https://doi.org/10.33451/florafauna.v32i1pp127-133
FLORA AND FAUNA ISSN 2456 - 9364 (Online)
2026 Vol. 32 No.1 PP 127-133 ISSN 0971 - 6920 (Print)

The appearance of colistin and azithromycin resistance in recent clinical isolates of *Enterobacter cloacae*, together with their antagonistic and synergistic interactions

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Received **:** 28.03.2026; ***Accepted*** : 08.05.2026

How to cite : Singh S, Singh AK, Nath G, Singh AP. The appearance of colistin and azithromycin resistance in recent clinical isolates of enterobacter cloacae, together with their antagonistic and synergistic interactions. *Flora and Fauna* 2026. 32(1) : 127-133.

ABSTRACT

Antibiotic resistance is a growing concern worldwide, and combination therapy has emerged as a promising strategy to address this issue. Combination therapy involves using two or more antibiotics at the same time to treat bacterial infections. The combination of colistin and azithromycin has demonstrated encouraging results in treating multidrug-resistant bacterial infections. Colistin disrupts the bacterial cell membrane, enhancing the uptake of azithromycin and ultimately leading to bacterial death. Azithromycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, preventing translocation and transpeptidation. This research article focuses on colistin and azithromycin-resistant isolates among *Enterobacter spp.* and their combination to investigate the synergistic and antagonistic relationships against these resistant isolates.

Figure : 01 References : 20 Tables : 04
KEY WORDS : Combinational therapy, *Enterobacter cloacae*, Synergistic effect.

Introduction

The digestive tract is the primary site for the anaerobic, Gram-negative bacterial strain *Enterobacter cloacae*, which is widely distributed in soil, water, and sewage. It is one of the most prevalent nosocomial bacteria that can cause infections, immunosuppression, and prolonged hospital stays in patients with underlying illnesses, particularly in intensive care and burn unit[15]. The bacteria seldom induce septic osteoarthritis but typically cause sepsis, urethritis, and lower respiratory tract infections[17]. Globally, antibiotic resistance is becoming an increasingly serious health concern[12]. Both Gram-positive and Gram-negative species are in the bacterial group known as ESKAPE. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae,* and *Enterobacter* species are among them. These microbes frequently cause nosocomial

ACKNOWLEDGEMENTS : SS thanks the Head of the Botony Department, C.M.P. College, Prayagraj (UP) India for allowing to do this experiment in the Bacteriophage research laboratory, IMS, BHU Varanasi (UP) India. We further thankfully acknowledge the laboratory and financial help provided by the Bacteriophage Research Laboratory and Viral Research Diagnostic Laboratory IMS, BHU, Varanasi, India.

TABLE-1: Resistance pattern of clinical (n=40) isolates of *Enterobacter cloacae* by broth diffusion method

Tested antibiotics	Range (µg/mL)	MIC Breakpoint (CLSI 2021)	Resistant %
Macrolides			
Azithromycin	0.76-3125	≤ 32 µg/mL	(26/40) 65 %
Lipopeptides			
Colistin	0.25-16750	≤ 4 µg/mL	(7/40) 17.5 %

infections that can be fatal in severely ill and immunocompromised individuals, and they may have pathways for medication resistance[16]. Combining various drugs can effectively treat antibiotic resistance[11]. Multidrug-resistant (MDR) Gram-negative bacteria in hospitals is a prominent cause of morbidity and mortality due to comorbidity and a lack of suitable treatment options[20]. Clinically available and efficacious medications are in short supply due to the rapid rise in extended-spectrum beta-lactamase-mediated bacterial resistance. The last resort for treating Gram-negative bacteria resistant to many drugs is colistin[18]. High-level colistin resistance, however, quickly arises due to chromosomal abnormalities in several genes, such as pmrAB, phoPQ, and mgrB[10]. When two antibiotics are combined, antagonistic, indifferent, or synergistic effects may occur. Combining the two medications results in microbial inhibition at doses lower than those of either drug alone[13]. Thus, two agents working together to produce notably more activity than acting alone is called synergy[14].

