

Article

Effects of Chronic Antidiabetic Drugs on Antibiotic Efficacy Against Intestinal *Escherichia coli* Isolates

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Citation: El-Din, N. W. K & Essa, M. A. Effects of Chronic Antidiabetic Drugs on Antibiotic Efficacy Against Intestinal *Escherichia coli* Isolates. American Journal of Biomedicine and Pharmacy 2026, 3(9), 205-212

Received: 10th Jun 2026

Revised: 21th Jul 2026

Accepted: 18th Aug 2026

Published: 25th Sep 2026



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Abstract: Background: Diabetic patients often need combined antimicrobial and antidiabetic treatment, however, the impact of chronic metabolic medications on antibiotic effectiveness is poorly understood. The objective of this study was to investigate these drug-modulatory effects on the antibacterial activity of antibiotics in vitro using commonly prescribed antidiabetic drugs (Metformin, Glimepiride, and Dapagliflozin). Methodology: The antibacterial interactions were evaluated against clinical isolates of *Escherichia coli* obtained from diabetic patients and healthy individuals, as well as a standard pathogenic strain O157:H7. Methods: In this study, we examined 11 different antibiotics and assessed all baseline susceptibility as well drug-drug interactions with antidiabetic drugs by the disk diffusion method. Results: Baseline testing demonstrated a significant multidrug resistance burden with absolute (100%) resistance to Trimethoprim, and Fusidic acid across diabetic clinical isolates, while fluoroquinolones (Levofloxacin, Ciprofloxacin) and Meropenem collectively retained complete (100%) susceptibility. Importantly, Metformin showed an extremely selective and microbiome-sparing inhibition only against the pathogenic *E. coli* O157:H7 strain. Pharmacodynamics and drug interactions assays demonstrated that potent, strain-dependent in vivo modulation of antibiotic efficacy could be achieved. Obligate antagonism was found with all combinations of Ampicillin tested (≤ 5 mm decrease in inhibition zones) and Levofloxacin to be a consistently reliable synergistic partner for >80% of antibiotics assessed, producing significantly larger inhibition zones. In addition, unique interaction profiles were identified between isolates from subjects with and without diabetes. Conclusion: These data undermine the assumed pharmacological neutrality of antidiabetic agents in the management of bacterial infections. The microbiome-mediated differential responses to these microbes in relation to the host microenvironment provide a clinical paradigm shift: when it comes to cohort of diabetics, in order to limit the risk of failure related to antibiotic treatment, empirical antibiotic selection has to deal not only with the pharmacokinetic and pharmacodynamics profile associated with concurrent antidiabetic treatment.

Keywords: Antidiabetic drugs; *Escherichia coli*; *E. coli* O157:H7 ; Drug-Drug Interactions; Therapeutic Synergism.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and insulin resistance, representing a massive global health burden. Patients with diabetes are exceptionally

susceptible to severe bacterial infections, particularly those caused by *E. coli*, due to hyperglycemia-induced impairments in innate immunity [1]. Treating these infections has become increasingly challenging due to the rapid global emergence of antimicrobial resistance (AMR), as Gram-negative pathogens like *E. coli* continuously evolve and disseminate complex resistance mechanisms against conventional therapies[2]. Consequently, developing novel therapeutic strategies and evaluating how current chronic medications influence infection management is of paramount importance.

The human body harbors approximately 100 trillion microbes, primarily concentrated in the gastrointestinal tract. First defined by Nobel laureate Joshua Lederberg as a symbiotic ecological community sharing the human body space [3], the gut microbiome is highly individualized and continuously shaped by both internal and external factors[4]. It is well established that antibiotic therapy can cause long-term disruptions to this microbial community[5], and notably, a positive correlation exists between the incidence of Type 2 Diabetes Mellitus (T2DM) and the frequency of antibiotic prescriptions[6].

