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In vitro cytotoxic evaluation of bioactive compounds derived from *Talaromyces minioluteus*

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Abstract

Objective

The prevalence of cancer has recently been increasing globally, highlighting the importance of investigation for new, more efficient and safer anticancer drugs. Different species of *Talaromyces* provide high-potential bioactive metabolites, such as phenolic, polyphenols, steroids, terpenoids, anthraquinones and alkaloids that can be widely used in several medical applications. However, the full pharmaceutical potential of such species, particularly those isolated from soil, is not fully documented. The aim of this study is to determine the cytotoxicity of the secondary metabolites of an isolated *Talaromyces* strain.

Materials and methods

The isolated fungal strain was identified and confirmed by both molecular and morphological analyses. Further, high-performance liquid chromatography (HPLC) was carried out to detect the secondary metabolites of isolated fungus. The MTT method was used to evaluate *in vitro* cytotoxic activity of the crude extracts of isolated fungus against human lung carcinoma (A549), colorectal carcinoma (SW480), and normal dermal fibroblasts (HDFn).

Results

The fungal identity as *Talaromyces minioluteus* was confirmed by morphological and ITS- based molecular analysis. HPLC detected several bioactive compounds in the crude extracts of isolated fungus. The crude extract of *Talaromyces minioluteus* was observed to have anticancer effects against A549 and SW480, the values of IC_{50} were 62.5 µg/mL for A549 and 78.2 µg/mL for SW480. The IC_{50} for normal HDFn was higher (>200 µg/mL), showing the high cytotoxicity against lung and colorectal carcinoma cells.

Conclusions

The crude extract of *Talaromyces minioluteus* has a high cytotoxicity against lung and colorectal carcinoma cells. The presence of secondary metabolites is responsible for this effect due to their main roles in apoptosis induction and tumour growth inhibition. Based on the current results, *Talaromyces minioluteus* is considered a valuable source of bioactive metabolites. Further research on this isolated fungus should be undertaken to investigate the underlying mechanisms by which bioactive metabolites exert their impacts.

Keywords: Bioactive compounds**,** cytotoxic activity**,** high-performance liquid chromatography**,** molecular identification**,** *Talaromyces minioluteus*

Paper Type: Research Paper.

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Introduction

In the past four decades, more than 60% of new small-molecule drugs have been derived from natural products, emphasizing the crucial role of these products in modern drug discovery (Newman & Cragg, 2016). The fungal kingdom has developed defence and communications mechanisms, including the biosynthesis of many bioactive chemicals known as secondary metabolites (Macheleidt et al., 2016; Wadhwa et al., 2024). Anticancer synthetic medications are often implicated with resistance and toxicity; secondary metabolites isolated from fungi provide effective therapies with low toxicity. It was demonstrated that these metabolites have variable structures of chemical and showed potential biological effects (Khabiri et al., 2023; Zhang et al., 2023). The most important clinical drugs, including antibacterial (e.g., penicillin), cholesterol-lowering (e.g., lovastatin), and immunosuppressive drugs (e.g., cyclosporine A), reflected the vital role of bioactive compounds isolated from fungi in drug discovery (Wang et al., 2018). The significant fungal genus, *Talaromyces*, contains many species with broad chemical diversity, potent bioactivities and unique structures (Lan & Wu, 2020; Nicoletti, et al., 2018). Based on these beneficial features, *Talaromyces* and its secondary metabolites can be used in many biotechnological and pharmaceutical applications. Therefore, pharmacologists and chemists pay their scientific interest and attention to study the major role of secondary metabolites produced by microorganisms such as polyphenols, steroids, alkaloids, terpenoids, and anthraquinones (Chen et al., 2019; Lei et al., 2022). For example, the meroterpenoids isolated from a *Talaromyces* strain had strong cytotoxicity against prostate, gastric and urinary bladder cancer (Kaur et al., 2017; Tang et al., 2024). However, the whole therapeutic impact of these bioactive compounds is still largely unknown (Zhai et al., 2016). The current work is one of the few studies that focused on *T. minioluteus* and its bioactive compounds. Understanding the therapeutic role of fungal secondary metabolites contributes to discovering novel anticancer drugs and directs future studies into more effective and safer chemotherapeutic compounds. The aim of this study is to isolate and identify a *Talaromyces* strain from soil and evaluate the cytotoxicity of its crude extract against lung and colorectal carcinomas.

