Development of screening system for antibiotics, antimalarial, and antihyperlipidemia drugs by using IPP synthesis pathways

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Isoprenoids, derived from the five-carbon units, isopentenyl diphosphate (IPP) and its isomer dimethylally diphosphate (DMAPP), are essential for survival in all organisms. Eukaryotes synthesize isoprenoids from the mevalonate pathway, and prokaryotes and malaria parasite synthesize isoprenoids from the MEP pathway. Inhibitor of the MEP pathway are expected to be antibiotics and antimalarial drugs. Inhibitor of the mevalonate pathway can be used for treating hyperlipidemia. This study suggests method for screening a substance capable of inhibiting either or both of the mevalonate pathway and the MEP pathway using *E. coli* cells. A wild type strain of *E. coli* MG1655 was used for screening the MEP pathway inhibitor. The mevalonate pathway inhibitor screening was carried with *E. coli* mutant which has an inactivated endogenous MEP pathway by deletion of *dxr* and a plasmid pDSNSA12Didi carrying mevalonate. Simvastatin and fosmidomycin, known specific inhibitiors to mevalonate and MEP pathway, respectively, were used to confirm our screening system. Cell growth of *E. coli* MG1655 and *E. coli Ddxr* harboring pDSNSA12Didi were completely inhibited with 20mM of fosmidomycin and 2mM of simvastatin, respectively. However, simvasatatin on *E. coli* MG1655 and fosmidomycin on *E. coli Ddxr* with mevalonate pathway had on cell growth inhibition at the same or even higher concentration tested above.

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