German Journal of Microbiology

eISSN: 2749-0149

Letter to the Editor

Arum Palaestinum-derived extracellular vesicles as antibacterial agents against ESKAPE pathogens

Ahmad Kadriya[1], Zenab Ali Saleh[1], Karolina Bierowiec[2], Wolfgang Eisenreich[3], Mizied Falah[1]*

[1]Medical Research Institute, The Holy Family Hospital Nazareth, Nazareth 16100; Azrieli Faculty of Medicine, Bar-Ilan University, Safed 1311502, Israel
[2]LWroclaw University of Environmental and Life Sciences, Department of Epizootiology and Clinic of Birds and Exotic Animals, Grunwaldzki Sq. 45, 50-366 Wrocław, Poland
[3]Structural Biochemistry of Membranes, Bavarian NMR Center, Technical University of Munich (TUM), Munich, Germany

Article History:
Received: 25-Dec-2023
Accepted: 12-Apr-2024
***Corresponding author:**
Mizied Falah
mizied.falah@gmail.com

Abstract

Plant phytosomes are tiny extracellular vesicles (EVs) that transport various molecules, facilitating communication both within and between cells. They can be found in different parts of plants and contain mir-RNA, m-RNA, DNA, lipids, proteins, and metabolites. These vesicles may play a critical role in plant immune response to microbial infections. EVs exert several biological activities, including anti-inflammatory, antioxidant, antiobesity, and anticancer effects. Recently, EVs have been used as a vehicle for drug delivery. Our recent preliminary data has identified antimicrobial effects of *Oleaceae*-derived EVs against multidrug-resistant bacteria such as *Staphylococcus aureus, Enterococcus faecalis,* and *Klebsiella pneumoniae.* This letter seeks scientists interested in studying the antimicrobial effects of EVs or their use in drug delivery using natural products against multi-drug resistance.

Keywords: *Arum Palaestinum*, antibacterial agents, extracellular vesicles, ESKAPE

Citation: Kadriya, A., Saleh, Z. A., Bierowiec, K., Eisenreich, W. and Falah, M. (2024). *Arum Palaestinum*-derived extracellular vesicles as antibacterial agents against ESKAPE pathogens. Ger. J. Microbiol. 3 (3): 16-19. https://doi.org/10.51585/gjm.2023.3.0027

Letter to Editor

Antibiotics were first introduced as an effective treatment option for serious bacterial infections in the mid-twentieth century. However, a few years later, bacteria developed resistance against these drugs, which has become a major global health concern (Hutchings et al., 2019). Antimicrobial resistance (AMR) is the ability of microorganisms such as bacteria, fungi, viruses, and parasites to stop the action of antimicrobial drugs, resulting in ineffective treatment and persistence of the infection. Currently, AMR is a global health threat, and its extensive use in farm animals, the food industry, and human and veterinary medicine has led to the emergence of multidrug-resistant (MDR) organisms. AMR is a leading cause of death worldwide, with the highest burdens in low-resource settings (Wagenlehner and Dittmar, 2022). It also results in a huge economic loss due to long stays in hospitals and increases in treatment complexity, posing a real challenge to the existing guidelines around the management of antibiotic resistance (Aljeldah, 2022). Some bacterial species naturally play a crucial role in healthy physiological processes (Sender et al., 2016). However, other bacteria that are opportunistic, parasitic, mentalistic, and invasive can still disturb such homeostasis processes and ultimately necessitate intervention (Llor and Bjerrum, 2014; Liyanarachi et al., 2022). Antibiotics have revolutionized modern medicine, but over the years, bacteria developed intricate mechanisms of resistance to many of the first-line antibiotics, and as such, bacteria could evade many of the potent actions of antibiotics (Munita and Arias, 2016). The World Health Organization (WHO) has recently identified MDR as among the three most important problems threatening human and animal health on a global scale (Santajit and Indrawattana, 2016). The main leading cause of nosocomial MDR infections is a group of bacteria known as ESKAPE pathogens, including *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species. Recently, ESKAPE, together with *Clostridioides difficile*, which is often caused by antibiotic-induced disruption of the native gut microbiota, the term changed to (ESKAPE+C). These pathogens collectively are the leading cause of nosocomial infections by diverse mechanisms of drug resistance, such as drug inactivation, active site modification, efflux pumps, and biofilm formation, leading to MDR strains (Weber et al., 2020).

