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Antimycobacterial potential of resorcinol type lipid isolated from *Chaetomium cupreum,* an endophytic fungus from *Mussaenda luteola*

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Abstract

An endophytic fungus *Chaetomium cupreum* was isolated from the ornamental plant *Mussaenda luteola*. A known metabolite named resorcinol type of lipid (compound 1) was isolated using column chromatography and structurally elucidated by spectroscopic studies includes UV-Vis, FT-IR, NMR, MS analysis and comparing with the existing data. The compound 1 was evaluated for antimycobacterial potential by microtitre plate alamar blue assay against *Mycobacterium tuberculosis* H37Rv (ATCC27294). It also estimated for DPPH free radical scavenging and antibacterial (agar well diffusion method) potentials. Compound 1 revealed to have significant inhibition of *Mycobacterium* with MIC of 6.3 µg/mL which is similar to the standard streptomycin drug. It also exhibited good DPPH free radical scavenging potential of 84.5 ± 0.4% and maximum inhibition of both *E. coli* (ATCC 25922) as well as *S. aureus* (ATCC 25923). Thus, endophytic fungus *C. cupreum* from *Mussaenda luteola* could be a potential source of novel lead antimicrobial agents for drug discovery.

Introduction

Medicinal plants, animals, microbes and marine organisms have historically proven their value as a source of bioactive molecules with therapeutic potentials and played a key role in medicinal chemistry to treat human diseases (Cragg and Newman, 2013).

Endophytes can be found in almost all plants and play a vital role in the growth of host plants against stressed condition (Li et al., 2013; Yu et al., 2017). Endophytes have the major impact on drug discovery (Awad et al., 2014) since it proved to be a valuable source of novel and structurally diverse secondary metabolites which may possess various biological potentials such as antimicrobial (Shen et al., 2012; Zhang et al., 2012; Zhang et al., 2015), anti-cancer (Shylaja and Sathiavelu 2017), immunosuppressant and others (Zhang et al., 2014; Strobel et al., 2005).

The genus *Chaetomium* is the prevalent group of saprophytic ascomycetes, commonly found in air, soil and plants. The bioactive secondary metabolites chaetoglobosins, chaetoviridins, cytoglobosins, pyrones, orsellides, cytochalasans, anthraquinone, chromanone were reported from *Chaetomium* spp. New azaphilones like rotiorinols, rotiorin and epi-isochromophilone had been isolated from the *C. cupreum* (Kanokmedhakul et al., 2006).

Mussaenda luteola is a vital source of bioactive compounds, predominantly iridoids, rutin, quercetin, gallic acid and triterpenes with pharmacological potentials such as cytotoxicity, anti-inflammatory, antipyretic, diuretic, antioxidant, antimicrobial and many others (Vidyalakshmi et al., 2008). The present study focussing