Increased activity or a synergistic effect is the primary justification for combining two drugs. Decreased toxicity is a secondary justification for permitting lower antibiotic doses. Combining two drugs can help to stop the emergence of antibiotic resistance[5]. The current study aimed to characterised the *in vitro* synergy effect of colistin and azithromycin, as well as the prevalence of colistin and azithromycin resistance in *Enterobacter* species recently isolated from clinical samples resistant to either colistin, azithromycin, or both antibiotics.

Materials and Methods

Isolation of *Enterobacter cloacae* from clinical specimens

The samples were collected from the bacteriological section at the Institute of Medical Sciences, Banaras Hindu University, Varanasi, between July 2021 and April 2023, yielding 51 clinical isolates of *Enterobacter*. Pus, blood, urine, faeces, and sputum samples were used to obtain these isolates.

Isolation and characterisation of clinical isolates

A total of 51 isolates of *Enterobacter* species were isolated using standard microbiological techniques. These isolates were subjected to PCR-based discrimination using specific primers targeting each species. The isolates were identified at the species level using EC-F (52 -TGAAAACCTTATCCGCGA-32) and EC-R (52 -GGCAGGCTGGAAGATAAA-32) primers (Ji et al. 2021). Positive control was *E. cloacae subsp. cloacae* ATCC 13047 type strains. For the reaction MQW (13.57 ìL), 2.5 ìL of 10x buffer, 2 ìL of dNTP, 0.8 ìL of each primer (forward and reverse), 5 ìL of DNA template, and 0.33 ìL of Taq Polymerase were mixed for a single PCR reaction (25 ìL). In brief, denaturation at 94ÚC for 30 s, annealing at 50ÚC for 30 s, an extension phase at 72ÚCfor 1 min, and a final extension at 72ÚC for 5 min. The amplified product was analysed by 1% agarose gel electrophoresis (GeNei TM Sl. No-07/19/F/328, Peenya, and Bangalore, India).

Antibiotic susceptibility test

The Clinical and Laboratory Standards Institute's Guidelines were used to identify the *Enterobacter* isolates, and the broth dilution method was accurately used to test for antibiotic susceptibility (CLSI 2021). The *Enterobacter cloacae subspecies cloacae* ATCC 13047 reference strain was used. Clinical isolates were subjected to assays for sensitivity to azithromycin and colistin methanesulfonate (CMS). The broth dilution method was used to determine the minimum inhibitory concentration (MIC) of colistin methanesulfonate and azithromycin. The CLSI (2021) recommended azithromycin ≥ 32 µg/mL and colistin ≥ 4 µg/mL as resistance breakpoints. Hi-Media Laboratories Pvt. Ltd. in Mumbai, India, supplied laboratory-standard powders of azithromycin and colistin methanesulfonate, which were then reconstituted according to their directions[18].

TABLE-2: *in vitro* activity of Colistin in combination with Azithromycin against Colistin-resistant clinical isolates of *Enterobacter cloacae*

Isolates	AZ MIC breakpoint (>32 µg/mL)	CO MIC breakpoint (>4 µg/mL)	CO+AZ MIC	FIC value of CO	FIC value of AZ	FICI index	Result
EC 01	12.205	65.07	4.065	0.06	0.33	0.39	Synergy
EC 12	24.41	130.155	65.07	0.49	2.66	3.15	Indifferent
EC 50	24.41	16.26	16.27	1.00	0.66	1.66	Indifferent
EC 45	24.41	32.53	32.55	1.00	1.33	2.33	Indifferent

Synergy studies against colistin and azithromycin-resistant isolates

The synergistic effectiveness of colistin and azithromycin *in vitro* was evaluated against seven colistin-resistant *Enterobacter cloacae* and twenty-six clinical isolates of *Enterobacter cloacae* that were resistant to azithromycin. Azithromycin resistance was also present in three (42.85 %) of the seven clinical isolates of *Enterobacter cloacae* that showed colistin resistance. The *in vitro* synergistic effectiveness of colistin and azithromycin was evaluated against seven colistin-resistant *Enterobacter cloacae* and twenty-six clinical isolates of *Enterobacter cloacae* resistant to azithromycin. Inoculum was applied to each well to achieve a final concentration of 1×10^5 CFU/well. For a whole day, the plates were incubated at 37°C. The MIC is the lowest concentration of the inhibitor that prevents detectable bacterial growth in the well. The fractional inhibitory concentration index (ÓFIC) was determined using the following formula.

