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LC–MS/MS Profiling the Dichloromethane Fraction of Endophytic *Fusarium proliferatum* CSBT2 Isolated from *Curcuma sumatrana* Miq

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Abstract. *Endophytic fungi are recognized as a rich source of structurally diverse secondary metabolites. However, the metabolite composition of endophytic fungi associated with the endemic medicinal plant Curcuma sumatrana Miq. remains largely unexplored. This study aimed to profile the major metabolites present in the dichloromethane (DCM) fraction of Fusarium proliferatum CSBT2 isolated from C. sumatrana. The fungus was cultivated in Potato Dextrose Broth (PDB) prepared according to the ATCC Medium 336 formulation, followed by extraction with ethyl acetate and fractionation to obtain the DCM fraction. Metabolite profiling was performed using LC–MS/MS, and compound annotation was based on accurate mass, fragmentation patterns, and database comparison. Several major metabolites were tentatively identified, including dehydrofusaric acid, fusaric acid, beauvericin, rhynchophylline, and solanidine. Most identified metabolites have previously been reported from Fusarium species, whereas the detection of solanidine may be associated with the potato-based cultivation medium. This study provides the first LC–MS/MS profile of the DCM fraction of F. proliferatum CSBT2 isolated from C. sumatrana. These findings expand the current knowledge of metabolites produced by Indonesian endophytic fungi and provide a basis for future isolation and biological evaluation of the detected compounds.*

Keywords: *Fusarium Proliferatum, Curcuma Sumatrana, Endophytic Fungi, LC–MS/MS Profilinng, Secondary Metabolites*

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INTRODUCTION

Natural products continue to represent one of the most productive sources of pharmaceutical lead compounds because of their remarkable chemical diversity and biological activities (Deshmukh et al., 2022; Chaachouay & Zidane, 2024; Singh et al., 2025; Najmi et al., 2022; Chassagne et al., 2019; Deshmukh et al., 2022). Among the various natural sources investigated over the past decades, endophytic fungi have attracted. These microorganisms inhabit healthy plant tissues without causing apparent disease and establish complex ecological interactions with their host plants that may influence the biosynthesis of unique metabolites (Waqar et al., 2024; Hardoim et al., 2015; Elhamouly et al., 2022; Trivedi et al., 2020).

The biosynthetic potential of endophytic fungi is attributed to their intimate association with host plants, where long-term ecological interactions can shape metabolic pathways and stimulate the production of chemically diverse secondary metabolites. Numerous studies have demonstrated that fungal endophytes produce a broad spectrum of compounds, including alkaloids, polyketides, terpenoids, peptides, quinones, xanthones, isocoumarins, and phenolic

derivatives, many of which exhibit significant pharmacological activities (Perincherry et al., 2019; Xu et al., 2023).

Indonesia recognized as one of the world's megabiodiversity countries, harboring an exceptional diversity of terrestrial and marine ecosystems that support an enormous wealth of plant, animal, and microbial resources (Von et al., 2017). This remarkable biodiversity provides a unique reservoir of microorganisms with untapped biosynthetic potential, particularly endophytic fungi that inhabit medicinal plants growing under diverse ecological conditions.

Despite this richness, the chemical diversity and biological potential of endophytic fungi associated with Indonesian medicinal plants remain substantially underexplored, but some endophytic fungi from Indonesian medicinal plant hasbeen published for their bioactive potential, yielding metabolites with notable antibacterial, cytotoxic, and other pharmacological properties (Handayani et al., 2024, 2023a, 2023b; Masri et al., 2025; Yulianis et al., 2024). Recent reviews have highlighted those numerous endophytic fungi isolated from Indonesian medicinal plants produce bioactive metabolites belonging to polyketides, terpenoids, peptides, quinones, steroids, alkaloids, and phenolic compounds (Sukmawaty et al., 2024).

