhibitory concentration (IC_{50}), E_{max}, as well as the comprehensive area under the effect curve (AUC). The PD modelling yielded highly robust fits that were validated by stringent goodness-of-fit coefficients (R^2>0.96), thereby ensuring the reliability of the derived parameters. The comparative analysis revealed striking divergences in antimicrobial potency amongst the tested OADs. In fact, metformin unequivocally demonstrated the highest antibacterial efficacy across the pathogen spectrum, achieving an impressive E_{max} of 70% against *S. aureus* and peaking at 78% against *E. coli*, while simultaneously generating the largest AUCs [1]. Gliclazide and vildagliptin exhibited moderate, yet notable, bacteriostatic activity. On the other hand, pioglitazone displayed the most attenuated effect against the Gram-positive *S. aureus* (with a minimal E_{max} of 28%), yet interestingly maintained a moderate inhibitory activity against the Gram-negative *E. coli* (with an E_{max} of 62%). A critical overarching trend in our experimental findings was the distinctly greater susceptibility of the Gram-negative

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strain: collectively, lower IC_{50} thresholds (predominantly converging at OAD concentrations of 2.0 mg/L) were required in order to actively inhibit *E. coli* compared to *S. aureus*, thereby suggesting specific target vulnerabilities related to different cell envelope architectures. Our *in vitro* study suggests that widely prescribed OADs harbour variable but highly quantifiable intrinsic antibacterial properties against foundational human pathogens [2,3]. The superior *in vitro* potency of metformin, followed by that of gliclazide and of vildagliptin, suggests a compelling secondary pharmacological benefit. While these molecules remain categorically defined by their vital role in metabolic management, their latent antimicrobial capacity could offer a clinical advantage in mitigating the severity of bacterial infections in vulnerable T2DM patient populations.

Keywords

antibacterial activity; gliclazide; *in vitro* pharmacodynamics; metformin; oral antidiabetic drugs

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Conflicts of interest statement

None to declare.

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