In a more direct fashion than antibiotics, glucose-lowering medications are known to alter the gut microbiome[7] therefore indirectly leading us towards clinical outcomes. For example, the most common prescribed oral antidiabetic Metformin alters gut microbiota composition shortly after its administration favouring *Lactobacillus*, *Bifidobacterium* and *Escherichia coli* growth while decreasing abundance of *Intestinibacter bartlettii*[8][9]. T2DM per se causes functional microbial changes, marked by elevated membrane transport of saccharides and downregulation of bacterial chemotaxis and flagellar assembly[10]. This microbial dysbiosis enhances gut permeability, leading to translocation of lipopolysaccharide (LPS) which activates the innate immune system and causes low-grade inflammation thereby aggravating insulin resistance[11][12]. Likewise, even the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin makes profound changes in microbial composition by reducing Firmicutes to Bacteroidetes ratio via modulating gut microbiota of mice influencing a large number of genes responsible for inflammation and metabolism level[13].

Despite the rising recognition of the modulatory effect of antidiabetic agents, including Metformin and Dapagliflozin as well as sulfonylureas such Glimepiride on both host microbiome and bacterial physiology direct pharmacological interactions between co-administered antibiotics remain dramatically under-explored. Diabetics most often receive concomitant therapy with metabolic control drugs and antimicrobial agents. To date, it has remained largely unknown if these antidiabetic medications exert either additive antibacterial benefits or antagonistic pro-therapeutic effects when given concomitantly. Such disparity in knowledge might help explain why empirical antibiotic therapies remain a hit or miss strategy to treat diabetes-associated infections.

The current research was conducted to evaluate the in vitro modulatory effects of three different antidiabetic agents (Metformin, Glimepiride & Dapagliflozin) on many common antibiotics. This study aims to identify synergistic or antagonistic interactions between these drug-drug assortments by comparing it against clinical *E. coli* isolates obtained from both diabetic and healthy patients as well a reference pathogenic O157:H7 type, in order to yield more effective AM treatment regimens for diabetics at base-level with standard of care approaches;

Materials and Methods

Bacterial Isolates and Identification: A total of five *Escherichia coli* isolates were utilized in this study. Two isolates were recovered from the stool of adult diabetic patients, two from healthy adults, and one standard strain of *E. coli* O157:H7 was included. All isolates were sourced, identified, and provided by the Department of Biology, College of Science, University of Mosul.

Antibiotic discs: Ten standard commercial antibiotic discs were utilized in this study. All antibiotic discs were supplied by Bioanalyse (Turkey). The tested panel included Amikacin (AK, 30 µg), Ampicillin (AMP, 25 µg), Amoxicillin-Clavulanic acid (AMC, 30 µg), Azithromycin (AZM, 15 µg), Ciprofloxacin (CIP, 10 µg), Doxycycline (DO, 10 µg), Fusidic acid (FA, 30 µg), Levofloxacin (LEV, 5 µg), Trimethoprim (TR, 23.75/1.25 µg), Meropenem (MRP, 10 µg), and Vancomycin (VA, 30 µg).

Antidiabetic Drugs: Three commercial antidiabetic medications for chronic diseases were utilized in this study. These drugs were procured from local pharmacies in Mosul, Iraq. The selected medications

comprised Metformin (Pioneer brand / , 500 mg) ; Glimepiride (Amaryl brand / , 2 mg) and Dapagliflozin (Diaglip brand / , 10 mg) .

Preparation of Antidiabetic Drug Solutions: The antidiabetic drugs were prepared as aqueous solutions followed by filtration. Specifically, a 50 mg/mL Metformin solution was prepared by dissolving a thoroughly crushed 500 mg tablet in distilled water to a final volume of 10 mL[14]. For Glimepiride (40 µg/mL), a 2 mg tablet was dissolved in a final volume of 100 mL of distilled water, requiring 30 minutes of shaking and mild heating (35–40°C) to facilitate dissolution due to its low aqueous solubility[15]. Finally, a 1% Dapagliflozin answer turned into formulated by stirring a pulverized 10 mg tablet in distilled water for 20–30 minutes before adjusting the final volume to ten mL[16]. All organized solutions have been filtered to cast off insoluble excipients and preserved in sterile tubes for next assays.

