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Repurposing Antifungal Drugs for Cancer Treatment: A Comprehensive Review of Mechanisms and Clinical Evidence

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ABSTRACT

Background and Objective: Cancer, as one of the most challenging diseases of the present era, has always required the discovery of novel therapeutic approaches. In recent years, extensive research has focused on repurposing existing drugs, including antifungal agents, for cancer treatment. The aim of this study is to provide a comprehensive review of the mechanisms and potential applications of antifungal drugs in cancer treatment.

Methods: In this review article, valid domestic and international databases, including PubMed, Web of Science, Google Scholar, and Scopus, were searched using the keywords "cancer," "fungal infection," "antifungal drugs," "drug repurposing," "apoptosis," and "cell cycle." Articles published up to June 2025 were reviewed. Duplicate articles, those without full text, or those irrelevant to the topic were excluded from the study.

Findings: Out of a total of 126 retrieved articles, 60 articles were selected for final review after initial screening and the removal of irrelevant or duplicate articles. The results showed that many antifungal drugs, in addition to their antifungal properties, exert significant anticancer effects through various mechanisms, such as inhibition of cell proliferation, induction of apoptosis and autophagy, reduction of angiogenesis, and regulation of cellular metabolism.

Conclusion: Based on the results of this study, almost all classes of antifungal drugs have demonstrated anticancer activity by targeting biological pathways shared between fungal and tumor cells, as well as through mechanisms independent of their primary target. However, further research is required to establish the efficacy of these drugs in the treatment of cancer patients.

Keywords: *Cancer, Fungal Infection, Antifungal Drugs, Drug Repurposing*.

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Introduction

Cancer, as one of the most complex and lethal diseases of the present era, has continually driven researchers to seek novel therapeutic approaches (1). Despite advances in diagnosis and treatment, drug resistance and the severe side effects of conventional therapies have made the need for new therapeutic agents essential (2, 3). Therefore, drug repurposing has emerged as an attractive strategy due to its potential to reduce the time and cost of drug development. In recent years, a close association has been demonstrated between fungal infections and the development and progression of certain cancers (4), creating new potential for cancer treatment (5).

Epidemiological studies indicate that individuals with certain fungal infections are at higher risk of developing some other types of cancer (4). Laboratory studies have shown that certain fungi, such as Malassezia and Candida, can directly damage healthy cells and transform them into cancerous cells (6). These findings underscore the significant role of the immune system in the development and progression of cancer, such that fungal infections may contribute to the growth and spread of cancer cells by weakening the immune system (7). Some antifungal drugs possess anticancer effects in addition to their antifungal properties. Their mechanisms include disruption of the cell membrane, inhibition of DNA and RNA synthesis enzymes, and enhancement of the antitumor immune response (8).

In light of these findings and the growing importance of drug repurposing in oncology, the present study was conducted with the aim of providing a comprehensive review of the repurposing of antifungal drugs in cancer treatment. This review examines the molecular mechanisms and clinical applications of these drugs in order to highlight their potential as novel therapeutic agents in the fight against cancer.

Methods

The present review study was conducted following approval by the Ethics Committee of Babol University of Medical Sciences (approval code: IR.MUBABOL.HRI.REC.1403.391), with the objective of collecting, analyzing, and summarizing the available information on the repurposing of antifungal drugs in cancer treatment. To identify relevant articles, searches were performed in valid electronic databases, including PubMed, Web of Science, Google Scholar, and Scopus. The keywords used in the search included the Persian and English terms cancer," "fungal infection," "antifungal drugs," "drug repurposing," "apoptosis," "cell cycle," "angiogenesis," and "cellular metabolism." Articles published up to the end of June 2025 were reviewed. Duplicate articles, review articles, articles lacking full text, and articles that did not directly address the relationship between antifungal drugs and cancer were excluded from the study. Following the initial search, all retrieved titles and abstracts were independently reviewed by two authors, and the findings were presented in a categorized manner with reference to credible sources.

