

## Supplementary information to:

### Letter to the editor:

## PLANT EXTRACTS: A POTENTIAL APPROACH TO COMBATING MULTIDRUG-RESISTANT BACTERIA

Sun Sik Kong<sup>1</sup>, Chang Ha Park<sup>2,\*</sup>

<sup>1</sup> College of General Education, Namseoul University, 91 Daehak-ro, Seonghwan-eup, Seobuk-gu, Cheonan-si, Chungcheongnam-do 31020, Republic of Korea

<sup>2</sup> Department of Smart Farm, Namseoul University, 91 Daehak-ro, Seonghwan-eup, Seobuk-gu, Cheonan-si, Chungcheongnam-do 31020, Republic of Korea

\* **Corresponding author:** Chang Ha Park, Department of Smart Farm, Namseoul University, 91 Daehak-ro, Seonghwan-eup, Seobuk-gu, Cheonan-si, Chungcheongnam-do 31020, Republic of Korea, Tel.: +82-41-580-3254, E-mail: [parkch@nsu.ac.kr](mailto:parkch@nsu.ac.kr)

<https://dx.doi.org/10.17179/excli2025-9282>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>).

**Supplementary Table 1:** Antibacterial activities and synergistic effects of phytochemicals against MDR pathogens

No	Compounds	Class	Strains	Effects	Reference
1	Xanthohumol, desmethylxanthohumol, lupulone	Phenolics	MRSA T28.1	Anti-biofilm activity	Bocquet et al., 2019
2	1,8-Cineole	Monoterpene	Clinical MRSA	Anti-biofilm activity	Merghni et al., 2018
3	Baicalin	Flavone	<i>S. aureus</i>	Anti-biofilm activity	Zhang et al., 2020
4	4-phenyl coumarin	Coumarin	MRSA ATCC 33591	Anti-biofilm activity and anti-adherence activity	da Cunha et al., 2020
5	Emodin	Anthraquinone	MRSA252	MRSA cell wall disruption	Cao et al., 2015
6	Artonin E	Xanthones	MRSA BAA-1720	MRSA membrane disruption	Zajmi et al., 2015
7	Oxyresveratrol	Phenolics	Clinically isolated strains and ATCC 33591	Structural alterations in bacterial septa formation	Joung et al., 2016b
8	reserpine, quinine, piperine, harmaline	Alkaloids	MRSA ATCC 25923/35931	Efflux pump inhibitory activity	Mohtar et al., 2009
9	Chelerythrine	Alkaloid	MRSA RN4220	Inhibition of multidrug efflux pumps	Gibbons et al., 2003

No	Compounds	Class	Strains	Effects	Reference
10	Ursolic acid	Triterpenoid	MRSA ATCC 33591	Inhibition of PBP2a uprotein by ursolic acid with oxacillin	Zhou et al., 2017
11	Sanguisorbigenin	Triterpenoid	MRSA ATCC 33591	Downregulation of penicillin-binding protein 2a and mecA genes	Wang et al., 2021
12	Shikonin	Naphthoquinone	MRSA ATCC 33591	Anti-MRSA activity via ABC transporter modulation and peptidoglycan binding	Lee et al., 2015
13	Cajanin Stilbene Acid	Stilbene	VRE ATCC 700802	Abnormal Energy Metabolism	Tan et al., 2020
14	6, 6'-dihydroxy-thiobinupharidine	Alkaloid	VRE FN-1, ATCC 51299	Downregulation of vanA gene.	Okamura et al., 2015