The FICs were evaluated in the manner described below:

FIC of Drug A =

$$\frac{\text{Minimum inhibitory concentration of Drug A in combination}}{\text{Minimum inhibitory concentration of Drug A alone;}}$$

FIC of drug B =

$$\frac{\text{Minimum inhibitory concentration of Drug B in combination}}{\text{Minimum inhibitory concentration of Drug B alone}}$$

The fractional inhibitory concentration index, or FICI, is the total FICs of drugs A and B. Synergy was defined as FICI $\leq$ 0.5, Indifference as FICI >0.5 and $\leq$ 4, and Antagonism as FICI >4.

Antibiotic susceptibility testing and minimum inhibitory concentration determination by the broth dilution Method

Of the 40 clinically isolated *Enterobacter cloacae*, 7 (17.5 %) were confirmed to be colistin-resistant.

Results

Identification of bacterial isolates

A species-specific primer identified 40 of the 51 (78.43 %) *Enterobacter* isolates as *Enterobacter cloacae* (Fig.1).

It was found that 29 out of 40 clinical isolates of *Enterobacter cloacae* (72.5%) were resistant to azithromycin (Table-1).

Enterobacter cloacae isolates (clinical) sensitive to colistin but resistant to azithromycin, sensitive to azithromycin and resistant to colistin, sensitive to both colistin and azithromycin and resistant to both colistin and azithromycin were found.

Synergy study of colistin-resistant *Enterobacter cloacae*

The *in vitro* synergy test for colistin and azithromycin combination examined four (4/40) clinical isolates with MIC valuese $\geq$ 4µg/mL and colistin resistant. Table-2 shows that the combination of azithromycin and colistin showed indifference against three isolates (75%), antagonism against 0 isolates (0%) and synergy against one isolate (25%). (Table-2).

Synergy study of azithromycin-resistant *Enterobacter cloacae*

The azithromycin and colistin combination demonstrated synergy against 6 (26.08%) isolates,

TABLE-3: *In vitro* activity of azithromycin and colistin against azithromycin-resistant clinical isolates of *Enterobacter cloacae*

Isolates	AZ MIC breakpoint (>32 µg/mL)	CO MIC breakpoint (>4 µg/mL)	CO+AZ MIC	FIC value of CO	FIC value of AZ	FICI index	Result
EC 51	1.015	48.82	8.137	8.016	0.16	8.182	Antagonism
EC 40	1.015	48.82	4.068	4.007	0.083	4.090	Indifferent
EC 47	1.015	97.65	8.137	8.016	0.083	8.099	Antagonism
EC 41	2.03	97.65	8.137	4.008	0.083	4.091	Indifferent
EC 44	2.03	48.82	4.068	2.003	0.083	2.086	Indifferent
EC 43	2.03	1562.5	4.068	2.003	0.002	2.005	Indifferent
EC 48	2.03	1562.5	4.068	1	0.002	2.0056	Indifferent
EC 34	2.03	48.82	2.03	1	0.041	1.041	Indifferent
EC 37	2.03	97.65	2.03	0.5	0.020	1.020	Indifferent
EC 36	4.06	195.31	2.03	4.007	0.01	0.51	Synergy
EC 22	1.015	1562.5	4.068	4.007	0.002	4.009	Indifferent
EC 19	1.015	195.31	8.137	8.016	0.041	8.057	Antagonism
EC 18	1.015	195.31	4.068	4.007	0.020	4.027	Indifferent
EC 17	2.03	195.31	1.015	0.5	0.0051	0.50	Synergy
EC 11	2.03	97.65	1.015	0.5	0.010	0.51	Synergy
EC 10	2.03	48.82	1.015	0.5	0.020	0.52	Synergy
EC 09	2.03	97.65	2.03	1	0.020	1.020	Indifferent
EC 06	2.03	48.82	4.068	2.003	0.083	2.086	Indifferent
EC 03	2.03	48.82	1.015	0.5	0.020	0.52	Synergy
EC 15	4.068	48.82	1.015	0.249	0.020	0.269	Synergy
EC 31	1.015	97.65	2.03	2	0.020	2.020	Indifference
EC 46	1.015	48.82	1.015	1	0.020	1.020	Indifference
EC 25	1.015	48.82	2.03	2	0.041	2.041	Indifference

