Iraqi Journal of Cancer and Medical Genetics

# Anticancer Compounds from Fungi: Review

Dhurgham A. H. Alhasan[1] , Hawraa F. H. AL-abedi[2]

1 College of Veterinary Medicine, University of Thi-Qar
2 Laser and Photonics Research Center, University of Al-Hamdaniya, Al-Hamdaniya, Nineveh, Iraq.

## Abstract

After cardiovascular disease, cancer represents an important one of the causative agents leading to mortality. Therefore, it is considered as a world major problem in, cancer defined as a disease when cells have uncontrolled abnormal proliferation and division. This disease can overcome immune responses leading to destroy other cells. Different chemotherapies are used for treating cancer but only a few have satisfied results. Gene or protein delivering drugs are used to destroy the cancer cells. Concerning anti-cancer agents, fungi play an important role in producing these agents. Taxol, obtained from Taxomyces andreanae, is a typical example of the fungal anti-cancer drugs that it is used for treating cancers of the breast and ovaries. Other fungi can produce the anti-cancer compounds which are Alternaria tenuissima, Aspergillus flavus, Aspergillus fumigatus, Aspergillus oryzae, Fusarium fujikuroi, Fusarium oxysporum, Fusarium graminearum, Penicillium expansum, Pyrenophora triticirepentis, Rhizoctonia solani, and Trichophyton rubrum. That can be mini-review summarized a topic related to the anti-cancer products are obtained from fungi.

***Key Words:*** *Fungi, Cancer, Anti-cancer Compounds.*

## Introduction:

Fungi possess benefits and one of them is their metabolites were used in medical applications; however, not all fungi can give the benefits and there are fungal species that can cause diseases in humans and animals. the antibiotics and anticancer compounds belonging to the fungal secondary metabolites (SMs) which are controlled by the biosynthesis gene clusters (BGCs) (Tran et al., 2019). Additionally, many secondary metabolites of endophytic fungi resulted in activity against the cell lines of the tumors (Deeksha et al., 2016). For instance, Taxol, a diterpenoid derivative that gave anti-tcancer efficiency against cancers of the breast and ovary. This anticancer agent was isolated from Taxomyces andreanae, a fungal endophyte (Ashraf et al., 2020).Therefore, fungi have an important role in biotechnology including industrial scales that are given by using bioreactors and processes are available. Regarding fungal metabolites, fungi can also produce enzymes, organic acids, and other compounds that have potential uses (Hyde et al., 2018).

**Corresponding Address:**
**Hawraa F. H. AL-abedi**
Laser and Photonics Research Center, University of Al-Hamdaniya, Al-Hamdaniya, Nineveh, Iraq
Email: hawraafaisal@uohamdaniya.edu.iq

Filamentous fungal groups such as Aspergillus, Penicillium and Talaromyces species represent factories for giving antibacterial, antifungal drugs as well as extracting anticancer agents (Abdulkawi et al., 2019). This aspect makes fungi represent an important source for discovering natural products (Hyde et al., 2019). Contextually, irofulven, a semi-synthetic derivative of illudin S; extracted from Omphalotus illudens resulted in activities against a variety of cancers in the clinical trials such as the cancers of the brain, breast, colon, lungs, ovaries, pancreas, and sarcoma (Topka et al., 2018; Hyde et al., 2019). Other researchers studied the anticancer activities against breast cancer cell lines using of purified vinblastine of Nigrospora sphaerica mycelia (Ayob et al., 2017).

Members of the genus Penicillium are amongst the most investigated fungi by means of herbal products chemists and are viewed a primary supply for drug discovery, the natural extract of the fungus Penicillium sp. gave two new compounds, named penicillatides A and B , collectively with cyclo(d-Pro–l-Phe) (cyclo(R-Pro–S-Phe) and cyclo(R-Pro–R-Phe) The antiproliferative and cytotoxic activities of the compounds against three human cancer cell lines as well as their antimicrobial activity against several pathogens were evaluated. Compounds 2–4 displayed variable cytotoxic and antimicrobial activities (Diaa

and Abdulrahman, 2018). In the same context, Aspergillus parasiticus produces sequoiamonascin A appeared cytotoxic effects on several cell lines belonging to leukemia and melanoma. In addition, sequoiamonascin A exhibited activities against cancers of the breast, lungs, and central nervous system (Bladt et al., 2013).