Results

Overall, 126 relevant articles were retrieved through the defined search strategy. Following initial screening based on title and abstract, and the exclusion of duplicate articles (30 articles), articles lacking full text (15 articles), and irrelevant articles (21 articles), a total of 60 articles were selected for full-text review. The key findings were categorized according to the mechanism of action of antifungal drugs as follows (Figure 1). The various types of antifungal drugs investigated under in vivo and in vitro conditions for the treatment of various cancers, along with their mechanisms of action, were also examined (Table 1).

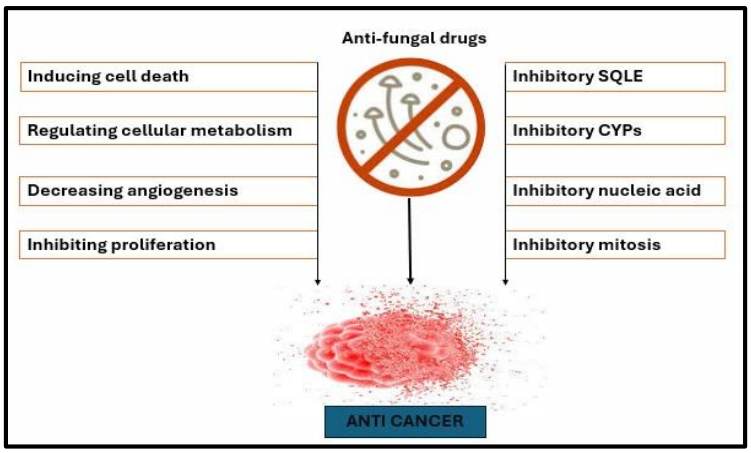


Figure 1. Summary of the mechanisms of action involved in the repurposing of antifungal drugs for the treatment of cancer

Table 1. Antifungal drugs repurposed for cancer treatment and their principal mechanisms of action (8)

Antifungal drug	Cancer type	Study type	Drug dose	Mechanism of action
Terbinafine	Hepatocellular carcinoma	In vitro / In vivo	0-50 µM / 80 mg/kg	SQLE inhibition
	Colorectal cancer	In vitro / In vivo	0-50 µM / 50 mg/kg	SQLE inhibition
	Promyelocytic leukemia	In vitro	0-30 µM	Induction of mitochondrial dysfunction and apoptosis
	Oral squamous cell carcinoma	In vitro	0-60 µM	Induction of G0/G1 cell cycle arrest
	Hepatic carcinoma	In vitro / In vivo	0-80 µM / 100 mg/kg	Regulation of AMPK-mTORC1 signaling
	Oral squamous cell carcinoma	In vitro	0-150 µg/µL	Suppression of Raf-MEK-ERK signaling
	Colon cancer	In vitro / In vivo	0-120 µM / 50 mg/kg	Induction of G0/G1 cell cycle arrest
Natamycin	Hepatocellular carcinoma	In vitro / In vivo	0-40 µM / 50 mg/kg	Induction of ROS accumulation and subsequent apoptosis
Itraconazole	Medulloblastoma and basal cell carcinoma	In vitro / In vivo	0-0.5 µM / 75 mg/kg	Hedgehog pathway inhibition
	Endometrial cancer	In vitro	0-10 µM	Hedgehog pathway inhibition
	Melanoma	In vitro / In vivo	0-4 µM / 0-100 mg/kg	Suppression of Hedgehog, Wnt, and PI3K/mTOR pathways
	Glioblastoma	In vitro / In vivo	0-4 µM / 75 mg/kg	Induction of autophagic cell death
	Endometrial cancer	In vitro	0-10 µM	Inhibition of AKT/mTOR signaling
	Cutaneous squamous cell carcinoma	In vitro / In vivo	0-4 µM / 0-80 mg/kg	Targeting the HMGCS1/ACSL4 axis