TABLE-4: *In-vitro* activity of azithromycin (AZ) and colistin (CO) against both colistin and azithromycin-resistant *Enterobacter* isolates

Isolates	AZ MIC breakpoint (>32 µg/mL)	CO MIC breakpoint (>4 µg/mL)	CO+AZ MIC	FIC value of CO	FIC value of AZ	FICI index	Result
EC 32	781.25	2082.5	520	0.250	0.666	0.9	Indifferent
EC 08	48.82	260	260	1	5.32	6.32	Antagonism
EC 21	97.65	65.07	16.27	0.25	0.166	0.416	synergy

antagonism against 3 (13.04 %), and indifference against 14 (60.86%) of the 23 clinical *Enterobacter cloacae* that were resistant to azithromycin (Table-3).

Synergy study of both colistin and azithromycin-resistant *Enterobacter cloacae*

Colistin and azithromycin together showed synergy against one isolate (33.33%), antagonism against one isolate (33.33%), and indifference against one isolate (33.33%) of the three clinical *Enterobacter cloacae* that were resistant to both antibiotics. (Table-4).

Discussion

Antibiotic combination therapy is finally used due to a shortage of novel, effective antibiotics. The primary objective of this study was to identify and collect antibiotic combinations that may be effective in combating colistin and azithromycin-resistant *Enterobacter cloacae*. The macrolide antibiotic azithromycin was used with imipenem, colistin, and fosfomycin, three commonly used antibiotics. It binds to the 50S ribosomal subunit at the 23S rRNA site, stopping translocation and transpeptidation during protein synthesis. Although colistin is a cationic antimicrobial peptide (CAMP), its nephrotoxicity and neurotoxicity led to the termination of its therapeutic usage. However, due to the emergence of multidrug-resistant (MDR) bacteria and the need for effective antimicrobials, the therapeutic potential of colistin is being reevaluated. Colistin primarily acts by breaking down bacterial membranes, which significantly alters the bacteria's permeability[3]. Because restricted entry or improved efflux frequently cause medication resistance, modest doses of colistin have been employed to make bacteria more sensitive to certain antimicrobials[2,9]. There has been evidence of *in vitro* synergy with low-dose colistin and other antimicrobials in *E. Coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [1,4,6,19]. Therefore, we examined the *in vitro* efficacy of colistin and azithromycin in treating 36 clinical isolates of drug-resistant *Enterobacter cloacae*. The antibiotic susceptibility of clinical isolates of *Enterobacter cloacae* was studied, as anticipated, using the broth dilution method to determine the minimum inhibitory concentration (MIC) of azithromycin and colistin. We found that *Enterobacter cloacae* clinical isolates exhibited greater resistance to azithromycin than colistin. In our investigation, we discovered that 69 % of *Enterobacter cloacae* from clinical specimens were resistant to azithromycin, while 16.6 % were resistant to colistin. Combination therapy is often suggested as an initial empirical treatment because there aren't many effective substances available to stop the growth of germs that are resistant to drugs. In light of this, we conducted *in vitro* tests using the colistin and azithromycin combination against seven colistin-resistant clinical isolates, yielding some interesting outcomes. Only synergy was seen in 25 % of the clinical isolates that were resistant to colistin. Similarly, 26 % of clinical isolates of *Enterobacter cloacae* resistant to azithromycin exhibited synergy. No information exists on the synergy between colistin and azithromycin against *Enterobacter cloacae* in any Indian report. One of the most plausible explanations for the synergy of colistin-azithromycin combinations is that colistin may increase the permeability of the bacterial outer membrane, allowing azithromycin to enter. In a similar vein, a previous study showed that colistin and high dosages of azithromycin (2.5 mg/litre) combined to combat colistin-resistant *E. coli* effectively isolates *in vitro* at a minimum inhibitory concentration (MIC) of just 25% to 50% of colistin[2].