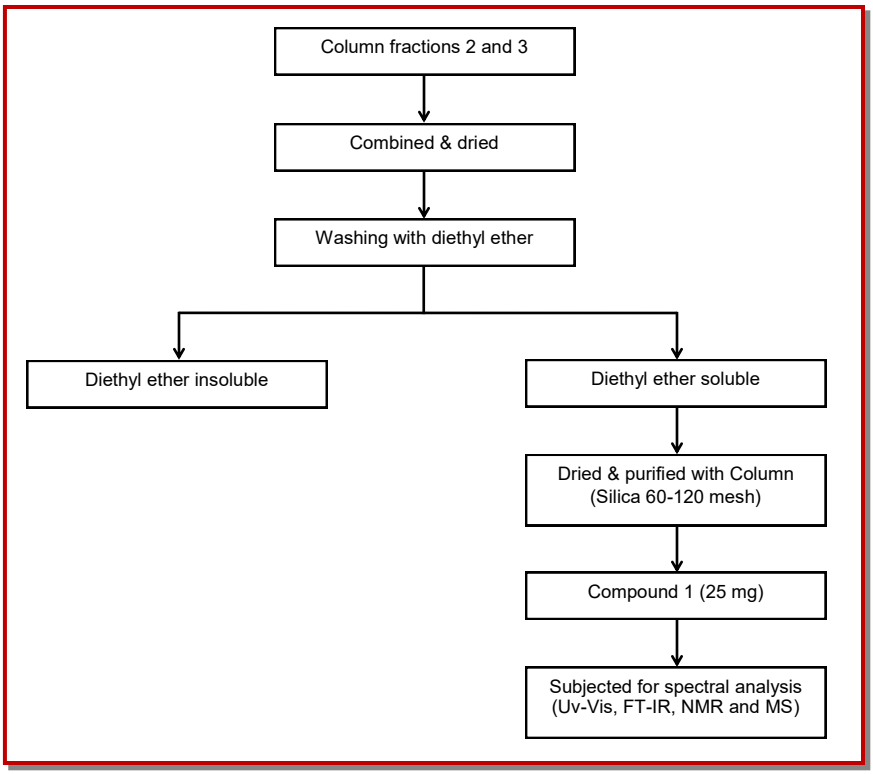

Figure 1: Flow chart for isolation of compound 1 from ethyl acetate extract of *C. cupreum*

on the isolation and identification of bioactive metabolite of the endophytic fungus *C. cupreum* from *M. luteola* and to evaluate the antioxidant, antibacterial and antimycobacterial potentials.

Materials and Methods

General experiments

The isolated compound was determined for maximum wavelength, λmax using UV–Vis spectrophotometer (Shimadzu UV-2401) range between 200–800 nm. FT-IR spectrum analysis was performed in KBr pellets on a (Shimadzu, FT-IR 8300) between 4000 and 400 cm^{-1}. NMR spectroscopic analysis of the sample was done for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) using Bruker Avance 400 NMR spectrometer. The chemical shifts were reported in parts per million relative to tetramethylsilane in deuterated chloroform (CH_dCl_3) as a solvent

Isolation, cultivation, and extraction of the fungal strain.

The fungus used in this study was isolated from the leaves of *M. luteola* (Schulz et al., 1993) and identified as *C. cupreum* on the basis of the rDNA internal transcribed spacer gene sequence. Seven-days grown colonies of the *C. cupreum* on PDA plate were cut into small pieces and dropped in 1L flask contained 400 mL of potato dextrose broth for fermentation and kept for incubation at 25°C for three weeks (Arivudainambi et al., 2011). The fermented fungal broth was filtered to remove fungal mycelium.

Extraction and metabolite isolation

The fungal filtrate was extracted with ethyl acetate and concentrated under vacuum. The obtained dried extract was fractionated by silica gel (60-120 mesh) column chromatography (Chang et al., 2017) using chloroform/methanol (100:00, 80:20, 60:40, 40:60, 20:80 and 0:100) gradient elution to provide 18 fractions. The fractions were determined for maximum wavelength, λmax using UV–Vis spectrophotometer. Fraction 2 and 3 showed the maximum wavelength of 502 λ_{max} and also similar thin layer chromatography profile. So, these fractions were combined and further purified by column over silica gel (60-120 mesh) using isocratic elution with diethyl ether (Figure 1). The solvent was removed under reduced pressure which afforded compound 1 (25 mg).

DPPH radical scavenging assay

Free radical scavenging potential of compound 1 from endophytic fungus was determined using DPPH method (Yadav et al., 2014). The absorbance was measured at 517 nm and ascorbic acid was used as reference compound. Each analysis was done in triplicate.

