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In Vitro and In Silico Prediction of Syringic Acid, a Cichorium intybus-Derived Ligand, as a Potential Antimicrobial Scaffold and Adjuvant Enhancing β-Lactam Susceptibility in Multidrug- Resistant *Staphylococcus aureus*

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Abstract

The emergence of multidrug-resistant (MDR) *Staphylococcus aureus* has created an urgent need for novel antimicrobial agents with improved pharmacological and safety profiles. The present study integrated *in vitro* antibacterial screening with comprehensive *in silico* molecular profiling to evaluate the therapeutic potential of *Cichorium intybus*-derived phytochemicals (CI-1 to CI-11) against MDR *S. aureus.* Among the medicinal plant extracts, ethanol extract of *C. intybus* demonstrated the strongest antibacterial activity with a 30 mm inhibition zone and highest antioxidant activity (68%), while *Mentha longifolia* exhibited 64% antioxidant activity. FTIR analysis confirmed the presence of bioactive functional groups including carboxylic acids, aromatic rings, alcohols, ethers, alkenes, and cyclohexyl groups associated with antibacterial potential. Molecular docking analysis revealed that CI-9 exhibited the strongest binding affinity against the selected target protein with a docking score of −11.1 kcal/mol, followed by CI-8 (−10.0 kcal/mol), CI-2 (−8.7 kcal/mol), and CI-5/CI-6 (−8.6 kcal/mol). The conceptual DFT of CI-6, CI-8, and CI-2 demonstrated lower HOMO–LUMO energy gaps, lower hardness, and higher softness values, indicating greater chemical reactivity and potential biological and electrophilicity index (0.7602), while CI-6 emerged as minimum hardness (0.021343) and maximum softness (23.427). PASS prediction further demonstrated that CI-9 possessed the highest predicted antibacterial activity (Pa = 0.677), antioxidant activity (Pa = 0.923), free radical scavenging activity (Pa = 0.988), and antineoplastic activity (Pa = 0.849). However, despite its superior docking affinity and biological activity, CI-9 demonstrated poor drug-likeness characteristics due to its very high molecular weight (610.52 g/mol), elevated TPSA (209.43 Å²), low predicted bioavailability (0.17), and multiple Lipinski rule violations, potentially limiting its oral therapeutic applicability. In contrast, CI-11 (syringic acid) exhibited comparatively moderate docking affinity but demonstrated the most balanced physicochemical, pharmacokinetic, and safety profile, characterized by favorable membrane permeability, balanced lipophilicity (Log P = 0.99), lower toxicity, excellent bioavailability radar characteristics, and strong drug-likeness properties. ADMET and STOPTOX analyses further identified CI-10 and CI-11 as the safest ligands, with CI-11 exhibiting 80% non-sensitization and 90% non-irritation confidence values. Additionally, CI-3 and CI-7 demonstrated the highest predicted bioavailability scores (0.85), whereas CI-1 showed the highest intestinal absorption (94.35%).

Conclusion, CI-9 may represent the biologically strongest antibacterial ligand, whereas CI-11 appears to be the most promising and safest lead compound for future anti-*S.aureus* drug development.

Keywords: *Therapeutic potential, FTIR, Antibiotic susceptibility, Antioxidant activity Molecular docking*