Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.60.009408

Metformin Beyond Diabetes: Antimicrobial Potential Against Resistant Pathogens

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ARTICLE INFO

Received: December 21, 2024

Published: January 06, 2025

Citation: Ingrid Thaís Nogueira dos Santos, Gessiane dos Santos de Souza, Karina Raquel Guilhon Machado, André Luís Serra Barbosa, Weldson Ricardo Silva Gomes and Camila Guerra Martinez. Metformin Beyond Diabetes: Antimicrobial Potential Against Resistant Pathogens. Biomed J Sci & Tech Res 60(1)-2025. BJSTR. MS.ID.009408.

ABSTRACT

Metformin, primarily used to manage type 2 diabetes mellitus (T2DM), improves insulin sensitivity and inhibits hepatic gluconeogenesis through AMP-activated protein kinase (AMPK) activation, regulating cellular energy homeostasis. It also affects mitochondrial respiration by inhibiting complex I, thereby altering ATP production and increasing intracellular AMP levels. Despite its widespread use, metformin can cause gastrointestinal side effects like nausea and diarrhea. Emerging research highlights metformin's antimicrobial properties. It disrupts quorum sensing (QS) in Pseudomonas aeruginosa by reducing acyl-homoserine lactone (AHL) production, impairing biofilm formation and virulence. Additionally, it demonstrated activity against multi-drug-resistant bacteria like Staphylococcus aureus and Klebsiella pneumoniae. These findings suggest metformin's potential as an adjuvant antimicrobial agent. Its ability to modulate bacterial communication and metabolism offers promising prospects for tackling antibiotic resistance, especially when used in synergy with traditional antibiotics. Further research could validate its clinical application in this context.

Keywords: Metformin; Antimicrobial Resistance; Bacterial Inflection; Virulence Factors

Introduction

Metformin, chemically identified as 1,1-dimethylbiguanide, is a small, hydrophilic molecule widely used in clinical medicine. Discovered in the 1920s and developed as a therapeutic drug in the 1950s, it is derived from galegine, a compound found in Galega officinalis (Werner, et al. [1,2]). The molecular structure of metformin allows it to be positively charged under physiological conditions, contributing to its hydrophilic nature and limited tissue permeability (Foretz, et al. [3]). Its widespread acceptance is attributed to its efficacy in managing metabolic disorders, particularly type 2 diabetes mellitus (T2DM), and its favorable safety profile compared to alternative therapies (Bailey, et al. [4]). Metformin has a typical dosage range of 500–2,500 mg daily, administered in divided doses or as an extended-release formulation. The absorption of metformin occurs within 6 hours after ingestion, with a bioavailability of 50% to 60%, and it is excreted unchanged in the urine, with 30% excreted in the feces (Bharath, et al. [5]). It acts primarily by inhibiting hepatic gluconeogenesis and improving insulin sensitivity in peripheral tissues (Lochhead, et al. [6,7]). Metformin exerts its effects through the activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis. By activating AMPK, metformin reduces ATP-consuming pathways, increases fatty acid oxidation, and downregulates gluconeogenic genes, including Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase) (Carling, et al. [8-10]).

Beyond AMPK, metformin also affects mitochondrial respiration by inhibiting complex I of the electron transport chain, leading to a mild reduction in ATP production and an increase in intracellular AMP levels (Fontaine, et al. [11]). In muscles, metformin increases the

translocation of glucose transporter 4 (GLUT4) to the cell membrane, facilitating glucose entry into cells and contributing to glycemic control (Zhou, et al. [12]). Additionally, metformin exerts beneficial effects on the gut microbiota, which, in turn, can influence glucose metabolism and insulin sensitivity. Changes in the microbiota composition can result in an increased production of short-chain fatty acids, which have anti-inflammatory effects and may improve glucose homeostasis (Mueller, et al. [13,14]). Metformin has also been shown to reduce intestinal glucose absorption by decreasing the expression of the Sodium-Glucose Cotransporter 1 (SGLT1) on the apical membrane of enterocytes in the jejunal region (Zubiaga, et al. [15]). The effects described thus far do not involve the direct stimulation of insulin secretion by pancreatic beta cells, as occurs with other antidiabetic drugs like sulfonylureas. Therefore, metformin is not considered a hypoglycemic medication (Bailey, et al. [4]). While generally well-tolerated, metformin can lead to adverse effects, primarily gastrointestinal symptoms such as diarrhea, nausea, and abdominal discomfort, which occur in up to 30% of patients (Bonnet, et al. [16]). Other reported effects include vitamin B12 deficiency after prolonged use, necessitating regular monitoring of hematological parameters in long-term therapy (Damião, et al. [17]).