Well Diffusion Assay for Inhibitory Activity: The biological activity of the antidiabetic drugs was evaluated using the agar well diffusion assay[17]. Bacterial suspensions were prepared by transferring colonies grown on nutrient agar into tubes containing 5 mL of sterile physiological saline. The turbidity was adjusted to match a 0.5 McFarland standard. The suspensions were evenly swabbed onto the surface of Muller-Hinton agar (MHA) plates using sterile cotton swabs and allowed to dry for 2–3 minutes. Wells of 6 mm in diameter were punched into the agar using a sterile cork borer, and 100 µL of each drug solution was added to the respective wells. Sterile distilled water was added to a separate well to serve as a negative control. After 24 hours of incubation at 37°C, the zones of inhibition were measured in millimeters.

Antimicrobial Susceptibility Testing: Antibiotic susceptibility test was performed by the modified Kirby-Bauer disk diffusion method according to the standard guidelines of WHO. Fresh, selected colonies were resuspended in 0.5 McFarland standards (densities equal to the standard using sterile saline adjusted for turbidity): Exponential phase cultures using double strength yeast nitrogen base with amino acids containing no measurable growth from fresh pure colonies of organism in discuss following areas The inoculum was distributed in multiple directions on the MHA plates. Antibiotic discs were then placed onto the agar surface using sterile forceps after a 2–3 minute drying phase. Plates were incubated at 37 °C for 24 h and inhibition zone diameters (in mm) were recorded and interpreted as resistance or susceptibility by Clinical and Laboratory Standards Institute[18].

Synergistic Effect Assay: In order to examine the combinations of antidiabetic medications and antibiotics, we performed paired testing between drugs found to have clear inhibitory effects with antibiotics that were known to confer resistance on each bacterial strain. Bacterial suspensions (adjusted to a 0.5 McFarland standard) were inoculated onto MHA plates. The selected antibiotic discs were then positioned on the agar after a 2–3 minute absorption interval. Ten µL of the active antidiabetic drug was then applied to each antibiotic disc by direct inoculation. To not contradict between the paper written we were used standard antibiotic discs at the same time without adding antidiabetic drug. The synergistic effect was assessed by recording the inhibition zones (mm) of combined discs versus alone antibiotic discs[19], after incubation of 37°C for 24hours with interpretation according to CLSI guideline (CLSI, 2023).

Results

The results in Table 1, showed antibiotics susceptibility patterns which revealed widespread multidrug resistance (MDR) among the tested *E. coli* isolates, and all isolates demonstrated uniform susceptibility (100%) to fluoroquinolones (Levofloxacin and Ciprofloxacin) and absolute resistance (100%) to Fusidic acid and Trimethoprim. Meropenem effectively inhibited all clinical isolates , but completely failed against the standard O157:H7 strain, which exhibited a severe MDR profile, (resisting 9 of the 11 tested antibiotics). Furthermore, while isolates from diabetic patients showed consistent resistance to β-lactams (Ampicillin and Amoxicillin-Clavulanic acid), isolates from healthy adults displayed variable susceptibility.

Table 1. Antibiotics susceptibility patterns of the studied *E. coli* isolates.

Isolate	AZM	AMP	AMC	MPR	VA	FA	DO	AK	TR	LEV	CIP
Diabetic 1	S	R	R	S	I	R	I	S	R	S	S
Diabetic 2	S	R	R	S	R	R	R	S	R	S	S
Healthy 1	S	S	S	S	R	R	I	I	R	S	S
Healthy 2	I	R	R	S	R	R	R	R	R	S	S
O157H7	R	R	R	R	R	R	R	R	R	S	S

S = Susceptible; I = Intermediate; R = Resistant.

The independent antibacterial activity of the studied antidiabetic drugs is detailed in Table 2. Neither Glimepiride nor Dapagliflozin exhibited any inhibitory activity against the tested *E. coli* isolates (0 mm). Metformin showed no antibacterial effect against any of the tested isolates recovered from both diabetic and healthy individuals, however, Metformin demonstrated a highly potent inhibitory effect against the standard strain, *E. coli* O157:H7, with inhibition zone of 26 mm.