Dispute: Because of the increased permeability of the Gram-negative outer membrane, which enables azithromycin to access the 50S ribosomal subunit, studies employing MDR *K. pneumoniae* have shown that azithromycin and colistin work in concert[8]. Interestingly,

25-26 % of the isolates exhibit synergy of clinical origin, meaning they are either azithromycin or colistin-resistant. It is necessary to look into the complex mechanism. However, because of its poor synergy, this combination is not recommended for empirically treating *Enterobacter cloacae* infections. This work is notable for its examination of antibiotic resistance patterns, minimum inhibitory concentrations, and the synergy of colistin and azithromycin in clinical isolates of *Enterobacter cloacae* strains. Furthermore, we demonstrated that the two medications synergise in clinical *Enterobacter cloacae* isolates resistant to both azithromycin and colistin, with certain isolates exhibiting a significant decrease in MIC values. According to the study's findings, clinical isolates develop high levels of drug resistance due to the strong selection pressure exerted by a range of antimicrobials present in the clinical setting.

Conclusion

Finally, based on the *in vitro* checker board experiment, we found that colistin and azithromycin synergistically inhibited *Enterobacter cloacae* isolates. The combination of colistin and azithromycin is also not promising, as it carries a risk of failure in more than 60% of cases of sickness caused by *Enterobacter cloacae.* This study raises serious concerns, as it implies that *Enterobacter cloacae* are also gaining ground in the last line of defence against infection treatment. Furthermore, *Enterobacter cloacae* infections are resistant to the current antibiotic arsenal, and due to their resistance to every antibacterial on the market, the bacteria have evolved into a superbug. We need to work on developing alternative antimicrobials, including synthetic chemicals, small polypeptides, bacteriophage treatment, and novel plant-based molecules.

