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RESEARCH ARTICLES

Enzyme inhibitors from endophytic *Xylaria feejeensis* isolated from *Cardiospermum halicacabum*

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Abstract
An endophytic fungus *Xylaria feejeensis* was isolated from the leaves of *Cardiospermum halicacabum* and identified using molecular means. The fungus was cultured on a large scale in potato dextrose broth medium. After 4 weeks, the fungal media and mycelium were extracted with ethyl acetate and subjected to chromatographic separation furnished eight compounds namely, (*R*)-(-)-5-methoxycarbonylmellein (**1**), (*S*)-(+)-mellein (**2**), (*S*)-(+)-*O*-methylmellein (**3**), cycloepoxytriol A (**4**), 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**5**), 2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**6**), phomopsiketone B (**7**) and 6-(1-hydroxypentyl)-4-methoxy-2*H*-pyran-2-one (**8**). Compounds **4** and **6** were isolated from the endophytic fungus *X. feejeensis* for the first time. Compound **1** exhibited α-glucosidase inhibitory activity with an IC_{50} value of 46.54 ± 8.08 µM, which was significantly lower than that of the positive control acarbose.

Keywords *Cardiospermum halicacabum* · Endophytic fungi · Secondary metabolites · *Xylaria feejeensis*

Introduction

Endophytic fungi are capable of producing bioactive substances that involve in a host-endophyte relationship (Strobel. 2003). We have previously reported several bioactive compounds produced by Sri Lankan plants (Bandara et al. 2015; Dissanayake et al. 2020; Kalinga et al. 2025; Kehelpannala et al. 2018, 2021; Munasinghe et al. 2017, 2021; Nilmini et al. 2025; Padmathilake et al. 2017; Piyasena et al. 2015; Qader et al. 2016, 2017, 2018; Rathnayake et al. 2018 & 2019; Samarakoon et al. 2025; Siriwardane et al., 2015; Sritharan et al. 2019; Thanabalasingam et al. 2015 & 2024). *Cardiospermum halicacabum* of the family Sapindaceae has multiple uses such as a vegetable, fodder, and diuretic, and is employed to treat various disorders such as rheumatism, lumbago, nervous diseases, orthitis and skeletal fractures (Veeramani et al. 2007). Enzymes have become targets for drug discoveries because of the high levels of disease association and target tractability (Copeland et al. 2007). In this paper, we report the inhibitory activities of the secondary metabolites isolated from an endophytic fungus *X. feejeensis* from *C. halicacabum* against α-amylase, α-glucosidase, acetylcholineesterase and lipase enzymes.

Materials and methods

General

The isolation of endophytic fungi and sub-culturing was carried out in a laminar flow cabinet (class II, NUAIRE, model no. NU-425-300E). As culture media Potato Dextrose Agar (PDA) (Dextrose-Avonchem, Oxon, UK), and Potato Dextrose Broth (PDB) (20% w/v potato extract, and 2.0% w/v dextrose) were used. DNA extraction was done by using Promega Wizard Genomic DNA Purification Kit (A1120), and the ITS region was amplified using universal eukaryotic primers ITS 1-F and ITS 4, with a thermal cycler (Applied Biosystems, Veriti). All the solvents used for chromatographic separation were redistilled before use. Silica gel-coated aluminum sheets (Merck TLC silica gel 60

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F254, Darmstadt, Germany, 0.20 mm thickness) were used for thin-layer chromatography (TLC) and preparative TLC (PTLC). The TLC and PTLC plates were visualized under UV light (Chromato Vue cabinet, model; CC-60) occurred at 254 nm and 365 nm wavelengths. Column chromatography utilized glass columns packed with silica gel (Merck grade 7734, Darmstadt, Germany) of 60 Å pore size, 70–230 nm mesh size, and 230–400 nm mesh size. Size exclusion chromatography employed Sephadex LH-20 (Fluka, Switzerland). High-performance liquid chromatography was carried out using a Shimadzu LC-6 A liquid chromatograph equipped with a UV/Vis detector (prominence SPD-20 A), system controller (SCL-6 A), chromatopac (C-R6A), and a reverse-phase C-18 column. UV absorbance was measured with a microplate reader (Synergy HTX Biotek Multimode reader, Biotek instruments, USA). All chemicals for bioassays were procured from Sigma Aldrich, unless specified otherwise. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM-ECP500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) or JEOL JNM-AL300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer. Optical rotations were measured on a JASCO P-2200 polarimeter.

