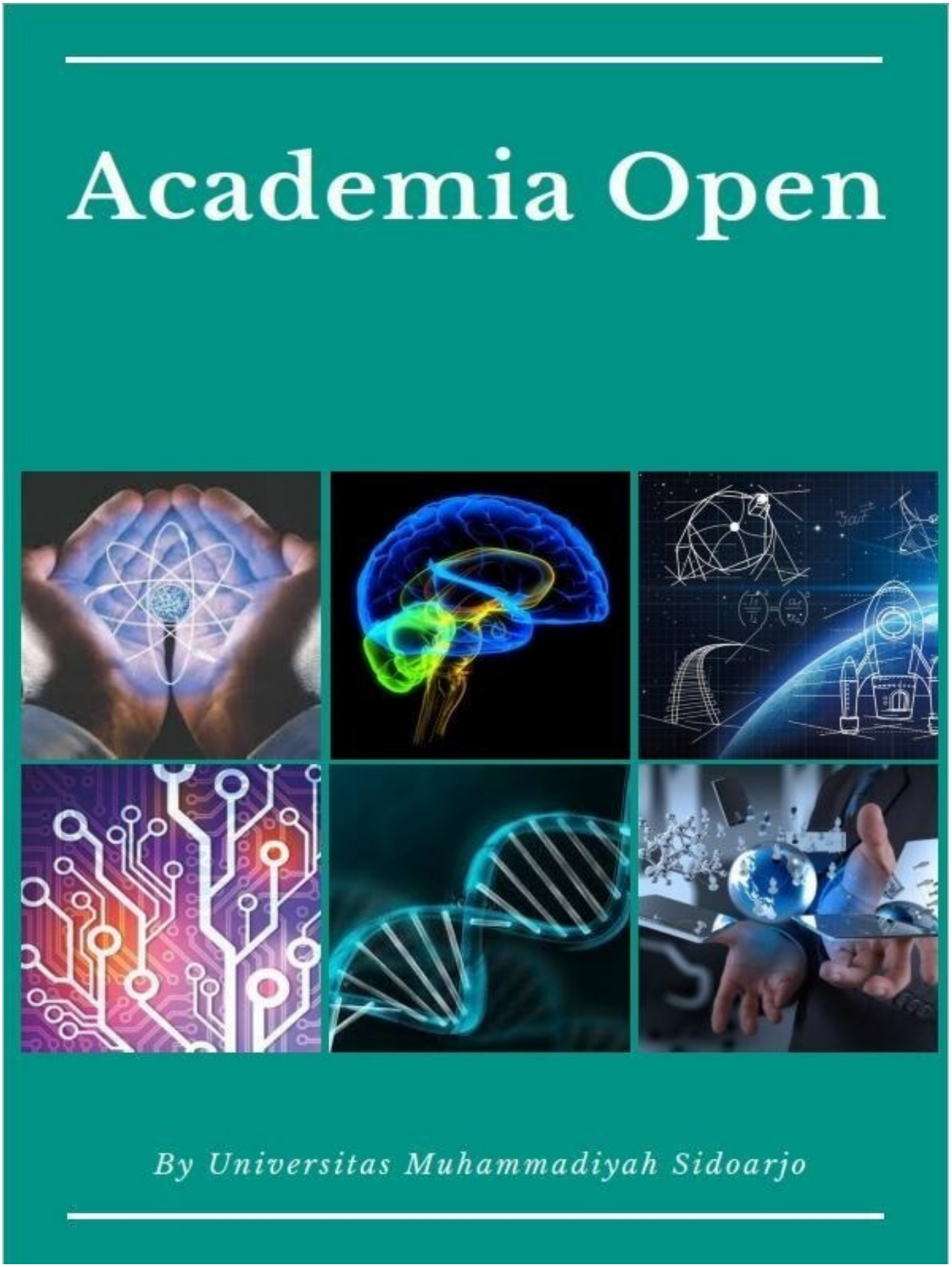
Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Table Of Contents

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

EDITORIAL TEAM

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Metformin Antibacterial Activity on Vaginal Isolates in Polycystic Ovarian Syndrome

Halah Dawood Salman, phar.halah.dawood@uobabylon.edu.iq,(1)

Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Al Hillah, Iraq

(1) Corresponding author

Abstract

General Background: Bacterial resistance to antibiotics continues to intensify worldwide, creating an urgent need for adjunct therapies that enhance antimicrobial efficacy. **Specific Background:** Metformin, a widely used antidiabetic drug, has shown immunomodulatory and antimicrobial properties, yet its effects on vaginal pathogens in women with and without polycystic ovary syndrome (PCOS) remain insufficiently explored. **Knowledge Gap:** Limited evidence exists regarding whether metformin can potentiate antibiotic activity against common vaginal bacterial isolates, particularly in PCOS patients who often exhibit reduced IL-10 levels and heightened inflammatory states. **Aims:** This study aimed to evaluate the adjuvant antibacterial effect of metformin when combined with standard antibiotics against Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa isolated from affected women. **Results:** Metformin enhanced antibiotic inhibition zones notably for K. pneumoniae and P. aeruginosa, while producing a moderate but less consistent synergistic effect on E. coli. Serum IL-10 levels were significantly lower in patients than controls, confirming an underlying inflammatory imbalance. **Novelty:** This research provides one of the first empirical assessments of metformin's antibacterial adjuvant role in vaginal infections among PCOS and non-PCOS women. **Implications:** Findings suggest metformin may serve as a promising supportive agent to strengthen antibiotic efficacy and help mitigate bacterial resistance.

Highlight :

- Metformin enhances the antibacterial effects on K. pneumoniae and P. aeruginosa.
- IL-10 is lower in PCOS patients, indicating inflammatory imbalance
- E. coli is the most common bacterium in vaginal infections.

Keywords : Metformin, Vaginal Infection, PCOS, Antibacterial Synergy, Antibiotic Resistance

Published date: 2025-12-05

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Introduction

Poly cystic ovarian syndrome (PCOS) is endocrine disorder with prevalence of 10% of women in age of reproduction, PCOS have multiple symptoms such as polycystic ovaries, hyperandrogenism, menstrual irregularities, systemic consequences of PCOS including mainly immunological and metabolic dysfunctions; actually PCOS patients often have more challenges especially infertility [1]. Inerleukin-10 is an antiinflammatory cytokine which produced from T helper 2 (TH2) cells, IL10 reduce immune responses also inflammation, it maintain immune homeostasis; therefore it's levels are crucial for balancing the inflammatory state in different conditions such as in PCOS, some researches had reported decrease in B cells that produce IL-10 in women having recurrent pregnancy loss [2]. PCOS affected young women; nearly (1 in 5) women may suffer from this abnormality in the ovaries which can be detected by ultrasound [3].

Pathogenesis of PCOS occurred as a consequence of chronic low-level inflamma¬tion as a major factor [4]; the expression of macrophage and Thelper-1 cells of proinflammatory cytokines is downregulated by interleukin10 as anti-inflammatory, that leading to dysfunction in ovaries [5].

Metformin, is drug using in treatment diabetes2, when it used as monotherapy; it would be effective as insulin or sulfonylureas and the efficacy had been shown to be independent of (age, insulin and C-peptide levels, body weight and the duration of diabetes) by mixing with diet it reduce the concentration of fasting glucose near 2.78 -3.90 mmol/L meaning 50 - 70 Mg/dL [6].

Metformin owing minimizing action on glucose chiefly resulted from minimized output of hepatic glucose which occur primarily by reduction of gluconeogenesis also attributed somewhat to the glycogenoglucos with increasing uptake of glucose stimulated by insulin in adipocytes and in muscles of skeletal system [7].

Mechanism of metformin in minimizing production liver glucose still unclear; however the primary site of metformin action is liver mitochondria where it rend oxidation of respiratory chain in complex I substrates [8].

Metformin usually used for treatment metabolic abnormalities of PCOS; it could minimized insulin level and testosterone, metformin produce protective effects of cardiovascular which interpret lowered level of LDL cholesterol; improvement the oxidative stress; reduce weight earning and others [9].

Metformin have impact on sensitivity to insulin in women with PCOS don't having diabetes; metformin impacts including elevated cyclicity of menstrual, reduced circulating level of androgen and improvement of ovulation [10].

Metformin can exhibit assistant effect as antimicrobial drug by many mechanisms consisting potentiation the antibiotic activity; modification immune response to infection; disrupting the bacterial outer membrane by increasing intracellular accumulation of many antibiotics [11]. Recently, there has been increasing attention about potential impacts of metformin on intestinal microbiota; some findings exhibited metformin may change composition and function of gut microbiota which may lead to immune and metabolic changing in health [12].

Metformin effect involve Gram+ and Gram- bacteria, like it's potential activity on tuberculosis bacteria through increasing efficacy of anti TB via enhancing autophagy process; while in tetracycline resistant Escherichia coli metformin restore susceptibility to antibiotic by intracellulary accumulation of doxycycline [13].

Moreover, it has been discovered that metformin can act on outer membrane of G-bacterial cell wall such as Klebsiella pneumoniae [14].

Metformin could Inhibit complex1 of mitochondria also transporting of electron by using as coassistant antibacterial agent may decrease supplement of energy that required in growthing of bacteria; in addition; metformin cause limitation of glycerol using in Krebs cycle leading to decreasing of bacterial virulence, moreover; metformin effect as antifolate could inhibit folate cycle of bacteria then suppression of bacterial growth [15].