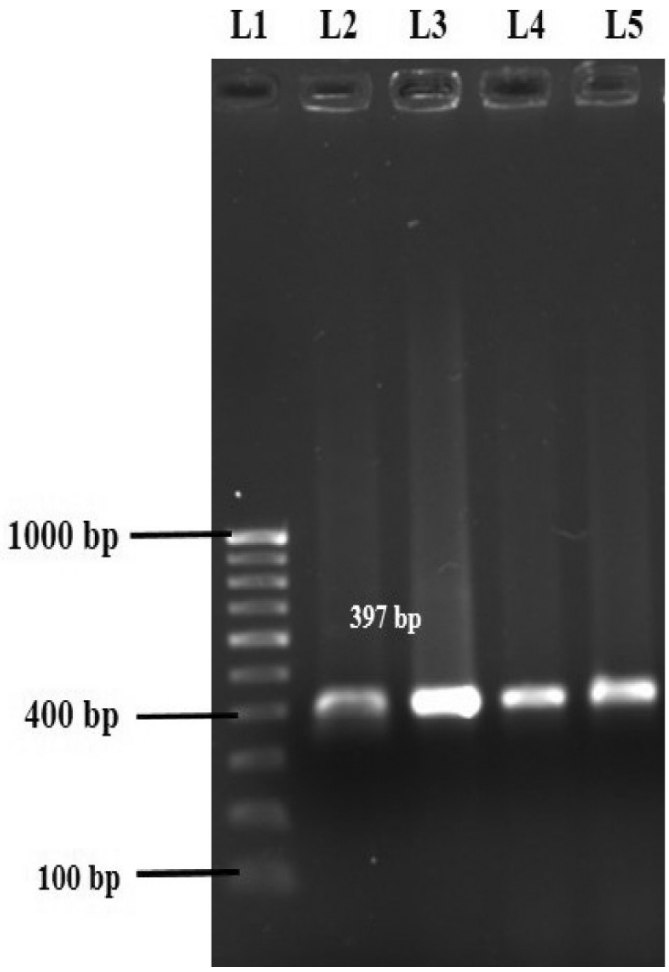

Fig.1 : Gel image showing molecular identification using a species-specific primer (Lane1: 100 bp Ladder, Lane 2: *Enterobacter cloacae* ATCC 13047 (Positive control), Lane 3, 4 & 5 showing clinical isolates (*Enterobacter cloacae subspecies cloacae*).

References

1. Al Atya, Ahmed K, Karima Drider-Hadiouche, Anne Vachee, Djamel Drider. "Potentialization of â-Lactams with Colistin: In Case of Extended Spectrum â-Lactamase Producing Escherichia Coli Strains Isolated from Children with Urinary Infections." *Research in Microbiology.* 2016; **167**(3) : 215–21. doi:10.1016/j.resmic.2015.12.002.

2. Armengol E, Domènech O, Fusté E, Pérez-Guillén I, J.H. Borrell JH, Sierra JM, Viñas M. "Efficacy of Combinations of Colistin with Other Antimicrobials Involves Membrane Fluidity and Efflux Machinery." *Infection and Drug Resistance.* 2019; **12** : 2031–38. doi:10.2147/IDR.S207844.

3. Bialvaei, Abed Zahedi, Hossein Samadi Kafil. "Colistin, Mechanisms and Prevalence of Resistance." *Current Medical Research and Opinion.* 2015; **31**(4) : 707–21. doi:10.1185/03007995.2015.1018989.

4. D'Souza, Beena Benita, Sunil Rao Padmaraj, Panchapaddy Devasya Rekha, Rouchelle Charmaine Tellis, Sudharshan Prabhu, Priyanka Pothen. "*In Vitro* Synergistic Activity of Colistin and Ceftazidime or Ciprofloxacin Against Multidrug-Resistant Clinical Strains of *Pseudomonas Aeruginosa*." *Microbial Drug Resistance.* 2014; **20**(6) : 550–54. doi:10.1089/mdr.2014.0006.

5. Haidari, Fatemeh, Mohammad Reza Rashidi, Seid Ali Keshavarz, Soltan Ali Mahboob, Mohammad Reza Eshraghian, Majid Mohamad Shahi. "Effects of Onion on Serum Uric Acid Levels and Hepatic Xanthine

Dehydrogenase/Xanthine Oxidase Activities in Hyperuricemic Rats." *Pakistan Journal of Biological Sciences.* 2008; **11**(14) : 1779–84. doi:10.3923/pjbs.2008.1779.1784.

6. Hong, Duck Jin, Jung Ok Kim, Hyukmin Lee, Eun-Jeong Yoon, Seok Hoon Jeong, Dongeun Yong, Kyungwon Lee. *"In Vitro* Antimicrobial Synergy of Colistin with Rifampicin and Carbapenems against Colistin-Resistant Acinetobacter Baumannii Clinical Isolates." *Diagnostic Microbiology and Infectious Disease.* 2016; **86**(2) : 184–89. doi:10.1016/j.diagmicrobio.2016.07.017.

7. Ji Yang, Peihong Wang, Tingting Xu, Yanzi Zhou, Rongchang Chen, Huaiqiu Zhu, Kai Zhou. "Development of a One-Step Multiplex PCR Assay for Differential Detection of Four Species (Enterobacter Cloacae, Enterobacter Hormaechei, Enterobacter Roggenkampii, and Enterobacter Kobei) Belonging to Enterobacter Cloacae Complex With Clinical Significance." *Frontiers in Cellular and Infection Microbiology.* 2021; **11** : 677089. doi:10.3389/fcimb.2021.677089.

