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Review Article

Repurposing strategies and benefits in light of itraconazole interrelated therapeutic activities and challenges

Marian N. Yassa[a*], Mai Mansour[b], Dalia G. ElKhateeb[c], Gehanne A. S. Awad[b]

[a]*Central Administration of Pharmaceutical Care, Egyptian Drug Authority, Cairo, Egypt*
[b]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*
[c]*Central Administration of Drug Control, Egyptian Drug Authority, Cairo, Egypt*

ABSTRACT

The accidental discovery of new indications for drugs outside their application span has encouraged many researchers to investigate the interrelation between various drugs, diseases, and specific targets. Systematic repositioning or repurposing using multiple data sources and methods of analysis has been addressed in various studies. Meanwhile, anticancer drugs generally exhibited relatively high toxicity and severe side effects in both affected and normal cells. Drug repurposing has helped to discover safer drug molecules with fewer side effects. Cancer and fungal pathogenesis were found to have overlapped modes of action opening the gate for using antifungals as adjuncts in cancer therapy for less toxicity and better tumor growth control. Preclinical and clinical data have proposed the use of itraconazole as a promising anticancer, However, itraconazole, as a weak basic compound with low solubility, poor absorption, and limited bioavailability, faces several formulation challenges. This review focuses on Itraconazole, with its dual antifungal anti-cancer activity, and the challenges facing its formulation.

Keywords: *Repurposing; Drug discovery; Antifungals; Itraconazole; Anticancer.*

***Correspondence** | Marian Nashat Yassa; Central Administration of Pharmaceutical Care, Egyptian Drug Authority, Cairo, Egypt.
Email: mariannashat@gmail.com

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1. Introduction

Lately, an exponential increase in the number of published articles mentioning drug repositioning or related terms like drug repurposing, drug reprofiling, drug redirecting, and drug discovery have been the subject of various publications.

Cancer treatment is among the expensive therapeutic approaches connected to numerous side effects affecting the patient, sometimes for years. In addition to introducing new modalities, researchers in the oncology field are focused on developing drugs with fewer side effects. Either strategy is lengthy, high cost, and accompanied by a high failure rate. Drug repurposing was hence suggested as an alternative novel cheaper approach using safer drugs with fewer side effects and efficient anticancer activity **[1]**.

Over the past few decades, various drugs initially approved for purposes other than cancer treatment have demonstrated a cytostatic effect on cancer cells **[2, 3]**. Prominent instances of drug repositioning are evident in anthelmintics,

antibiotics, antifungals, antivirals, antihypertensives, psychopharmaceuticals, and antidiabetics, owing to their substantial immunomodulatory, antiproliferative, pro-apoptotic, and antimetastatic capabilities. These drugs could potentially be combined with existing anticancer treatments.

Although repurposing the antihypertensive Sildenafil and the antidiabetic Semaglutide was accidentally discovered, systematic repositioning approaches were suggested and applied by pharmaceutical companies. They addressed the exploration of the interrelation between drugs, diseases, and targets. Sildenafil was introduced into the market as an antianginal drug but repurposed as a drug for erectile dysfunction **[4]**. In 2021, manufacturers of Semaglutide (Novo Nordisk) got approval for the drug to be used also for the chronic management of obesity under the brand name Wegovy® **[5]**.

1.1. Data integration for repurposing

Investigation of a drug for a new indication is generally directed towards an untackled application or uncommon group of patients outside the range approved. Poorly efficient drugs and those retracted due to safety problems were also revised **[6]**. Thalidomide recently repurposed for cancer, was, firstly, developed as a sedative for pregnant women and retracted for its teratogenicity, then approved as an antileprotic and in 2006, for multiple myeloma due to its antiangiogenic activity. A well-known example of repurposing in the approach to disease was to employ an anticancer drug for psoriasis. Cancer and psoriasis both have the same uncontrolled cell growth as a biological mechanism **[7]**. The discovery of a link between a confirmed target and a new indication was a target-centric perspective for the use of tyrosine-kinase inhibitors in Parkinson's disease (PD). The oxidative stress accompanying neurodegenerative diseases such as Parkinson's and Alzheimer's is known to activate -Abl tyrosine kinase. Accordingly, Nilotinib, a potent and selective tyrosine kinase inhibitor, with moderated brain penetration was tried in PD disease where it proved a delay in disease evolution in acute animal model **[8]**.