Enzymatically, L-asparaginase was extracted from Aspergillus niger that exhibited effects against different cancer cell lines (Vala et al., 2018). This enzyme is used to treat acute clinical forms of leukemia in children (Munir et al., 2019). Furthermore, Penicillium rubens, remoted from a garden soil in Madurai district of Tamil Nadu, was once located to produce a highly promising anti-cancer metabolite. The percentage viabilities of HepG2, HeLa and MCF-7 most cancers cells treated with the bioactive fraction (P5) isolated from P. rubens, ranged between 40-50% after 96 h (Prerana and Varalakshmi et al., 2021). Concerning endophytic fungi, indole derivatives are the varioloid A and varioloid B exhibited cytotoxic effects on cancer cell lines of humans. The derivatives were given by Paecilomyces variotii, an endophytic fungus of marine- algae. In the same situation, Aspergillus ochraceus , marine algae-endophytic species, produced insulicolide A possesses anticancer activity (Deshmukh et al., 2018). Sclerotiorin produced by a Cephalotheca faveolata, an endophytic species, appeared anti-prolative results against cancer cell lines in which the compound encourages apoptosis of the colon cancer cells (Giridharan et al., 2012). In connection with the same context, ergoflavin had an antitumor activity that the compound was isolated from an endophytic fungus of Mimosops elengi , medicinal plant (Deshmukh et al., 2018). Therefore, endophytic fungi have an important role in producing compounds including anticancer agents (Uzma et al., 2018; Teixeira et al., 2019).Medicinal mushrooms have necessary health advantages and showcase a large spectrum of pharmacological activities, including antiallergic, antibacterial, antifungal, anti-inflammatory, antioxidative, antiviral, cytotoxic, immunomodulating, antidepressive, antihyperlipidemic, antidiabetic, digestive, hepatoprotective, neuroprotective, nephroprotective, osteoprotective, and hypotensive activities (Giuseppe et al., 2021).

**Types of Fungal Anti-Cancer Compounds**

**1- Aphidicolin**

Aphidicolin was extracted from Cephalosporium aphidicola, fungal species is currently named Akanthomyces muscarius, however; this anti-cancer compound is also given by Nigrospora sphaerica (Ayob et al., 2017). Chemical characterization of the compound is a form of the tetracyclic diterpene which has the capability of competing to bind on a position of DNA polymerase of α and δ besides ε enzymes. Aphidicolin was clinically tested but no interesting results (Ayob et al., 2017).

**2- Irofulven**

The chemical sturcture of irofulven is derivative of illudin S as semi-synthetic preparation that the illudin S is a toxin of Omphalotus illudens, Irofulven belongs to a household of anticancer compounds referred to as the acylfulvenes. Irofulven's mechanism of action involves apoptosis (programmed cell death) of most cancers cells. Phase two trials of Irofulven are being performed in refractory or recurrent advanced epithelial ovarian cancer, hormone-refractory prostate cancer, recurrent malignant glioma, and inoperable liver cancer. Ongoing phase 1 studies are evaluating aggregate chemotherapy. Side effects from Irofulven consist of low white blood cell and platelet counts, nausea, vomiting, fatigue, and visual disturbance (Topka et al., 2018).

**3- L-Asparaginase**

L-asparaginase (ASNase) was described as a hydrolase enzyme and has another name is L-asparagine amidohydrolase. This enzyme can convert asparagine into L-aspartic acid and ammonia through catalyzing and hydrolyzing processes (Paul and Tiwary, 2020). Therefore, L-asparaginase is used in clinical trials of cancer treatment where clinical action of this enzyme results in depending on different levels of metabolic pathways of normal and cancer cells. Scientists have reported several strains of fungi that can produce L-asparaginase that are Alternaria tenuissima, Aspergillus flavus, Aspergillus fumigatus, Aspergillus oryzae, Fusarium fujikuroi, Fusarium oxysporum, Fusarium graminearum, Penicillium expansum, Pyrenophora triticirepentis, Rhizoctonia solani, and Trichophyton rubrum (Paul and Tiwary, 2020).

**4- Anti-Cancer Polyketide Derivative Products**

Polyketides belong to the most valuable natural products, including diverse bioactive compounds, such as antibiotics, anticancer drugs, antifungal agents, immunosuppressants and others (Ewa and Wolfgang, 2018). Many enzymes participate in the biosynthesis of the polyketides that belong to non-reduced or partly reduced ones (Klejnstrup et al., 2012). An example of the compound is lovastatin that demonstrated apoptosis induction in some ovarian cancer cell lines at which IC50 values were reported in a range of 2-39 μM (Martirosyan et al., 2010). Concerning, Penicillium griseofulvum and Aspergillus parasiticus were reported to be producers for polyketide anti-cancer agents that the compounds of spiro ring products and sequoiamonascin were given by them (Stierle et al., 2003). Researchers showed that apoptosis induction of lung and breast cancer, as well as melanoma, were inhibited by simvastatin (Relja et al., 2010) at which encouraging findings resulted in using this drug for the treatment of cancer clinically (Osmak et al., 2012).