Recently, metformin used as inhibitor of efflux pump in K.pneumoniaea also as inhibitor of quorum sensing in P.aeruginosa [16].

In addition, metformin is effective beside safe in treatment number of neonatal diseases which was tested as antivirulence factor for neonatal MDR K.pneumoniae [17]. Previous researches exhibited that metformin effectively minimized the production of virulence factors such as hemolysins and proteases in P. aeruginosa [18].

Metformin could stimulate expression of antimicrobial peptides LL-37 and RANase; also stimulation multiple responses regarding protective in the host which resulted in elevated intra with extracellular killing of E. coli, moreover in Serratia marcescens metformin can inhibit formation of biofilm, production of hemolysins and proteases [19].

Research Methodology

Bacterial Samples : eighty seven samples had been collected and 80 women without (PCOS or bacterial vaginal infections as a control) in childbearing age for the time of(April 2024 tooJuly-2024) female patients having bacterial infections in vagina; they attended clinic of gynecology in hospital of Gynecology and obstetrics teaching / Hillah/ Iraq; patient's age ranging 19-50 yrs., several data had been collected by questioner sheet including: (age, family history, blood pressure, metformin in therapy, Diabetes, vaginal bacterial inflammations, besides other data. The bacterial samples had been diagnosed (only aerobic bacteria) then reserved for next investigation; bacterial diagnosis and identification achieved using VITEK-2 compact-system from (BioMérieux,,France); then other tests that consisting of: culturing, biochemical, sensitivity to antibiotic, ELISA kit of (Elabscience /USA) was used with principle of Sandwich method for determining serum level of IL-10; all samples taken from patients after obtaining approval from hospital and each patient.

Metformin Experiment:

Metformin (500 mg) had been diluted by adding 10 ml of distilled water to it, transfer (10 ml) prepared metformin after dilution through sterile dropper on Mulller-Hinton agar; diffusion of diluted metformin by sterile glass diffuser; let the agar dry totally; then antibiotic sensitivity achieved by method Kirby bour using tested antibiotic discs after culturing of Mulller-Hinton agar plates with E.coli, K. pneumoniae and P. aeroginosa; same mentioned experiment performed without diluted metformin; all cultured media incubated in 37˚C for 18-24 hours; then results of inhibition zone recorded by measuring of zone diameter. Antibiotic used: Ciprofloxacin, Cefotaxime, Amikacin, Gentamicin, Flucloxacillin, Amoxicillin-clavulanic acid, Ceftazidime, Cefoxitin.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Results

Table (1) summarizes the demographic characteristics of the study sample, which consisted of 87 patients. The age distribution shows that the majority of participants were young adults: 46 patients (52.8%) were between 19–30 years, followed by 35 patients (40.2%) aged 30–40 years, while only 6 patients (6.89%) fell within the 40–50 years age group [20].

Table (1): Demographic Characteristics of Patients (part 1)

Patients (total=87)		
Age	(19-30)	46 **(52.8%)**
	(30-40)	35**(40.2%)**
	(40-50)	6 **(6.89%)**
Married / unmarried		82 / 5 **(32.1% / 5.7%)**
Age of marriage		19-37 **(21.8% /42.5%)**
Type of delivery : Cs / Normal		78 /9 **(89.6% / 10.3%)**
Weight		45-92 **kg**
Education Level	Primary	6 **(6.89%)**
	Secondary	19 **(21.8%)**
	Postsecondary	62 **(71.2%)**
Occupation	House Wife	20 **(22.98%)**
	Student	26 **(29.8%)**
	employee	41 **(47.1 %)**
Residence: Urban/Rural		87/0**(100%)**

Table (2) presents additional demographic and clinical characteristics of the 87 patients included in the study. Family history of diseases revealed that 70 patients (80.4%) had no family history of chronic illness [21]. Among those with a positive history (17 patients; 19.5%), specific conditions included: diabetes in 11 patients (12.6%), combined diabetes and hypertension in 4 patients (4.9%), and thyroid disorders in 2 patients (2.2%) [22].

Table (2): Demographic Characteristics of Patients (part 2)

Patients(total=87)		
Family History of Diseases	70 / No (80.4 %)	*4 / Diabetic & Hypertension **(4.9 %)** * 11/Diabetes **(12.6 %)** * 2 / Thyroid **(2.2 %)**
		Total: 17 (19.5 %)
Polycystic Ovary Syndrome (PCOS)	46/ yes **(52.8%)**	41/ No **(47.1 %)**

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Hypertension	85/ No **(**97.7%)	2/ Yes**(2.2 %)**
Heart Disease	86/ No **(98.8 %)**	1/ Arrhythmia**(1.1 %)**
Cigarette Smoking	87/ No **(100 %)**	0/No **(0 %)**

In this study, which included 87 patients, the majority did not have diabetes, as reported by 63 participants (72.4%). Meanwhile, 24 patients (27.5%) were diagnosed with diabetes [23]. Among those with diabetes, a significant proportion 20 patients (83.3%) also had polycystic ovary syndrome (PCOS), suggesting a notable association between PCOS and the presence of diabetes (Table 3).

