Journal of Elementology ISSN 1644-2296

Beňovič, P., Kašlíková, K., Meluš, V. and Krajčovičová, Z. (2026)
'An integrated in silico assessment of natural compounds targeting lipoteichoic acid synthase in *Staphylococcus aureus*',
*Journal of Elementology*, 31(4), ,
available: https://doi.org/10.5601/jelem.2026.31.3.3875

RECEIVED: 17 August 2026
ACCEPTED: 28 October 2026

**ORIGINAL PAPER**

# An integrated *in silico* assessment of natural compounds targeting lipoteichoic acid synthase in *Staphylococcus aureus**

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**Abstract**

*Staphylococcus aureus* remains a major cause of community and hospitalacquired infections, with its clinical relevance amplified by the emergence of methicillinresistant strains (MRSA). Lipoteichoic acid synthase (LtaS), an essential $Mn^{2+}$ dependent enzyme involved in lipoteichoic acid biosynthesis, represents an attractive but underexplored antibacterial target. While recent virtual screening studies have proposed potential LtaS inhibitors, most emphasize highthroughput docking with limited mechanistic insight into binding stability. In this study, an integrated *in silico* workflow combining molecular docking, redocking validation, molecular dynamics (MD) simulations, and ADME profiling was applied to a focused set of 13 bioactive natural compounds with reported anti*Staphylococcus aureus* activity. Docking identified several ligands with favorable binding scores; however, MD simulations revealed pronounced differences in binding behavior. Rigid polyphenolic scaffolds, particularly galangin and rosmarinic acid, retained stable interactions within the $Mn^{2+}$dependent catalytic site of LtaS, whereas more flexible phenylpropanoid derivatives rapidly dissociated or adopted nonproductive surfacebinding modes despite favorable docking energies. Analysis of RMSD, RMSF, intermolecular distances, and hydrogen-bond occupancy suggests that higher ligand rigidity may contribute to active-site stabilization and binding persistence. ADME predictions further supported galangin as a promising lead compound with acceptable druglikeness and low predicted toxicity. Overall, this work highlights the limitations of dockingbased ranking alone and underscores the importance of MD simulations for identifying true LtaS binders relevant to antiMRSA drug discovery.

**Keywords:** *Staphylococcus aureus,* lipoteichoic acid synthase, molecular dynamics simulations, natural products, anti-MRSA agents

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* The source of funding: KEGA 003TnUAD-4/2024.