Throughout the centuries, plants have been studied for therapeutics, and their compounds have been purified and tested on various disease models; phytogenic compounds have antimicrobial properties against bacteria, fungi, protozoa, and viruses. They can also help boost the immune system of patients who have a weakened immune system. The mechanism of antibacterial effects can be attributed to the damage of the cell membrane by targeting the phospholipids of Gram-positive and Gram-negative bacteria. Bioactive substances or their metabolites are incorporated into the membrane, causing alteration of its physiological function (Nourbakhsh et al., 2022).

Recently, plant-derived extracellular vesicles isolated from edible plants were found to be an abundant source of nanovesicles with remarkable therapeutic properties and minimal side effects (Xiao et al., 2018; Yang et al., 2018; Bokka et al., 2020). In this letter, we will highlight the extracellular vesicle as a potentially promising approach to metabolites. These phytosomes have been identified in various plant parts, indicating their potential role in the plant immune response during microbial infection. In this letter, we will highlight the extracellular vesicle as a potentially promising approach to combat MDR. The emerging field of extracellular vesicles (EVs) in plants, termed phytosomes, presents a fascinating avenue for such research. Similar to mammalian cell-derived EVs, plant phytosomes facilitate intercellular and intracellular communication by transporting a diverse cargo of molecules, including mir-RNA, m-RNA, DNA, lipids, proteins, and metabolites. These phytosomes have been identified in various plant parts, indicating their potential role in the plant immune response during microbial infection. In the context of plant infections, investigations have unveiled how plants leverage phytosomes to harbor antifungal and antibacterial cargos, effectively countering the virulence agents of pathogens. A study conducted on Arabidopsis cells, commonly known as rockcress, elucidated a phenomenon termed cross-kingdom interference. This phenomenon underscores the intricate interaction between host cells of Arabidopsis and invading fungi, wherein the plant cells secrete phytosomes containing small RNAs (s-RNAs) to silence the virulence genes of pathogens such as Botrytis. The transferred s-RNAs, specifically TAS1c-siR483 and TAS2-siR453, effectively silenced the vesicle-trafficking pathways of the fungi, as demonstrated in the study by (Cai et al., 2018). Similarly, research on wheat cells has revealed the presence of micro-RNAs (miR1023) that target a potential gene of the pathological fungus *Fusarium graminearum* (Jiao and Peng, 2018). We have previously showcased the potential use of plant-derived phytosomes as an anticancer remedy (Kadriya and Falah, 2023), and now we aim to initiate a study and investigate deeper to unravel the antimicrobial capacity. Plants employ a diverse array of defense mechanisms involving physiological and biochemical responses to fend off invasive pathogens effectively. Upon infection, pathogens activate plant immune responses, and thereby, phytosomes are produced to play key roles in plant-pathogen interactions, transferring the plant defense-related cargos that are taken up by pathogens, resulting in reducing their virulence (Zhou et al., 2022). Plant-derived EVs pertain to several exciting potentials (Figure 1).

Our recent preliminary data has identified antimicrobial effects of *Oleaceae*-derived EVs against multidrug-resistant bacteria such as *Staphylococcus aureus, Enterococcus faecalis,* and *Klebsiella pneumoniae* (see Figure 2, Figure 3), which are reference strains purchased from ATCC (Satroious, Israel). Given the publication's pivotal role in facilitating discourse and disseminating cutting-edge scientific discoveries, we are confident that providing details about this forthcoming research endeavor to your esteemed readership will significantly enhance its visibility and influence. This letter is a call for scientist interested in developing natural products in order to investigate in detail the antimicrobial effects of phytosomes or their use in drug delivery.