Computational methods based on drug disease and drug target associations drew attention to similarities between proteins and genes. Focusing on the resemblance between the modes of action of drugs, new indications were found, as well as disease-drug and drug-drug associations. Relying on one type of data in this study method will need to find genes affecting the required information which once identified and targeted modification in gene expression might occur misguiding the results **[9]**. So, a recent study, using what's called the IDDI-DNN matrices model was able to integrate between different sources of data applied using a convolution neural network **[10, 11]**. In the applied method, matrices fusion was applied following separate matrices construction for drug and disease-related properties and drug-disease relationships, thus finding a new association between drugs and diseases **[12]**.

2. Fungi and cancer correlation

The relationship between viral and fungal infections on one side and cancer has been widely discussed and was demonstrated in various researches **[13, 14]**. Initially, some species of fungi had been condemned not only to develop cancer but also to enhance tumor growth and metastasis. These fungi were found to affect different cell components and DNA, increasing the risk of cancer. Fungi may also stimulate cytokines and various inflammatory mediators, promoting the risks of cancer. Furthermore, numerous fungi were at the origin of numerous anticancer drugs like paclitaxel, camptothecin, and vincristine **[15, 16]** due to the secretion of various bioactive compounds that can be used as

lead compounds for the production of anticancer drugs. Finally, both fungal pathogenesis and malignancies affect the immune system where a strong relation was found between immunological reaction towards fungal infections and cancer causation.

For example, cancer progression is enhanced by squalene epoxidase which is an enzyme important in cholesterol biosynthesis by catalyzing the conversion of squalene to 2,3(*S*)-oxidosqualene. Squalene inhibition is a target in fungal infection treatment, as well as for anticancerous activity **[17]**. Moreover, thymidylate kinase may be an important enzyme in the regulation of DNA synthesis. Meanwhile, genetic studies have proved that yeast mutant cell division lacks thymidylate kinase. On the other hand, a marked increase in thymidylate kinase was found in some tumor cells including those of Ehrlich ascites and hepatoma cells **[18, 19]**. Doulabi *et al*. also reported a high enzyme activity in tumor cells and confirmed the findings of Zhou et al who suggested the use of the enzyme as an essential cellular proliferation tumor biomarker **[20, 21]**. The inhibition of thymidylate kinase was reported to be the basis of the antifungal activity of 2-chloro-N-phenylacetamide and was targeted to inhibit the growth of Candida albicans **[22, 23]**. Accordingly, the mechanism of actions of different antifungals and their effect in combating fungi make them suitable candidates for repurposing them for anticancer activity. **Table 1** shows different antifungals that have been repurposed for the treatment of different cancer types.

Table 1. Repurposed antifungals loaded in Nanosystems for cancer therapy

Antifungal	Nano-system	Type of Cancer	Reference
Ketoconazole+sunitinib	Exosomes	Renal cell carcinoma	Greenberg et al 2021 **[24]**
Clotrimazole	Nanomicellar Formulation	Human Breast Cancer Cells	Marcondes et al 2015 **[25]**
Sertaconazole	Nanoparticle	lung cancer	Liu et al 2023 **[26]**
Miconazole	Nanoemulsions	Melanoma	Amado et al 2023 **[27]**
Ketoconazole and Bevacizumab	Liposomes	Endometrial Cancer	Wang et al 2024 **[28]**
Miconazole and Metronidazole	Silver Complexes	Melanoma	Fabijańska et al 1805 **[29]**
Terbinafine Hydrochloride	pH-Responsive Eudragit-Coated Mesoporous Silica Nanostructures	Targeted Colon Cancer	Alyami et al 2023 **[30]**

Concurrently, it was proved that tumor growth can stop at a size of 2-3 mm unless it can recruit its vascularization. Thus, there is a correlation between tumorigenesis and metastasis in tumors with rich blood supply. VEGF (vascoendothelial growth factor) is characterized around malignant cells and boosted by a toxic environment will promote tumor size and growth

[31]. The use of monoclonal antibodies to target VEGF was accompanied by significant cytotoxicity. In the meantime, itraconazole (ITZ) proved a potential antiangiogenic effect where it was found to inhibit both proliferation and migration of non-small cell lung cancer while enhancing significantly the cisplatin effect on tumor cells **[32]**.