	Hepatocellular carcinoma	In vitro	0-8 µg/mL	Regulator of Wnt, PI3K/AKT/mTOR, and ROS pathways
	Colon cancer	In vitro / In vivo	0-10 µM / 75 mg/kg	Hedgehog pathway inhibition
	Oral squamous cell carcinoma	In vitro / In vivo	0-5 µM / 50 mg/kg	Hedgehog pathway inhibition
	Pancreatic cancer	In vitro	0-80 µM	Bak-1 activation
	Breast cancer	In vitro / In vivo	0-20 µg/mL / 30 mg/kg	Hedgehog pathway inhibition
	Gastric cancer	In vitro	0-10 µM	Hedgehog pathway inhibition
	Nasopharyngeal carcinoma	In vitro	0-20 nM	Ferroptosis inducer
	Lung cancer	In vitro / In vivo	0-3 µM / 100 mg/kg	Inhibition of angiogenesis and tumor growth
Ketoconazole	Colon and breast cancer	In vitro	0-30 µM	Induction of cell cycle arrest
	Colorectal and hepatocellular carcinoma	In vitro	0-20 µM	Induction of G0/G1 cell cycle arrest
	Hepatic carcinoma	In vitro / In vivo	0-20 µM / 50 mg/kg	Induction of mitophagy and apoptosis
	Glioblastoma	In vitro / In vivo	0-10 µM / 25 mg/kg	Targeting HK2
Miconazole	Colon carcinoma	In vitro / In vivo	0-50 µM / 50 mg/kg	Induction of G0/G1 cell cycle arrest and apoptosis
	Bladder cancer	In vitro	0-100 µM	Induction of apoptosis
	Osteosarcoma	In vitro	0-100 µM	Induction of increased intracellular Ca^{2+}
	Breast cancer	In vitro	0-50 µM	Induction of increased intracellular Ca^{2+}
	Lung cancer	In vitro / In vivo	0-20 µM / 50 mg/kg	Suppression of STAT3 activation
	Bladder cancer	In vitro	0-50 µM	Induction of apoptosis
Econazole	Lung cancer	In vitro / In vivo	0-20 µM / 50 mg/kg	Inhibition of PI3K activity and promotion of apoptosis
	Colon cancer	In vitro / In vivo	0-60 µM / 50 mg/kg	Induction of G0/G1 cell cycle arrest and apoptosis
	Gastric cancer	In vitro	0-20 µM	Induction of p53-dependent apoptosis
	Pancreatic cancer	In vitro / In vivo	0-40 µM / 50 mg/kg	Induction of autophagic arrest and apoptosis
Clotrimazole	Breast cancer	In vitro	0-100 µM	Induction of apoptosis and G1 arrest
	Lung, colon cancer, and melanoma	In vitro / In vivo	0-10 µM / 120 mg/kg	Depletion of intracellular Ca^{2+} stores
	Endometrial cancer	In vitro / In vivo	0-20 µM / 20 µM	Blockade of IKCa1 channels

	Lung carcinoma and colon adenocarcinoma	In vitro	0-50 µM	Reduction of glycolysis and survival
	Breast cancer	In vitro	0-50 µM	Disruption of glycolysis
	Breast cancer	In vitro	0-100 µM	Disruption of glycolysis
	Melanoma	In vitro	0-50 µM	Reduction of glycolysis and ATP levels
Sertaconazole	Lung cancer	In vitro / In vivo	0-40 µM / 75 mg/kg	Induction of proapoptotic autophagy
5-Fluorocytosine	Glioblastoma	In vivo	NA	Gene-directed enzyme prodrug therapy (GDEPT)
Griseofulvin	Ovarian cancer	In vitro	0-120 µM	Suppression of mitotic spindle microtubule dynamics
	Colorectal cancer	In vitro / In vivo	0-60 µM / 50 mg/kg	Induction of apoptosis and G2/M cell cycle arrest
GF-15	Colon cancer and multiple myeloma	In vitro / In vivo	0-1.25 µM / 100 mg/kg	Inhibition of centrosome clustering

Clinical Trials: Some antifungal drugs, particularly itraconazole and ketoconazole, have entered clinical trials for the treatment of various types of cancer and have shown promising results (Table 2).

