

Bioactive Compounds From Saudi Arabian Fungi: A Systematic Review of Anticancer Potential

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Abstract: Cancer remains the second leading cause of death worldwide, highlighting the urgent need for novel therapeutic approaches. Fungi are a rich source of bioactive metabolites, some of which exhibit potent anticancer properties. This scoping review evaluates the current research on fungal metabolites with anticancer potential, focusing on species native to Saudi Arabia's unique ecosystem. Following PRISMA 2020 guidelines, a comprehensive literature search was conducted using PubMed, Google Scholar, and Web of Science. Out of approximately 14,000 records, 11 studies met the inclusion criteria (2000–2024). A total of 16 distinct fungal species were identified, with their metabolites tested against various human cancer cell lines. Compounds derived from *Penicillium sp. RO-II*, *Fusarium venenatum*, *Chaetomium globosum*, *Bipolaris sorokiniana*, and *Aspergillus sydowii* demonstrated notable cytotoxic effects. Reported IC₅₀ values ranged from as low as 0.2 µg/mL to over 600 µg/mL, indicating varying levels of potency. *Penicillium sp. RO-II* (emodin, IC₅₀ = 2 ± 7.6 µM) and *Fusarium venenatum* (IC₅₀ = 0.3779 µg/mL against HCT8 cells) emerged as the most potent candidates. These metabolites exerted their effects by inducing apoptosis, inhibiting proliferation, and disrupting oncogenic signaling pathways. The findings underscore the therapeutic potential of fungal-derived compounds and highlight the importance of further research to isolate and characterize the most effective strains for biomedical applications. Expanding investigations into Saudi Arabia's fungal diversity may yield promising candidates for future cancer treatments.

Keywords: fungal metabolites, anticancer agents, Saudi Arabian fungi, cytotoxicity, marine fungi, terrestrial fungi

Introduction

Cancer is one of the leading causes of death worldwide.^{1–5} It is projected that by 2025 that over 2,000,000 new cases of cancer will be newly diagnosed, and cancer deaths being over 600,000 in the United States alone.⁶ According to⁵ approximately one in five individuals will develop cancer in their lifetime, with about one in nine men and one in twelve women dying from the disease. In Saudi Arabia, cancer is also a major health issue, with breast, colorectal, prostate, brain, lymphoma, kidney, and thyroid cancers being the most prevalent.⁷ Despite current interventions such as prevention efforts, chemotherapy/immunotherapy, and surgical approaches, treatment outcomes often remain suboptimal, indicating a need for improved strategies.

Current cancer treatments face several challenges, including limited effectiveness, diminishing response rates, significant side effects and the immune evasion, where cancer cells develop strategies to evade detection and destruction by the immune system, thereby limiting the effectiveness of immunotherapies.^{1,8,9} Moreover, Drug resistance is responsible for more than 90% treatment failure and mortality in tumor patients.^{10,11} In addition, these treatments impose soaring costs on healthcare systems. Treatment plans also vary widely among patients due to numerous individual factors, increasing the complexity and uncertainty of cancer care.¹² This growing complexity, coupled with rising cancer

incidence, indicates the urgent need for new and improved cancer therapies. Consequently, the exploration of novel anti-cancer agents has become important. Fungi, with their rich source of structurally diverse compounds, represent a promising option for potential anticancer activity.

By systematically exploring diverse fungal species and characterizing their bioactive metabolites, it is possible to discover compounds with unique mechanisms of action and enhanced efficacy against cancer cells.^{13–15} Research studies on fungal metabolites show significant potential for anticancer activities. A survey conducted by Newman and Giddings¹⁶ examined the origins of 191 chemotherapeutic agents introduced between the late 1930s and the end of 2012, revealing that 89 were derived directly from natural products or their modified forms, and 39 were synthetic compounds with natural origins. Thus, only 63 anticancer agents (33%) could be classified as entirely synthetic. Moreover, fungal-derived compounds can enhance the efficacy of existing therapies while minimizing side effects.^{13,17,18}

Fungi have long been a source of bioactive compounds with therapeutic applications.^{19,20} From penicillin to cyclosporine, fungal-derived drugs have transformed modern medicine. Nonetheless, a vast number of fungal species remain unexplored for their pharmacological potential. Recent research increasingly focuses on identifying novel fungi and exploring their mechanisms of action, particularly in the context of cancer therapy.^{15,17,21,22} The diverse and unique ecosystem of Saudi Arabia offers significant opportunities for drug discovery and development.²³ This region may harbor previously unknown fungal species with mechanisms of action that could lead to novel anti-cancer agents.²⁴ For example, research conducted at King Abdulaziz University in Jeddah²⁴ utilized pyrosequencing to reveal a rich fungal biodiversity. Over 450 species were identified from samples collected in Khulais, Mecca Old Road, Thuwal, and Asfan Road.

Despite the rich fungal diversity within Saudi Arabia's ecosystems, there remains a significant gap in understanding the anticancer potential of fungi native to this region. Although previous reviews have examined the anticancer properties of fungi from various geographical areas, none has specifically focused on the fungal species found in Saudi Arabia's diverse ecological niches. A systematic review addressing this knowledge gap would potentially reveal new avenues for anticancer drug discovery tailored to the region's unique fungal diversity. This systematic review aims to thoroughly examine fungal-derived compounds isolated from Saudi Arabia's ecosystems that have been investigated for their potential anticancer properties. It will summarize existing research and evaluate the findings to assess the prospects for developing future anticancer treatments derived from these fungal metabolites.

Materials and Methods

Search Strategies

The systematic review adhered to the (PRISMA) 2020 guidelines, ensuring a thorough and transparent approach. The search was conducted through the electronic databases of PubMed, Google Scholar, and Web of Science and only studies published post-2000 were included to ensure relevance and accuracy, avoiding outdated information. The studies were evaluated in depth, with details regarding fungi sources, anticancer activities, test results, and an overall conclusion and recommendation. The review exclusively focuses on the studies that examine the anticancer properties of fungal metabolites in Saudi Arabia (Figure 1).