Materials and methods

Fungal strain isolation and identification: The agricultural soil samples were collected from Basrah, Iraq, to isolate the fungus. The plate dilution method was used to isolate the fungal strain. Potato dextrose agar (PDA) provided with 100 μg/mL of streptomycin were used to culture the isolated fungus and incubated at 25 ± 0.5 °C for seven days.

Morphological identification: The morphological properties including colony colour, growth rate, texture, and sporulation, were recorded after seven days of incubation. Microscopic observations including conidia, conidiophores, phialides, and branching patterns, were recorded using the light microscope supplied with a digital camera.

Molecular identification: Internal Transcribed Spacer (ITS) sequencing of fungal ribosomal DNA, a highly conserved genetic marker, was used for molecular identification (Ebaya et al., 2020).

Genomic DNA isolation and amplification: To extract the genomic DNA, a small portion from the edges of an actively growing fungal colony was excised and inoculated onto a yeast extract-peptone-dextrose plate for approximately 5–7 days at 30 ± 1°C. Approximately 0.2 g of mycelium from solid culture was employed for DNA extraction using Geneaid DNA Isolation Kit for Yeast (Cat. No. GEY004). The NanoDrop spectrophotometer (Thermo Scientific) was employed to assess the DNA's concentration and purity. Extracted DNA was preserved at -20°C for further analysis.

Sequencing and analysis: The ITS region was amplified by using primers ITS1, ITS4 and genomic DNA as the template (White et al., 1990). Amplification was carried out under standard cycling conditions (Bahi & Shekhany, 2023), and the resulting product was purified and sequenced by Macrogen Company. ITS sequences were analysed using BLAST against related sequences in GenBank/ NCBI database. The high similarity with *T. minioluteus* confirmed the molecular identity of the isolated fungus.

Extraction of secondary metabolites: The confirmed strain of *T. minioluteus* was cultured in 250 mL flasks of potato dextrose broth (100 mL) for seven days at 25 ± 0.5°C in a rotary shaker set at 140 rpm. Following the incubation time, the broths were filtered using filter paper Whatman No. 1 to isolate the mycelium. Subsequently, the culture filtrate was extracted three times using same amount of ethyl acetate. Under reduced pressure, the collected organic layer was concentrated with a rotary evaporator to obtain the crude extract for further analysis.

Isolation and identification of secondary metabolites: The high-performance liquid chromatography (HPLC), provided with a UV detector (SYKAM Germany), was used to detect the secondary metabolites in the crude extract of *T. minioluteus.* The C18 Octadecylsilane (ODS) column was used to separate phenolic acids and flavonoids, and a mixture of methanol, distilled water, and formic acid (70:25:5) was employed as a mobile phase at a flow rate of 1 mL min–1 to facilitate separation. The samples' retention times were compared with those of the standards at 280 nm to detect phenolic acids and flavonoids. Several standard compounds were used to identify phenolic compounds, including caffeic, gallic, chlorogenic, syringic, vanillic acids, and p-coumaric Quercetin, hesperidin, and kaempferol were used to detect flavonoids.

Cells culture reagents: Roswell Park Memorial Institute medium (RPMI-1640), foetal bovine serum (FBS), phosphate-buffered saline (PBS), dimethyl sulfoxide (DMSO), and sodium bicarbonate were obtained from Sigma-Aldrich (USA). Antibiotics, including benzyl penicillin and streptomycin were obtained from Ajenta Pharm (India). The MTT cytotoxicity assay kit was supplied by Intron Biotech (Korea). Lung carcinoma (A549), colorectal carcinoma (SW480), and normal human dermal fibroblasts (HDFn) were provided ethically by Department of Pharmacology, College of Medicine, Malaya University.