Table 2. Inhibitory Activity of Antidiabetic Drugs Against the Studied Isolates (Inhibition Zone Diameter, mm)

Isolate	Drug Type		
	Metformin	Glimepiride	Dapagliflozin
Diabetic 1	0	0	0
Diabetic 2	0	0	0
Healthy 1	0	0	0
Healthy 2	0	0	0
O157H7	26	0	0

The antibiotics that have undergone studies for interaction with antidiabetic drugs, and their interactions are presented in Tables 3–5. When looking at the antibiogram-centered approach, LEV was a highly synergistic drug in 8/9 drug-isolate combinations without exhibiting any antagonism. On the other hand, Ampicillin (AMP) was antagonized under all conditions. In summary, antibiotics such as AZM, AMC and CIP showed highly strain-dependent behavior with respect to antagonism in some combinations while being synergistic or indifferent amongst other strains. In healthy adults, isolates displayed the same interaction paradigm for all antidiabetic drugs studied where they would consistently synergize in combination with AK, MRP, LEV and CIP whilst showing an antagonistic effect with AZM, AMP and AMC. In the presence of diabetic isolates, LEV and AMC were consistent synergistic partners, while interactions with other antibiotics (e.g. AK) fluctuated. Metformin and Glimepiride acted synergistically only on AZM and LEV in an almost identical manner, while Dapagliflozin synergized with FA only in the O157:H7 strain.

Table 3. Drug Interaction Between Antibiotics and Metformin Against Bacterial Isolates

Isolate	No. of Synergistic Antibiotics	Synergistic Antibiotics	No. of Antagonistic Antibiotics	Antagonistic Antibiotics
Diabetic	4	AZM, AMC, AK, LEV	3	AMP, MRP, CIP
Healthy	4	AK, MRP, LEV, CIP	3	AZM, AMP, AMC
O157:H7	2	AZM, LEV	3	AMC, AK, CIP

Table 4. Drug Interaction Between Antibiotics and Glimipride Against Bacterial Isolates

Isolate	No. of Synergistic Antibiotics	Synergistic Antibiotics	No. of Antagonistic Antibiotics	Antagonistic Antibiotics
Diabetic	4	AZM , AMC , LEV , CIP	2	AMP, AK
Healthy	4	AK,MRP, LEV, CIP	3	AZM, AMP, AMC
O157:H7	2	AZM, LEV	3	AMC, AK, CIP

Table 5. Drug Interaction Between Antibiotics and Dapoflozin Against Bacterial Isolates

Isolate	No. of Synergistic Antibiotics	Synergistic Antibiotics	No. of Antagonistic Antibiotics	Antagonistic Antibiotics
Diabetic	4	AMC , MRP AK , LEV	2	AZM , CIP
Healthy	4	AK , MRP , LEV , CIP	3	AZM, AMP, AMC
O157:H7	1	FA	2	AZM , CIP

Discussion

Antibiotic susceptibility test results, interpreted according to the CLSI guidelines, recorded a high prevalence of multidrug-resistant (MDR) *E. coli* strains among the studied isolates, consistent with the global health threat of antimicrobial resistance [20]. The 100% absolute resistance observed with Trimethoprim and Fusidic acid across all diabetic isolates represents a major shortcoming in traditional therapeutic options for this highly at-risk patient group with published data showing elevated MDR burdens and impaired bacterial clearance reported among diabetic cohorts[21]. In light of the dramatic difference in susceptibility shown by clinical isolates to fluoroquinolones (Levofloxacin and Ciprofloxacin) and Meropenem, it appears that both drugs are reliable options for empirical therapy. But shocking is the resistance of standard pathogen *E. coli* O157:H7 to Meropenem. This resistance indicates an intrinsic or acquired mechanism of carbapenem-resistance, namely the horizontal acquisition of carbapenems-encoding genes and outer membrane porin channel alterations, which are key drivers of Enterobacteriales carbapenem resistance[22], thus, more molecular studies might be required.