Metformin as an Antibacterial Agent

Recent research has explored metformin's potential antimicrobial activity, revealing effects against various bacterial pathogens. The literature suggest that metformin could be repurposed as an adjuvant in antimicrobial therapy, offering a novel approach to combatting antimicrobial resistance. Its ability to modulate bacterial metabolism and interaction presents an intriguing avenue for further investigation, particularly in synergy with conventional antibiotics to enhance efficacy and reduce resistance development.

Pseudomonas Aeruginosa: Pseudomonas aeruginosa is gram-negative, bacilliform and aerobic bacterium. It is a highly adaptable and opportunistic pathogen associated with severe nosocomial infections, particularly in immunocompromised individuals (Wilson, et al. [18]). Its infections are prevalent in cases such as ventilator-associated pneumonia, cystic fibrosis, urinary tract infections, and wound infections (Silva, et al. [19]). The organism's ability to resist multiple antibiotics is driven by mechanisms like efflux pumps, enzymatic degradation, and reduced membrane permeability. This resistance complicates treatment and significantly contributes to morbidity and mortality globally. In recent years, multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains have emerged, representing a critical challenge in healthcare (Seung, et al. [20]). XDR strains, resistant to multiple antibiotic classes, are associated with mortality rates exceeding 40% in some studies, especially among patients with bloodstream infections or bacteremia (Montero, et al. [21]). Given its genomic plasticity and adaptability, *P. aeruginosa* remains a priority pathogen for the development of innovative antimicrobial agents. Collaborative global efforts are essential to mitigate its impact and address the growing threat of antimicrobial resistance effectively. Quorum sensing (QS) in Pseudomonas aeruginosa is a sophisticated communication system that enables bacterial cells to coordinate gene expression based on population density (Miranda, et al. [22]).

This process involves the production, release, and detection of signaling molecules called autoinducers, primarily N-acyl homoserine lactones (AHLs) (Smith, et al. [23]). These molecules bind to specific receptor (LasR and RhlR), triggering the expression of virulence factors and biofilm formation (Elnegery, et al. [24]). QS plays a critical role in regulating processes like toxin production and resistance mechanisms, making it a significant target for antimicrobial strategies (Smith, et al. [25]). Studies have shown that disrupting QS can reduce the pathogenicity and antibiotic resistance of *P. aeruginosa* (Skindersoe, et al. [26]). Metformin can inhibit QS in Pseudomonas aeruginosa PAO1 by suppressing QS genes and reducing the production of AHL (Abbas, et al. [27]). Additionally, molecular docking study suggests that metformin could bind to AHL receptor, LasR, by hydrogen bonding and electrostatic interaction and to RhlR by hydrogen bonding only (Abbas, et al. [27]). By interfering in the production and interaction of AHLs, metformin could disrupt the biofilm structure and make planktonic cells more susceptible to antibiotics action. In Pseudomonas aeruginosa PA14, QS is regulated by three circuits: two that use AHL signals and one that uses quinolone signals. These circuits regulate the expression of hundreds of genes, including many that code for virulence factors (Miranda, et al. [22]). Targeting QS is an effective way to reduce bacterial virulence. PA14 is a highly virulent strain of *P. aeruginosa* that can cause disease in a wide range of organisms (Mikkelsen, et al. [28]).

Metformin significantly reduced the production of AHLs in PA14 in a concentration-dependent manner. At 1/16 MIC, total AHLs were reduced by 20.8% and at 1/8 MIC, AHL production was further lowered by 43.1% (Chadha, et al. [29]). Conventional treatments for Pseudomonas aeruginosa infections include a combination of an antipseudomonal beta-lactam and an aminoglycoside. However, Pseudomonas aeruginosa can be resistant to many antibiotics, so new treatment options are needed (Khayat, et al. [30]). The interference of metformin in the QS sytems holds promise in reducing bacterial resistance and enhancing treatment outcomes when used in combination with conventional therapies.