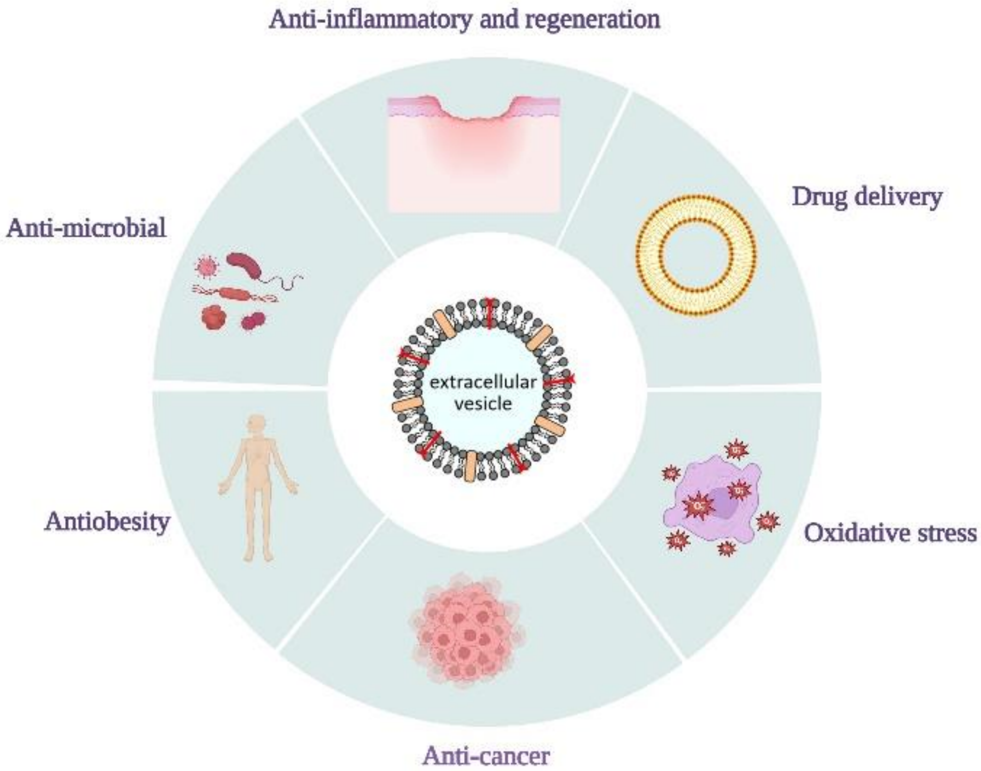

Figure 1: Potential applications of plant-derived extracellular vesicles.