**5- Compounds of Anticancer Nitrogen-Containing Products**

Fungi can produce these compounds are nitrogen-containing natural products. Generally, the compounds represent types of formations that possess building blocks of amino acids that are often incorporated into the compounds of the complex heteroaromatic structures e.g., benzodiazepines, diketopiperazines, and quinazolines (Frisvad et al.,2004). Fungal endophytes are the most typically used endophytes for the isolation of quite a number distinctive kinds of bioactive molecules. These bioactive molecules can be used as antimicrobial, antibacterial and anticancer agents. Fungal endophytes like Taxomyces andreanae isolated from Yew plant have the conceivable to produce an anti-cancer compound referred to as Paclitaxel (Ejaz et al., 2020). Other specific fungal endophytic species produce a va-

riety of different sorts of anticancer compounds like camptothecin, podophyllotoxin, torreyanic acid, vincristine, and vinblastine. This evaluate is prepared to describe the established find out about of herbal bioactive molecules or secondary metabolites secreted by using fungal endophytes as novel sources of anticancer drugs. The major cause of this evaluation is to prepare the tremendous compound of the fungal endophytes for most cancers treatments (Ejaz et al., 2020).

**6- Derivatives of Anticancer Terpenoid Products**

Terpenes belong to the largest category of secondary metabolites and essentially consist of 5 carbon isoprene devices which are assembled to every different (many isoprene units) with the aid of hundreds of ways. Terpenes are easy hydrocarbons, whilst terpenoids are modified classification of terpenes with distinctive functional groups and oxidized methyl group moved or removed at various positions. Terpenoids are divided into monoterpenes, sesquiterpenes, diterpenes, sesterpenes, and triterpenes depending on its carbon devices. Most of the terpenoids with the variant in their structures are biologically active and are used global for the treatment of many diseases. Many terpenoids inhibited special human most cancers cells and are used as anticancer drugs such as Taxol and its derivatives (Shagufta and Areej, 2018).

**7- Taxol and Taxomyces andreanae are Typical Examples**

Endophytic fungi from Taxus spp. opened a new avenue for industrial Taxol manufacturing due to their speedy growth, value effectiveness, independence on climatic changes, feasibility of genetic manipulation. However, the anticipation of endophytic fungi for industrial Taxol manufacturing has been challenged by means of the loss of its productivity, due to the metabolic reprograming of cells, downregulating the expression of its encoding genes with subculturing and storage. Thus, the goals of this overview had been to (1) Nominate the endophytic fungal isolates with the Taxol producing efficiency from Taxaceae and Podocarpaceae; (2) Emphasize the distinct tactics such as molecular manipulation, cultural optimization, co-cultivation for bettering the Taxol productivities; (3) Accentuate the genome mining of the rate-limiting enzymes for fast screening the Taxol biosynthetic machinery; (4) Triggering the silenced rate-limiting genes and transcriptional elements to prompts the biosynthetic gene cluster of Taxol (Ashraf et al., 2020).

Following the National Cancer Institute (NCI) application of looking out for novel anticancer compounds in 1960, Taxol and camptothecin have been the first explored compounds with strong antiproliferative activity. Taxol has been clinically investigated by means of NCI medical trials in the following phases: Phase I (breast, liver, ovarian epithelial, lymphoma and childhood leukemia), Phase II (colon, head and neck, renal cell, prostate, small cell lung cancers, esophageal most cancers and melanoma) and Phase III (metastatic breast most cancers and ovarian epithelial cancer) (Ashraf et al., 2020).

**The current approaches for Taxol production are:**

1- Natural sources from the bark of T. brevifolia (most productive source), however, the yield of taxol based totally on this strategy was once ranged from 0.001–0.05%, consequently for producing of one gram purified Taxol it need about 8–10 kg of plant bark, which collected from about 4 to 5 plants (Malik et al.,2011)

2- Semisynthetic procedure with the aid of 10-decaetylbaccatin III intermediate from the needles of T. baccata is the modern method for taxol manufacturing however, the decrease yield of this intermediate, selectivity over undesirable byproducts, heterogeneity, reproducibility, in addition to the epigenetic and mutational changes of T. baccata are the current hurdles (El-Sayed et al., 2017).

3- Endophytic fungi from Taxus spp. opened a new avenue for industrial Taxol production due to their speedy growth, value effectiveness, independence on climatic changes and feasibility for genetic manipulation ( Ashraf et al., 2020).