**Supplementary Table 2:** Antibacterial activities and synergistic effects of phytochemicals against MRSA and VRE

No	Compounds	Class	Strains	Synergy effect	Reference
1	Brazilin	Catechols	Clinical MRSA	Aminoglycosides	Zuo et al., 2014
2	Sophoraflavanone G	Flavanone	MRSA ATCC 33591	Ampicillin	Cha et al., 2009
3	Rhein	Anthraquinone glycoside	Clinical MRSA	Ampicillin	Joung et al., 2012
4	Luteolin	Flavones	Clinical MRSA	Ampicillin/Oxacillin	Joung et al., 2016a
5	Baicalin	Flavonoid	MRSA NCTC 11940	Benzylpenicillin, methicillin, ampicillin, cefotaxime	Liu et al., 2000
6	Clerodane	Diterpenoids	MRSA-ST2071	Ciprofloxacin, norfloxacin, ofloxacin	Gupta et al., 2016
7	Chrysoeriol	Flavonoids	Clinical MRSA	Ciprofloxacin, oxacillin	Lan et al., 2021
8	Diosmetin	Flavonoids	MRSA RN4220	Erythromycin	Chan et al., 2015
9	Salvianolate	Coumaric	Clinical MRSA	Fosfomycin, erythromycin, piperacillin-tazobactam, clindamycin	Cheng et al., 2013
10	Carnosic acid	Diterpenoids	MRSA ATCC 29213	Gentamicin	Vázquez et al., 2016
11	Galangin	Flavonoid	Clinical MRSA	Gentamicin	Lee et al., 2008
12	Fremontone	Isoflavone	MRSA ATCC 1708	Methicillin	Kumarihamy et al., 2022
13	Theasinsensin A	Polyphenol flavonoid	Clinical MRSA	Oxacillin	Hatano et al. 2003
14	Berberine	Alkaloids	Clinical MRSA	Oxacillin	Yu et al., 2005

No	Compounds	Class	Strains	Synergy effect	Reference
15	Silibin	Flavonoid	MRSA ATCC 33591	Oxacillin, ampicillin	Kang et al., 2011
16	Allicin	Thiosulfonates	MRSA strain	Silver nanoparticles	Sharifi-Rad et al., 2014
17	Artocarpin	Flavone	DMST 20654	tetracycline, ampicillin, norfloxacin	Septama and Panichayupakaranant, 2016
18	Sophoraflavanone G	Flavanone	Clinical MRSA	Vancomycin	Sakagami et al., 1998
19	Rosmarinic acid	Polyphenol	Clinical MRSA	Vancomycin	Ekambaram et al., 2016
20	Stigmasterol / $\beta$ -caryophyllene oxide	Terpenoids	MRSA ATCC 33592	$\beta$ -lactam antibiotics	Alagasamy et al., 2021

### Conflict of interest

The authors declare no conflict of interest.

### Artificial Intelligence (AI) – assisted technology

The authors used an LLM exclusively for improving English language clarity and readability in the manuscript preparation.

### REFERENCES

Alagasamy SV, Ramanathan S, Chear NJY, Tan WN, Ramachandram DS, Ching-Ga AFT, et al. The potentiation of beta-lactam and anti-bacterial activities of lipophilic constituents from *Mesua ferrea* leaves against methicillin-resistant *Staphylococcus aureus*. *J Complement Integr Med*. 2021;18(2):339–345.

Bocquet L, Sahpaz S, Bonneau N, Beaufay C, Mahieux S, Samaillie J, et al. Phenolic compounds from *Humulus lupulus* as natural antimicrobial products: new weapons in the fight against methicillin resistant *Staphylococcus aureus*, *Leishmania mexicana* and *Trypanosoma brucei* strains. *Molecules*. 2019;24(6):1024.

Cao F, Peng W, Li X, Liu M, Li B, Qin R, et al. Emodin is identified as the active component of ether extracts from *Rhizoma Polygoni Cuspidati*, for anti-MRSA activity. *Can J Physiol Pharmacol*. 2015;93(6):485–493.

Cha JD, Moon SE, Kim JY, Jung EK, Lee YS. Antibacterial activity of sophoraflavanone G isolated from the roots of *Sophora flavescens* against methicillin-resistant *Staphylococcus aureus*. *Phytother Res*. 2009;23(9):1326–1331.

Chan BC, Han XQ, Lui SL, Wong CW, Wang TB, Cheung DW, et al. Combating against methicillin-resistant *Staphylococcus aureus* - two fatty acids from Purslane (*Portulaca oleracea* L.) exhibit synergistic effects with erythromycin. *J Pharm Pharmacol*. 2015;67(1):107–116.