8. Kumaraswamy M, Lin L, Olson, Sun CF, Nonejuie P, Corriden R, Döhrmann S, Ali SR, Amaro D, Rohde M, Pogliano J, Sakoulas G, Nizet V. "Standard Susceptibility Testing Overlooks Potent Azithromycin Activity and Cationic Peptide Synergy against MDR *Stenotrophomonas Maltophilia*." *Journal of Antimicrobial Chemotherapy.* 2016; **71**(5) : 1264–69. doi:10.1093/jac/dkv487.

9. Lenhard, Justin R, Roger L. Nation, Brian T. Tsuji. "Synergistic Combinations of Polymyxins." *International Journal of Antimicrobial Agents.* 2016; **48**(6) : 607–13. doi:10.1016/j.ijantimicag.2016.09.014.

10. Li, Yanqin, Xiaohuan Lin, Xuan Yao, Yan Huang, Wenguang Liu, Tao Ma, Binghu Fang. "Synergistic Antimicrobial Activity of Colistin in Combination with Rifampin and Azithromycin against Escherichia Coli Producing MCR-1." *Antimicrobial Agents and Chemotherapy.* 2018; **62**(12) : e01631-18. doi:10.1128/AAC.01631-18.

11. Lv, Ji, Senyi Deng, and Le Zhang. "A Review of Artificial Intelligence Applications for Antimicrobial Resistance." *Biosafety and Health.* 2021; **3**(1) : 22–31. doi:10.1016/j.bsheal.2020.08.003.

12. Murray, Christopher JL, Kevin Shunji Ikuta, Fablina Sharara, Lucien Swetschinski, Gisela Robles Aguilar, Authia Gray, Chieh Han, et al. "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis." *The Lancet.* 2022; **399**(10325) : 629–55. doi:10.1016/S0140-6736(21)02724-0.

13. Olajuyigbe OO. "Synergistic Influence of Tetracycline on the Antibacterial Activities of Amoxicillin Against Resistant Bacteria." *Journal of Pharmacy and Allied Health Sciences.* 2012; **2**(1) : 12–20. doi:10.3923/jpahs.2012.12.20.

14. Orhan, Gani, Aysen Bayram, Yasemin Zer, Iclal Balci. "Synergy Tests by E Test and Checkerboard Methods of Antimicrobial Combinations against *Brucella Melitensis*." *Journal of Clinical Microbiology.* 2005; **43**(1) : 140–43. doi:10.1128/JCM.43.1.140-143.2005.

15. Sanders WE, Sanders CC. "Enterobacter Spp.: Pathogens Poised to Flourish at the Turn of the Century." *Clinical Microbiology Reviews.* 1997; **10**(2) : 220–41. doi:10.1128/CMR.10.2.220.

16. Santajit Sirijan, Nitaya Indrawattana. "Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens." *BioMed Research International.* 2016; 1–8. doi:10.1155/2016/2475067.

17. Shirtliff, Mark E, Jon T. Mader. "Acute Septic Arthritis." *Clinical Microbiology Reviews.* 2002; **15**(4) : 527–44. doi:10.1128/CMR.15.4.527-544.2002.

18. Singh Srishti, Singh Alok Kumar, Singh Sudhir Kumar, Yadav Virendra Bahadur, Kumar Akshay, Nath Gopal. "Current Update on the Antibiotic Resistance Profile and the Emergence of Colistin Resistance in Enterobacter Isolates from Hospital-Acquired Infections." *The Microbe.* 2025; **8** : 100432. doi:10.1016/j.microb.2025.100432.

19. Singkham-in, Uthaibhorn, Netchanok Muhummudaree, Tanittha Chatsuwan. *"In Vitro* Synergism of Azithromycin Combination with Antibiotics against OXA-48-Producing Klebsiella Pneumoniae Clinical Isolates." *Antibiotics.* 2021; **10**(12) : 1551. doi:10.3390/antibiotics10121551.