Isolation, identification, large-scale culturing, extraction and isolation of compounds from endophytic fungi

C. halicacabum leaves were collected from home gardens in Kandy. First, the samples were washed under running water to remove all the debris and sterilized by sequentially immersing in 96% ethanol for one minute, sodium hypochlorite (2% available chlorine v/v) for three min and 96% ethanol for 30 s. Then, they were rinsed in sterile distilled water. This procedure was triplicated. After that, leaves were cut into small pieces of approximately 5 mm x 5 mm and placed on PDA medium. The emerged fungus was repeatedly sub-cultured until get the pure fungal culture. The fungus is deposited at the National Institute of Fundamental Studies. Internal Transcribed Spacer (ITS) of the ribosomal DNA, ITS-1 F and ITS-4 were amplified. All PCR amplifications were carried out in a total of 40 µL volume using a Thermal Cycler. The PCR program consisted of an initial denaturation at 95 °C for 4 min, 35 cycles of denaturation at 95 °C for 30 s, annealing at 54 °C for 30 s, extension at 72 °C for 45 s and a final extension at 72 °C for 7 min. The fungus was cultured on a large scale in ninety 1 L Erlenmeyer flasks containing 400 mL of PDB medium and autoclaved at 121 °C for 20 min, followed by inoculation with the fungus and incubated at room temperature for 21 days. After incubation, the broth was filtered under reduced pressure and partitioned three times with ethyl acetate (EtOAc). Mycelia were crushed and extracted into EtOAc. Solvents were evaporated using a rotary evaporator at 40 °C to obtain crude extracts. Both extracts were combined according to the similarities in TLC (16.19 g) and subjected to chromatographic separation using gravity columns with silica gel and gradient elution of n-hexane: EtOAc: MeOH, and n-hexane: CH_2Cl_2: MeOH solvent systems. Additional separation steps involved using Sephadex LH-20 columns, with 70% MeOH: 30% $CHCl_3$ and 100% MeOH solvent systems. HPLC separation with reverse phase C-18 columns and 35% water: 65%MeOH system afforded eight compounds: **1** (25 mg, $[\alpha]_D^{20}$ -172 (*c*, 0.56, MeOH) (lit., $[\alpha]_D$ -151 for (*R*)-compound (Sumarah et al. 2008), **2** (35 mg, $[\alpha]_D^{20}$ +86.4 (*c*, 0.67, MeOH) (lit., +88.6 for (*S*)-compound (Dimitriadis et al. 1997), **3** (30 mg, $[\alpha]_D^{20}$ +205 (*c*, 0.40, MeOH) (lit., +238 for (*S*)-compound) (Kerti et al. 2007), **4** (36 mg), **5** (128 mg), **6** (27 mg), **7** (11 mg) and **8** (30 mg, $[\alpha]_D^{20}$ -28.5 (*c*, 0.57, MeOH).

Conducting enzyme inhibitory bioassays

Enzyme inhibitory assays were conducted for the crude extract and pure compounds, which were dissolved in distilled water with 1%. DMSO. For crude extract a concentration series was prepared from 1000 mg/L to 31.25 mg/L using half-dilutions, and for pure compounds a concentration series was prepared from 100 mg/L to 3.125 mg/L. All the experiments were triplicated. For the negative control of the experiments solvent which was used to dissolve the extracts was used in the same volume, instead of the samples and for the reaction blanks equal volume of buffer was used instead of the enzyme. Percentage inhibitions of the enzymes were calculated using below Eq. (1), and the graphs were plotted between percentage inhibition and sample concentration and the sample concentration resulting in 50% inhibition of the enzyme (IC_{50}) was determined using the graph.

$$Percentage\ enzyme\ inhibition = \frac{\delta\ \text{A control} - \delta\ \text{A sample}}{\delta\ \text{A control}} \times 100\ \% \quad (1)$$

Where; δA *control*=Absorbance$_{control}$-Absorbance$_{control\ blank}$
δA *sample*=Absorbance$_{sample}$-Absorbance$_{sample\ blank}$

α-amylase inhibitory assay

The sample solution and 100 µL of α-amylase (from porcine pancreas) solution were mixed and incubated at room temperature for 30 min. 100 µL of starch solution was added and the mixture was re-incubated for 10 min at room temperature. 100 µL of 3,5-dinitrosalicylic acid (DNSA) solution was added and the mixture was re-incubated in a water bath at 85.5 °C. After 15 min samples were taken out and

diluted with 900 µL of distilled water. 200 µL of each diluted solution was added to a 96 microwell plate and absorbance values were measured at 540 nm using a microplate reader (Alakolanga et al. 2015). Acarbose was used as the positive control.