Cytotoxicity evaluation: MTT cytotoxic assay was applied to evaluate the cytotoxicity (van de Loosdrecht et al., 1994). Cells were nourished with RPMI-1640 media enriched with 1% sodium bicarbonate, 10% FBS, 103 IU penicillin, and 0.001 g streptomycin in 96-well plates at a density of 1 × 10^4 cells/mL (100 µL/well). Cells were incubated in a 5% CO2 incubator

(Gallenkamp, England) at 37°C. Twenty-four hours post-seeding, cells received treatment with medium containing 25, 50, 100, 200, and 400 µg/mL, followed by incubation for 24 h. MTT (10 µL) was added to each well, and following 4 h of incubation, formazan crystals were dissolved and absorbance measured at 575 nm. The IC_{50} was calculated for the crude extract against both cancer cell lines (A549 and SW480) and compared with the normal HDFn cell line to determine the selective cytotoxicity.

Statistical analysis: Results were expressed as mean ± standard deviation (SD) and analysed using GraphPad Prism (version 9.4). One-way analysis of variance (ANOVA) and Duncan's post hoc test were used to assess differences among groups. A p-value ≤ 0.05 was considered indicative of statistical significance.

Results

Morphological and molecular identification of isolated fungus: The isolate formed yellow-green colonies measuring 25–30 mm in diameter after 7 days of incubation on PDA (Figure 1A). Microscopic observations revealed the biverticillate conidiophores; stipes smooth-walled, phialides acerose, three to five per metulae (Figure 1B and C), conidia smooth-walled, ellipsoidal to subglobose 2.58 × 2.24 µm (Figure 1D). The genetic analysis using ITS rDNA sequencing confirmed the morphological identification of the isolated fungus. The phylogenetic result showed high similarity of isolated fungal strain to *T. minioluteus* (Figure 2). Therefore, the combined morphological and molecular evidence confirmed the classification of the isolated fungus as *T. minioluteus* under accession number PV991116, (https://www.ncbi.nlm.nih.gov/nuccore/PV991116).

Secondary metabolites identification by HPLC: The HPLC result of *T. minioluteus* extract revealed the presence of flavonoids, particularly quercetin and several phenolic acids, including p-coumaric, syringic, vanillic, hydroxybenzoic, caffeic, gallic, and chlorogenic acids (Figure 3). Quantification was conducted with a standard calibration curve. The concentrations of the identified compounds from the analysed sample are summarized in Table 1.

Cytotoxic activity: The cytotoxicity of the extract was determined using the MTT method against A549, SW480, and HDFn cell lines. All cell types were treated with a range of concentrations (25, 50, 100, 200, and 400 µg/mL) of the crude extract for 24 h. The crude extract showed a dose-dependent reduction in A549 and SW480 cell viability, with IC_{50} values of 62.5 µg/mL for A549 and 78.2 µg/mL for SW480. The IC_{50} was more than 200 µg/mL for normal HDFn (Figure 4). This result shows that *T. minioluteus* produces interesting bioactive compounds that inhibit tumour cells with less toxicity to normal cells.