Table 2. Antifungal drugs currently under clinical investigation for cancer treatment (8)

Antifungal drug	Cancer type	Clinical trial identifier	Main finding
Itraconazole	Basal cell carcinoma	NCT01108094 (Phase II)	Itraconazole reduced cell proliferation by up to 45% and Hedgehog pathway activity by up to 65%.
	Esophageal cancer	NCT02749513 (Phase I)	Itraconazole blocked HER2/AKT signaling.
	Lung cancer	NCT00769600 (Phase II)	Overall survival was longer in patients receiving itraconazole (median 32 months) compared with the control group (8 months).
	Lung cancer	NCT02157883 (Phase I)	Itraconazole can be administered concurrently with Osimertinib.
Ketoconazole	Prostate cancer	NCT00673127 (Phase II)	The response rate to ketoconazole, hydrocortisone, and dutasteride was at least comparable to previous studies of ketoconazole alone, while time to progression was significantly longer.
	Breast cancer	NCT00544804 (Phase I)	Ketoconazole was able to increase lapatinib exposure.
	Breast cancer	NCT00212082, NCT00212095 (Phase II)	Ketoconazole-modulated docetaxel led to reduced docetaxel clearance.
	Prostate cancer	NCT00460031 (Phase II)	The combination of ketoconazole and lenalidomide was well tolerated.

	Prostate cancer	NCT00298155 (Phase I)	The combination with ketoconazole showed a greater number of complete and near-complete responses compared with bicalutamide and dutasteride alone.
	Prostate cancer	NCT01199146 (Phase II)	Abiraterone showed moderate clinical efficacy in patients with prostate cancer previously treated with ketoconazole.
5-Fluorocytosine	Glioma	NCT02414165 (Phase I)	Toca 511 and Toca FC showed promising survival and excellent tolerability in recurrent high-grade glioma.
	Glioma	NCT01470794 (Phase I)	Toca 511 + Toca FC showed durable multi-year responses.

Mechanisms Involved in the Anticancer Role of Antifungal Drugs, Categorized According to Their Primary and Secondary Targets:

Squalene Epoxidase (SQLE) Targeting: Studies have demonstrated that squalene epoxidase (SQLE) is upregulated in cancers, and dysregulation of SQLE can result in disrupted cholesterol metabolism, which constitutes a key event in cancer dysregulation (8). SQLE catalyzes the epoxidation of squalene, which is subsequently converted to 2,3-oxidosqualene (9). The most common allylamine antifungal agents include naftifine, terbinafine, and butenafine, which have demonstrated considerable efficacy and safety in this context. In recent years, an association has been shown between cholesterol dysregulation and cancer progression in various malignancies, including kidney, breast, and colorectal cancer (CRC). In addition, statins possess preventive and therapeutic properties against cancer (10). SQLE promotes carcinogenesis through cholesterol ester and nicotinamide adenine dinucleotide phosphate ($NADP^+$), which epigenetically silences PTEN via the ROS-DNA methyltransferase A3 axis and stimulates the PTEN/PI3K/AKT/mTOR pathway (11). He et al. reported that SQLE is highly upregulated in colorectal cancer (12).

Targeting Cytochrome P450 Monooxygenase Family Members: CYP51 mediates the conversion of lanosterol to ergosterol by demethylating the 14α position, which is another essential step in ergosterol synthesis. Azoles are broad-spectrum drugs used in clinical applications and exert their inhibitory effect on CYP51 by interacting with the heme group (13). CYPs, owing to their function as metabolic enzymes, exert at least two important effects on cancer cells: they play a role in the conversion of procarcinogens into active carcinogenic compounds and in catalyzing antitumor drug reactions (14).