α-glucosidase inhibitory assay

The experiment was carried out in a 96 microwell plate. 100 µL of buffer was mixed with 25 µL of the sample solution and 25 µL of α-glucosidase (from *Saccharomyces cerevisiae*) solution, and the whole was incubated at 37 °C for five min. Then, 50 µL of 4-nitrophenyl α-D-glucopyranoside (PNPG) solution was added and re-incubated at 37 °C for 30 min. Subsequently, the color formation was measured at 410 nm. As the positive control acarbose was used (Sathya et al. 2020).

Acetylcholinesterase inhibitory assay

The experiment was conducted in a 96 microwell plate. 100 µL of phosphate buffer (pH 8), 25 µL of the sample solution and 50 µL of acetylcholinesterase (from electric eel) solution were added to the well and incubated at room temperature for 10 min. Thereafter, 50 µL of 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) solution and 25 µL of acetylthiocholine iodide solution were added and again incubated for 10 min at room temperature. Subsequently, absorbance values were measured at 412 nm. As the positive control donepezil was used (Sathya et al. 2020).

Lipase inhibitory assay

The experiment was carried out in a 96-microwell plate. 100 µL of buffer solution was mixed with 25 µL of lipase enzyme (from porcine pancreas) solution and 25 µL of the sample solution and the mixture was incubated at 37 °C for 15 min. Afterward, 25 µL of 4-nitrophenyl butyrate (PNPB) solution was added and the mixture was re-incubated for 30 min at 37 °C. Then, absorbance was measured at 400 nm using a microplate reader. As the positive control orlistat was used (Fernando et al. 2019).

Results and Discussion

The isolated fungus from *C. halicacabum* leaves was identified as *Xylaria feejeensis* through sequence analysis of the ITS region of the rDNA gene. Based on the ITS sequence the strain was identified as *X. feejeensis* (GenBank accession no. MG881827.1). The crude EtOAc extract of the fungus exhibited α-amylase inhibitory activity with an IC_{50} value of 583.17 ± 41.13 mg/L as well as α-glucosidase inhibition (IC_{50} = 61.23 ± 1.77 mg/L) and acetylcholinesterase inhibition (IC_{50} = 224.46 ± 15.75 mg/L), but not lipase inhibitory activity. Chromatographic separations of the EtOAc extract using Sephadex LH-20 columns, silica gel columns, PTLC and HPLC with reverse phase C-18 columns furnished eight metabolites (Fig. 1). Their structures were elucidated by spectroscopic analysis and comparison with the reported spectral data. They were identified as (*R*)-(-)-5-methoxycarbonylmellein (**1**) (Sumarah et al. 2008), (*S*)-(+)-mellein (**2**) (Chacón-Morales et al. 2013), (*S*)-(+)-*O*-methylmellein (**3**) (Kerti et al. 2007; Islam et al. 2007), cycloepoxytriol A (**4**) (Hussain et al. 2009), 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**5**) (Tansuwan et al. 2007), 2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**6**) (Tansuwan et al. 2007), phomopsiketone B (**7**) (Tang et al. 2017) and 6-(1-hydroxypentyl)-4-methoxy-2*H*-pyran-2-one (**8**) (Rathnayake et al. 2019). The isolated compounds were assessed for their inhibitory activity against α-amylase, α-glucosidase, acetylcholinesterase and lipase enzymes. Against α-glucosidase only compound **1** exhibited significant inhibitory activity with an IC_{50} value of 46.54 ± 8.08 µM, which was significantly lower ($p < 0.05$) than the positive control acarbose (IC_{50} = 115.30 ± 14.00 µM). In contrast, the activity of (*S*)-mellein (**2**) (6.71 ± 0.98% inhibition at a concentration of 561.23 µM) was much weaker than acarbose.