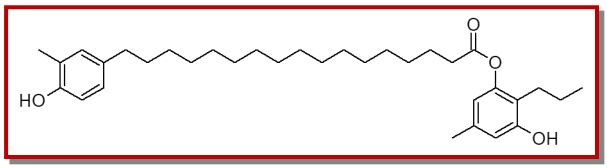

Figure 2: Structure of resorcinol type lipid isolated from *C.cupreum*

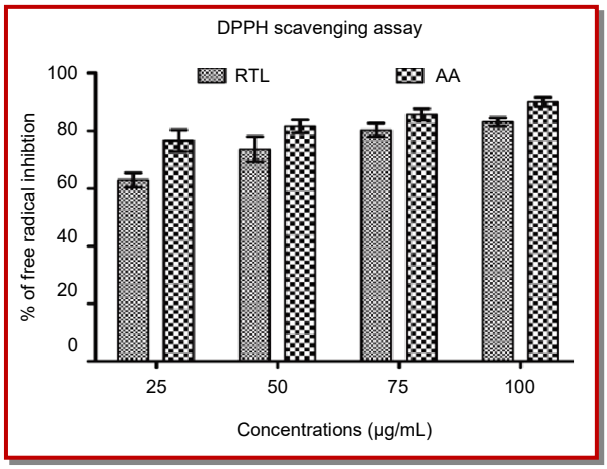

Figure 3: DPPH free radical scavenging activity of resorcinol type lipid isolated from *C. cupreum*

Note: RTL- Resorcinol Type Lipid; AA- Ascorbic acid

Antibacterial assay

The antibacterial efficacy of compound 1 was determined by agar-well diffusion method (Ahmad and Beg, 2001) against bacterial strains Gram positive, *Staphylococcus aureus* (ATCC 25923) and Gram negative *Escherichia coli* (ATCC 25922). The compound 1 was dissolved in dimethyl sulfoxide (1 mg/mL) and prepared four concentration range from 0.500, 0.250, 0.125 and 0.061 mg/mL. 40 µL of each concentration was added to wells (6 mm) made from the MHA plates. The plates were kept for overnight incubation at 37°C.

Determination of in vitro antimycobacterial activity against M. tuberculosis H37Rv

The antimycobacterial potential of compound 1 was assessed based on the microplate alamar Blue assay (MABA) (Collins and Franzblau, 1997) against *Mycobacterium tuberculosis* H37Rv (ATCC27294). Briefly, the stock solution of compound 1 was prepared in dimethyl sulfoxide and added 100 µg/mL concentration to the well of a microplate containing Middlebrook 7H12 broth (Falzari et al., 2005) and 2-fold serial dilutions were done in 7H12 media to yield a final concentrations ranging from 100 to 0.2 µg/mL. 40 µL *M. tuberculosis* H37Rv culture (3 x 105 CFU/mL) was added to all wells except media control well. Pyrazinamide, ciprofloxacin and streptomycin were used as standard controls. Then *Mycobacteria* plus dimethyl sulfoxide and media alone used as a negative control. The microplate was sealed and incubated for 6 days at 37°C. After incubation, 25 µL of alamar blue reagent was added to all wells and re-incubated for 24 hours at 37°C. The color change from blue to pink indicated the reduction of resazurin due to bacterial growth. The lowest concentration in which the drug is preventing the color change was determined as minimum inhibitory concentration.

Results

The endophytic fungus *C. cupreum* was isolated from the leaves of *M. luteola.* The fungus was identified based on morphological and molecular studies (GenBank ID: KY806554). A crude ethyl acetate extract of *C. cupreum* was subjected to silica gel column to yield resorcinol type lipid.

Resorcinol type lipid (1)