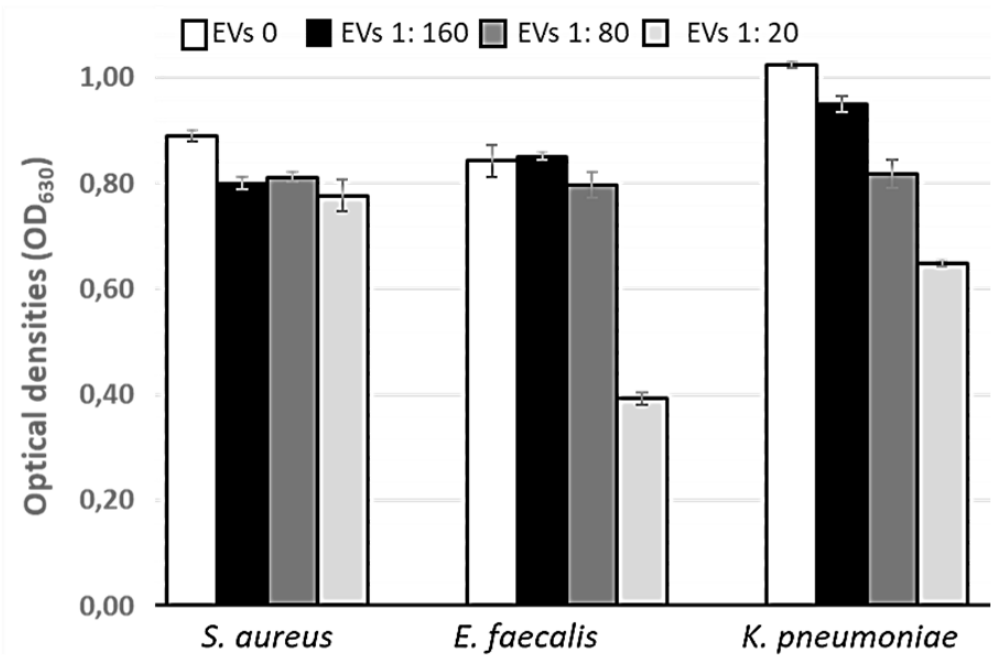

Figure 2: Antimicrobial effect of *Oleaceae*-derived EVs. A colony of bacteria suspended in growth media (Luria broth) was grown overnight (16 hours) at 37 °C rocking at 130 rpm, then diluted to OD_{630}=0.1 with growth media in a 96-well plate (200 µL per well) and incubated overnight with EVs at the indicated dilutions. The OD was read using a Varioskan plate reader at 630 nm. The results are represented in the form of mean ± standard error from three experiments (n = 3).

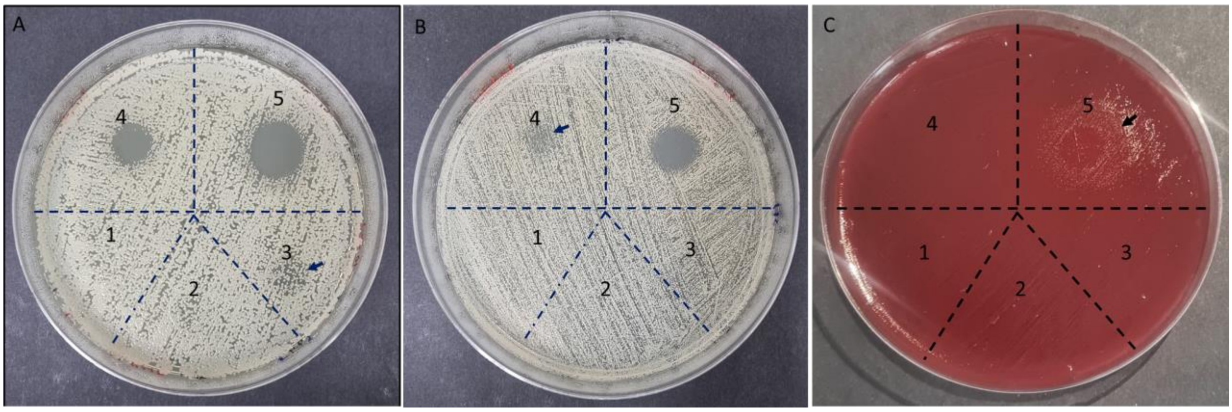

Figure 3: Inhibition zones of EVs against resistant bacteria on both Mueller Hinton and blood agar. Panel A depicts *Klebsiella pneumoniae,* Panel B shows *Staphylococcus aureus,* and Panel C illustrates *Enterococcus faecalis*. The numbers indicate different dilutions of EVs: 1 = PBS (No treatment), 2 = 1:10, 3 = 1:5, 4 = 1:2, 5 = undiluted EVs. Arrows indicate partial effects. The determined inhibition zones are as follows: A4 = 11mm, A5 = 14mm, B5 = 12mm, C5 = 12mm.

Article Information
Conflict of Interest. The authors declare to have no competing interests.
Funding. The authors did not receive any funds for this work
Acknowledgments. Not applicable
Authors' contributions. All authors participated in preparing and approving the submitted manuscript.