The anti-cancer action of taxol involves microtubule stabilization at which obtrusion occurs to stop a division of cancer cells leading to make the cell proliferation being inhibited. This action occurs when taxol interferes with that cells and 10 result in binding to β subunit in the tubulin heterodimer structures of the cells leading to their cytotoxicity (Isah, 2015). Related to diterpene taxanes, they possess 11 different structural compounds resulting in a change in the shattering, rearranging original taxane core or the compounds is produced by the change in transannular C-C bonds within the core. Therefore, cyclotaxanes possess various kinds of transannular C-C bonds (Schneider et al., 2021). Because of several reasons such as small amounts of natural taxol source (Taxus brevifolia) because of its exploitation for producing taxol that peoples threat their yield of this shrubs; scientists have been investigated to get other sources for obtaining taxol and related compounds (Isah, 2015).

**Conclusion:**

This review summarizes the anticancer potential of fungal metabolites, highlighting the function of complete synthesis outlining the feasibility of modern synthetic methods that facilitate the improvement of fungal metabolites into drugs that may also grow to be a actual future perspective.

## References:


1. Abdulkawi Ali Al-Fakih and Wael Qasem Abdulgabbar Al-maqtri . Overview on antibacterial metabolites from terrestrial Aspergillus spp. Mycology Vols. 2019; 10(4). P 101- 209.
2. Ashraf S.A. El-Sayed.; Manal T. El-Sayed.; Amgad M. Rady.; Nabila Zein.; Gamal Enan.; Ahmed Shindia.; Sara El-Hefnawy.;Mahmoud Sitohy.; and Basel Sitohy. Exploiting the Biosynthetic Potency of Taxol from Fungal Endophytes of Conifers Plants; Genome Mining and Metabolic Manipulation. Molecules. 2020; 25(13): P 3000.
3. Ayob F.W.; Simarani K.; Abidin N.Z.; Mohamad, J. First report on a novel Nigrospora sphaerica isolated from Catharanthus roseus plant with anticarcinogenic properties. Microb. Biotech. 2017; 10(4): P 926–932.
4. Bladt T.T.; Frisvad J.C.; Knudsen P.B.; Larsen T.O. Anticancer and Antifungal Compounds from Aspergillus, Penicillium and Other Filamentous Fungi. Molecules. 2013; 18: P 11338-11376.
5. Deeksha Sharma.; Avijit Pramanik.; Pavan Kumar Agrawal-corresponding. Evaluation of bioactive secondary metabolites from endophytic fungus Pestalotiopsis neglecta BAB-5510 isolated from leaves of Cupressus torulosa D.Don. Biotech. 2016; 6(2): P 210.
6. Deshmukh S.K.; Prakash V.; Ranjan N. Marine fungi: A source of potential anticancer compounds. Front. Microbiol. 2018; 8: P 1-24.
7. Diaa T. A. Youssef and Abdulrahman M. Alahdal. Cytotoxic and Antimicrobial Compounds from the Marine-Derived Fungus, Penicillium Species. Molecules. 2018; 23(2): P 394.
8. Ewa Maria Musiol-Kroll and Wolfgang Wohlleben. Acyltransferases as Tools for Polyketide Synthase Engineering. Antibiotics (Basel). 2018; 7(3): P 62.
9. El-Sayed A.S.A.; Abdel-Ghany S.E.; Ali, G.S. Genome editing approaches: Manipulating of lovastatin and taxol synthesis of filamentous fungi by CRISPR/Cas9 system. Appl. Microbiol. Biotechnol. 2017; 101: P 3953–3976.
10. Frisvad J.C.; Smedsgaard J.; Larsen T.O.; Samson R.A. Mycotoxins, drugs and other extrolites produced by species in Penicillium subgenus Penicillium. Stud. Mycol.2004; 49: P 201–241.
11. Giridharan P.; Verekar S. A.; Khanna A.; Mishra P D.; Deshmukh, S.K. Anticancer activity of sclerotiorin, isolated from an endophytic fungus Cephalotheca faveolata Yaguchi, Nishim. and Udagawa. Indian. J. Exp.Biol. 2012; 50 (7): P 464-468.