Inclusion and Exclusion Criteria

The studies included in this review met the following criteria. Studies focus on fungal metabolites; terrestrial and marine fungi used in the study must be extracted from the Saudi Arabian ecosystem, and fungal metabolites must be tested against cancer cell lines. Articles were excluded if they did not perform cytotoxicity, studies did not contain original data, were not in English, or if they were review articles, systematic reviews, or unpublished articles, the terms excluded “antiviral” and “agriculture”. Two independent reviewers who conducted the initial filtering based on titles and abstracts identified the aforementioned strategy. Data extraction was performed for articles that met the inclusion criteria.

Identification of studies via different database

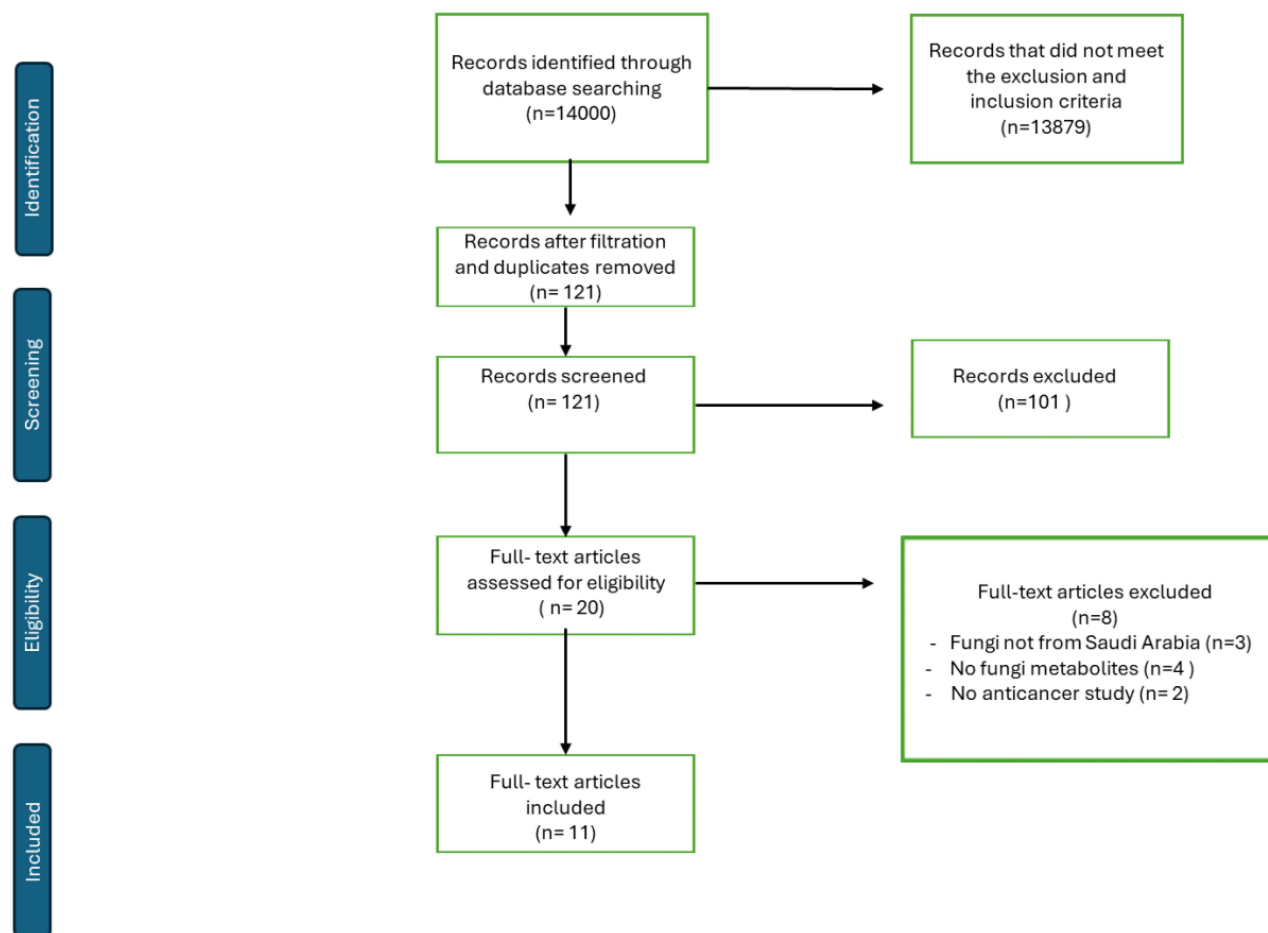


Figure 1 A flow diagram illustrating the study selection process conducted in accordance with PRISMA 2020 guidelines.

Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.²⁵

Results

The Red Sea is a highly diverse ecosystem, featuring coral reefs that stretch over 2000 km along its coastline (Figure 2). It hosts more than 1000 invertebrate species, along with over 200 kinds of both soft and hard corals. This remarkable biodiversity, combined with relatively limited research, makes the Red Sea an underexplored reservoir for the discovery of novel bioactive marine natural products. In parallel, the Arabian Gulf (also shown in Figure 2) represents another important aquatic region with distinct environmental pressures and biological diversity.