CYPs also play a role in the activation and inactivation of chemotherapeutic agents (8). Through CYP metabolism, inactive antitumor drugs are converted into cytotoxic compounds within cancer cells, and the CYP2 and CYP3 isoforms are the most common subfamilies responsible for catalyzing anticancer agents (14). Conversely, some CYPs are involved in the inactivation of antitumor agents, such that increased CYP expression in tumor tissue is positively associated with chemotherapy resistance, and inhibition of specific CYPs improves treatment response. CYPs may regulate cancer proliferation, invasion, angiogenesis, apoptosis, or differentiation as upstream molecules of signaling pathways in cancer, including MAPK, PI3K/Akt, and NF-κB. Ketoconazole is a broad-spectrum antifungal agent that has been identified as an inhibitor of 17α-hydroxylase/17,20-lyase (CYP17A1) and CYP3A4 (8).

Ketoconazole, itraconazole, and posaconazole inhibit CYP3A4 activity with varying potencies. CYP3A4 is responsible for the detoxification of various common antitumor drugs in clinical practice, including docetaxel, irinotecan, gefitinib, cisplatin, paclitaxel, tamoxifen, and vinorelbine. Overexpression of CYP3A4 limits chemotherapy response; therefore, reducing CYP3A4 expression may improve therapeutic

response. Consequently, ketoconazole is used in combination with standard therapies due to its function in catalyzing antitumor drugs into inactive derivatives. Results from several clinical studies indicate that ketoconazole may increase drug exposure or reduce the clearance of lapatinib, docetaxel, and irinotecan (15).

Targeting Nucleic Acids: 5-Fluorocytosine (5-FC), which is used for the treatment of infections caused by Candida and Cryptococcus, has recently been proposed as a basis for gene-directed enzyme prodrug therapy (GDEPT), which is characterized by the selective conversion of drugs into cytotoxic metabolites within malignant cells, leading to maximal concentrations of cytotoxic drugs in the tumor region and reduced toxicity in normal tissues (16). Recently, Toca 511 + 5-FC therapy has been ranked as an advanced therapy by the Food and Drug Administration (FDA), while the European Medicines Agency supports its use for the treatment of high-grade glioma. In addition, various clinical trials focusing on the CD/5-FC system based on novel targets, including APS001F and TG6002, are currently underway (17).

Targeting Mitosis: Griseofulvin is an antifungal agent that inhibits fungal growth by blocking mitosis. Since uncontrolled proliferation is a hallmark of cancer and mitosis is the most common method of cell division in the human body, drugs that target mitosis by suppressing microtubule dynamics, such as paclitaxel and Vinca alkaloids, are effective chemotherapeutic agents. Studies focusing on the anticancer activity of griseofulvin based on its inhibitory effect on mitosis and its low toxicity have attracted considerable attention (18). Yu et al. reported that griseofulvin inhibits colorectal cancer growth by inducing G2/M cell cycle arrest and apoptosis, and that griseofulvin exhibits synergistic effects with nocodazole, a classic microtubule inhibitor (19).

Inhibition of Cancer Cell Proliferation: Excessive proliferation is one of the most notable biological capabilities of cancer cells. Growth factors bind to cell surface ligands and activate intracellular kinases. A large number of studies indicate that certain antifungal drugs inhibit cancer cell proliferation by interfering with the cell cycle. Forgue-Lafitte et al. reported that ketoconazole suppresses cell proliferation and H3-thymidine incorporation in colon and breast cancer cells (20). Chen et al. also demonstrated that ketoconazole induces inhibition of cell growth and G0/G1 arrest in CRC and HCC (21). Miconazole also prevents the proliferation of human cancer cells through cell cycle arrest, induction of ROS production, and intracellular Ca^{2+} release (22). Recently, the Hedgehog (Hh) signaling pathway has emerged as a critical regulator in cancer cell proliferation. Aberrant hyperactivation of the Hh signaling pathway leads to carcinogenesis in various cells; therefore, its inhibitors have been proposed as therapeutic targets, including SMO and glioma-associated oncogene (GLI).