Compounds **1**, **6** and **7** exhibited acetylcholinesterase inhibitory activity with IC_{50} values of 576.50 ± 76.28, 678.77 ± 44.02 and 280.98 ± 7.5 µM, respectively. All the values obtained were significantly higher ($p < 0.05$) than the positive control donepezil (IC_{50} = 2.00 ± 0.29 µM). In the lipase enzyme inhibitory assay compounds **4**, **5** and **6** showed significantly lower ($p < 0.05$) inhibitory activities with IC_{50} values of 1765.49 ± 300.20, 4477.32 ± 578.75 and 3716.73 ± 448.04 µM, respectively, when compared to the positive control orlistat (IC_{50} = 5.51 ± 1.78 µM). None of the compounds showed α-amylase inhibitory activity. Compounds **4** and **6** were isolated from endophytic *X. feejeensis* for the first time. It is known that *Xylaria* species produce mellein-type compounds. (*R*)-(-)-5-Methoxycarbonylmellein (**1**) was previously isolated as a metabolite of *Xylaria* sp. SWUF09-62 (Patjana et al. 2021) among others. (*R*)-(-)-Mellein is a well-known secondary metabolite of plants and fungi. Its antipode, (*S*)-(+)-mellein (**2**) was also isolated from several endophytic fungi including from *Xylaria* sp. (Patjana et al. 2021). (*S*)-(+)-*O*-Methylmellein (**3**) was isolated from *Xylaria* sp. (Patjana et al. 2021), together with (3*S*,4*R*)-(+)- and (3*S*,4*S*)-(+)-4-hydroxymelleins, and from *X. feejeensis* associated with *Hintonia latifolia* (Rivera-Chávez et al. 2015). On the other hand, isolation of (*R*)-(-)-*O*-methylmellein was reported from *X. feejeensis* SRNE2BP

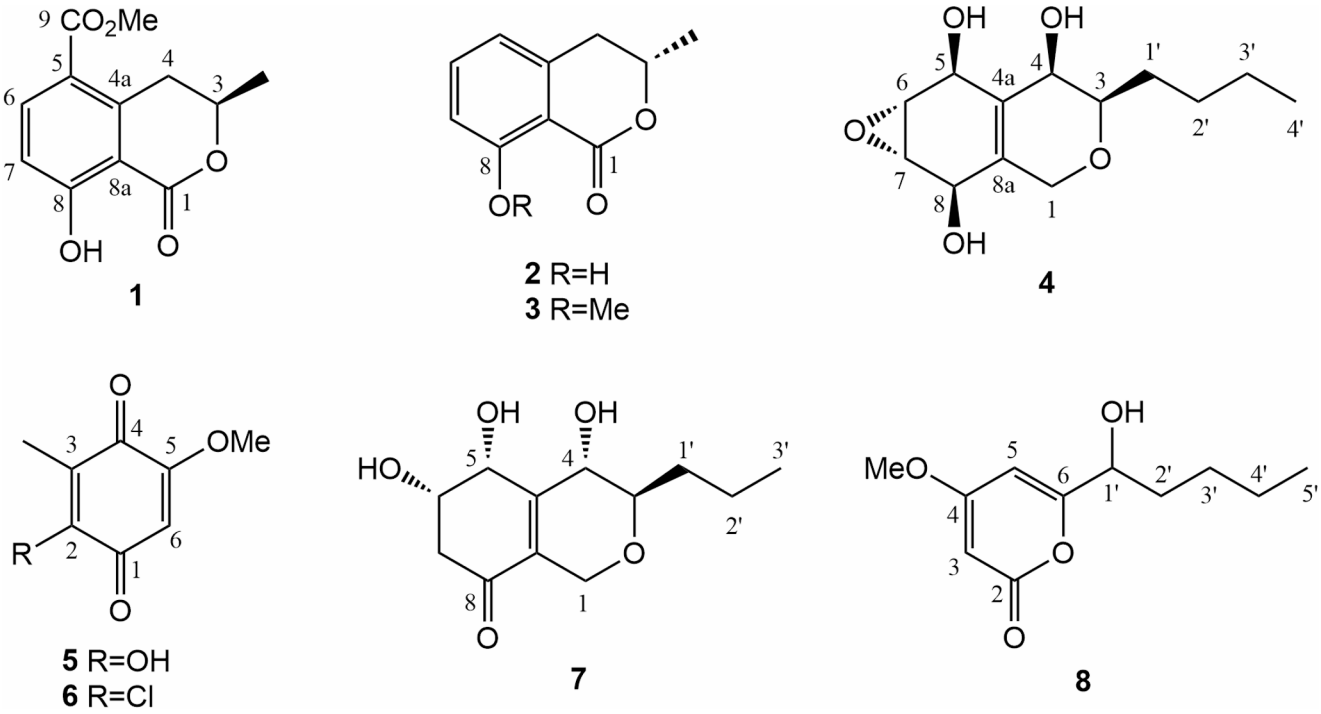

Fig. 1 Chemical structures of compounds **1**–**8** isolated from *Xylaria feejeensis*

