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Chlorflavonin, a flavone-type fungal metabolite with potent and selective antitubercular activity

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Abstract

Mycobacterium tuberculosis, the etiologic agent of tuberculosis (TB), is one of the leading causes of mortality and morbidity caused by pathogenic microorganisms. Treatment of TB is currently facing serious problems due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) M. tuberculosis strains. The latter is practically untreatable with the currently available anti-TB drugs on the market and thus that there is an urgent need for novel antibiotics against TB. During our ongoing search for new potential anti-TB drug leads, we investigated the endophytic fungus Mucor irregularis, which was isolated from the Cameroonian medicinal plant Moringa stenopetala. The ethyl acetate extract of M. irregularis yielded two flavonoid-type derivatives, chlorflavonin and dechlorflavonin, the latter only differing by the absence of a chlorine atom in the B ring.

The design of the mediation modification using complete genome sequencing, chemical supplementation tests, and cell suspension tests and enzymatic descriptions revealed that chlorflavonin specifically inhibits acetohydroxyacid synthase catalytic subunit IlvB1, which produces auxotic chain amxotrophies and pantothenic acid. While showing the bacteriostatic effect on monotreatment treatment, chlorflavonin has shown the effects of first-line anti-antibiotic isoniazid interaction and especially with delamanid, which has led to the complete closure of the fluid civilization in combination therapy.

Using a fluorescent reporter type, the intracellular activity of chlorflavonin against Mycobacterium tuberculosis within infected macrophages was demonstrated and was superior to streptomycin treatment.

In contrast to dechlorflavonin, chlorflavonin exhibited strong growth inhibitory activity against M. tuberculosis, indicating that chlorination plays an important role for anti-TB activity. Importantly, chlorflavonin showed no cytotoxicity against the human fibroblast (MRC-5) and macrophage-like human acute monocytic leukemia (THP-1) cell lines up to concentrations of 100 µM. Mapping of resistance-mediating mutations revealed that chlorflavonin specifically inhibits the acetohydroxyacid synthase IlvB1, which mediates the first step in branched chain amino acids and pantothenic acid biosynthesis. Chlorflavonin displayed synergistic effects in combination with the first-line antibiotic isoniazid leading to a complete sterilization and no resistance in liquid culture during combination treatment. Moreover, chlorflavonin exhibited potent activity against XDR M. tuberculosis strains, which highlights the potential of this compound as a promising anti-TB agent.

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