Table(3): Diabetes in Patients

			Patients (total=87)
Diabetes	24/ Yes **(27.5 %)** * 20 with POS **(83.3 %)**	63 / No **(72.4 %)**	
Diabetes during pregnancy	11 / Yes **(12.6 %)**	76/ no **(87.3 %)**	
Date of having diabetes	4 **(4.5 %)** 3- 5 mos	15**(17.2%)** 1-5 yrs	5 **(5.7 %)** 5-8 yrs

Among the 87 patients included in the study, infection was highly prevalent, with 84 patients (96.5%) reporting the presence of an infection, while only 3 patients (3.4%) had no infection [24]. Analysis of infection types revealed that more than half of the cases were bacterial infections, affecting 53 patients (60.9%). Meanwhile, 31 patients (35.6%) showed no microbial growth on laboratory testing [25]. These findings demonstrate that infections particularly bacterial ones are a major clinical concern within this patient group (Table 4).

Table (4): Infection and Infection Types

		Patients (total=87)
Infection	84/ Yes **(96.5 %)**	3 / No **(3.4%)**
Type of infection	53 / Bacterial **(60.9 %)**	31/No Growth**(35.6 %)**

Out of the 87 patients included in the study, 53 patients were confirmed to have bacterial vaginal infections [26]. Among these bacterial isolates, E. coli was the most prevalent organism, identified in 25 cases (47.1%), making it the leading cause of infection in this group [27]. Klebsiella pneumoniae was the second most common isolate, found in 19 patients (35.8%), while Pseudomonas aeruginosa was detected in 9 patients (16.9%) (Table 5).

Table (5): Bacterial Isolates of Vaginal Infection

			Patients (total=87)
Bacterial Isolate	***E.coli***	***K.pneumoniae***	***P.aeroginosa***
Isolate's Counts	25 **(47.1%)**	19**(35.8 %)**	9**(16.9 %)**
Total Bacterial Infections			**53 out of 87**

Among the 87 patients included in the study, metformin was used as part of therapy by 48 patients (55.1%), while 39 patients (44.8%) reported not using metformin [28]. Among those receiving metformin treatment, the duration of use varied [29]. The largest proportion (32 patients, 36.7%) had been using metformin for 6–12 months, followed by 11 patients (12.6%) who had used it for 1–6 months [30]. A smaller number, 5

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

patients (5.7%), had been on metformin therapy for 12–24 months. In total, all 48 patients (55.1% of the sample) represented those currently receiving metformin treatment (Table 6).

Table (6): Metformin (Presence in Therapy and Duration)

		Patient (total=87)
Metformin Present In Therapy	48/ Yes**(55.1 %)**	39 /No**(44.8 %)**
		Duration for Metformin in Treatment
	1-6 months	11**(12.6 %)**
	6-12 months	32**(36.7 %)**
	12- 24 months	5**(5.7 %)**
	Total	48**(55.1 %)**

Table (7) presents the serum levels of Interleukin-10 (IL-10) in the study population. The control group, consisting of 80 individuals, had an IL-10 level of 4.55 pg/ml, whereas the patient group (87 individuals) showed a lower mean IL-10 level of 2.15 ± 0.51 pg/ml [31].

Table(7): level of Inerleukin-10 in patients and control

IL-10 (pg/ml)	**Control (80)**	**Patient (87)**
	4.55	**2.15 ± 0.51**

Table (8) presents the antibiotic sensitivity of three bacterial isolates *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* tested with standard antibiotics alone and in combination with metformin [32]. The antibiotic susceptibility was measured by the diameter of the inhibition zone (mm).

Table (8): Antibiotic Sensitivity of *k.pneumoniae*, *P.aeroginosa* and *E.coli* alone and with Mixing with Metformin

Antibiotic	**Diameter of Inhibition Zone forAntibiotics only(by millimeter)**			**Diameter of Inhibition Zone for Antibiotics with Metformin(by millimetre)**		
	k.pneumoniae	***P.aeroginosa***	***E.coli***	***k.pneumonia***	***P.aeroginosa***	***E.coli***
CIP	20	25	20	27	30	20
CTX	16	0	26	20	10	22
AK	17	30	28	20	34	25
GEN	19	30	28	28	38	20
F	15	30	23	16	34	25
AMC	0	0	12	23	20	10
CAZ	0	0	0	0	0	0
FOX	0	0	0	0	0	0