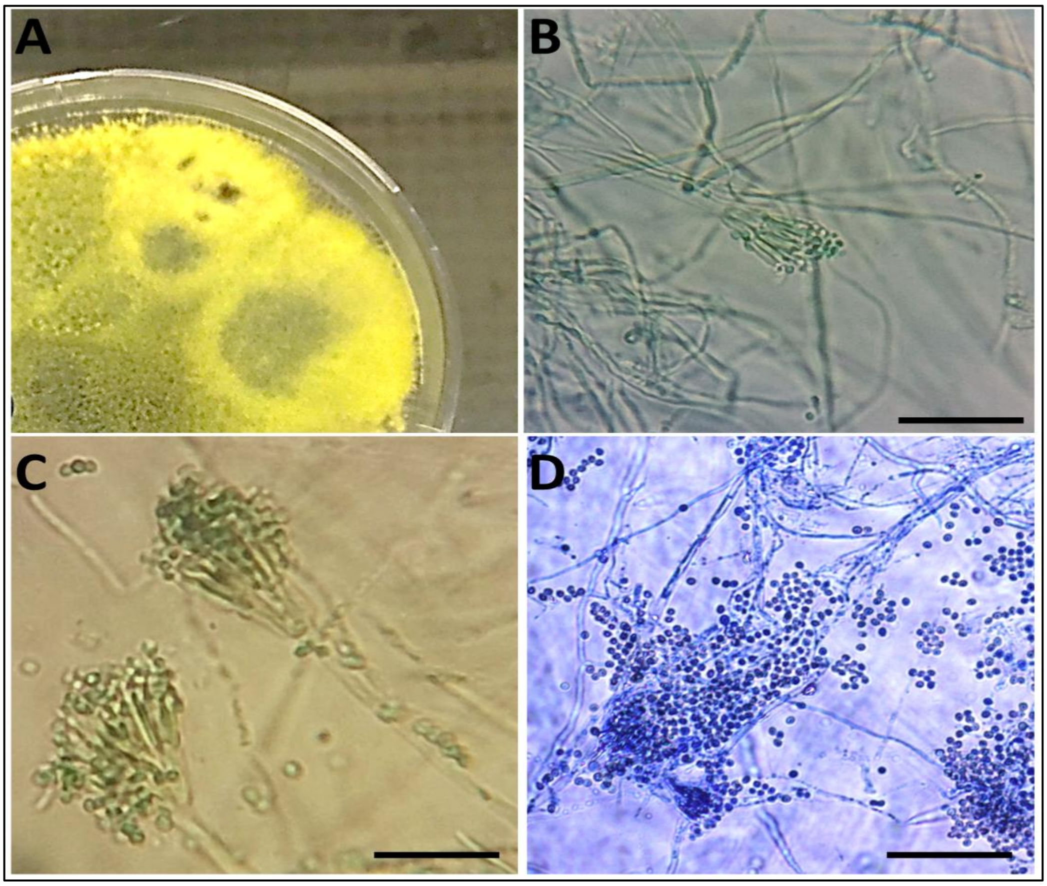

Figure 1. Morphological features of *Talaromyces minioluteus*. (A) Colonies, (B–D) Conidiophores and conidia and (E) Conidia. 400× magnification and 10 µm scale bars

Discussion

Recently, there has been growing interest in identifying non-toxic secondary metabolites. The bioactive compounds formed by biological processes have shown high selectivity and safety toward target organisms compared to their synthetic chemical agents. Based on these investigations, this study isolated a soil-derived fungal strain from southern Iraq and screened its bioactive compounds. The soil-derived fungal strain, *T. minioluteus*, was successfully isolated and identified in this study. The taxonomic identity of *T. minioluteus* was confirmed by both morphological and molecular techniques using ITS rDNA sequencing with high accuracy and reliability. A previous study aligns completely with the fungal classification reported in this study (Pyrri et al., 2021). Molecular analysis of the studied fungal strain supplied deep confirmation of *T. minioluteus* taxonomic identity. ITS rDNA region was effectively sequenced and amplified. BLAST examination confirming the morphological identification of the isolated fungus by showing a high similarity between the gained sequence and *T. minioluteus* sequences that are available in GenBank.