Among Indonesian medicinal plants, species belonging to the genus *Curcuma* (Zingiberaceae) have received considerable scientific attention because of their long history of traditional medicinal use and their rich repertoire of biologically active phytochemicals (Subositi & Wahyono, 2019; Destryana et al., 2024; Sun et al., 2017). Members of this genus are widely recognized for producing curcuminoids, sesquiterpenoids, diarylheptanoids, and other specialized metabolites exhibiting antimicrobial, antioxidant, anti-inflammatory, and anticancer activities (Alolga et al., 2022; Rajkumari and Sanatombi, 2017). *Curcuma sumatrana* Miq. is an endemic wild turmeric species native to Sumatra, Indonesia, with a restricted geographical distribution and limited scientific documentation (Ardiyani et al., 2011; Syafira et al., 2024).

Recent ecological studies have expanded knowledge of its distribution and habitat preferences, yet investigations into its phytochemistry, associated endophytic fungi, and microbial secondary metabolites remain scarce (Feskaharny et al., 2023; Tamara et al., 2022). This lack of information represents an important knowledge gap, considering that host plant species can strongly influence the composition of endophytic fungal communities and their biosynthetic capabilities. Our preliminary investigation revealed that this endemic species harbors a diverse community of endophytic fungi with promising biological activities (Suhetris, 2025).

Among the endophytic fungi isolated from *Curcuma sumatrana* in our unpublished preliminary investigation (Suhetris, 2025), *Fusarium proliferatum* CSBT2 was selected for further chemical investigation because of its potential to produce structurally diverse secondary metabolites (Proctor et al., 2009). Species belonging to the genus *Fusarium* are recognized as prolific producers of natural products, including polyketides, non-ribosomal peptides, terpenoids, alkaloids, quinones, and other bioactive metabolites with diverse chemical scaffolds (Qu et al., 2024). Numerous metabolites isolated from *Fusarium* species have been reported to possess significant pharmaceutical and agricultural relevance, while comparative metabolomic studies continue to reveal the remarkable chemical diversity within this genus (Summerell et al., 2011).

The production of fungal secondary metabolites is profoundly affected by the composition of the cultivation medium. Potato Dextrose Broth (PDB) is among the most widely used media for submerged cultivation of filamentous fungi because it supports rapid mycelial growth and provides a nutrient-rich environment favorable for secondary metabolite production (Wang et al., 2022). Moreover, liquid fermentation in PDB enables homogeneous nutrient distribution, facilitates metabolite secretion into the culture medium, and simplifies downstream extraction processes, making it particularly suitable for metabolite profiling studies.

Therefore, PDB was employed in the present study as the cultivation medium for *F. proliferatum* CSBT2. Following fermentation, the crude extract was fractionated using solvents of increasing polarity to reduce sample complexity prior to chemical analysis. Among these fractions, the dichloromethane (DCM) fraction was selected because medium-polarity solvents are known to efficiently concentrate semipolar fungal metabolites reported from filamentous fungi (Dame et al., 2016; Picicci et al., 2026). Consequently, focusing on the DCM fraction provides a practical strategy for characterizing chemically diverse semipolar metabolites produced by endophytic fungi. In this study, we also performed liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis of the dichloromethane fraction of Fusarium proliferatum CSBT2 cultured in Potato Dextrose Broth to characterize its major metabolites and provide fundamental chemical information for future investigations of endophytic fungal metabolites.

METHODS

Material

The endophytic fungus Fusarium proliferatum CSBT2 used in this study was isolated from the stem of Curcuma sumatrana Miq. and identified by molecular analysis in a previous unpublished study. The isolate was designated as F. proliferatum CSBT2. Details regarding the molecular marker and sequence accession number are not available in the present study and should be provided from the original molecular identification data(Suhetris, 2025).

Cultivation dan fermentation

Rice (50 g) was placed in a clean glass bottle and moistened overnight with 55 mL of distilled water. The bottles were then sterilized by autoclaving at 121 °C for 20 min. Fungal cultures previously grown on Sabouraud Dextrose Agar (SDA) for 7–10 days were aseptically cut into 1–2 cm^2 fragments and inoculated onto the sterilized rice substrate. The inoculated cultures were incubated under static conditions for 2–3 weeks until the fungal mycelia fully colonized the rice substrate. The number of fermentation replicates, incubation temperature, exact inoculum quantity, and uninoculated rice control were not reported in the original experimental data and should therefore be clarified if these records are available (Handayani et al., 2024; Kjer et al., 2010).