Yellowish orange powder; The molecular ion peak at m/z 526.8306 [M+ H]+ by HRESIMS indicated the molecular formula of **1** was $C_{34}H_{52}O_4$ (Calcd. 524.786 g/mol); UV –Vis ($CHCl_3$) λmax (log ϵ) 502, 295 and 208 nm; FT-IR (KBr) ν_{max} signal bands were 3298, 2960, 2873, 1722, 1612, 1450, 1368, 1201, 1045, 947, 879, 790, 731, 574, 482 cm^1. ^1H NMR($CDCl_3$) spectrum represent the peaks corresponding to chemical shifts (52 protons) at ppm δ 4.18 (1H, t, H-2), δ 4.16 (1H, t, H-5), δ 4.15 (1H, t, H-6), δ 4.14 (1H, t, H-27), δ 4.15 (1H, t, H-29), δ 7.51 (1H, t, C-4 OH), δ 7.53 (1H, t, H-26), δ 0.83 (3H, s, H-32), δ 0.84 (3H, s, H-33), δ 0.85 (3H, s, H-34), δ 2.85 - 2.328 (2H, m, H-7 to H-22), δ 2.31 (2H, m, H-30) and δ 2.311 (2H, t, H-31). ^{13}C NMR($CDCl_3$) spectrum represent the peaks corresponding to chemical shifts (34 carbon) at ppm δ 129.69 (C-1), δ 114.07 (C-2), δ 129.69 (C-3), δ 128.81 (C-4), δ 128.07 (C-5), δ 128.06 (C-6), δ 68.17 (C-7), δ 65.18 (C-8), δ 45.39 (C-9), δ 37.11 (C-10), δ 34.12 (C-11), δ 31.93 (C-12), δ 29.70 (C-13), δ 29.46 (C-14), δ 30.37 (C-15), δ 28.93 (C-16), δ 30.05 (C-17), δ 32.79 (C-18), δ 34.16 (C-19), δ 38.74 (C-20), δ 65.05 (C-21), δ 70.28 (C-22), δ 174.96 (C-23), δ 173.96 (C-24), δ 129.69 (C-25), δ 128.81 (C-26), δ 111.27.0 (C-27), δ 129.66 (C-28), δ 109.10 (C-29) and δ 68.40 (C-30), δ 24.48 (C-31), δ 20.54 (C-32), δ 23.75 (C-33) and δ 22.70 (C-34). The FT-IR, NMR and MS data obtained from compound 1 (Figure 2) were identical to the published data of resorcinol type of lipid (2-propyl-3-hydroxy-5-methyl phenyl 17-(3-methyl-4-hydroxy phenyl) heptadecane ester) (Venil et al., 2014).

Antioxidant assay

The isolated compound showed significant DPPH scavenging potential of 84.5 ± 0.4% compared to the standard ascorbic acid (89.9 ± 0.1%) at a concentration of 100 µg/mL. The percentage inhibition of DPPH and ascorbic acid are shown in Figure 3.

Table I

Antimicrobial potential of resorcinol type lipid isolated from *C. cupreum*

Dose (µg)/well	Zone of inhibition (mm)	
	E.coli	*S. aureus*
05	10	10
10	11	12
20	12	13
40	14	14

Table II

Antimycobacterial activity of *C. cupreum* against *Mycobacterium tuberculosis* H37Rv

Strain	Minimum inhibition concentration (µg/mL)			
Strain	RTL	PZA	CIP	STM
M. tuberculosis $H_{37}R_V$	6.3	3.1	3.1	6.3

RTL: Resorcinol type lipid; PZA: Pyrazinamide; CIP: Ciprofloxacin; STM: Streptomycin

Antibacterial assay

The compound 1 exhibited strong inhibition against both test pathogens of Gram positive *S. aureus* and Gram negative *E. coli* with the zone of inhibition of 14 mm at the concentration of 40 µg/mL (Table I).

Antitubercular assays

Results for the investigation of isolated resorcinol type lipid (1) against *M. tuberculosis* H37Rv are presented in Table II. It was observed that compound 1 possess significant inhibition of *Mycobacterium* with MIC 6.3 µg/mL which was similar to the standard streptomycin.

Discussion

The genus *Mussaenda* is an ornamental plant with many pharmacologically active phytochemicals (Gunasekaran et al., 2015). The compound resorcinol type lipid was isolated from ethyl acetate extract of *C. cupreum* by column chromatography. Resorcinolic lipids have been extensively found in both plants and microorganisms. It possesses many biological applications with the characteristic of 1, 3-dihydroxybenzene core with saturated chains at 5-position of the aromatic ring (Nagy et al., 1998).

The Infrared (IR) of compound 1 showed a peak at 3298 cm^{-1} which may be due to the presence of hydroxyl group, while the peak at 1722 and 1612 cm^{-1} may be due to the presence of carbonyl group (C–O). These two peaks may likely be due to the presence of carboxylic acid functional group or ester (COOH). The shifts in carbonyl and the hydroxyl absorption spectra of the pigment can be related to strong chelation (Nagy et al., 1998; Deveoglu et al., 2012). The peak at 1368 cm^{-1} may be due to the presence of tri-substituted olefinic group, while the peak at 1201 cm^{-1} may be due to the presence of –CH3 and –CH2- signals. The peak at 2960 and 2873 cm^{-1} may be due to the presence of C-H stretch for alkanes. This signal suggests that the molecule may be highly saturated. Also, the absorption bands at 947 to 482 cm^{-1} are due to asymmetric C–H stretching in alkyl hydrocarbons which corresponds to the resorcinol type lipid (flexirubin class of pigment) (Bej, 2011).