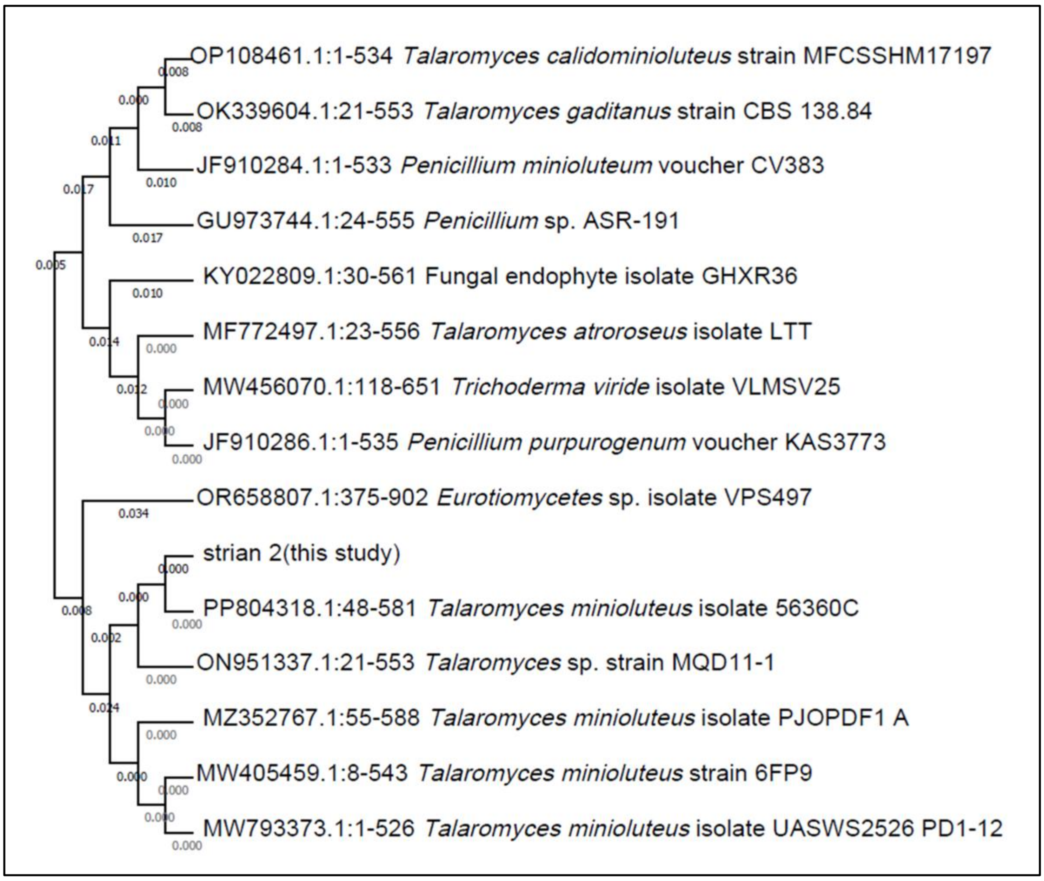

Figure 2. Genetic analysis using ITS rDNA sequences of *Talaromyces minioluteus*. Phylogenetic analysis showing the close relationship between the isolated strain and reference sequences from GenBank