Among the important conclusions in the results of this is the selective inhibitory Metformin activity against *E. coli* O157:H7 strain. Glimepiride and Dapagliflozin did not present any independent action against bacteria; Metformin only inhibited the O157:H7 strain and did not inhibit clinical isolates collected from non-diabetic patients or diabetic patients. The specificity of this targeting is particularly significant; the recent microbiome-pharmacology paradigms indicate how many non-antibiotic drugs are capable of site- or strain-specific antimicrobial effects without broad-spectrum disruption of the commensal intestinal flora. Thus, it implies that Metformin broadly does not disturb the normal gastrointestinal microbiome and specifically inhibits metabolic pathways, membrane structures or virulence determinants produced by this O157:H7 serotype. This selective inhibition of virulence would also set Metformin apart in terms of drug repurposing against certain pathogens, which is an important tactic to ensure the efficacy of traditional antibiotics will be maintained in view of worrying levels of antimicrobial resistance [23][24].

The interaction studies of antidiabetic drugs with antibiotics showed highly significant effects on antibacterial effect. The establishment of high reproducibility and isolation of pure synergistic interactions were enabled by using single-source antidiabetic agents, which avoids the variability associated with drug formulation. Therapeutic synergism is enormously valuable clinically, especially its ability to overcome bacterial resistance (reverse resistant mechanisms), improve the inhibition effects of antibiotics, reduced time in treatment and prevent the rise of multidrug-resistant pathogens[25]. In

this study, substantial synergism (defined as an increase in the inhibition zone diameter by ≥ 5 mm)[26][27] was frequently found among the clinical isolates.

The same interaction profile observed in isolates from healthy individuals (synergy with AK, MRP, LEV and CIP) suggests a stable genetic and metabolic background established among the normal physiological flora. In contrast, variable interaction patterns seen with diabetic isolates imply selective pressure from the diabetic microenvironment (e.g., chronic hyperglycemia), which may lead to changes in bacterial outer membrane permeability and/or overexpression of efflux pumps that elicit unpredictable responses to drug combinations. Importantly, Levofloxacin (LEV) always proved the most robust synergetic partner in all combinations. This synergy is probably that antidiabetic drugs exposure alters the bacterial outer membrane permeability itself where they compete for binding to the outer membrane and promote a greater intracellular accumulation of fluoroquinolone, necessitating interaction with DNA gyrase[28]. In contrast, Ampicillin (AMP) often displayed antagonism. Current molecular models predict that the response to external factors is an adaptive envelope response, in which diverse added stresses or even non-antibiotic drugs rapidly downregulate outer membrane porin channels and decrease permeability before blocking β -lactam antibiotics like Ampicillin from reaching their targets, the penicillin-binding proteins (PBPs)[29][30]. In conclusion, although these synergistic and antagonistic profiles in vitro are an important starting point for finding optimized treatment regimens—especially in diabetic patients vulnerable to severe infections—in vivo studies are necessary to provide the specific pharmacokinetic and pharmacodynamic mechanisms of the interactions of the pairs of drugs inside a living host.

Conclusion

Here we show that chronic antidiabetic drugs (Metformin, Glimepiride, Dapagliflozin) are an extremely potent modulator of antibiotic activity fundamentally altering the paradigm of their presumed pharmacological neutrality in treating infections. Levofloxacin was one of the most reliable synergistic partners across regimens; meanwhile, Ampicillin combinations consistently triggered intense strict antagonism to a humanized therapy whilst incurring an unmanageable risk for therapeutic failure. Furthermore, our finding of changed interaction patterns in isolates from diabetic patients is particularly important as it reinforces the idea that host microenvironment is an active modifier of bacterial drug responses. These considerations, along with the result that metformin exhibits selective anti-virulence activity against *E. coli* O157:H7, require one change to clinical practice: Empirical antimicrobial selection for patients with diabetes needs to consider concurrent antidiabetic therapies. These interactions require immediate validation through their translation into clinical relevance with in vivo studies for precision prescribing.

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