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

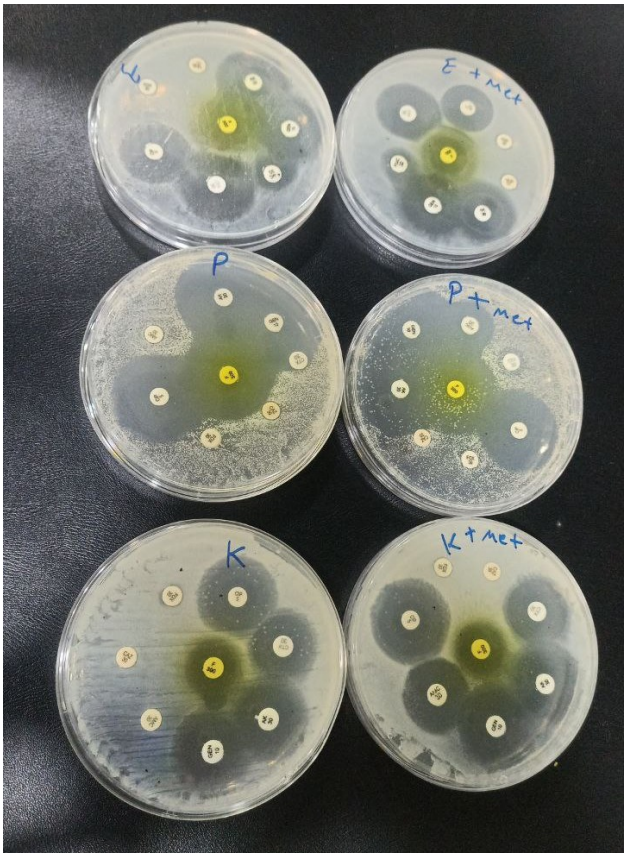


Figure-(1) Antibiotic Sensitivity Tests (Antibiotic only; Antibiotic Mixed with Metformin) on Causative Bacteria

Figure (1) illustrates the antibiotic sensitivity of three causative bacterial isolates *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* when treated with antibiotics alone and in combination with metformin [33].

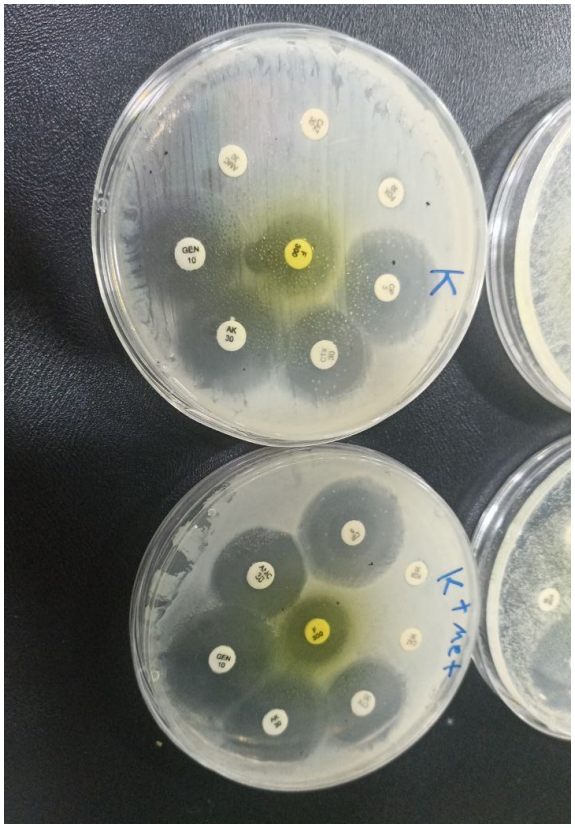


Figure-(2) Antibiotic Sensitivity Tests (Antibiotic only and Antibiotic Mixed with Metformin) on *Klebsiella pneumoniae*

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.13026

Figure (2) illustrates the antibiotic sensitivity of *Klebsiella pneumoniae* when treated with antibiotics alone and in combination with metformin. The data show that the inhibition zones increased for most antibiotics when combined with metformin, indicating an enhanced antibacterial effect [34].

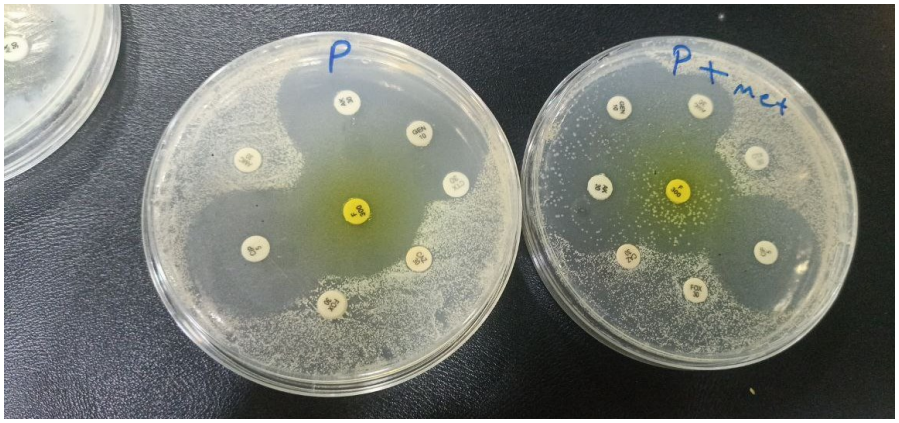


Figure-(3) Antibiotic Sensitivity Tests (Antibiotic only and Antibiotic Mixed with Metformin) on *Pseudomonas aeroginosa*