Marine fungi inhabiting these environments face significant challenges compared to their terrestrial counterparts. These include high salinity levels leading to osmotic and ionic stress, ultraviolet radiation exposure, and low temperatures.²⁶ Additionally, fungi must adapt to limited access to substrates for growth, hydrostatic pressure in some regions, and the unique dispersal challenges posed by aquatic environments.²⁷

Acremonium sp

Fungal isolates from the coasts of the Red Sea and the Arabian Gulf were collected to discover marine fungi with potent bioactivities against pathogenic bacteria, fungi, and cancer cells. The research also focused on identifying strains with



Figure 2 Map of Saudi Arabia showing the Red Sea and Arabian Gulf. (Downloaded from Google map location: 28°12'42"N 32°57'37"E).

strong antioxidant properties.²⁶ The Red Sea, characterized by high salinity and warm temperatures, and the Arabian Gulf, the hottest sea globally, offered distinct habitats for microbial diversity.²⁷ Marine fungi were collected from 15 different coastal locations around the Arabian Peninsula. The isolates were evaluated for their antioxidant activity, antibacterial and antifungal potential, and cytotoxic effects against various cancer cell lines. Among the isolates, *Acronium* sp. was identified as one of the most bioactive genera, demonstrating substantial multifunctional potential across diverse assays. *Acronium* sp. exhibited exceptional cytotoxicity against skin cancer cells (A431) by 98%± 5%, while also displaying strong antioxidant activity with 97% DPPH radical scavenging. The strain demonstrated broad-spectrum cytotoxic effects, inhibiting breast cancer cells (MCF-7) by 85%±9%, and lung cancer cells (A549) by 93%±9%. Additionally, the isolates showed notable antibacterial and antifungal activities, further highlighting their therapeutic potential. Particularly, *Acronium* strains isolated from the Red Sea exhibited superior bioactivities compared to those from other locations. These findings demonstrate the biomedical significance of *Acronium* species and the potential of marine fungi from extreme environments as sources of novel bioactive compounds.²⁶

Acrocalymma sp

Acrocalymma sp., including *A. africana* and *A. medicaginis*, was isolated from the coasts of the Arabian Gulf and the Red Sea.²⁶ The isolates demonstrated significant cytotoxic and antioxidant activities. *A. africana* inhibited the proliferation of skin cancer cells (A431) by 65% and liver cancer cells (HepG2) by 70%, while *A. medicaginis* showed 52% inhibition of breast cancer cells (MCF-7) and 66% inhibition of liver cancer cells (HepG2). Both species exhibited strong antioxidant properties, with DPPH scavenging activities of 83% and 86%, respectively. These findings indicate the potential of *A. medicaginis* as a promising candidate for further investigation.

Aspergillus oryzae

Aspergillus oryzae is another marine fungus isolated from Red Sea sediment. It was found at a depth of 50 meters near Jeddah, Saudi Arabia, and cultivated for four weeks on a solid rice medium.²⁸ This cultivation yielded asporychalasin, a novel bioactive cytochalasin compound with a distinctive 6/6/11 skeleton. Researchers found asporychalasin as the primary compound as well as other known CYTOCHALASINS but focused on its unique structure and biological features. Asporychalasin exhibited significant cytotoxic activity, with IC₅₀ values of 0.3 µg/mL for A549, 0.2 µg/mL for HepG2, and 0.4 µg/mL for MCF-7 compared to doxorubicin-treated cells, used as the positive control. Cell viability was expressed as a percentage of mean absorbance in treated samples compared to control samples. The mechanisms of action of the bioactive compound involved disruption of actin polymerization, impairing cytokinesis, and inducing the formation of multinucleated cancer cells. These outcomes highlight the potential of asporychalasin as an anticancer agent.

Marine Fungi with Anticancer Activity

Marine fungi represent a remarkable source of bioactive secondary metabolites with potential therapeutic applications, including anticancer activity as summarized in (Table 1). These fungi thrive in unique and often extreme marine environments, enabling them to produce structurally diverse and biologically potent compounds. Recent studies have highlighted various marine fungal species capable of synthesizing metabolites with significant cytotoxic effects against a broad range of cancer cell lines. (Table 1) below provides a summary of key marine fungi, their bioactive metabolites, and the corresponding anticancer activities reported in the literature. This compilation emphasizes their promise as a resource for drug discovery and development in oncology.

Table 1 Summarizing the Marine Fungi with Anticancer Activity

Fungus	Metabolites	Source	Cell Lines	IC ₅₀ or GI ₅₀ Concentration	Mechanism of Action	Reference
<i>Aspergillus oryzae</i>	Asporychalasin cytochalasan	Isolated from the Red Sea	HeLa, HUVEC	IC ₅₀ : 0.3 µg/mL (A549); 0.2 µg/mL (HepG2); 0.4 µg/mL (MCF-7)	Disruption of actin polymerization	[29]
<i>Aspergillus neoniger</i> A	Asperazine, Asperazine A	Ficus carica from Wadi Fatima, Makkah	HeLa, HUVEC, K-562	CC ₅₀ : 6.2 µg/mL (HeLa); GI ₅₀ : 5.9 µg/mL (K-562); 4.8 µg/mL (HUVEC)	Inhibition of cancer cell growth	[30]
<i>Acremonium</i>	Gliotoxin and acremonamide	Arabian Gulf and Red Sea coasts	A549, A431, MCF-7	MCF-7: 85%; A549: 93%; A431: 98%	Inhibition of cancer cell growth	[28]
<i>Acrocalymma</i>	No specific secondary metabolites explicitly identified	Arabian Gulf and Red Sea coasts	A431, MCF-7, HepG2	A431: 65%; HepG2: 70%; MCF-7: 52%	Inhibition of cancer cell growth	[28]
<i>Aspergillus flavus</i>	Gregatin B, Pulvinulin	Sabkha Marsh, Jeddah	HepG2, HCT8, HCT116, MDA-MB-231, KAIMRC1, KAIMRC2	IC ₅₀ : 15.63–38.43 µg/mL	Inhibition of cancer cell growth	[31]
<i>Aspergillus niger</i>	Fonsecin B, Funalenone, Rubrofusarin, Aurasperone E, Aurasperone D, Nigerone, αβ-dehydrocurvularin	Sabkha Marsh, Jeddah	HepG2, HCT8, HCT116, MDA-MB-231, KAIMRC1, KAIMRC2	IC ₅₀ : 91.06–615.4 µg/mL	Inhibition of cancer cell growth	[31]
<i>Penicillium</i> sp. RO-11	Emodin (Compound 4), Austinol (Compound 3)	Ghamiqa Hot Springs, Makkah	HTB-176	IC ₅₀ : 2 ± 7.6 µM (Emodin); IC ₅₀ : 10 ± 3.92 µM (Austinol)	Inhibition of cancer cell growth	[32]

Notes: The following abbreviations are used in the table above: IC₅₀ (50% inhibitory concentration), GI₅₀ (50% growth inhibition concentration), and CC₅₀ (50% cytotoxic concentration). Cell lines include HeLa (human immortal cervical cancer cells), HUVEC (human umbilical vein endothelial cells), A549 (lung carcinoma cells), HepG2 (hepatoma cells), MCF-7 (breast carcinoma cells), A431 (skin carcinoma cells), HCT8 and HCT116 (colorectal adenocarcinoma cells), MDA-MB-231 (drug-resistant metastatic breast carcinoma cells), KAIMRC1 (epithelial-like breast carcinoma cells), KAIMRC2 (triple-negative breast carcinoma cells), K-562 (chronic myelogenous leukemia cells), and HTB-176 (human lymphoma cell line). Concentrations are reported in µg/mL (micrograms per milliliter) and µM (micromolar).