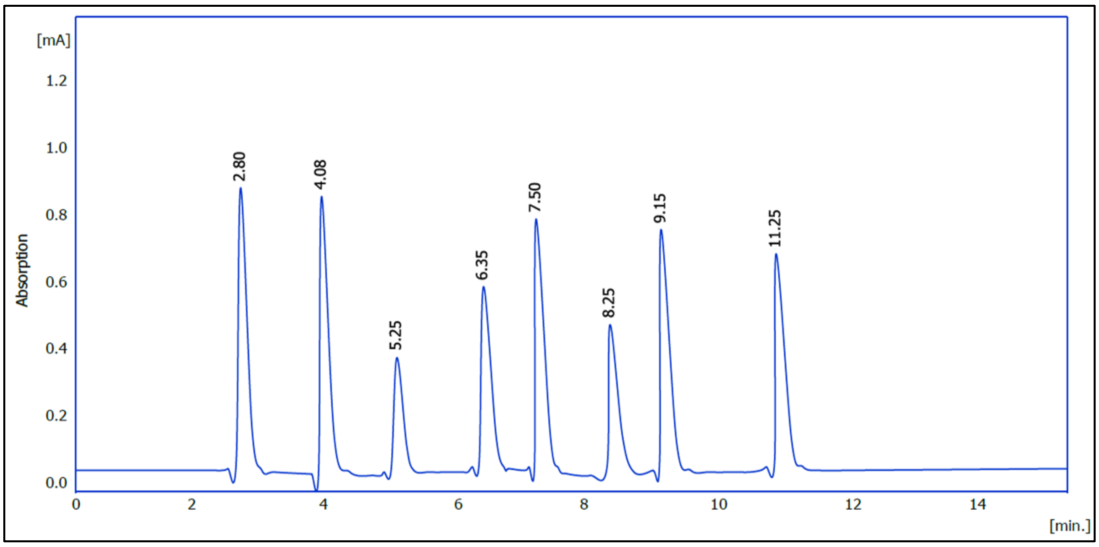

Figure 3. HPLC analysis of major bioactive compounds in the crude extracts of *Talaromyces minioluteus*

Table 1: Retention times and concentrations of bioactive compounds in the crude extract of *Talaromyces minioluteus*

No.	Name	Rt.	Con. (ppm)
1	Caffeic acid	2.88	124.9
2	Gallic acid	4.08	147.8
3	Vanillic acid	5.25	62.7
4	Hydrobenzoic acid	6.30	88.9
5	Syringeic acid	7.55	64.9
6	Quercetin	8.25	80.9
7	p-Coumaric acid	9.12	70.9
8	Chlorogenic acid	11.25	55.9

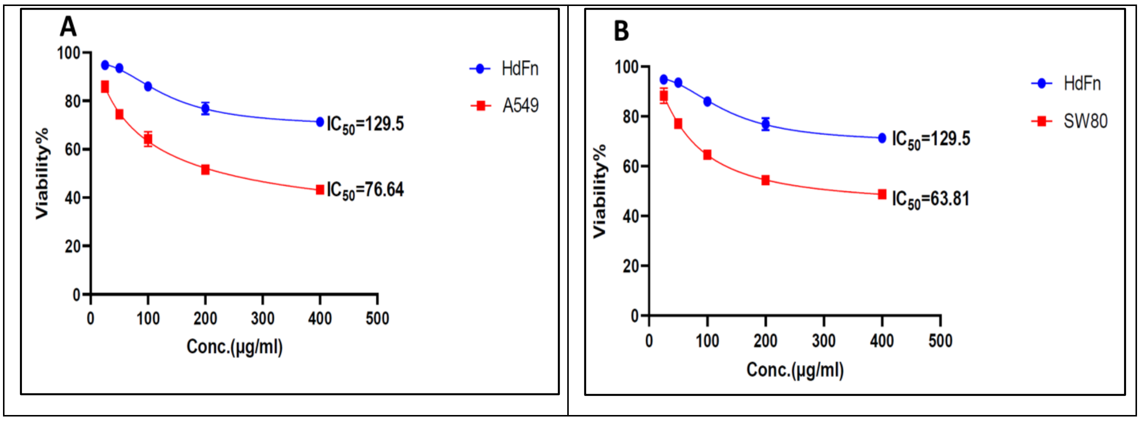

Figure 4. Cell viability of human cancer cell lines treated with crude extract from *Talaromyces minioluteus.* (A) Cell viability (%) of human lung carcinoma (A549) compared with the normal human dermal fibroblasts (HDFn). (B) Cell viability of human colorectal adenocarcinoma (SW480) compared with normal HDFn cells. All cell lines were treated with different concentrations of crude extract of *T. minioluteus*. Statistical analysis was applied using one-way ANOVA and Duncan's subtest. All experiments were conducted in triplicate

The phylogenetic tree obtained validates the molecular identification by showing strong bootstrap support. ITS sequencing is mainly considered a universal DNA barcode for fungi, giving strong resolution for species-level identification (Nilsson et al., 2019; Schoch et al., 2012).