Figure 3 depicts the antibiotic sensitivity of *Pseudomonas aeruginosa* when treated with antibiotics alone and in combination with metformin [35].

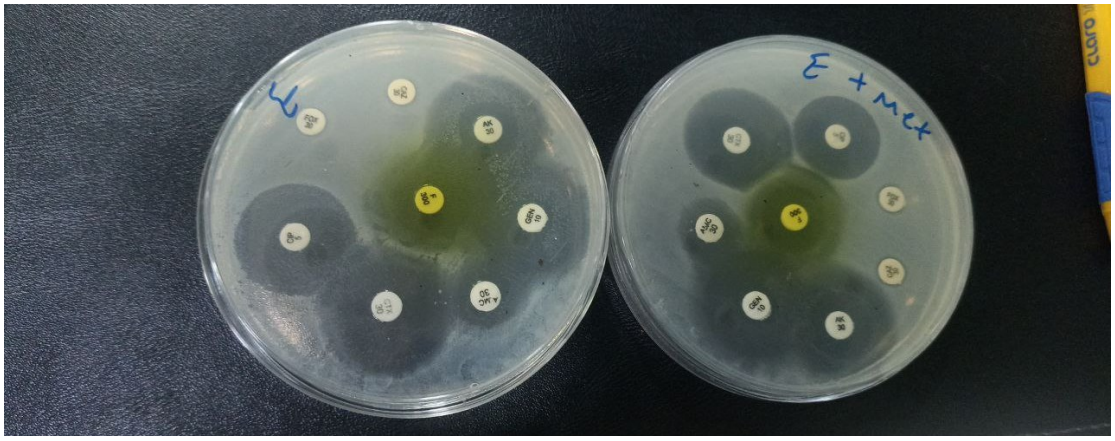


Figure-(4) Antibiotic Sensitivity Tests (Antibiotic only and Antibiotic Mixed with Metformin) on *E.coli*

Figure (4) presents the antibiotic sensitivity of *Escherichia coli* when treated with antibiotics alone and in combination with metformin. The results demonstrate that the inhibition zones increased for most antibiotics when combined with metformin, indicating a synergistic enhancement of antibacterial activity [36].

Discussion

Recently, emerging and spreading of resistance to antibiotics has considered as a potent threating for health globally, slowing the scare progression of resistance bacteria through antibiotic policies [37].

PCOS Patients exhibited decreasing in plasma Inter¬leukin-10, multiple diseases such as PCOS including antiinflammatory cytokine like IL-10 which has immune suppressive effect, recent findings showed that PCOS women had significantly lowered IL-10 serum levels [38].

Results of present research indicated that isolation of bacteria responsible for vaginal infections consisting only K.pneumoniae, P.aeroginosa and E.coli from women of (19-50) years enrolled in this research; while other cultures indicated no growth as appeared in which have been interpreted as anaerobic bacteria or other microorganisms such as viral, fungal, or parasites [39]. In addition, the current research indicated that metformin activity may raise on K.pneumoniae also on P. aeroginosa compared to effect of antibiotics alone, while on E.coli metformin activity mixed with tested antibiotics leading to moderately effects that was lowering the assistant effect of metformin comparing to that on other tested isolates [40].

In the current study that is roughly in consistent with results of the current study, indicated isolation of E.coli (15%) as a principle pathogens; followed by K.pneumoniae (2%) and S.aureus (9%) while Candida (16%); moreover, same research indicated that E.coli, S.aureus, Candida spp. with percentage of 18%, 12%, 18% have been reported in women with diabetes while 12%, 6%, 14% respectively, have been showed in nondiabetic women [41]. Multiple previously published researches indicated that metformin has potential activity to increase antibacterial action when combined with other antibiotics [42]; additionally, metformin can minimize bacterial resistance which effectively restores the activity of the antibiotics [43]. These findings along with others emphasize metformin as antimicrobial potential when used alone or mixed with antibacterial drugs [44, 45]