Terrestrial Fungi Extracted in Saudi Arabia

Fusarium venenatum

Fusarium venenatum, as reported by,³¹ was isolated in Almuzahimiyah, Saudi Arabia, and demonstrated notable anti-proliferative activity against breast and colorectal cancer cell lines.³¹ Among the breast cancer cell lines tested, *F. venenatum* exhibited a lower IC₅₀ value of 12.52 µg/mL against the drug-resistant metastatic breast cancer cell line (MDA-MB-231). In colorectal cancer cell lines, *F. venenatum* showed potent activity, particularly against the HCT8 cell line, with an IC₅₀ of 0.3779 µg/mL. This value was comparable to the IC₅₀ of the positive control Mitoxantrone (0.32 µg/mL). However, the activity against the HCT116 colorectal cancer cell line was moderate in comparison. These findings suggest that *F. venenatum* possesses promising anti-cancer properties.

Chaetomium globosum

Chaetomium globosum, isolated in Tabuk, Saudi Arabia, exhibited differential anti-proliferative activity against various cancer cell lines. When tested against the estrogen receptor (ER)-positive, progesterone receptor-positive, and HER2-negative breast cancer cell line (MCF-7), it showed minimal activity with an IC₅₀ of 335.6 µg/mL. In contrast, significant activity was observed against the drug-resistant metastatic breast cancer cell line (MDA-MB-231) and the epithelial-like breast carcinoma cell line (KAIMRC1), with IC₅₀ values of 23.61 µg/mL and 75.12 µg/mL, respectively. The most potent effect was noted against the colorectal cancer cell line HCT8, where *Chaetomium globosum* demonstrated strong anti-proliferative activity, achieving an IC₅₀ of 8.7 µg/mL. These results highlight the potential of *Chaetomium globosum* as a source of bioactive compounds for targeting specific cancer types, particularly metastatic breast cancer and colorectal cancer.

Bipolaris sorokiniana

Bipolaris sorokiniana, isolated in Al Qasab, Saudi Arabia, displayed selective anti-proliferative activity against certain cancer cell lines.³¹ The crude extract of *Bipolaris sorokiniana* showed no activity against estrogen receptor (ER)-positive, progesterone receptor-positive, and HER2-negative breast cancer cells (MCF-7) or epithelial-like breast carcinoma cells (KAIMRC1). However, the extract demonstrated modest activity against the human drug-resistant metastatic breast cancer cell line (MDA-MB-231), with an IC₅₀ of 39.93 µg/mL. Furthermore, it exhibited moderate anti-proliferative activity against the colorectal cancer cell line HCT116, achieving an IC₅₀ of 18.97 µg/mL. These findings suggest that *Bipolaris sorokiniana* may hold potential for further research as a source of anticancer compounds, particularly for colorectal and drug-resistant metastatic breast cancers.

Aspergillus sydowii

Aspergillus is considered an important medically fungal genus, with *A. fumigatus*, *A. flavus*, and *A. terreus* being frequently identified as etiological agents of infection.³² *A. sydowii* is an opportunistic non-dermatophytic filamentous fungus that has been linked to multiple diseases such as skin infection (onychomycosis), keratitis, and peritonitis.³³ A research team identified the chemical structures of secondary metabolites produced by *Aspergillus sydowii*, as illustrated in (Figure 3). The fungus was isolated from soil samples collected in Rabigh City, located in the Makkah region of Saudi Arabia. Its anticancer potential was evaluated against several cancer cell lines, including those derived from breast, liver, and colorectal cancers. Notably, the study also incorporated two newly developed, Saudi-specific breast cancer cell lines—KAIMRC1 and KAIMRC2—designed to better represent the local population. *A. sydowii* demonstrated excellent anticancer activity in all tested cell lines showing IC₅₀ values of 48.56 for the epithelial-like breast carcinoma cells KAIMRC1, 68.33 for and the triple-negative breast carcinoma cells KAIMRC2, 27.38 for human drug-resistant metastatic breast cancer cell line MDA-MB-231, 121.7 for hepatoma cell line HepG2, 134.5 for colorectal cancer cell lines HCT8, and 55.25 for colorectal cancer cell lines HCT116.³³

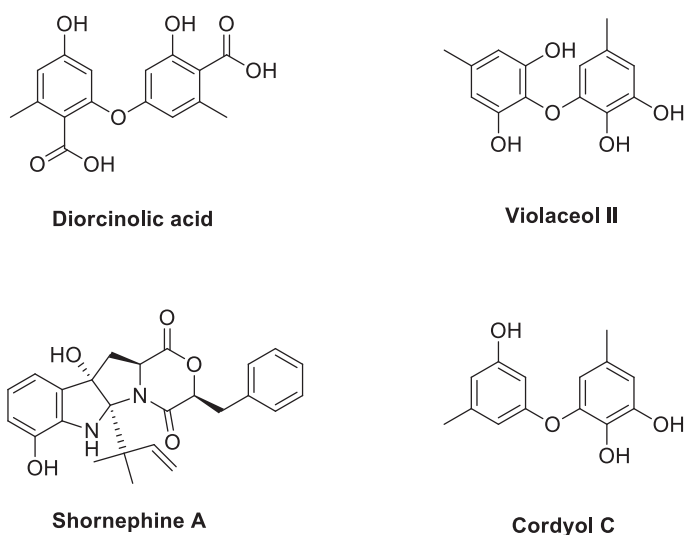


Figure 3 Chemical structures of secondary metabolites identified in *Aspergillus sydowii*.