Extraction and fractionation

The extraction and fractionation procedures were conducted following the protocol described. After cultivation, the solid rice cultures were homogenized and extracted with ethyl acetate (EtOAc) at a 1:1 ratio. The extraction was performed three times, with each extraction cycle conducted for 24 h. The EtOAc extracts were subsequently evaporated to dryness to obtain the crude extract. The crude extract was suspended in 90% methanol and successively partitioned with hexane, dichloromethane (DCM), and water-saturated methanol. Each resulting fraction was concentrated under reduced pressure using a rotary evaporator to obtain the respective hexane, DCM, and methanol fractions. The exact solvent volumes, partitioning cycles, extraction yields, and storage conditions were not reported and should be added only if supported by the experimental records (Kjer et al., 2010).

Cytotoxic Assay

A preliminary cytotoxicity study was conducted using the Brine Shrimp Lethality Test (BSLT) method, as described in previous research reports. Preliminary cytotoxicity was evaluated using the Brine Shrimp Lethality Test (BSLT). Each extract and fraction was tested at concentrations of 1,000, 500, 250, and 125 ppm. *Artemia salina* eggs were hatched in fresh seawater, and freshly hatched nauplii were exposed to serial dilutions of each sample concentration. After 24 h of incubation in the dark at room temperature, the number of surviving nauplii in each vial was counted. The median lethal concentration (LC_{50}) was calculated using probit analysis. Based on the results, the crude EtOAc extract showed no significant cytotoxicity, with an LC_{50} value exceeding 1,000 µg/mL, whereas the DCM fraction exhibited weak cytotoxicity

with an LC_{50} of 710.4 µg/mL. The number of nauplii per vial, number of replicates, solvent, exposure volume, positive and negative controls, statistical software, and confidence intervals were not reported in the original data and should be included if available from the experimental records.

LC-MS/MS analysis

The DCM fraction was selected for LC–MS/MS analysis because, among the fractions evaluated, it showed detectable cytotoxic activity in the BSLT, with an LC_{50} value of 710.4 µg/mL. The DCM fraction was dissolved in HPLC-grade methanol and analyzed using an ultraperformance liquid chromatography (UPLC) system equipped with a C18 column (1.8 µm, 2.1 × 100 mm) coupled to an XEVO G2-S Q-TOF mass spectrometer. The mobile phase consisted of solvent A, water containing 5 mM ammonium formate, and solvent B, acetonitrile containing 0.05% formic acid. The analysis was performed using gradient elution at a flow rate of 0.2 mL/min with a total run time of 23 min. Mass spectrometric detection was performed using electrospray ionization (ESI) in positive-ion mode over an *m/z* range of 50–1,200. The data were processed using MassLynx software version 4.1 to detect prominent peaks and determine tentative molecular formulas. Putative metabolite annotation was based on accurate mass measurements, ion type, molecular formula prediction, mass error, and MS/MS fragmentation patterns. The observed ions were compared with entries in PubChem, MassBank, and ChemSpider databases and with relevant literature reports. The chromatographic and mass spectral data included retention time, observed *m/z*, ion type, molecular formula, Δppm, and key MS^2 fragments. Because the detected compounds were not confirmed using authentic reference standards, all reported metabolites were described as tentatively or putatively annotated. The analysis resulted in the putative annotation of metabolites including dehydrofusaric acid, fusaric acid, fusaric acid-like compounds, rhynchophylline, rubrofusarin, bikaverin, beauvericin, and boviquinone-4, in addition to one unidentified compound. Definitive identification requires compound isolation, structural elucidation, and comparison with authentic standards.