12. Giuseppe Venturella.; Valeria Ferraro.; Fortunato Cirlincione.; Maria Letizia Gargano. Medicinal Mushrooms: Bioactive Compounds, Use, and Clinical Trials. Int J Mol Sci. 2021; 22(2): P 634.
13. Hyde K.D.; Chaiwan N.; Norphanphoun C.; Boonmee S. et al. Mycosphere notes 169-224 Article . Mycosphere. 2018; 9: P 271–430.
14. Hyde K.D.; Xu. J.; Rapior S.; Jeewon R.; Lumyong S. et al. The amazing potential of fungi: 50 ways we can exploit fungi industrially. Fung. Divers. 2019; 97: P 1–136.
15. Isah T. Natural sources of taxol. BJPR. 2015; 6(4): 214- 227.
16. Klejnstrup M.L.; Frandsen R.J.N.; Holm D.K.; Nielsen M.T.; Mortensen U.H.; Larsen T.O.; Nielsen J.B. (2012). Genetics of polyketide metabolism in Aspergillus nidulans. Metabolites. 2012; 2(1): P100–133.
17. Malik S.; Cusidó R.M.; Mirjalili M.H.; Moyano E.; Palazón J.; Bonfill M. Production of the anticancer drug taxol in Taxus baccata suspension cultures: A review. Process Biochem. 2011; 46: P 23–34.
18. Martirosyan A.; Clendening J.W.; Goard C.A.; Penn L.Z. (2010). Lovastatin induces apoptosis of ovarian cancer cells and synergizes with doxorubicin: potential therapeutic relevance. BMC Cancer. 2010; 10: P 103.
19. Ejaz M.; Javed S.; Hamza M.;Tabassum S.; AbubakarM.; Ullah I. Fungal endophytes are effective alternatives and novel sources of anticancer drugs. Punjab Univ. J. Zool. 2020; 35(1): P 13-24.
20. Munir N.; Zia M. A.; Sharif S.; Tahir I.M.; Jahangeer M.; Javed I.; Riaz M.; Sarwar M.U.; Akram M.; Ali Shah S.M. L-Asparaginase potential in acrylamide mitigation from foodstuff: a mini-review. Progr. Nutr. 2019; 21(3): P 498-506.
21. Paul V. and Tiwary B.N. An investigation on the acrylamide mitigation potential of l-asparaginase from Aspergillus terreus BV-C strain. Biocatal. Agric. Biotechnol. 2020; 27: P101677.
22. Prerana Venkatachalam and Varalakshmi Kilingar Nadumane. Modulation of Bax and Bcl-2 genes by secondary metabolites produced by Penicillium rubens JGIPR9 causes the apoptosis of cancer cell lines. Mycology. 2021; 12(2): P 69-81.
23. Relja B.; Meder F.; Wilhelm K.; Henrich D.; Marzi I.; Lehnert M. Simvastatin inhibits cell growth and induces apoptosis and G0/G1 cell cycle arrest in hepatic cancer cells. Int. J. Mol. Med. 2010; 26: P 735–741.
24. Schneider F.; Pan L.; Ottenbruch M.; List T.; Gaich,T. The chemistry of nonclassical taxane diterpene. Acc. Chem. Res. 2021; 54 (10): P 2347–2360.
25. Shagufta Perveen and Areej Al-Taweel. Introductory Chapter: Terpenes and Terpenoids. Books. 2018.
26. Stierle D.B.; Stierle A.A.; Bugni, T. Sequoiamonascins A–D: Novel anticancer metabolites isolated from a redwood endophyte. J. Org. Chem. 2003; 68: P 4966–4969.
27. Tran P.N.; Yen M.R.; Chiang C.Y.; Lin H.C.; Chen P.Y. Detecting and prioritizing biosynthetic gene clusters for bioactive compounds in bacteria and fungi. Appl. Microbiol. Biotechnol.2019; 103: P 3277–3287.
28. Teixeira T.R.; Santos G.S.D.; Armstrong L.; Colepicolo P.; Debonsi H.M. Antitumor potential of seaweed derived-endophytic fungi. Antibiotics ( Basel). 2019; 8 (4): P 205.
29. Topka S.; Khalil S.; Stanchina E.; Vijai J.; Offit K. Preclinical evaluation of enhanced irofulven antitumor activity in an ERCC3 mutant background by in vitro and in vivo tumor models. Cancer Research. 2018; 78: P 3258- 3258
30. Uzma F.; Mohan C.D.; Hashem A.; Konappa N.M.; Rangappa S et al. Endophytic fungi—alternative sources of cytotoxic compounds: A review. Front. Pharmacol. 2018; 9 (309): P 1- 37.
31. Vala, A.K.; Sachaniya, B.; Dudhagara, D. ;Panseriya, H.Z.; Gosai, H.; Rawal, R. and Dave, B.P. Characterization of L-asparaginase from marine-derived Aspergillus niger AKV-MKBU, its antiproliferative activity, and bench scale production using industrial waste. Int. J. Biolog.Macroml. 2018; 108: P 41-46.