Aspergillus neoniger

The fig tree (*Ficus carica* L.), belonging to the Moraceae family, has been widely recognized in traditional medicine for its therapeutic potential. It has been reported to alleviate various conditions, including gastrointestinal, cardiovascular, respiratory, and ulcerative disease.³⁴ The leaves of *F. carica* have demonstrated benefits for gastrointestinal disorders, respiratory illnesses, skin ailments, cardiovascular conditions, hemorrhoids, diabetes, ulcers, and the dissolution of blood clots caused by injuries. A study identified a total of 126 chemical constituents in *F. carica* leaves, and found their anticancer, antioxidant, antidiabetic, anticholinesterase, anti-inflammatory, hepatoprotective, anti-Herpes simplex virus type 1 (anti-HSV-1), antibacterial, and renoprotective properties.³⁵ These findings highlight the diverse pharmacological potential of *F. carica*.

Aspergillus neoniger was isolated from *Ficus carica*, a plant collected from Wadi Fatima, Makkah, Saudi Arabia.³⁶ The extraction process yielded two compounds, Asperazine and Asperazine A. The extract from *A. neoniger* cultivated in MPG medium demonstrated strong cytotoxic effects against HeLa cells ($CC_{50} = 6.2 \mu\text{g/mL}$) and antiproliferative effects against K-562 and HUVEC cell lines ($GI_{50} = 5.9$ and $4.8 \mu\text{g/mL}$, respectively). The anticancer properties of these isolates were evaluated using Human immortal cervical cancer cells (HeLa), Human umbilical vein endothelial cells (HUVEC), and human immortalized myelogenous leukemia cells (K-562). Asperazine exhibited a CC_{50} value of $19.2 \mu\text{g/mL}$ against HeLa cells, with GI_{50} values of 31.4 and $24.6 \mu\text{g/mL}$ against HUVEC and K-562 cells, respectively. Asperazine A showed moderate cytotoxic activity against HeLa cells ($CC_{50} = 34.4 \mu\text{g/mL}$) and weak cytostatic activity against HUVEC and K-562 cells, with GI_{50} values of 40.5 and $50 \mu\text{g/mL}$, respectively. These findings highlight the potential of *Aspergillus neoniger* A and its metabolites as candidates for anticancer therapies.

Aspergillus flavus

The Sabkha desert sites in Saudi Arabia present extreme conditions such as high salinity, neutral pH, and variable moisture levels, making them seemingly inhospitable for many organisms. Despite these harsh conditions, recent studies revealed the exceptional adaptability of diverse fungal species in the Sabkha environment, demonstrating their capacity to endure extreme environmental stresses.^{29,37} One such fungus, *Aspergillus flavus*, was isolated from the Sabkha marsh near Jeddah, Saudi Arabia, using dilution and blotter methods and subsequently incubated at $25 \pm 2^\circ\text{C}$ for a week. The pure cultures were maintained on potato dextrose agar and identified for further analysis. The cytotoxic potential of *Aspergillus flavus* was evaluated using an MTT Cell Viability Assay with a 48-hour incubation period. The IC_{50} values were determined for six cancer cell lines: HepG2, HCT8, HCT116, MDA-MB-231, KAIMRC1, and KAIMRC2, ranging from $15.63 \mu\text{g/mL}$ to $38.43 \mu\text{g/mL}$. Among the metabolites identified, Gregatin B and Pulvinulin A exhibited the highest

bioactivity, with Pa values of 0.902 and 0.880, respectively. Notably, the most significant effects were observed in the KAIMRC1, KAIMRC2, and MDA-MB-231 cell lines, indicating the potential of *Aspergillus flavus* metabolites in biomedical applications.

Aspergillus niger

A. niger was extracted from the Sabkha marsh, Jeddah, Saudi Arabia.²⁹ The sample was isolated using dilution and blotter techniques and was then incubated at 25 ± 2 °C for one week. The pure samples were stored in potato dextrose agar and identified. An MTT Cell Viability Assay with a 48-hour incubation period was used to assess the IC₅₀ on Six different cell lines, which consisted of HepG2, HCT8, HCT116, MDA-MB-231, KAIMRC1, and KAIMRC2. The IC₅₀ of *Aspergillus Niger* ranged from 91.06 µg/ml to 615.4µg/ml and had pa values ranging from 0.709 to 0.854.

Penicillium rubens

Endophytes are microorganisms residing within plant tissues in a symbiotic relationship, providing mutual benefits without causing any visible signs of disease.³⁸ These microorganisms have been found to produce bioactive compounds that act like those synthesized by their host plants during their mutualistic interactions.¹ Since the discovery of taxol from *T. andreanae*, endophytic fungi have gained increasing recognition as valuable sources of bioactive compounds. Numerous metabolites derived from endophytic fungi with potential applications in breast cancer treatment have been identified, and researchers continue to investigate their molecular mechanisms of action to explore their biological activity. Additionally, these endophytes are capable of synthesizing unique secondary metabolites with novel structures and, in some cases, hybrid chemical scaffolds.³⁹

Endophytic fungi were isolated from *Avicennia marina* mangroves in Jazan, Saudi Arabia, along the Red Sea. Among the isolates, *Aspergillus niger* and *Penicillium rubens* showed the highest isolation frequency (80%), relative density (12.5%), and antimicrobial activity. *P. rubens* demonstrated superior antimicrobial and anticancer activities compared to *A. niger* and *A. alternata*, confirmed via ITS rRNA gene sequencing. GC-MS analysis of *P. rubens* filtrate revealed compounds such as acetic acid ethyl ester, *N*-(4,6-Dimethyl-2-pyrimidinyl)-4-(4-nitrobenzylideneamino) benzenesulfonamide, 1,2-benzenedicarboxylic acid, octadecanoic acid and hexadecanoic acid. Unlike *A. alternata* and *A. niger*, *P. rubens* extract exhibited negligible cytotoxicity against normal WI-38 cells and inhibited prostate cancer (PC-3) proliferation with 75.91% and 76.2% mortality at 200 µg/mL and 400 µg/mL, respectively.¹⁷