RESULT AND DISCUSSION

The endophytic isolate CSBT2 was confirmed as *F. proliferatum* by molecular analysis in our previous unpublished study (Suhetris, 2025). LC–MS/MS profiling of the DCM fraction of *F. proliferatum* CSBT2 isolated from *C. sumatrana* revealed a chemically diverse metabolite profile, reflecting the remarkable biosynthetic capacity of this endophytic fungus. Members of the genus *Fusarium* are well recognized for producing structurally diverse secondary metabolites, including polyketides, terpenoids, alkaloids, and nitrogen-containing compounds and others. The diversity of metabolites observed in the present study supports the view that endophytic *F. proliferatum* possesses a versatile secondary metabolism that may be influenced by its ecological niche and host association (Picicci et al., 2026). The LC–MS chromatogram of the DCM fraction of *F. proliferatum* CSBT2 is shown in Figure 1.

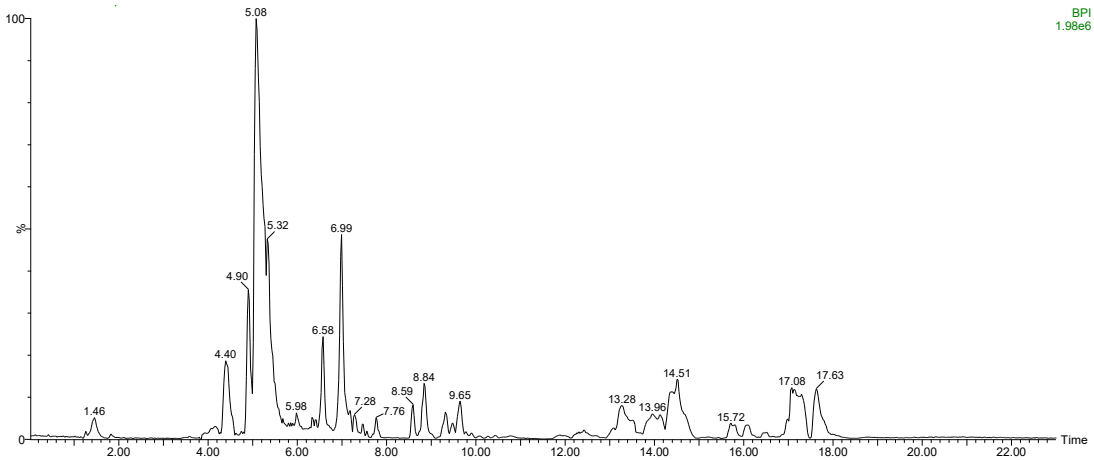


Figure 1. The LC–MS Chromatogram of the DCM Fraction of *F. proliferatum* CSBT2

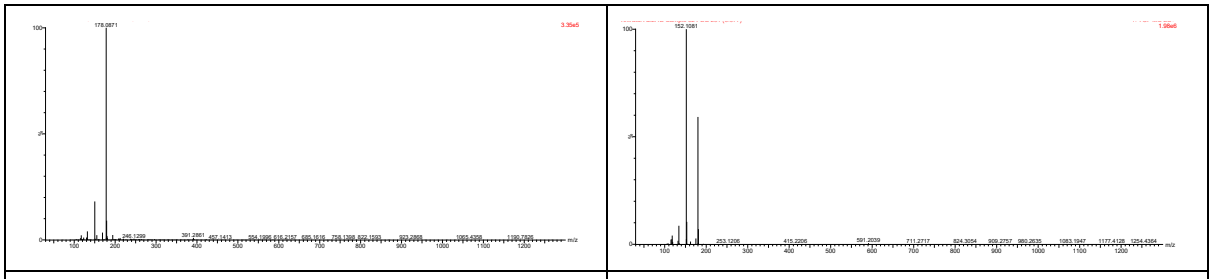
The use of dichloromethane as the extraction solvent likely contributed to the enrichment of semi-polar metabolites in the analyzed fraction. Dichloromethane preferentially extracts compounds with intermediate polarity, including aromatic polyketides, quinones, alkaloids, and several classes of fungal secondary metabolites. Several metabolites tentatively identified in this study have previously been reported from *F. proliferatum* isolated from different host plants and ecological environments. This finding indicates that certain biosynthetic pathways are conserved within the species regardless of host origin. Previous metabolomic studies have demonstrated that *F. proliferatum* associated with maize, rice, garlic, asparagus, and other agricultural crops produces a wide range of secondary metabolites, including fusaric acid, beauvericin, fumonisins, fusarins, moniliformin, and various polyketides. While some of these metabolites were also tentatively detected in the present study, differences in the overall metabolite profile suggest that the endophytic isolate from *C. sumatrana* exhibits a distinct chemical composition. The tentatively identified metabolites detected in *F. proliferatum* CSBT2 are presented in Table 1.