Staphylococcus Aureus: *Staphylococcus aureus* is a gram-positive bacterium and a prominent human pathogen responsible for a wide spectrum of diseases, ranging from superficial skin infections to severe conditions like endocarditis, pneumonia, and septicemia (Bush, et al. [31]). Its ability to adapt and develop resistance to antibiotics, including methicillin and vancomycin, has made it a global health challenge. Methicillin-resistant *S. aureus* (MRSA) emerged in the 1960s and continues to evolve with variants such as vancomycin-resistant strains (VRSA), posing significant therapeutic difficulties (Cong, et al. [32]). Recent advances in research have focused on alter-

native treatments, including bacteriophages, monoclonal antibodies, and new antibiotics (REF). Efforts to develop effective vaccines have faced challenges due to the complexity of its virulence mechanisms and immune evasion strategies (REF). Nevertheless, ongoing trials of innovative vaccine candidates and therapeutic approaches offer hope for better management of *S. aureus* infections in the future. Mechanistically, metformin can impair bacterial energy metabolism and enhance host immune responses, promoting autophagy and modulating cytokine production. Metformin can reduce the secretion of cytokines induced by *S. aureus*, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IFNγ, IL-1α, IL-6, monokine induced by gamma interferon (MIG/CXCL9), and transforming growth factor β (TGFβ), and prevent changes in the epithelial tight junction proteins of the airways induced by *S. aureus* (Garnett, et al. [33]).

Studies with hyperglycaemic db/db mice demonstrate that metformin (40 mg/kg - intraperitoneally every day from day 2 before infection) can reduce bacterial growth at lung (Garnett, et al. [33]). The bacterial load in livers and kidneys of mice infected with *S. aureus* ATCC 6538 previously treated with metformin was lower when compared to untreated bactéria (Abbas, et al. [34]). One possibility, still not tested in the literature, would be the combination of metformin with antibiotics such as vancomycin or daptomycin in MRSA-infected models. These effects would be particularly valuable in addressing infections where biofilm formation limits antibiotic penetration, such as in prosthetic joint infections and endocarditis caused by *S. aureus*. Nonetheless, the repurposing of metformin represents a novel and cost-effective strategy to augment current antimicrobial therapies against one of the most challenging pathogens in clinical medicine.

Klebsiella Pneumoniae: *Klebsiella pneumoniae* is a Gram-negative pathogen responsible for various community- and hospital-acquired infections, including pneumonia, urinary tract infections, bacteremia, and wound infections (Effah, et al. [35]). Its increasing resistance to antibiotics, particularly carbapenems, poses significant challenges to public health. Carbapenem-resistant K. pneumoniae (CRKP) arises primarily due to the acquisition of carbapenemase genes such as bla_KPC and bla_NDM, alongside mechanisms like porin mutations and efflux pump overexpression (Effah, et al. [35,36]). These adaptations complicate treatment, as CRKP often shows resistance to last-resort antibiotics, including ceftazidime/avibactam and colistin (Effah, et al. [35,37]). CRKP is prevalent in intensive care units, where immunocompromised patients are at higher risk of severe outcomes (Karampatakis, et al. [36]). Mortality rates for infections with CRKP remain alarmingly high, driven by the limited therapeutic options and the pathogen's capacity for rapid genetic adaptation under antibiotic pressure (Effah, et al. [35,38]). Effective management strategies require robust antimicrobial stewardship, infection control measures, and novel therapeutic approaches, such as combination antibiotic regimens and potential vaccine development. Additionally, advanced diagnostics are essential for the timely identification and treatment of multidrug-resistant K. pneumoniae infections.

Metformin has a inhibitory effect on the production of K. pneumoniae virulence factors. When used to treat mice infected with K. pneumoniae previously treated with metformin (1 mg/ml), it was observed a 60% increase in survival (Shafik, et al. [39]) Research on metformin's impact against CRKP has demonstrated synergistic effects when combined tigecycline, one of the last effective options against multidrug resistance bacteria. This combination enhances bacterial clearance and reduces resistance development, especially in biofilm--associad infections, by the disruption of function of efflux pump, thereby increasing the intracellular concentration of the antibiotic (Xiao, et al. [40]). Moreover, metformin's anti-inflammatory properties may mitigate host immune dysregulation caused by Kp infections. Despite these promising findings, more *in vivo* and clinical studies are necessary to optimize dosing strategies and fully understand the mechanisms underlying metformin's antimicrobial effects. With the increasing prevalence of MDR pathogens like Kp, exploring metformin's repurposing offers a valuable avenue for developing innovative therapies that complement existing antibiotics and address the global antimicrobial resistance crisis (Bell, et al. [41].

Conclusion

The increasing bacterial resistance to conventional antibiotics represents a significant challenge in contemporary medicine. Metformin, due to its safety profile and ability to affect the microbiota and immune response, emerges as a potential addition to existing therapeutic strategies. The combined use of metformin with antibiotics could not only enhance treatment efficacy but also reduce the burden of bacterial resistance. It is crucial that future studies are conducted to fully understand the mechanisms by which metformin influences the development of bacterial infections and to establish guidelines for its use in clinical contexts. Randomized clinical trials are needed to validate these findings and explore the possibility of implementing metformin as part of integrated preventive strategies against various types of infections.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.60.009408

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