Pulicaria undulata

Pulicaria undulata, found in central regions of Saudi Arabia, was evaluated for its anticancer potential using a water-ethanol extract.⁴⁰ The extract was tested against normal human fibroblasts and cancer cell lines, including estrogen receptor (ER)-positive, progesterone receptor-positive, pancreatic carcinoma cells (PANC-1, and HER2-negative breast cancer cells (MCF-7), and myelogenous leukemia cells (K562). Concentrations ranging from 6.25 µg/mL to 1000 µg/mL were applied and showed a dose-dependent effect on cell viability. Among the tested cell lines, MCF-7 exhibited the highest inhibition rates, ranging from $39.09 \pm 2.44\%$ to $104.87 \pm 2.74\%$ as the dose increased, followed by K562 cells ($44.31 \pm 0.65\%$ to $67.35 \pm 2.11\%$) and PANC-1 cells ($55.14 \pm 1.75\%$ to $95.75 \pm 1.8\%$). The extract demonstrated significant cytotoxic activity, with the lowest IC₅₀ value observed in MCF-7 cells (519.2 µg/mL), followed by K562 (1212 µg/mL) and PANC-1 (1535 µg/mL). In contrast, the IC₅₀ value for normal fibroblast cells was significantly higher at 4048 µg/mL. This indicates selective cytotoxicity towards cancer cells and suggests the potential of *P. undulata* extract as a selective anticancer agent.

Preussia africana

P. africana is an endophytic fungus isolated from *Aloe vera* collected in the Asir desert, Saudi Arabia. It was identified through sequence analysis of the ITS1, ITS4, and 5.8S internal spacer regions.¹⁸ The crude extract of *P. africana* exhibited notable bioactivities, including potent antioxidant properties with an 87% DPPH scavenging rate at a concentration of 500 µg/mL. It also showed significant wound-healing activity, achieving 42.6% healing at 48 hours with a 100 µg/mL concentration. Furthermore, the extract demonstrated broad-spectrum anticancer activity against

multiple cancer cell lines, such as MCF-7, HepG2, A549, HeLa, LN-229, and A-431, and also against the kidney cell line HEK 293T, at a concentration of 50 µg/mL. These findings highlight the therapeutic potential of *P. africana* in addressing severe medical challenges. The isolation and characterization of *P. africana* from *Aloe vera* in the Asir desert highlight its promising antioxidant, wound-healing, and anticancer properties.¹⁸

Penicillium sp. RO-11

Thermophilic fungi are distinct eukaryotic organisms capable of surviving at elevated temperatures ranging from 45 to 60°. ^{41,42} These fungi are prevalent in various composting systems and extreme environments such as hydrothermal vents, hot springs, and volcanic regions. A key representative of this group, the genus *Thermomyces*, is phylogenetically related to mesophilic genera like *Aspergillus* and *Penicillium*, although it has significantly reduced genome sizes. This unique adaptation enables thermophilic fungi to endure extreme heat while producing novel bioactive secondary metabolites.⁴³ Temperature plays a significant role in influencing the structural and functional properties of biomolecules produced by thermophilic fungi, as well as preserving the integrity of their cellular components. These biomolecules have attracted considerable interest from chemists and biotechnologists for their potential applications in natural product discovery and biotechnology.^{43,44} One of the most abundant fungal genera, *Penicillium*, includes over 300 recognized species found in diverse habitats, including terrestrial, marine, and extremophilic regions. Since the discovery of penicillin G from *P. notatum*, *Penicillium* has been recognized for its ability to produce numerous bioactive secondary metabolites, highlighting its potential in natural product development.⁴⁵

In the search for novel bioactive metabolites from extremophilic fungi, Orfali et al isolated *Penicillium sp. RO-11* from sediment samples collected at the Ghamiqa hot springs, 180 km south of Makkah, Saudi Arabia. Cultivation of *Penicillium sp.* on a solid rice medium yielded two novel compounds: 3-(furan-12-carboxylic acid)-6-(methoxycarbonyl)-4-hydroxy-4-methyl-4,5-dihydro-2H-pyran (Compound 1) and 3 α -methyl-7-hydroxy-5-carboxylic acid methyl ester-1-indanone (Compound 2). Additionally, three known metabolites—austinol (Compound 3), emodin (Compound 4), and 2-methyl-penicinoline (Compound 5)—were identified. The structures of the newly identified compounds were assessed through comprehensive spectroscopic analyses, including one-dimensional and two-dimensional nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry. The cytotoxic potential of these metabolites was evaluated against the HTB-176 human lymphoma cell line using the MTT assay. Among the isolated compounds, emodin (Compound 4) exhibited the strongest anticancer activity with an IC₅₀ value of 2 ± 7.6 µM. Austinol (Compound 3) showed moderate cytotoxicity, with an IC₅₀ value of 10 ± 3.92 µM, while Compound 2 displayed weaker activity, with an IC₅₀ value of 22 ± 2.94 µM. The remaining compounds, Compound 1 and Compound 5, were inactive in this assay. These findings highlight the potential of emodin as an anticancer agent among the metabolites derived from *Penicillium sp. RO-11*, further indicating the potential of extremophilic fungi in natural product-based drug discovery.⁴⁵

Terrestrial Fungi with Anticancer Activity

Terrestrial fungi are prolific producers of diverse secondary metabolites, many of which exhibit promising anticancer properties as listed below in (Table 2). Found in soil, plants, and other terrestrial ecosystems, these fungi synthesize bioactive compounds that target various cancer cell types through distinct mechanisms, such as inducing apoptosis, inhibiting cell proliferation, and disrupting tumor angiogenesis. The unique chemical diversity of these metabolites makes terrestrial fungi a valuable resource for the discovery of novel anticancer agents. (Table 2) below highlights notable terrestrial fungal species, their active metabolites, and the specific anticancer activities documented in recent studies, showcasing their potential for therapeutic development.

