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Two new compounds and the anti-mycobacterial activity of the constituents from *Zanthoxylum leprieurii* root bark

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ABSTRACT

The emergence of resistance to the existing TB drugs necessitated a search for new anti-mycobacterial compounds from *Z. leprieurii* root bark, which is used locally for the treatment of tuberculosis (TB) in Uganda. Two new compounds: (*E*)-*N*-isobutyl-3-(4-((3-methylbut-2-en-1-yl)oxy)phenyl)acrylamide (**1**) and 4-(5,5a,6,8,8a,9-hexahydrofuro[3′,4′:6,7]-naphtha[2,3-*d*][1,3]dioxol-5-yl)-2-methoxyphenol (**2**), were isolated from the dichloromethane (DCM) extract. In addition, sixteen known compounds were isolated from the DCM and methanol extracts, with two of them, *N*-isobutylcinnamamide (**9**) and (*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-isobutylacrylamide (**14**), being reported from a natural source for the first time. The structures of the isolates were elucidated by a combination of spectroscopic techniques. The isolated compounds were subjected to anti-mycobacterial activity testing using the microplate Alamar blue assay (MABA). Five compounds, **10** (MIC, 0.98 μg/mL), **11** (MIC, 7.82 μg/mL), **12** (MIC, 1.95 μg/mL), **13** (MIC, 3.91 μg/mL), and **14** (MIC, 3.91 μg/mL) exhibited significant anti-mycobacterial activities against the susceptible ($H_{37}Rv$) strain and could provide vital templates for developing new and highly effective TB drugs. Also, compounds **4** (MIC, 62.50 μg/mL), **7** (MIC, 62.50 μg/mL) and **16** (MIC, 62.50 μg/mL) exhibited moderate activity against $H_{37}Rv$.

1. Introduction

Tuberculosis, a communicable disease, is among the leading causes of illness worldwide. Before the onset of the coronavirus (COVID-19) pandemic, TB was the main cause of death resulting from a single infectious agent and was ranked above HIV/AIDS (WHO, 2021; 2022), and the emergence of drug-resistant strains of TB has worsened this problem (WHO, 2017).

In Uganda, *Zanthoxylum leprieurii*, one of the species from the rutaceous genus *Zanthoxylum* native to tropical and subtropical regions, is used traditionally to manage TB as well as to treat malaria, rheumatic pain, urinary infections, and HIV/AIDS-related symptoms (Misra et al., 2013; Ngoumfo et al., 2010). In addition, *Z. leprieurii* root bark extract has previously been shown to exhibit activity against *M. tuberculosis*, the TB-causing bacterium (Oloya et al., 2022).

Previous phytochemical investigations on *Z. leprieurii* stem and root barks revealed a wide range of secondary metabolites, including triterpenoids, alkaloids, coumarins, lignans, and flavonoids (Bunalema et al., 2017; Misra et al., 2013; Ngoumfo et al., 2010; Oloya et al., 2021). It is important to note that some of the alkaloids isolated from *Z. leprieurii* stem bark, including hydroxy-1, 3-dimethoxy-10-methyl-9-acridone, and *trans*-fagaramide have shown significant anti-mycobacterial activities (Bunalema et al., 2017; Oloya et al., 2021). A medium polarity solvent, dichloromethane, was selected as one of the extraction solvents in this study because such a solvent is capable of extracting constituents of the plant which are lipophilic and can easily permeate across the *M. tuberculosis* cell wall and hence, hindering its growth. It is also expected that extractions carried out using medium polarity solvents contain secondary metabolites like terpenoids, polyphenols, and alkaloids, which have activity against microbes (Cowan, 1999; Kumar et al., 2008; Parekh et al., 2005).

In an attempt to identify anti-mycobacterial compounds from

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