References

Aljeldah, M.M., 2022. Antimicrobial resistance and its spread is a global threat. Antibiotics (Basel) 11, 1082. https://doi:10.3390/antibiotics11081082

Bokka, R., Ramos, A.P., Fiume, I., Manno, M., Raccosta, S., Turiák, L., Sugár, S., Adamo, G., Csizmadia, T., Pocsfalvi, G., 2020. Biomanufacturing of tomato-derived nanovesicles. Foods 9, 1852. https://doi:10.3390/foods9121852

Cai, Q., Qiao, L., Wang, M., He, B., Lin, F.-M., Palmquist, J., Huang, S.-D., Jin, H., 2018. Plants send small RNAs in extracellular vesicles to fungal pathogens to silence virulence genes. Science 360, 1126–1129. https://doi:10.1126/science.aar4142.

Hutchings, M.I., Truman, A.W., Wilkinson, B., 2019. Antibiotics: past, present and future. Current Opinion in Microbiology 51, 72–80. https://doi:10.1016/j.mib.2019.10.008.

Jiao, J., Peng, D., 2018. Wheat microRNA1023 suppresses invasion of *Fusarium graminearum* via targeting and silencing FGSG_03101. Journal of Plant Interactions 13, 514–521. https://doi:10.1080/17429145.2018.1528512.

Kadriya, A., Falah, M., 2023. Nanoscale phytosomes as an emerging modality for cancer therapy. Cells 12, 1999. https://doi:10.3390/cells12151999.

Liyanarachi, K.V., Solligård, E., Mohus, R.M., Åsvold, B.O., Rogne, T., Damås, J.K., 2022. Incidence, recurring admissions, and mortality of severe bacterial infections and sepsis over a 22-year period in the population-based HUNT study. PLoS One 17, e0271263. https://doi:10.1371/journal.pone.0271263.

Llor, C., Bjerrum, L., 2014. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Therapeutic Advances in Drug Safety 5, 229–241. https://doi:10.1177/2042098614554919.

Munita, J.M., Arias, C.A., 2016. Mechanisms of antibiotic resistance. Microbiology Spectrum 4. https://doi:10.1128/microbiolspec.VMBF-0016-2015.

Nourbakhsh, F., Lotfalizadeh, M., Badpeyma, M., Shakeri, A., Soheili, V., 2022. From plants to antimicrobials: Natural products against bacterial membranes. Phytotherapy Research 36, 33–52. https://doi:10.1002/ptr.7275.

Santajit, S., Indrawattana, N., 2016. Mechanisms of antimicrobial resistance in ESKAPE pathogens. BioMed Research International 2016, 1–8. https://doi:10.1155/2016/2475067.

Sender, R., Fuchs, S., Milo, R., 2016. Revised estimates for the number of human and bacteria cells in the body. PLoS Biology 14, e1002533. https://doi:10.1371/journal.pbio.1002533.

Wagenlehner, F.M.E., Dittmar, F., 2022. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet 399, 629–655. https://doi:10.1016/S0140-6736(21)02724-0.

Weber, K.L., LeSassier, D.S., Kappell, A.D., Schulte, K.Q., Westfall, N., Albright, N.C., Godbold, G.D., Palsikar, V., Acevedo, C.A., Ternus, K.L., Hewitt, F.C., 2020. Simulating transmission of ESKAPE pathogens plus *C. difficile* in relevant clinical scenarios. BMC Infectious Diseases 20, 411. https://doi:10.1186/s12879-020-05121-4.

Xiao, J., Feng, S., Wang, X., Long, K., Luo, Y., Wang, Y., Ma, J., Tang, Q., Jin, L., Li, X., Li, M., 2018. Identification of exosome-like nanoparticle-derived microRNAs from 11 edible fruits and vegetables. PeerJ 6, e5186. https://doi:10.7717/peerj.5186.

Yang, C., Zhang, M., Merlin, D., 2018. Advances in plant-derived edible nanoparticle-based lipid nano-drug delivery systems as therapeutic nanomedicines. Journal of Materials Chemistry B 6, 1312–1321. https://doi:10.1039/C7TB03207B.

Zhou, Q., Ma, K., Hu, H., Xing, X., Huang, X., Gao, H., 2022. Extracellular vesicles: Their functions in plant-pathogen interactions. Molecular Plant Pathology 23, 760–771. https://doi:10.1111/mpp.13170.