Apoptosis induction: Numerous antifungal drugs, such as terbinafine, natamycin, itraconazole, econazole, and miconazole, regulate apoptosis levels in cancer cells. Sobecks et al. reported that miconazole induces apoptosis in human T-cell leukemia cells (23). Terbinafine also possesses anticancer activity against promyelocytic leukemia cells through the induction of apoptosis. Other studies have reported that econazole also induces caspase-8-independent apoptosis in colon cancer cells and p53-dependent apoptosis in gastric cancer cells (24).

Reduction of Angiogenesis: Angiogenesis is primarily driven by growth factors secreted by tumor cells, including vascular endothelial growth factor-A (VEGF-A). Several studies have reported the anti-angiogenic effect of itraconazole, which is mediated through inhibition of the VEGF pathway, the basic fibroblast growth factor (bFGF) pathway, or the platelet-derived growth factor pathway. Aftab et al. reported the potential anti-angiogenic activity of itraconazole in non-small cell lung cancer (25). Terbinafine also possesses anti-angiogenic activities, such as cell cycle arrest and inhibition of vascular endothelial cell migration (26).

Regulation of Cellular Metabolism: Tumor cells independently regulate their metabolic pathways to meet the intense demands of bioenergetics and biosynthesis. The Warburg effect is a well-known phenomenon of cancer metabolic reprogramming. Tumor cells preferentially utilize aerobic glycolysis rather than oxidative phosphorylation, even in the presence of sufficient oxygen. Hexokinase is an essential enzyme involved in the glycolytic pathway and plays an important role in tumor growth. Given the importance of glycolysis in malignancies, inhibition of hexokinase represents a potential anticancer therapeutic strategy. Most studies on the antitumor properties of clotrimazole relate to its role in disrupting glycolysis (8).

Other studies have also reported that clotrimazole disrupts glycolysis in breast cancer and melanoma cells (27, 28). Existing research has focused on the repurposing of antifungal drugs in cancer, which exert their antitumor effects by modulating cancer hallmarks (29). Currently, with the increase in tumor molecular biology studies, this strategy will find broader application.

Discussion

Drug repurposing offers a promising approach owing to its reduction of associated time and costs and possesses the potential for more rapid entry into clinical applications. Today, the repurposing of existing drugs has become one of the most attractive strategies in the field of drug discovery—an approach that, by considerably reducing development time and costs, paves the way for the more rapid entry of well-known compounds into clinical practice (30). Early clinical successes, including reports of improved survival in patients with advanced prostate cancer following itraconazole administration (31) and the observation of the anti-angiogenic effects of this drug in preclinical models (32), promise a bright future for this field.

One of the most serious challenges is pharmacokinetic differences; that is, conventional antifungal doses are often insufficient to achieve effective concentrations in solid tumors, and conversely, dose escalation is associated with risks such as hepatotoxicity and serious drug interactions (33).

Overcoming these obstacles appears to require the application of creative strategies. The use of novel drug delivery systems, such as lipid and polymeric nanoparticles, which selectively direct the drug to tumor tissue and reduce its effect on healthy tissues, can significantly widen the therapeutic window (34). Another strategy is the design of combination regimens with conventional chemotherapeutic drugs—an approach that, while reducing the required dose, also decreases the likelihood of compensatory mechanisms and drug resistance. The present study emphasizes that antifungal drugs, beyond inhibiting fungal pathogens, possess considerable antitumor properties. Repurposing these drugs represents a promising and cost-effective pathway for novel cancer treatment that requires continuous and multidisciplinary clinical research.

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