The ^{1}H-NMR spectrum of compound 1 showed three singlets methyl groups at δ 0.85, 0.84, and 0.83 (H- 32, 33, and 34). The olefinic proton at C-2, C-5, C-6, C-27 and C-29 appeared at δ 4.18, 4.16, 4.15, 4.14 and 4.152 as a triplet (J=3.5Hz) respectively. A one proton double doublet at δ 2.85 was assigned to H-18 on the basis of its chemical shift as well as multiplicity pattern reported for H-18 with β-stereochemistry.

^{13}C-NMR spectrum of compound 1 exhibited thirty-four carbon peaks. The peak at δ 174.37 may be due to the presence of carbonyl group assigned to C-23. The two peaks at δ 129.69, 114.07, 111.27, 109.10, 128.81, 128.07, and 128.06 may be due to the presence of a pair of sp2 hybridized carbon atoms assigned in two benzene ring between C1 to C6 and C-24 to C-29. While the seven peaks at δ 22.70, 23.75 and 20.54 are attributable to the three methyl groups which are assigned to C-32, C-33 and C-34 respectively. Therefore, compound 1 could be assigned as 2-propyl-3-hydroxy-5-methyl phenyl 17-(4-hydroxy-3-methyl phenyl) heptadecane (Resorcinol type lipid).

The isolated compound 1 found to be a resorcinol type lipid contain chromophores of phenyl octaenic acid esterified with resorcinol carrying three hydroxyl group and one hydrocarbon chains (1,4,5 trihydroxy -3-propyl benzene). The chemical structure of compound 1 is characterized by non-isoprenoid phenyl-substituted poly alkane carboxylic acid (Reichenbach and Kleinig, 1974). This basic chemical structure of resorcinol type lipid may be modified length variation and branching of the hydrocarbon chains on the resorcinol. In this way, a large diversity of different resorcinol type lipid arises along with changes in physical properties (Stafsnes and Bruheim, 2013).

Free radicals, a major responsible for many chronic diseases, due to toxicity and many health threats the synthetic antioxidants can be replaced by natural sources (Wong et al., 2006). Pestacin and iso–pestacin major antioxidant agents isolated from endophyte *Pestalotiopsis microspore* of the plant *Terminalia morobensis* (Guo et al., 2008). DPPH free radical scavenging assay is the most precise and extensively used assay for determining antioxidant activity (Yadav et al., 2014). In this study, the isolated compound had inhibition of

DPPH similar to the ascorbic acid.

Chaetoglobosins A and C were reported from the endophytic fungus *C. globosum* of the plant *Ginkgo biloba* was found to have antibacterial property against *Mucor miehei*. A novel peptide cryptocandin from *Cryptosporiopsis quercina* revealed antibacterial activity against *C. albicans* and also many other compounds had been identified from endophytic fungus as antimicrobials (Yu et al., 2010).

Tuberculosis is a deadly and transmittable disease caused by *M. tuberculosis*. More than 8.8 million new cases and 1.5 million deaths were accounted worldwide in 2010 as indicated by the most recent WHO report (Alvin et al., 2014). Tuberculosis was stated to be a global health emergency because of the high incident in HIV co-infection and the existence of multidrug-resistant (MDR) and extensively drug-resistant strains (XDR-TB) (Lienhardt et al., 2012). New anti-mycobacterial entities with unique mechanisms of action are therapeutically needed for treating resistant forms of tuberculosis. Endophytes an alternate source of novel antimycobacterial compounds. Penialidin C and citromycetin from the endophytic fungus *Penicillium sp.* were found to be most effective in inhibition of *Mycobacterium* sp. with MIC of 15.6 and 31.2 µg/mL respectively (Jouda et al., 2016).

Conclusion

The compound resorcinol type lipid isolated from the endophytic fungus *C. cupreum* has a significant anti-mycobacterial and antioxidant properties. It can be used as a lead molecule for drug development process.

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Conflict of Interest

Authors declare no conflict of interest

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