Table 1. The Tentatively Identified Metabolites Detected in *F. proliferatum* CSBT2

TR (min)	*m/z* Observed	Ion Type	Molecular Formula	Proposed Compound	Ref
4.40	178.0870	$[M^+H]^+$	$C_{10}H_{11}NO_2$	Dehydrofusaric acid	(Capasso et al., 1996)
5.08	180.1031	$[M^+H]^+$	$C_{10}H_{13}NO_2$	Fusaric acid	(Capasso et al., 1996; Niehaus et al., 2014)
6.99	385.2119	$[M^+H]^+$	$C_{20}H_{14}O_8$	Rhyncophylline	(Ndagijimana et al., 2013)
8.84	398.3423	$[M^+H]^+$	$C_{27}H_{43}NO$	Solanidine	(Niehaus et al., 2014)
14.37	784.4169 801.4433	$[M^+H]^+$ $[M^+NH4]^+$	$C_{45}H_{57}N_3O_9$	Beauvericin	(Wang and Xu, 2012)
17.12	413.2672	$[M^+H]^+$	$C_{26}H_{36}O_4$	Boviquinone-4	(Heinke et al., 2013)

LC–MS/MS analysis of the DCM fraction of *F. proliferatum* CSBT2 isolated from *C. sumatrana* resulted in the putative annotation of ten metabolites, including dehydrofusaric acid, fusaric acid, solanidine, rhynchophylline, beauvericin, and boviquinone-4, (Table 1). The metabolite profile demonstrates the broad biosynthetic capability of *F. proliferatum*, which is recognized as one of the most chemically diverse species within the genus *Fusarium*. Besides producing economically important mycotoxins such as fumonisins, *F. proliferatum* also synthesizes numerous polyketides, alkaloids, cyclic peptides, terpenoids, and nitrogen-containing metabolites through multiple biosynthetic gene clusters (Picicci et al., 2026).

Among the detected metabolites, dehydrofusaric acid at retention time (RT) 4.40 *m/z* 178.0870 and fusaric acid at TR 5.08 *m/z* 180.1031 belong to the picolinic acid derivatives that are considered characteristic metabolites of *Fusarium* species. Fusaric acid has been consistently reported from *F. proliferatum* isolated from maize, rice, garlic, asparagus, and several other hosts, indicating that its biosynthesis is highly conserved within the species. The detection of dehydrofusaric acid together with fusaric acid may reflect sequential biosynthetic or oxidative transformations occurring during secondary metabolism, as dehydrofusaric acid has been proposed as a biosynthetic intermediate or structural analogue in the fusaric acid pathway. Recent metabolomic investigations have shown that *Fusarium* species produce numerous modified fusaric acid analogues that remain incompletely characterized, highlighting the chemical complexity of this metabolite family (Zaman et al., 2026).



(A) (B)

Figure 2. Ion mass spectrum of the chromatographic peak corresponding to the tentative identification of (A) dehydrofusaric acid; and (B) fusaric acid.