3. ITZ anticancer activity and modulations for enhanced efficiency

According to a screening study done for approved small molecule drugs, ITZ was found to inhibit angiogenesis with IC50 of 160 nM) and hedgehog pathway (Hh) with an IC50 = 690 nM. **[33]**. Besides, ITZ inhibits the AKT/mTOR signaling pathway in glioblastoma, melanoma cells, endometrial carcinoma (EC), and human umbilical vein endothelial cells (HUVECs). It counteracts the chemoresistance brought on by P-glycoprotein, controlling Hh signal transduction pathways and preventing cancer cells from angiogenesis, hence it was repurposed as an anticancer drug. **Fig. 1** shows the mechanism of action of ITZ as an anticancer.

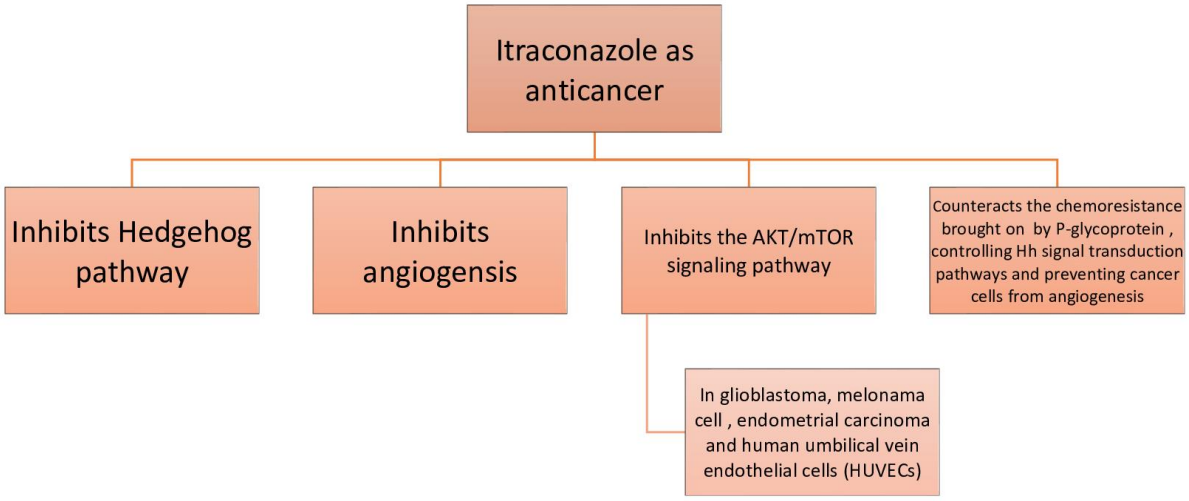

Fig. 1. Mechanism of action of Itraconazole in cancer therapy

ITZ is currently being studied as an anticancer drug against acute myeloid leukemia, non-small cell lung cancer, basal cell carcinoma, and prostate cancer. ITZ has shown antiangiogenic activity through suppression of the mTOR signaling system. Specifically, ITZ's strong anti-melanoma action has been recently reported by Liang *et al*., suggesting that it could work in concert with other anti-cancer medications to avoid the emergence of chemo-resistance **[34]**.

According to the biopharmaceutical classification system (BCS), ITZ is a class II drug practically insoluble in water with a pKa of 3.7. It has a relatively high partition coefficient (n-octanol/aqueous buffer pH 8.1) of 5.66 **[35, 36]**. The marketed ITZ oral and parenteral solutions (Sporanox®) are solubilized by cyclodextrin with the oral solution having a higher bioavailability than the capsules.

Recently, the field of pharmaceutical nanotechnology has polished up our heads to the possibility of solving drug solubility, stability, and bioavailability issues. **Table 2** shows the different nanosystems used for encapsulating ITZ as an anticancer.