The molecular features of several previous phylogenetic studies on *Talaromyces* species are consistent with the current results (Pyrri et al., 2021; Yilmaz et al., 2014). Interestingly, *T. minioluteus* produced some bioactive compounds and HPLC analysis confirmed the presence of quercetin, p-coumaric, syringic, vanillic, hydroxybenzoic acids, caffeic acid, gallic acid, and chlorogenic acids. The bioactive compound quercetin, a type of flavonoid, is a strong antioxidant, anti-inflammatory, and anticancer agent. It was demonstrated that synergistic or more anticancer effects can be obtained when quercetin is used in combination with other anticancer therapies (Kundur et al., 2019; Lewandowska et al., 2014; Tang et al., 2017). The phenolic acids are well-documented for their anti-inflammatory, antioxidant, and anticancer activities (Soleimanizadeh et al., 2025). The identification of these compounds is consistent with previous results on the chemical diversity of *Talaromyces* species, which are highly recognized due to their pharmacologically active compounds (Wu et al., 2016). Cytotoxicity assays are widely used to screen cytotoxic compounds. The screened soil-derived fungal extract possessed a variety of anticancer compounds. The current findings demonstrated a dose-dependent cytotoxic effect of the crude extract on A549 and SW480 with IC_{50} values of 62.5 μg/mL and 78.2 μg/mL, respectively, compared with a significantly lower cytotoxicity in HDFn cells. The obtained selective cytotoxicity indicates that the extract may have a selective toxicity against cancer cells, a key feature of a promising anticancer candidate. Quercetin, one of the secondary metabolites isolated from Talaromyces species, exhibits anticancer properties through promoting apoptosis and reducing cancer cell proliferation (Asgharian et al., 2022; Hashemzaei et al., 2017). Herein, the exact mechanism responsible for the cytotoxic activity was not evaluated; therefore, further studies on apoptosis and reactive oxygen species assays are needed. Additionally, the anticancer effects were assessed only *in vitro* and by using three cell lines, which may not fully reflect the *in vivo* therapeutic effects. Further, the crude extract was identified without isolating and purification all individual compounds. Therefore, the determination of which specific metabolites are responsible for the observed cytotoxicity is difficult.

Conclusion: Our study highlights that the Iraqi isolate of *T. minioluteus* secretes many secondary metabolites with strong anticancer effects. HPLC analysis investigated several bioactive compounds such as quercetin and several phenolic acids. The crude extract isolated from *T. minioluteus* showed high cytotoxicity against A549 and SW480 cells, with lower toxicity towards normal HDFn cells. These results suggest the vital role of soil-derived *Talaromyces* as an interesting source of novel therapeutic agents.

List of abbreviations

A549: Human lung carcinoma cell line, ANOVA: Analysis of variance, DMSO: Dimethyl sulfoxide, EDTA: Ethylenediaminetetraacetic acid, ELISA: Enzyme-linked immunosorbent assay, FBS: Fetal bovine serum, HDFn: Normal human dermal fibroblasts, HPLC: High-performance liquid chromatography, ITS: Internal transcribed spacer (ribosomal DNA region), MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, ODS: Octadecylsilane, PBS: Phosphate buffered saline: PDA: Potato dextrose agar, RPMI-1640:Roswell park memorial institute medium, SD: Standard deviation, SW480: Human colorectal adenocarcinoma cell line, and UV: Ultraviolet.

Author contributions

Conceptualization, K.K. and Z.A.; methodology, K.K.; software, Z.A.; validation, K.K., Z.A. and R.A.; formal analysis, R.A.; investigation, R.A.; resources, K.K.; data curation, Z.A.; writing original draft preparation, R.A.; writing review and editing, K.K. and Z.A.; visualization, K.K.; supervision, K.K.; project administration, K.K. and Z.A; funding acquisition, K.K. All authors have read and agreed to the published version of the manuscript.