Among the metabolites tentatively identified in the DCM fraction, detection of solanidine at RT 8.84 min *m/z* 398.3423 may be associated with the use of PDB prepared from fresh potatoes according to the ATCC Medium 336 formulation. As solanidine is a naturally occurring steroidal alkaloid aglycone found in potato tissues, its presence in the extract may reflect residual potato-derived constituents retained in the culture medium rather than de novo biosynthesis by *F. proliferatum* CSBT2. The detection of solanidine highlights an important methodological consideration when fresh potato-based PDB is used for metabolomic studies. The Potato-derived metabolites may remain in the fermentation broth and subsequently co-extract with fungal metabolites. Therefore, the contribution of medium-derived constituents to the LC–MS/MS profile cannot be completely excluded (Nielsen et al., 2020).

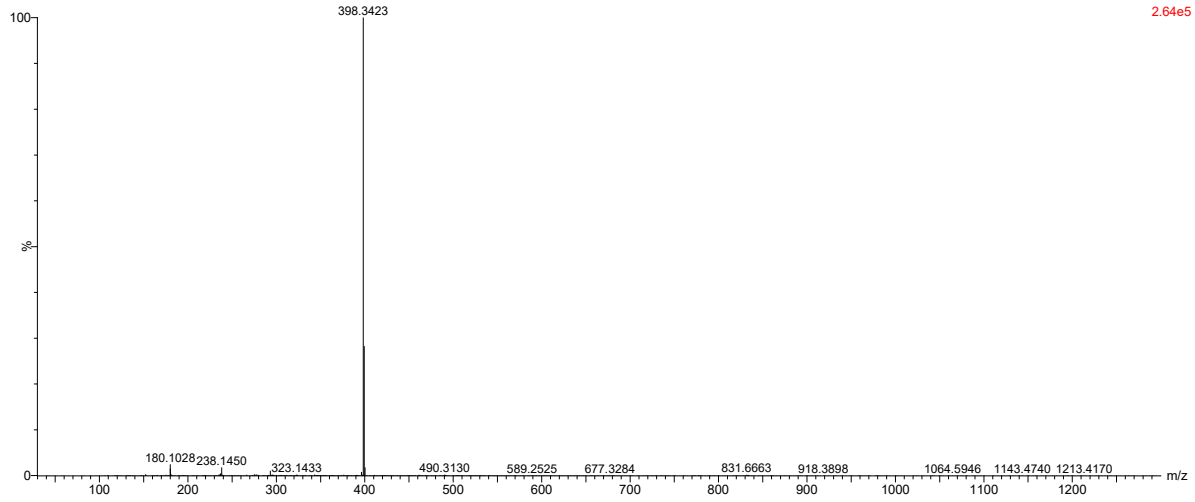


Figure 3. Ion Mass Spectrum of The Chromatographic Peak Corresponding to The Tentative Identification Of Solanidine.

The detection of beauvericin at TR 14.37 *m/z* 801.4396 is also consistent with previous reports describing this cyclic hexadepsipeptide as one of the characteristic secondary metabolites of *F. proliferatum*. Beauvericin production has been reported in isolates obtained from maize, corn fodder, garlic, and green Chinese onion, and its biosynthetic gene cluster has been experimentally characterized in *F. proliferatum*. The repeated occurrence of beauvericin in isolates from diverse hosts suggests that its biosynthesis is conserved across geographically and ecologically distinct populations of the species (Handayani et al., 2021; Zhang et al., 2013). The tentative annotation of boviquinone-4 expands the diversity of quinone-derived metabolites detected in *F. proliferatum* CSBT2. Quinone metabolites have frequently been reported from *Fusarium* species, reflecting the diversity of fungal polyketide biosynthesis. Nevertheless, reports specifically describing boviquinone derivatives in *F. proliferatum* remain limited. Therefore, confirmation of this annotation will require purification and structural elucidation using spectroscopic techniques such as nuclear magnetic resonance (NMR) (Heinke et al., 2013).