Cheng C, Liu Y, Song H, Pan L, Li J, Qin Y, et al. Marinopyrrole derivatives as potential antibiotic agents against methicillin-resistant *Staphylococcus aureus* (II). *Marine Drugs*. 2013;11(8):2927–2948.

da Cunha MG, de Cássia Orlandi Sardi J, Freires IA, Franchin M, Rosalen PL. Antimicrobial, anti-adherence and antibiofilm activity against *Staphylococcus aureus* of a 4-phenyl coumarin derivative isolated from Brazilian geophilic. *Microb Pathogen*. 2020;139:103855.

Ekambaram SP, Perumal SS, Balakrishnan A, Marappan N, Gajendran SS, Viswanathan V. Antibacterial synergy between rosmarinic acid and antibiotics against methicillin-resistant *Staphylococcus aureus*. *J Intercult Ethnopharmacol*. 2016;5(4):358–363.

Gibbons S, Leimkugel J, Oluwatuyi M, Heinrich M. Activity of *Zanthoxylum clava-herculis* extracts against multi-drug resistant methicillin-resistant *Staphylococcus aureus* (mdr-MRSA). *Phytother Res*. 2003;17(3):274–275.

Gupta VK, Tiwari N, Gupta P, Verma S, Pal A, Srivastava SK, et al. A clerodane diterpene from *Polyalthia longifolia* as a modifying agent of the resistance of methicillin resistant *Staphylococcus aureus*. *Phyto-medicine*. 2016;23(6):654–661.