20. Vardakas, Konstantinos Z, Petros I. Rafailidis, Athanasios A. Konstantelias, Matthew E. Falagas. "Predictors of Mortality in Patients with Infections Due to Multi-Drug Resistant Gram Negative Bacteria: The Study, the Patient, the Bug or the Drug?" *Journal of Infection.* 2013; **66**(5) : 401–14. doi:10.1016/j.jinf.2012.10.028.

Nat Rev Endocrinol. 2019; **15** : 261-273.

3. Cani PD, Amar J, Iglesias MA. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007; **56** : 1761-1772.
4. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol.* 2019; **16** : 461-478.
5. Devillard E, McIntosh FM, Duncan SH, Wallace RJ. Metabolism of linoleic acid by human gut bacteria. *J Bacteriol.* 2007; **189** : 2566-2570.
6. Devillard E, McIntosh FM, Paillard D, Thomas NA, Shingfield KJ, Wallace RJ. Differences between human subjects in the composition of the faecal bacterial community and metabolism of linoleic acid. *Microbiology.* 2009; **155** : 513-520.
7. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol.* 2021; **19** : 55-71.
8. Gurung M, Li Z, You H. Role of gut microbiota in type 2 diabetes pathophysiology. *E Bio Medicine.* 2020; **51** : 102590.
9. Hollister EB, Gao C, Versalovic J. Compositional and functional features of the gastrointestinal microbiome and their effects on human health. *Gastroenterology.* 2014; **146** : 1449-1458.
10. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol.* 2015; **21** : 8787-8803.
11. Karlsson FH, Tremaroli V, Nielsen J, Bäckhed F. Assessing the human gut microbiota in metabolic diseases. *Diabetes.* 2013; **62** : 3341-3349.
12. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell.* 2016; **165** : 1332-1345.
13. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006; **444** : 1022–1023.
14. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. *Proc Nutr Soc.* 2003; **62** : 67-72.
15. Markowiak P, Slizewska K. Effects of probiotics, prebiotics and synbiotics on human health. *Nutrients.* 2017; **9** : 1021.
16. O'Hara AM, Shanahan F. The gut flora as a forgotten organ. *EMBO Rep.* 2006; **7** : 688-693
17. Pedersen HK, Gudmundsdottir V, Nielsen HB, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature.* 2016; **535** : 376-381.
18. Picard C. Non-alcoholic fatty liver diseases: from role of gut microbiota to microbial-based therapies. *Eur J Clin Microbiol Infect Dis*. 2020; **39** : 613–627.
19. Raygan F, Rezavandi Z, Bahmani F. The effects of probiotic supplementation on metabolic status in type 2 diabetic patients with coronary heart disease. *Diabetol Metab Syndr.* 2018; **10** : 51.
20. Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature.* 2019; **576** : 51-60.
21. Sartor RB. Microbial influences in inflammatory bowel diseases. *Gastroenterology.* 2008; **134** : 577-594.
22. Schloissnig S, Arumugam M, Sunagawa S, et al. Genomic variation landscape of the human gut microbiome. *Nature.* 2013; **493** : 45-50.
23. Sekirov I, Russell SL, Antunes LCM, Finlay BB. Gut microbiota in health and disease. *Physiol Rev.* 2010; **90** : 859-904.
24. Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. *Nature.* 2016; **535** : 56-64.
25. Swidsinski A, Loening-Baucke V, Lochs H, Hale LP. Spatial organization of bacterial flora in normal and inflamed intestine. *World J Gastroenterol.* 2005; **11** : 1131-1140.
26. Tilg H, Zmora N, Adolph TE, Elinav E. The intestinal microbiota fuelling metabolic inflammation. *Nat Rev Immunol.* 2020; **20** : 40 54.
27. Turroni F. Bifidobacteria as probiotic agents: physiological effects and clinical benefits. *Aliment Pharmacol Ther.* 2005; **22** : 1045–1055.
28. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science.* 2018; **359** : 1151-1156.