Conclusion

Metformin drug have property against bacteria; by mixing to other antibiotics; metformin exhibit antimicrobial activity when investigated on multiple isolates of bacteria, therefore may be conducted to be as a new assistant to antibiotic. These findings suggest that metformin may act as

a potent adjuvant to conventional antibiotics, potentially improving treatment outcomes and reducing bacterial resistance. Therefore, metformin could be considered as a novel supportive agent in antibacterial therapy, and further clinical studies are warranted to explore its therapeutic potential and mechanisms of action in combination with standard antibiotic treatments

References

1. World Health Organization, "Polycystic Ovary Syndrome," 2023, Available: https://www.who.int/
2. A. M. Elsayed et al., "Clinical Phenotypes of PCOS: A Cross-Sectional Study," Reproductive Sciences, vol. 1, pp. 1–12, 2023.
3. D. Fang and J. Zhu, "Molecular Switches for Regulating the Differentiation of Inflammatory and IL-10-Producing Anti-Inflammatory T-Helper Cells," Cellular and Molecular Life Sciences, vol. 77, pp. 289–303, 2020, doi: 10.1007/s00018-019-03282-4.
4. J. Liu, Q. Liu, and X. Chen, "The Immunomodulatory Effects of Mesenchymal Stem Cells on Regulatory B Cells," Frontiers in Immunology, vol. 11, 551680, 2020, doi: 10.3389/fimmu.2020.551680.
5. C. M. Farquhar et al., "The Prevalence of Polycystic Ovaries on Ultrasound Scanning in a Population of Randomly Selected Women," Australian and New Zealand Journal of Obstetrics and Gynaecology, vol. 34, pp. 67–72, 1994.
6. M. Rostamtabar et al., "Pathophysiological Roles of Chronic Low-Grade Inflammation Mediators in Polycystic Ovary Syndrome," Journal of Cellular Physiology, vol. 236, pp. 824–838, 2021.
7. T. Artimani et al., "Evaluation of Pro-Oxidant–Antioxidant Balance and Its Association With Inflammatory Cytokines in Polycystic Ovary Syndrome," Gynecological Endocrinology, vol. 34, pp. 148–152, 2018.
8. L. S. Hermann et al., "Therapeutic Comparison of Metformin and Sulfonylurea, Alone and in Various Combinations: A Double-Blind Controlled Study," Diabetes Care, vol. 17, pp. 1100–1109, 1994.
9. UKPDS Group, "Effect of Intensive Blood Glucose Control With Metformin on Complications in Overweight Patients With Type 2 Diabetes," Lancet, vol. 352, pp. 854–865, 1998.
10. R. A. DeFronzo and A. M. Goodman, "Efficacy of Metformin in Patients With Non-Insulin-Dependent Diabetes Mellitus," New England Journal of Medicine, vol. 333, pp. 541–549, 1995.
11. K. Johansen, "Efficacy of Metformin in the Treatment of NIDDM: Meta-Analysis," Diabetes Care, vol. 22, pp. 33–37, 1999.
12. A. J. Garber et al., "Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial," American Journal of Medicine, vol. 103, pp. 491–497, 1997.
13. M. B. Davidson and A. L. Peters, "An Overview of Metformin in the Treatment of Type 2 Diabetes Mellitus," American Journal of Medicine, vol. 102, pp. 99–110, 1997.
14. C. J. Bailey and R. C. Turner, "Metformin," New England Journal of Medicine, vol. 334, pp. 574–579, 1996.
15. K. Cusi and R. A. DeFronzo, "Metformin: A Review of Its Metabolic Effects," Diabetes Reviews, vol. 6, pp. 89–131, 1998.
16. H. Yki-Jarvinen, K. Nikkila, and S. Makimattila, "Metformin Prevents Weight Gain and Improves Metabolic Parameters in Abdominally Obese Women With and Without Polycystic Ovary Syndrome," Journal of Clinical Endocrinology and Metabolism, 1999.
17. L. J. Dominguez et al., "Effects of Metformin on Tyrosine Kinase Activity, Glucose Transport, and Intracellular Calcium in Rat Vascular Smooth Muscle," Endocrinology, vol. 137, pp. 113–121, 1996.
18. D. Argaud et al., "Metformin Decreases Gluconeogenesis by Enhancing the Pyruvate Kinase Flux in Isolated Rat Hepatocytes," European Journal of Biochemistry, vol. 213, pp. 1341–1348, 1993.
19. A. Dresner et al., "Effects of Free Fatty Acids on Glucose Transport and IRS-1-Associated PI3-Kinase Activity," Journal of Clinical Investigation, vol. 103, pp. 253–259, 1999.