In support of these findings, Figure 4 presents a comprehensive heatmap analysis of IC₅₀ values for various fungal metabolites tested across multiple cancer cell lines. The heatmap visually illustrates the differential cytotoxic potency of these compounds, with darker green shades indicating stronger anticancer activity (lower IC₅₀ values) and red shades representing weaker effects (higher IC₅₀ values). Notably, compounds derived from *Fusarium venenatum*, and *Chaetomium globosum* displayed strong cytotoxic profiles, particularly against colorectal (HCT8) and triple-negative breast cancer cell lines (MDA-MB-231). The clear stratification of potency across cell lines in the heatmap further emphasizes the selective efficacy of certain fungal species and supports their prioritization for downstream drug

Table 2 Terrestrial Fungi with Anticancer Activity

Fungal Species	Source (Location in Saudi Arabia)	Active Metabolites	Tested Cell Lines	Potency (IC50/GI50)	Mechanism	Reference
Fusarium venenatum	Soil (Almuzahimiyah)	Ethyl acetate crude extracts	MCF-7, MDA-MB-231, KAIMRC1, KAIMRC2, HCT8, HCT116	12.52 µg/mL (MDA-MB-231)	Growth inhibition	[46]
Chaetomium globosum	Soil (Tabuk)	Ethyl acetate crude extracts	MCF-7, MDA-MB-231, KAIMRC1, KAIMRC2, HCT8, HCT116	8.7 µg/mL (HCT8)	Growth inhibition	[46]
Aspergillus sydowii	Soil (Makkah)	Diornicolic acid, β-d-glucopyranosyl Aspergillusene A, Violaceol II, Cordyol C, etc.	MDA-MB-231, KAIMRC1, KAIMRC2, HCT8, HCT116, HepG2	27.38 µg/mL (MDA-MB-231)	Growth inhibition	[39]
Penicillium rubens	Mangrove plants (Jazan)	Acetic acid ethyl ester, Hexadecanoic acid, Octadecanoic acid, etc.	PC-3, WI-38	24.09% viability at 200 µg/mL (PC-3)	Growth inhibition	[14]
Preussia africana	Asir Desert	Unspecified metabolites	HepG2, HeLa, A549, MCF-7, A-431, LN-229, HEK 293T	78% activity at 50 µg/mL (HeLa)	Growth inhibition	[15]
Alternaria tenuissima	Soil (Ha'il)	Unspecified metabolites	HepG2, WST-38	IC50: 0.52 mM (43.33% viability)	Growth inhibition	[47]

Abbreviations IC50, half-maximal inhibitory concentration; GI50, 50% growth inhibition; MCF-7, breast adenocarcinoma; MDA-MB-231, triple-negative breast cancer; HCT8/HCT116, colorectal carcinoma; KAIMRC1/KAIMRC2, King Abdullah International Medical Research Center cell lines; HepG2, liver cancer; PC-3, prostate cancer; WI-38, normal lung fibroblasts; PANC-1, pancreatic cancer; K562, leukaemia cell lines; HeLa, cervical cancer; A549, lung adenocarcinoma; A-431, skin carcinoma; LN-229, glioblastoma; HEK 293T, embryonic kidney cells.

development. Additionally, the clustering of potent responses across multiple cell lines for specific extracts suggests the presence of broad-spectrum bioactive metabolites, warranting further mechanistic investigation and in vivo validation.

Discussion

The present systematic review explores the anticancer potential of fungi from diverse ecosystems in Saudi Arabia, underscoring their valuable contributions to cancer drug discovery. The IC₅₀ values reported for the fungal metabolites tested against various cancer cell lines exhibit a considerable range, extending from as low as 0.2 µg/mL to over 600 µg/mL. This broad spectrum reflects the differing levels of potency among the compounds.

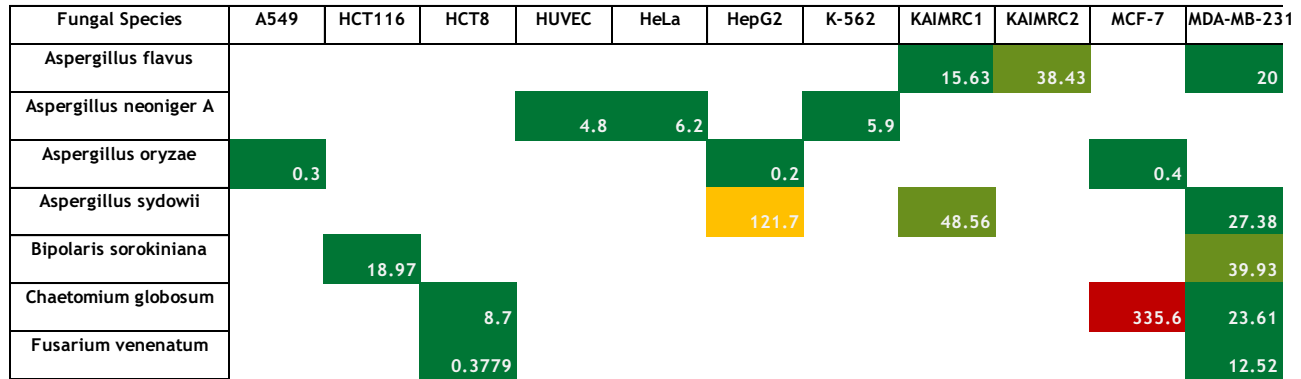


Figure 4 Heatmap of IC₅₀ values for the fungal metabolites tested against various cancer cell lines. Lower IC₅₀ values (darker green) indicate higher anticancer potency while higher IC₅₀ (red) indicate weak anticancer potency.