Table 2. Repurposed itraconazole-loaded in nanosystems for cancer therapy

Drug	Nanosystem	Type of Cancer	Reference
Itraconazole	Topical SLN formulation	Skin Cancer treatment	Carbone et al 2018 **[37]**
Itraconazole	Miltefosine-modified lipid nanocapsules	Breast cancer	El-Sheridy et al 2021 **[38]**
Co-delivery of repurposing Itraconazole and VEGF siRNA	Nanoparticulate System	Breast Cancer	Jin et al 2022 **[39]**
Itraconazole	Ethosomal gel	skin cancer	Saraf et al 2018 **[40]**
Itraconazole	Lipid Nanocapsules	Skin Cancer	El-Sheridy et al 2022 **[41]**
Co-Delivery of Itraconazole and Docetaxel	Core/Shell Lipid Nanocells	Breast cancer	Okeke et al 2017 **[42]**
Itraconazole	PLGA Nanoparticles	Lung Cancer	Alhakamy et al 2019 **[43]**
Doxorubicin and Itraconazole	Pluronic® P123 coated liposomes	Breast cancer	Lin et al 2018 **[44]**

By mingling the administration of ITZ with a coating layer of di-dodecyl-dimethyl-ammonium bromide, Carbone *et al*., have created an enhanced topical solid lipid nanoparticles (SLN) formulation that repurposes the drug's effectiveness through synergistic skin anticancer efficacy. For the tumoral cell lines A431 and SK-MEL-5, there was a dose-dependent decline in cell viability, with the A431 cancer cell line viability being significantly lower. The reduction of the cancer cells treated was able to increase by nearly 20% upon the addition of the medication molecule to the uncoated nanoparticles. As a promising stable and safe method to significantly reduce the viability of skin cancer cells, their results show the potential for repurposing ITZ activity by using the combined nanoencapsulation strategy with the positively charged coating layer on SLN **[37]**.

An endeavor for the topical manipulation of ITZ as a treatment of Basal cell carcinoma represents a new yearning in skin cancer. ITZ-loaded ethosomes were prepared and characterized by vesicular shape, vesicular size, and entrapment efficiency. Saraf *et al*. could successfully develop ethosomal gels loaded with ITZ. Physicochemical characterization of the prepared ethosomes showed that they exhibit a nanometric size range of average particle size 169.0 nm and homogenous size distribution. ITZ was highly loaded inside the ethosomes with an entrapment efficiency of 82%. And was substantially more cytotoxic than the drug alone on the BCC1/KMC cell line **[40]**.

Another attempt for the usage of ITZ to treat skin cancer was proposed by El Sheridy *et al.*, who developed drug nanoparticles with enhanced anticancer efficacy. The nano-formulae comprise lipid nano-capsules with or without the amphiphiles bio-additives miltefosine or the biosurfactant surfactin. Lipid nano-capsules showed a very small particle size (42-45 nm) with depot release of ITZ that was highly entrapped inside the nano-capsules (98%) **[41]**. The lipid nanocapsules significantly increased the ITZ anticancer efficacy and selectivity for cancer cells in cytotoxicity assays utilizing malignant SCC 9 cells and normal human fibroblasts. Additionally, intradermal tumor-bearing mice treated with ITZ nano gels as opposed to ITZ and 5-FU single gels showed considerable reduction of tumor growth, which was markedly amplified by the bio-additives, in addition to skin architecture recovery. These authors offered further proof that a variety of strategies, including drug repurposing, nanotechnology, and the use of bioactive amphiphiles as formulation-enhancing additives, can be used to effectively

treat low-risk skin carcinogenesis topically **[41]**.

The same authors tried their lipid nanocapsules on MCF-7 breast cancer cells and found notably higher anticancer activity and selectivity for the prepared nanocapsules than both solution (ITZ-sol) and unmodified ITZ-LNC. In vivo, the results of therapy of mouse mammary pad Ehrlich tumors supported this pattern **[38]**. The ITZ-induced tumor growth inhibition, proliferation, and necrosis were most enhanced in lipid formulations. Tumor content of Gli 1, caspase-3, and vascular endothelial growth factor confirmed the effect of miltefosine in augmenting the inhibitory effects of ITZ on the apoptotic, antiangiogenic, and Hh pathway at the molecular level.

