Antimicrobial and drug-synergistic potential of *Alpinia conchigera* Griff.-derived phenylpropanoids against *Mycobacterium smegmatis*

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**ABSTRACT**

Aims: This study aimed to evaluate the antimicrobial activity of naturally derived phenylpropanoids from *Alpinia conchigera* (*A. conchigera*) Griff. and its synthetic analogues, as well as interactions between selected compounds with first-line tuberculosis (TB) drug, rifampicin, against *Mycobacterium smegmatis*, a potential opportunistic nontuberculous mycobacterium (NTM) and a surrogate organism for TB.

Methodology and results: Twelve phenylpropanoids of *A. conchigera* were evaluated for antimicrobial activity against *M. smegmatis* (ATCC 14468). The phenylpropanoid compound from *A. conchigera* with the lowest minimum inhibitory concentration and bactericidal (MIC, MBC) values were selected for checkerboard tetrazolium microplate assay (TEMA) with rifampicin to determine drug interactions. A majority of the compounds had antimicrobial activity, however, purified natural compound 1'S-1'-acetoxychavicol acetate (ACA) showed the highest antimicrobial activity with an MIC value of 62.5 µg/mL against *M. smegmatis*. The combination of ACA and rifampicin produced indifferent interaction with fractional inhibition concentration (FIC) index of 1.5, while the combination of rifampicin and ACA synthetic analogue 4-allyl-2,6-methoxyphenyl isobutyrate produced a synergistic interaction effect with FIC index of 0.5. None of the compounds tested were bactericidal but appear to be bacteriostatic.

Conclusion, significance and impact of study: This study presents the first report on the antimicrobial potential of natural *A. conchigera*-derived ACA against *M. smegmatis* as well as the synergistic interaction of 4-allyl-2,6-methoxyphenyl isobutyrate with rifampicin which warrants further investigation.

**Keywords:** plant phenylpropanoids, natural products, tuberculosis, non-tuberculous mycobacteria, minimum inhibition concentration assay

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**INTRODUCTION**

Despite being an ancient disease that has plagued humankind since 3000 BC (Barberis et al., 2017), tuberculosis (TB) caused by *Mycobacterium tuberculosis* remains among the top 10 causes of disease and death worldwide, resulting in an estimated 1.6 million deaths in 2018. According to the Global Tuberculosis Report 2018 by World Health Organization (WHO), TB can affect all age groups including children. Active pulmonary and extra-pulmonary TB, which infects the lungs or other parts of the body, respectively, is prevalent worldwide with the highest number of cases reported in South-East Asia and Western Pacific regions. The risk of contracting TB increases in conditions of crowding, poverty, and immunocompromised states, and TB is currently the primary cause of death in HIV-infected individuals. This situation challenges efforts to achieve the Sustainable Development Goals (SDGs) to "End TB" by 2030 (Lönnroth and Raviglione, 2015).

Additionally, the emergence of *M. tuberculosis* strains that are resistant to antibiotics has become a global concern. Drug resistance has largely arisen from inappropriate and/or incomplete treatments, among which adverse effects of standard first-line TB drugs such as isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, is an important factor (Liang et al., 2012). It has been estimated by WHO in 2017 that 558,000 patients were infected with MTB strains resistant against rifampicin, a standard first-line drug for TB treatment. However, in the case of multidrug-resistant TB (MDR-TB), which exhibits resistance against both rifampicin and isoniazid — treatment and cure may still be achieved through second-line drugs. A more significant challenge is