- Hatano T, Kusuda M, Hori M, Shiota S, Tsuchiya T, Yoshida T. Theasinensin A, a tea polyphenol formed from (-)-epigallocatechin gallate, suppresses antibiotic resistance of methicillin-resistant *Staphylococcus aureus*. *Planta Med.* 2003;69(11):984–989.
- Joung DK, Joung H, Yang DW, Kwon DY, Choi JG, Woo S, et al. Synergistic effect of rhein in combination with ampicillin or oxacillin against methicillin-resistant *Staphylococcus aureus*. *Exp Ther Med.* 2012;3(4):608–612.
- Joung DK, Lee YS, Han SH, Lee SW, Cha SW, Mun SH, et al. Potentiating activity of luteolin on membrane permeabilizing agent and ATPase inhibitor against methicillin-resistant *Staphylococcus aureus*. *Asian Pac J Trop Med.* 2016a;9(1):19–22.
- Joung DK, Mun SH, Choi SH, Kang OH, Kim SB, Lee YS, et al. Antibacterial activity of oxyresveratrol against methicillin-resistant *Staphylococcus aureus* and its mechanism. *Exp Ther Med.* 2016b;12(3):1579–1584.
- Kang HK, Kim HY, Cha JD. Synergistic effects between silibinin and antibiotics on methicillin-resistant *Staphylococcus aureus* isolated from clinical specimens. *Biotechnol J.* 2011;6(11):1397–1408.
- Kumarihamy M, Tripathi SK, Khan S, Muhammad I. Schottiiin, a new prenylated isoflavones from *Pso-rothamnus schottii* and antibacterial synergism studies between methicillin and fremontone against methicillin-resistant *Staphylococcus aureus* ATCC 1708. *Nat Prod Res.* 2022;36(12):2984–2992.
- Lan JE, Li XJ, Zhu XF, Sun ZL, He JM, Zloh M, et al. Flavonoids from *Artemisia rupestris* and their synergistic antibacterial effects on drug-resistant *Staphylococcus aureus*. *Nat Prod Res.* 2021;35(11):1881–1886.
- Lee YS, Kang OH, Choi JG, Oh YC, Chae HS, Kim JH, et al. Synergistic effects of the combination of galangin with gentamicin against methicillin-resistant *Staphylococcus aureus*. *J Microbiol.* 2008;46:283–288.
- Lee YS, Lee DY, Kim YB, Lee SW, Cha SW, Park HW, et al. The mechanism underlying the antibacterial activity of shikonin against methicillin-resistant *Staphylococcus aureus*. *Evid Based Complement Altern Med.* 2015;2015:520578.
- Liu IX, Durham DG, Richards RM. Baicalin synergy with  $\beta$ -lactam antibiotics against methicillin-resistant *Staphylococcus aureus* and other  $\beta$ -lactam-resistant strains of *S. aureus*. *J Pharm Pharmacol.* 2000;52(3):361–366.
- Merghni A, Noumi E, Hadded O, Dridi N, Panwar H, Ceylan O, et al. Assessment of the antibiofilm and anti-quorum sensing activities of *Eucalyptus globulus* essential oil and its main component 1,8-cineole against methicillin-resistant *Staphylococcus aureus* strains. *Microb Pathog.* 2018;118:74–80.
- Mohtar M, Johari SA, Li AR, Isa MM, Mustafa S, Ali AM, et al. Inhibitory and resistance-modifying potential of plant-based alkaloids against methicillin-resistant *Staphylococcus aureus* (MRSA). *Curr Microbiol.* 2009;59:181–186.
- Okamura S, Nishiyama E, Yamazaki T, Otsuka N, Taniguchi S, Ogawa W, et al. Action mechanism of 6,6'-dihydroxythiobinupharidine from *Nuphar japonicum*, which showed anti-MRSA and anti-VRE activities. *Biochim Biophys Acta.* 2015;1850(6):1245–1252.
- Sakagami Y, Mimura M, Kajimura K, Yokoyama H, Iinuma M, Tanaka T, et al. Anti-MRSA activity of sophoraflavanone G and synergism with other antibacterial agents. *Lett Appl Microbiol.* 1998;27(2):98–100.
- Septama AW, Panichayupakaranant P. Synergistic effect of artocarpin on antibacterial activity of some antibiotics against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. *Pharm Biol.* 2016;54(4):686–691.
- Sharifi-Rad J, Hoseini-Alfatemi S, Sharifi-Rad M, Iriti M. Antimicrobial synergic effect of Allicin and silver nanoparticles on skin infection caused by methicillin resistant *Staphylococcus aureus* spp. *Ann Med Health Sci Res.* 2014;4(6):863–868.
- Tan S, Hua X, Xue Z, Ma J. Cajanin stilbene acid inhibited vancomycin-resistant *Enterococcus* by inhibiting phosphotransferase system. *Front Pharmacol.* 2020;11:473.
- Vázquez NM, Fiorilli G, Guido PAC, Moreno S. Carnosic acid acts synergistically with gentamicin in killing methicillin-resistant *Staphylococcus aureus* clinical isolates. *Phytomedicine.* 2016;23(12):1337–1343.
- Wang F, Liu H, Li J, Zhang W, Jiang B, Xuan H. Australian propolis ethanol extract exerts antibacterial activity against methicillin-resistant *Staphylococcus aureus* by mechanisms of disrupting cell structure, reversing resistance, and resisting biofilm. *Braz J Microbiol.* 2021;52:1651–1664.
- Yu HH, Kim KJ, Cha JD, Kim HK, Lee YE, Choi NY, et al. Antimicrobial activity of berberine alone and in combination with ampicillin or oxacillin against methicillin-resistant *Staphylococcus aureus*. *J Med Food.* 2005;8(4):454–461.

Zajmi A, Mohd Hashim N, Noordin MI, Khalifa SA, Ramli F, Mohd Ali H, et al. Ultrastructural study on the antibacterial activity of artonin e versus streptomycin against *Staphylococcus aureus* strains. *PLoS One*. 2015;10(6):e0128157.

Zhang S, Hu B, Xu J, Ren Q, Wang Z, Wang S, et al. Baicalin suppress growth and virulence-related factors of methicillin-resistant *Staphylococcus aureus* in vitro and vivo. *Microb Pathog*. 2020;139:103899.

Zhou T, Li Z, Kang OH, Mun SH, Seo YS, Kong R, et al. Antimicrobial activity and synergism of ursolic acid 3-O- $\alpha$ -L-arabinopyranoside with oxacillin against methicillin-resistant *Staphylococcus aureus*. *Int J Mol Med*. 2017;40(4):1285–1293.

Zuo G, Han Z, Hao X, Han J, Li Z, Wang GC. Synergy of aminoglycoside antibiotics by 3-Benzylchroman derivatives from *Caesalpinia sappan* against clinical methicillin-resistant *Staphylococcus aureus* (MRSA). *Phytomedicine*. 2014;21(7):936–941.