20. G. Patane et al., "Metformin Restores Insulin Secretion Altered by Chronic Exposure to Free Fatty Acids," Diabetes, vol. 49, pp. 735–740, 2000.
21. C. Wilcock and C. J. Bailey, "Reconsideration of Inhibitory Effect of Metformin on Intestinal Glucose Absorption," Journal of Pharmacy and Pharmacology, vol. 43, pp. 120–121, 1991.
22. J. E. Nestler, "Metformin for the Treatment of the Polycystic Ovary Syndrome," New England Journal of Medicine, vol. 358, pp. 47–54, 2008.
23. M. Pollak, "The Effects of Metformin on Gut Microbiota and the Immune System," Diabetologia, vol. 60, pp. 1662–1667, 2017.
24. E. Thursby and N. Juge, "Introduction to the Human Gut Microbiota," Biochemical Journal, vol. 474, pp. 1823–1836, 2017.
25. D. Stepensky et al., "Pharmacokinetic–Pharmacodynamic Analysis of Metformin in Diabetic Rats," Drug Metabolism and Disposition, vol. 30, no. 8, pp. 861–868, 2002.
26. G. G. Graham et al., "Clinical Pharmacokinetics of Metformin," Clinical Pharmacokinetics, vol. 50, no. 2, pp. 81–98, 2011.
27. B. D. Novita et al., "Metformin-Induced Autophagy in Diabetes–Tuberculosis Co-Infection: A Case Study," Indian Journal of Tuberculosis, vol. 66, no. 1, pp. 64–69, 2019.
28. Y. Liu et al., "Metformin Restores Tetracycline Susceptibility Against Multidrug-Resistant Bacteria," Advanced Science, vol. 7, no. 12, 1902227, 2020, doi: 10.1002/advs.201902227.
29. C. T. Bramante et al., "Metformin and Risk of Mortality in Hospitalized COVID-19 Patients," Lancet Healthy Longevity, vol. 2, pp. e34–e41, 2021.
30. K. Maniar et al., "Metformin–Butyrate Synergism and Gut Microbiome Modification," Pharmacological Research, vol. 117, pp. 103–128, 2017.
31. W. A. H. Hegazy et al., "Repurposing Anti-Diabetic Drugs to Cripple Quorum Sensing in Pseudomonas Aeruginosa," Microorganisms, vol. 8, p. 1, 2020.
32. J. L. Tarry-Adkins, C. E. Aiken, and S. E. Ozanne, "Neonatal, Infant, and Childhood Growth After Metformin vs Insulin for Gestational Diabetes," PLoS Medicine, vol. 16, pp. 1–20, 2019.
33. W. A. H. Hegazy et al., "Repurposing Anti-Diabetic Drugs to Cripple Quorum Sensing in Pseudomonas Aeruginosa," Microorganisms, vol. 8, 1285, 2020.
34. W. A. H. Hegazy et al., "Repurposing Antidiabetics as Serratia Marcescens Virulence Inhibitors," Brazilian Journal of Microbiology, vol. 52, pp. 627–638, 2021.
35. M. M. Masadeh et al., "Metformin as a Potential Adjuvant Antimicrobial Agent," Clinical Pharmacology, vol. 13, pp. 83–90, 2021.
36. S. A. Gnanadass, Y. D. Prabhu, and A. V. Gopalakrishnan, "Association of Metabolic and Inflammatory Markers With PCOS," Archives of Gynecology and Obstetrics, vol. 303, pp. 631–643, 2021.
37. R. M. Chugh et al., "Mesenchymal Stem Cell Therapy Restores Fertility in a PCOS Mouse Model via IL-10," Stem Cell Research and Therapy, vol. 12, pp. 1–19, 2021.
38. M. Umar, K. S. Sastry, and A. I. Chouchane, "Role of Vitamin D Beyond Skeletal Function," International Journal of Molecular Sciences, vol. 19, 1618, 2018.
39. Lakshmi et al., "Bacterial Vaginal Infections in Diabetic and Non-Diabetic Women," BMC Infectious Diseases, vol. 12, suppl. 1, P63, 2012.
40. T. R. P., S. Patil, S. Patil, and A. Patil, "Antimicrobial Potential of Metformin," International Journal of Pharmacognosy and Phytochemical Research, vol. 11, no. 3, pp. 230–234, 2019.

41. A. Mor et al., “Metformin and Glucose-Lowering Drugs and Infection Rates,” BMJ Open, vol. 6, e011523, 2016.
42. Y. Xiao et al., “Metformin Promotes Innate Immunity Through a PMK-1/p38 MAPK Pathway,” Virulence, vol. 11, no. 1, pp. 39–48, 2020.
43. Y. Liu et al., “Metformin Restores Tetracycline Susceptibility Against Multidrug-Resistant Bacteria,” Advanced Science, 1902227, 2020.
44. F. Nasrin, “Antimicrobial and Antioxidant Potential of Metformin,” International Journal of Pharmaceutical and Drug Analysis, pp. 220–224, 2014.
45. S. K. Gi et al., “Increased Airway Glucose Increases Airway Bacterial Load in Hyperglycemia,” Scientific Reports, vol. 6, p. 1, 2016.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo