Synergistic Effect of Chlorogenic Acid and Caffeic Acid with Fosfomycin in Growth Inhibition of a Resistant *Listeria monocytogenes* Strain

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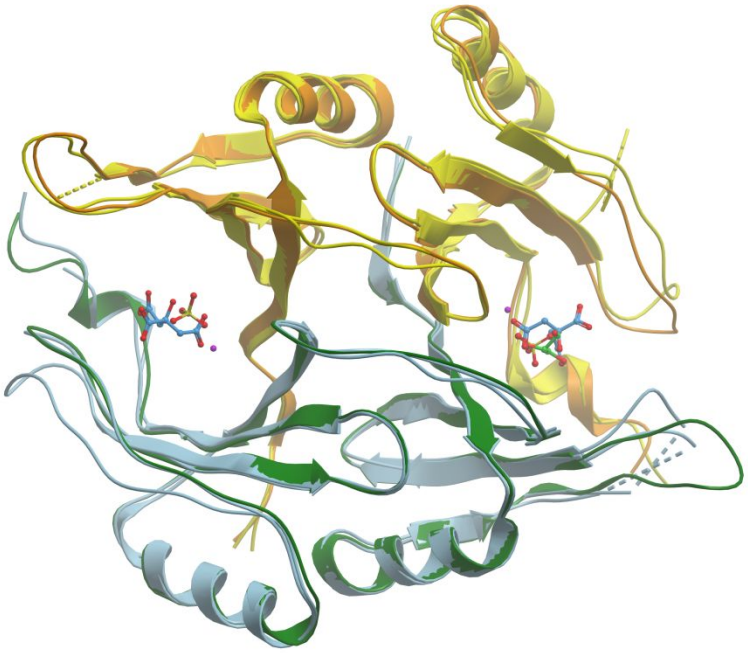
Supporting Information

1. Analysis of X-ray Crystal structures of FosX protein

A)



B)

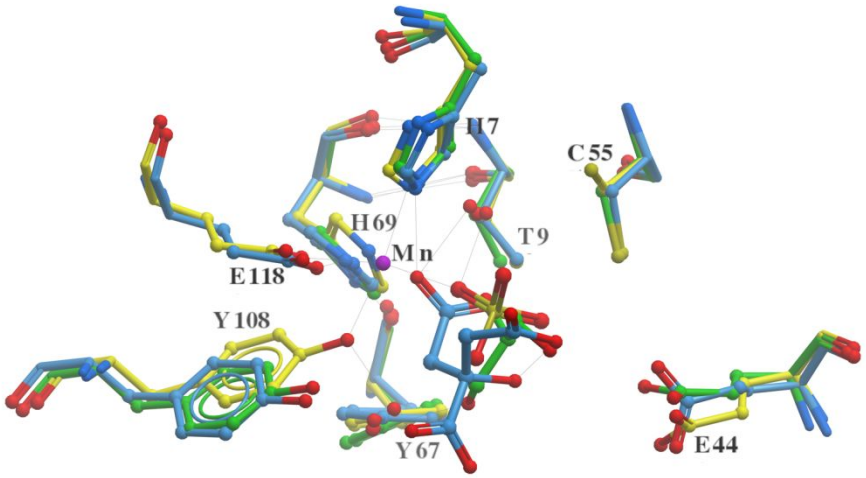
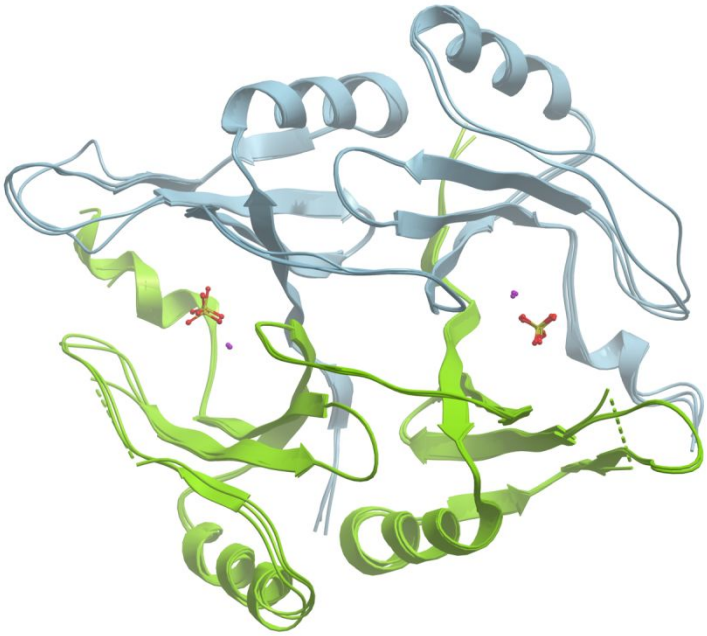


Figure S1. (A) global superimpose of FosX protein binding with various ligands FosX-sulfate ion complex (2p7p), FosX-glycerol complex (2p7l), and FosX-citric acid complex (2p7k). (B) conserved residues within catalytic sites of the three complexes which are colored respectively (yellow, green, blue). Different ligands binding might not significantly change the loop structure. Residues in catalytic site are conserved in ligand binding. Y108, E118, H69 and H7, T9 participate in binding of ligands. E44 are proposed acting as a general base in the catalytic mechanism of FosX. Therefore, structures with ligand bind would be rational for virtual screening. Additionally, the position of bound sulfate ion is expected to be a good indicator of the position of the phosphonate group in the substrate or product complexes. Docked conformation of each ligands was evaluated being overlapping with the sulfate ion.

A)



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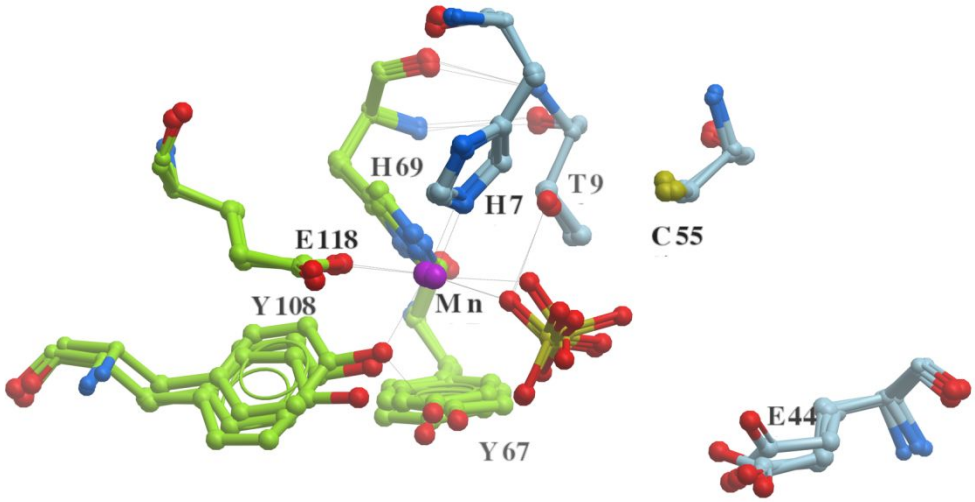

Figure S2. (A) global structure superimposes of dimers of FosX protein extracted from chain AB, CD, and EF of a FosX structure (PDB code 2p7p) (B) conserved residues within catalytic site of FosX protein with MN(II) and sulfate ion. The chains A, C, and E are colored with green; chain B, D, and F are colored in light blue. The structure of three dimers are identical and residues with catalytic site e.g. E44, T9, E118, Y108, Y67, H69, H7, and C55. Due to the missing residues in loops around catalytic site in chain AB and CD, only FosX dimer formed by Chain EF were simply modified as docking receptor.

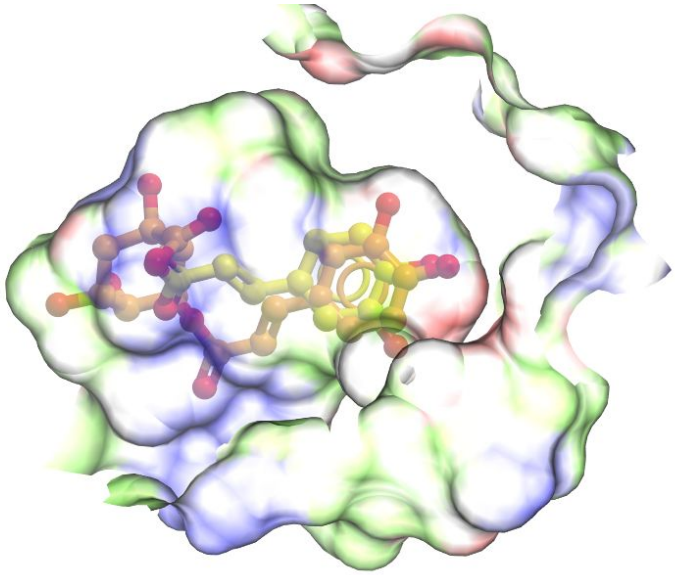

Figure S3. Docked conformation of caffeic acid (yellow)/chlorogenic acid (orange) within the catalytic site of the dimeric FosX Protein.

2. Cell growth test of lower concentrations of Chlorogenic acid/Caffeic acid and 50mg/L Fosfomycin

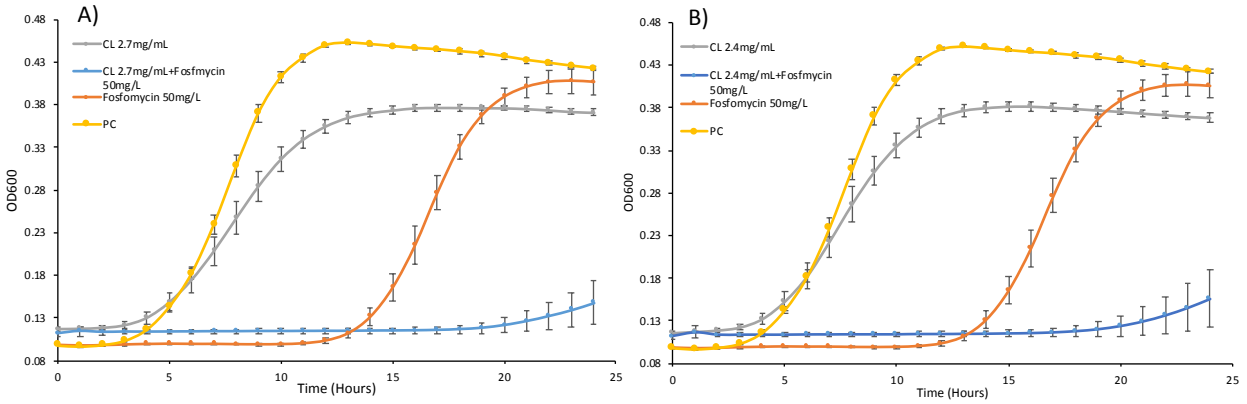

Figure S4. Cell growth test with Fosfomycin and lower concentration of chlorogenic acid. A) Comparison of growth curves of *L. monocytogenes* under 2.7mg/mL chlorogenic acid and/or 50mg/L Fosfomycin; B) Comparison of growth curves of *L. monocytogenes* under 2.4mg/mL chlorogenic acid and/or 50mg/L Fosfomycin. CL: chlorogenic acid; triplicate samples; Error bar: Standard deviation; PC: positive control (diluted *L.monocytogenes* overnight culture with 5% DMSO).

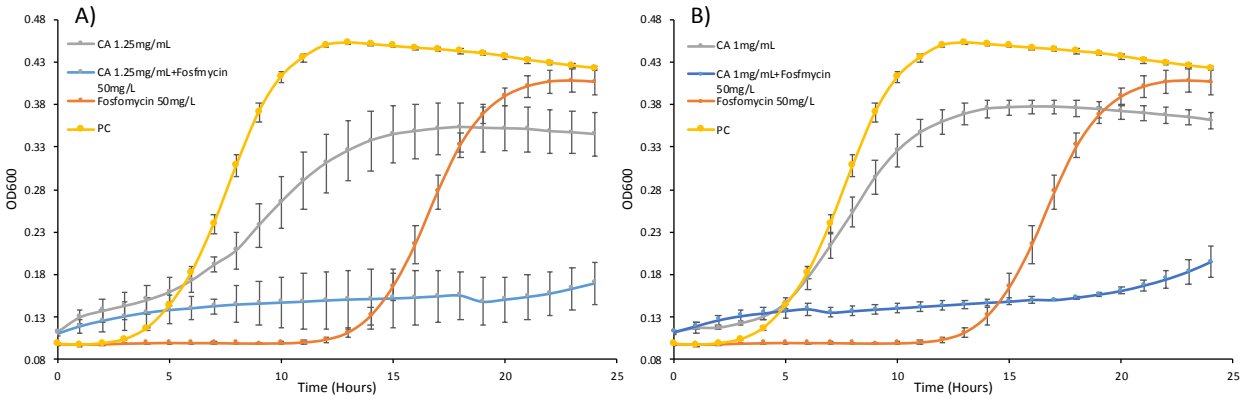

Figure S5. Cell growth test with caffeic acid and Fosfomycin. A) Comparison of growth curves of *L. monocytogenes* under 1.25mg/mL caffeic acid and/or 50mg/L Fosfomycin; B) Comparison of growth curves of *L. monocytogenes* under 1mg/mL chlorogenic acid and/or 50mg/L Fosfomycin. CA: caffeic acid; triplicate samples; Error bar: Standard deviation; PC: positive control (diluted *L.monocytogenes* overnight culture with 5% DMSO).