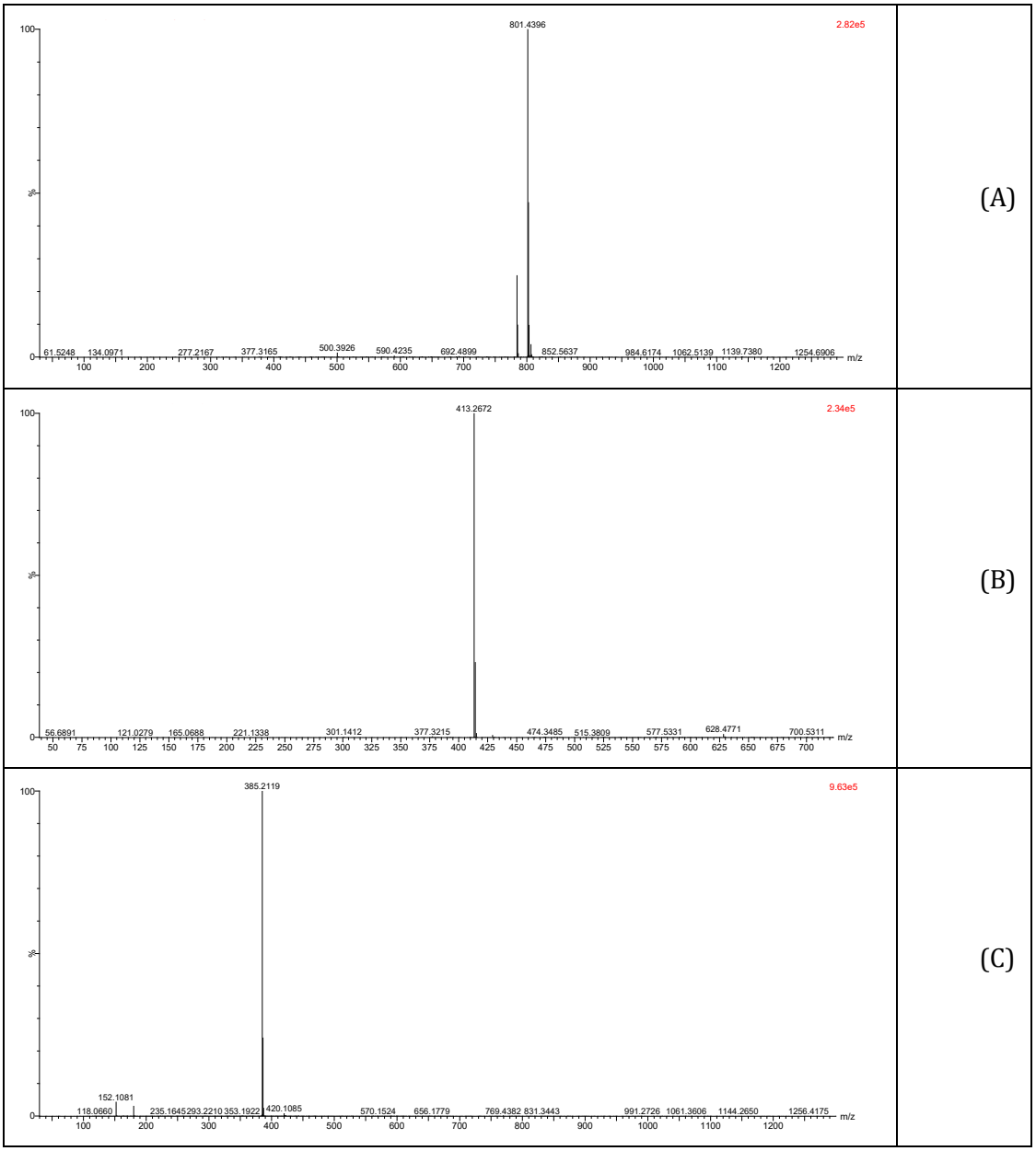


Figure 4. Ion mass spectrum of the chromatographic peak corresponding to the tentative identification of (A) beauvericin; (B) boviquinone-4; and (C) rhynchophylline.