isolated from a mangrove tree (Brooks et al. 2022) and from the mangrove-derived fungus *Xylaria cubensis* PSU-MA34 (Klaiklay et al. 2012). Rivera-Chávez and co-workers reported that **(**3*S*,4*R*)- and (3*S*,4*S*)-4-hydroxymelleins showed α-glucosidase inhibitory activity, comparable to the positive control acarbose, but (*S*)-mellein and (*S*)-*O*-methylmellein did not showed the activity (Rivera-Chávez et al. 2015). Compound **1** characteristically possesses a CO_2Me group at C-5 and (*R*) configuration at C-3. According to our results, IC_{50} values of α-glucosidase inhibition exhibited the following order: compound **1** < acarbose << compound **2**. These findings suggest the α-glucosidase inhibitory activity is related to the substituents on the mellein backbone rather than the C-3 configuration. Further studies are needed to establish detailed structure-activity relationships between variously substituted mellein-type compounds and their α-glucosidase enzyme inhibitory activity.

Cycloepoxytriol A (**4**) is a very rare fungal metabolite and was isolated only from an endophytic *Phomopsis* sp. from *Laurus azorica* (Hussain et al. 2009). Compounds **5** was previously isolated from *Xylaria* sp. (Tansuwan et al. 2007), X. *feejeensis* (Rivera-Chávez et al. 2015)d *feejeensis* from *Sapium macrocarpum* (García-Méndez et al. 2016). Compound **6** was isolated as a metabolite from *Xylaria* sp. (Tansuwan et al. 2007), mangrove-derived *X. cubensis* (Klaiklay et al. 2012)d *plebeja* (Rukachaisirikul et al. 2013). Compound **6** was reported to show in vitro activity against *Plasmodium falciparum* and cytotoxicity against African green monkey kidney fibroblasts (Vero cells). Compound **7** was isolated from *Phomopsis* sp. (Tang et al. 2017)d *feejeensis* SRNE2BP isolated from a mangrove tree (Brooks et al. 2022). For compound **8** (6-(1-hydroxypentyl)-4-methoxy-2*H*-pyran-2-one), the (1'*R*)-(+)-form, i.e., PC-2 (lit. $[\alpha]_D$ +78.5 (MeOH) (Kimura et al. 1978) hasTH been reported as a metabolite of several *Penicillium* species (Kimura et al. 1978) and a marine-derived fungus *Xylaria* sp. (Evidente et al. 2012). We previously isolated (1'*R*)-(+)-compound ($[\alpha]_D$ +76 (MeOH) from *Pestalotiopsis microspora* isolated from *Manilkara zapota* fruits (Rathnayake et al. 2019). On the other hand, the (1'*S*)-(+)-form, i.e., (1'*S*)-dehydropestalotin was isolated from an endophytic fungus *Pestalotiopsis phitinae* and a wood-inhabiting cup fungus *Urnula craterium* (Ayer et al. 2000; Ding et al. 2012). Furthermore, co-occurrence of both antipodes in the metabolites of *X. feejeensis* isolated from a sponge *Stylissa massa* was reported (Wang et al. 2018). Compound **8** showed $[\alpha]_D$ +28.8 (*c*, 0.57, MeOH), indicating that compound **8** could be an approximately 2:1 mixture of (1'*S*)- and (1'*R*)-antipodes.

Conclusions

In this study *Xylaria feejeensis* was isolated as an endophytic fungus from the leaves of *Cardiospermun halicacabum*. The fungus was cultured in PDB medium and chromatographic separation of the EtOAc extract of the broth and mycelium

furnished (*R*)-(-)-5-methoxycarbonylmellein (**1**), (*S*)-(+)-mellein (**2**), (*S*)-(+)-*O*-methylmellein (**3**), cycloepoxytriol A (**4**), 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**5**), 2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**6**), phomopsiketone B (**7**) and 6-(1-hydroxypentyl)-4-methoxy-2*H*-pyran-2-one (**8**). In the enzyme inhibitory assays, compound **1** exhibited a potent inhibitory activity against α-glucosidase enzyme. This finding suggests a possibility that compounds with α-glucosidase inhibitory activity could exist among mellein-type secondary metabolites, and further study will be an interesting area of research that could potentially lead to the discovery of interesting lead compounds for the treatment of type 2 diabetes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42535-025-01495-5.

Author contributions We all are equally contributed this paper.

Data availability All data will be available upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

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