Data availability statement

All relevant data supporting the findings of this study are included in the article.

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Ethical considerations

The study was approved by the Human Research Ethics Committee, College of Pharmacy, University of Basrah (Approval No. EC79). All experiments were performed in accordance with institutional and international ethical guidelines.

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Conflict of interest

All authors declared no conflict of interest, financial or otherwise.

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ارزیابی سیتوتوکسیک In vitro ترکیبات بیواکتیو مشتق‌شده از Talaromyces minioluteus

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چکیده

هدف: شیوع سرطان اخیراً در سطح جهانی افزایش یافته است، که این امر بر اهمیت بررسی داروهای ضدسرطانی جدید، کارآمدتر و ایمن‌تر تأکید می‌کند. گونه‌های مختلف Talaromyces متابولیت‌های بیواکتیو با پتانسیل بالا مانند فنولیک‌ها، پلی‌فنول‌ها، استروئیدها، ترپنوئیدها، آنتراکینون‌ها و آلکالوئیدها را فراهم می‌کنند که می‌توانند به طور گسترده در کاربردهای پزشکی مختلف استفاده شوند. با این حال، پتانسیل دارویی کامل این گونه‌ها، به ویژه آن‌هایی که از خاک جدا شده‌اند، به طور کامل مستند نشده است. هدف این مطالعه تعیین سمیت سلولی متابولیت‌های ثانویه یک سویه جدا شده Talaromyces است.

مواد و روش‌ها: سویه قارچی جدا شده با استفاده از تحلیل‌های مولکولی و مورفولوژیکی شناسایی و تأیید شد. علاوه بر این، کروماتوگرافی مایع با کارایی بالا (HPLC) برای شناسایی متابولیت‌های ثانویه قارچ جدا شده انجام شد. روش MTT برای ارزیابی فعالیت سیتوتوکسیک in vitro عصاره‌های خام قارچ جدا شده در برابر کارسینوم ریه انسانی (A549)، کارسینوم کولورکتال (SW480) و فیبروبلاست‌های درمال طبیعی (HDFn) استفاده شد.

نتایج: هویت قارچی به عنوان Talaromyces minioluteus با تحلیل مورفولوژیکی و مولکولی مبتنی بر ITS تأیید شد. HPLC چندین ترکیب بیواکتیو را در عصاره‌های خام قارچ جدا شده شناسایی کرد. عصاره خام Talaromyces minioluteus اثرات ضدسرطانی علیه A549 و SW480 نشان داد، که مقادیر IC50 آن ۶۲/۵ میکروگرم بر میلی‌لیتر برای A549 و ۷۸/۲ میکروگرم بر میلی‌لیتر برای SW480 بود. IC50 برای HDFn طبیعی بالاتر (بیشتر از ۲۰۰ میکروگرم بر میلی‌لیتر) بود، که سمیت سلولی بالا علیه سلول‌های کارسینوم ریه و کولورکتال را نشان می‌دهد.

نتیجه‌گیری: عصاره خام Talaromyces minioluteus سمیت سلولی بالایی علیه سلول‌های کارسینوم ریه و کولورکتال دارد. وجود متابولیت‌های ثانویه مسئول این اثر است، زیرا نقش اصلی آن‌ها در القای آپوپتوز و مهار رشد تومور است. بر اساس نتایج فعلی، Talaromyces minioluteus به عنوان منبع ارزشمندی از متابولیت‌های بیواکتیو در نظر گرفته می‌شود. تحقیقات بیشتری بر روی این قارچ جدا شده باید انجام شود تا مکانیسم‌های زیربنایی که متابولیت‌های بیواکتیو اثرات خود را اعمال می‌کنند، بررسی شود.

کلمات کلیدی: ترکیبات بیواکتیو، شناسایی مولکولی، فعالیت سیتوتوکسیک، کروماتوگرافی مایع با کارایی بالا، Talaromyces minioluteus

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