Interestingly, rhynchophylline at RT 6.99 *m/z* 385.2119 was also tentatively annotated in the DCM fraction. Rhynchophylline is classically recognized as an oxindole alkaloid from plants of the genus *Uncaria* and has rarely been reported from fungi. Its annotation should therefore be interpreted cautiously because LC–MS/MS-based annotation relies on spectral similarity and accurate mass matching. Structural isomers or compounds with highly similar fragmentation patterns may generate comparable annotations. Consequently, definitive identification of this metabolite requires isolation of the compound followed by comprehensive spectroscopic characterization and comparison with an authentic standard (Ndagijimana et al., 2013). The presence of an unidentified metabolite suggests that the current fungal metabolite databases may not fully represent the chemical diversity of endophytic fungi. Further isolation and spectroscopic characterization are required to elucidate its structure.

The preliminary cytotoxicity of the crude ethyl acetate (EtOAc) extract and dichloromethane (DCM) fraction of *F. proliferatum* CSBT2 was evaluated using the Brine Shrimp Lethality Test (BSLT). Each sample was tested at concentrations of 125, 250, 500, and 1,000 ppm.

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Artemia salina eggs were hatched in fresh seawater, and freshly hatched nauplii were exposed to the respective sample concentrations. After 24 h of incubation in the dark at room temperature, the surviving brine shrimp were counted, and the LC_{50} value was determined using probit analysis.

The crude EtOAc extract did not reach 50% lethality within the tested concentration range. Therefore, its LC_{50} could not be accurately estimated and is reported as LC_{50} >1,000 µg/mL within the tested concentration range. This result should not be interpreted as "no significant cytotoxicity," as no statistical significance test was performed. In contrast, the DCM fraction exhibited weak cytotoxicity, with an LC_{50} value of 710.4 µg/mL. According to the BSLT toxicity criterion, samples with LC_{50} values below 1,000 µg/mL are considered toxic. However, based on the LC_{50} value obtained, the cytotoxic activity of the DCM fraction can be classified as weak.

Table 2. Cytotoxicity of the EtOAc extract and DCM fraction of *F. proliferatum* CSBT2 against *Artemia salina*

Sample	Tested concentration (µg/mL)	LC_{50} (µg/mL)	Interpretation
Crude EtOAc extract	125, 250, 500, 1,000	>1,000*	LC_{50} not reached within the tested range
DCM fraction	125, 250, 500, 1,000	710.4	Weak cytotoxicity

*The LC_{50} value could not be accurately estimated because 50% lethality was not reached at the highest tested concentration. Therefore, the result is reported as LC_{50} >1,000 µg/mL within the tested concentration range

CONCLUSION

The present study demonstrated that the DCM fraction of endophytic *F. proliferatum* CSBT2 isolated from *C. sumatrana* contains a diverse range of secondary metabolites as revealed by LC–MS/MS analysis. Tentative metabolite annotation identified compounds that have previously been reported from Fusarium species, including fusaric acid, dehydrofusaric acid, and beauvericin, together with other detected metabolites. To our knowledge, this is the first report describing the LC–MS/MS profile of the DCM fraction of *F. proliferatum* CSBT2 isolated from the endemic medicinal plant Curcuma sumatrana Miq., providing baseline chemical information for future studies on this endophytic fungus. The metabolite profile observed in *F. proliferatum* CSBT2 showed similarities with previously reported metabolites from *F. proliferatum* obtained from different host plants, while also reflecting the influence of host association and environmental conditions on fungal secondary metabolism. LC–MS/MS profiling provided valuable preliminary information for metabolite dereplication and prioritization of compounds for further chemical investigation. However, the identified compounds remain putative annotations and require further confirmation through isolation, NMR spectroscopy, and comparison with authentic standards.

SUGGESTION

Future studies should focus on the purification and structural elucidation of the major metabolites detected in the DCM fraction, particularly compounds that are uncommon or remain unidentified. Comparative metabolomic studies involving *F. proliferatum* isolates from different host plants and cultivation conditions are also recommended to better understand the influence of ecological factors on secondary metabolite production and to explore the chemical diversity of endophytic fungi from Indonesian medicinal plants.

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