HepG2 and MCF-7 cell lines were most used possibly due to their generalizability on the local population and being accessible to researchers. Notably, *Penicillium* sp. RO-11, isolated from the Ghamiqa Hot Springs near Makkah, exhibited the most potent anticancer activity. Its secondary metabolite, emodin, demonstrated a strong cytotoxic effect with an IC_{50} of $2 \pm 7.6 \mu M$ against HCT116 cells, positioning it as the most effective compound among the fungal metabolites studied. For context, the clinically used anticancer drug paclitaxel typically shows IC_{50} values ranging from 2.5 to $7.5 \mu M$ ⁴⁸ under similar in vitro conditions, highlighting the comparable potency of emodin and its promise as a natural lead compound. While Austinol showed moderate cytotoxicity with an IC_{50} value of $10 \pm 3.92 \mu M$. *Preussia africana*, collected from the central part of the Asir desert, also showed significant potential, achieving 78% activity against HeLa cells at 50 $\mu g/mL$, with comparable results across multiple cell lines, including Hep G2, A549, and MCF-7, indicating broad-spectrum anticancer activity. Additionally, *Alternaria tenuissima* AUMCI434, sourced from Al Shihiyah in Ha'il, demonstrated moderate activity against HepG cells, with an IC_{50} of 0.52 mM and a viability of 43.33%.

These findings align with the global efforts to identify selective and safer anticancer agents, emphasizing the significance of Saudi Arabia's fungal biodiversity. Although many studies have attempted to diversify their collection sites, many geographically diverse sites exist, such as the eastern region of the Kingdom of Saudi Arabia, specifically the Empty Quarter. As it is inhabitable and possesses great biodiversity⁴⁷ it could be a candidate for future exploration. Compared to studies in other regions, such as Southeast Asia and Europe, Saudi fungi stand out for their resilience in extreme environments, which may contribute to their unique metabolite profiles. For instance, fungi, such as *Aspergillus sydowii*, adapted to arid and saline conditions, produce metabolites that are effective against triple-negative breast cancer (MDA-MB-231). This adaptability mirrors findings from marine ecosystems globally, where extreme conditions drive the evolution of bioactive compounds with distinctive mechanisms of action.^{49–51} Such comparisons underscore the potential of Saudi Arabian fungi to fill gaps in the existing therapeutic pipelines, particularly for drug-resistant cancers.

Despite these important findings, several gaps need to be addressed. For example, many studies, have not evaluated the cytotoxicity of the identified compounds against normal human cell lines, Furthermore, the site of isolation was not accurately mentioned in certain studies, and none of the reviewed papers included in vivo models, which is a critical step in validating the clinical relevance of these metabolites. Mechanistic studies, such as exploring apoptotic pathways or immune modulation, exploring secondary metabolites, and testing their anti-cancer activity separately were largely absent, and many studies have focused on the same areas of sample collection, leaving behind a vast range of unexplored areas. Addressing these gaps is crucial to advancing the translational potential of these findings. Future research should prioritize building on these discoveries. In vivo Validation of fungal metabolites in animal models to assess their efficacy and safety in complex biological systems. Mechanistic insights include investigating the molecular pathways targeted by these metabolites, such as apoptosis, angiogenesis inhibition, and immune modulation. Advanced Analytical Techniques, employing genomics and bioinformatics to uncover biosynthetic pathways and optimize compound production. Synergistic Studies exploring combinations of fungal metabolites with existing chemotherapy agents to enhance efficacy and reduce resistance and studying the activity of the secondary metabolites separately to recognize the active metabolites are important for future drug development.

Conclusions

This review underscores the potential of fungal metabolites from the diverse ecosystems of Saudi Arabia as promising anti-cancer agents. The findings indicate that various fungal species exhibit selective cytotoxicity against multiple cancer cell lines while preserving the viability of normal cells. For instance, *Penicillium rubens* shows significant efficacy against prostate cancer, and *Pulicaria undulata* demonstrates broad-spectrum activity. However, notable gaps persist, including a lack of in vivo studies and limited clinical research. Additionally, many studies relied heavily on computational approaches (eg, molecular docking) without experimental validation, which hinders the advancement of this field. To propel further progress, future research should focus on in vivo validation of cytotoxicity and pharmacokinetics, mechanistic studies to elucidate cellular pathways targeted by fungal metabolites, and the use of omics technologies (genomics, proteomics, metabolomics) to uncover novel bioactive compounds. Exploring synergistic effects with conventional chemotherapeutic agents, conducting structure-activity relationship (SAR) analyses, and evaluating toxicological profiles in animal models are also recommended. Moreover, compounds such as emodin from *Penicillium* sp.

RO-11 exhibit potency comparable to existing chemotherapeutics, justifying further investigation in preclinical and clinical studies to advance their therapeutic applications.

Abbreviations

MDA-MB-231, Human drug-resistant metastatic breast carcinoma cells; KAIMRC1, Human epithelial-like breast carcinoma cells (Saudi-specific); KAIMRC2, Human triple-negative breast carcinoma cells (Saudi-specific); HCT8, Human colorectal adenocarcinoma cells; HCT116, Human colorectal adenocarcinoma cells; HepG2, Human hepatoma cells; WI-38, Normal human lung fibroblast cells; PC-3, Human prostate cancer cells; PANC-1, Human pancreatic carcinoma cells; K562, Human chronic myelogenous leukemia cells; HeLa, Human immortal cervical cancer cells; HUVEC, Human umbilical vein endothelial cells; A549, Human lung carcinoma cells; A431, Human skin carcinoma cells; HEK293T, Human embryonic kidney cells; HTB-176, Human lymphoma cell line; GI₅₀, 50% Growth Inhibition Concentration; IC₅₀, 50% Inhibitory Concentration; SP., Species; PDA, Potato Dextrose Agar; DPPH, 2,2-diphenyl-1-picrylhydrazyl (used in antioxidant assays); NMR, Nuclear Magnetic Resonance; GC-MS, Gas Chromatography–Mass Spectrometry; ITS, Internal Transcribed Spacer (used in fungal identification); ER, Estrogen Receptor; HER2, Human Epidermal Growth Factor Receptor 2; SAR, Structure-Activity Relationship.

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Disclosure

The authors declare that there is no conflict of interest.

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