. Nacev *et al*. also investigated the anticancer mechanism of ITZ in breast cancer and found its ability to block VEGF and VEGF receptor 2 (VEGFR2) binding **[39]**. Furthermore, the monoclonal antibodies against VEGF and ITZ worked more synergistically together. This drew Jin *et al*., to design a combination of two distinct VEGF inhibitors that act against angiogenesis and can prevent the growth of breast cancer tumors along with (ITZ), Their goal was to examine the anti-angiogenesis efficacy and synergistic anticancer effect of composite nanoparticles co-loaded with VEGF and ITZ siRNA for breast cancer. The nanoparticles had a particle size of 117.9 nm with a modest positive surface charge of +6.69 mV. In vitro, the nanoparticles also effectively escaped from endosomes and inhibited cell growth and death. Experiments conducted in vitro and in vivo showed that the nanoparticles could successfully suppress VEGF-related expressions and have anti-angiogenesis properties. Additionally, the co-loaded ITZ-VEGF siRNA NPs demonstrated low toxicity and adverse effects, while significantly inhibiting tumor growth confirming ITZ repositioning as a strong contender for antitumor therapy **[45, 39]**.

The antiangiogenic activity of ITZ combined with the anticancer activity of doxorubicin was also explored by Lin *et al.,* **[44]**. Liposome-coated Pluronic® P123-containing codelivery nanoparticulate system comprising hydrophilic doxorubicin (DOX) and hydrophobic ITZ (ITZ/DOX-PLip) were prepared. The inhibitory effect of ITZ/DOX-Plip on tumor growth was found to be superior to that of free DOX or DOX-loaded liposome (DOX-Lip) based on cytotoxicity against 4T1 murine breast cancer cells and cellular uptake results. Furthermore, biodistribution tests in xenograft 4T1 bearing BALB/c mice showed that ITZ/DOX-PLip exhibited reduced distribution in the heart and increased drug accumulation in tumors when compared to free DOX. Interestingly, when compared to the same dose of ITZ injection or DOX-Lip, ITZ/DOX-PLip dramatically reduced tumor volume, tumor weight, liver metastasis, and micro-vessel density.

Conclusion

Driven by the tremendous benefits of drug repurposing including cost, shorter time of approval, and safety, a wide variety of systematic studies have been carried out to find different interrelations between drugs, diseases, and targets. They aimed to replace the accidental discovery of new drug indications with systematic data handling. Anticancer medications typically showed severe side effects with a comparatively high level of toxicity in both normal and afflicted cells. Repurposing drugs was specially targeted to the field of malignancy to develop safer, less harmful medicinal compounds. Due to the overlap between fungal pathogenesis and cancer, antifungals were proposed as adjuncts in cancer therapy for reduced toxicity and improved tumor growth control. The antifungal ITZ being a drug of class II in BCS classification suffers from low

solubility limiting its bioavailability. While shedding light on its anticancer mechanism of action, this review focused on various nano platforms adopted to improve its bioavailability.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that there is no conflict of interest.

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Author's contribution

All authors contributed to the study conception and design, the first draft of the manuscript was written by Marian Nashat Yassa and all authors commented on previous versions of the manuscript

All authors read and approved the final manuscript

4. References

1. Li CL, Fang ZX, Wu Z, Hou YY, Wu HT, Liu J. Repurposed itraconazole for use in the treatment of malignancies as a promising therapeutic strategy. Biomed Pharmacother. 2022;154:1–41. https://doi.org/10.1016/j.biopha.2022.113616
2. Hanusova V, Skalova L, Kralova V, Matouskova P. Potential Anti-cancer Drugs Commonly Used for Other Indications. Curr Cancer Drug Targets. 2015;15(1):35–52. https://doi.org/10.2174/1568009615666141229152812
3. Yang CFJ, Chan DY, Speicher PJ, Gulack BC, Wang X, Hartwig MG, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol. 2016;34(10):1057–64. https://doi.org/10.1200/JCO.2015.63.8171
4. Israr J, Alam S, Kumar A. Approaches of pre-clinical and clinical trials of repurposed drug. Prog Mol Biol Transl Sci. 2024;205:259–75. https://doi.org/10.1016/bs.pmbts.2024.03.024
5. Basolo A, Fierabracci P, Salvetti G, Santini F. Comment on: Semaglutide and cardiovascular outcomes in obesity without diabetes. J Endocrinol Invest. 2024;47(5):1047–9. https://doi.org/10.1007/s40618-023-02290-2
6. Pauly BA. Accelerating Drug Development: Unleashing the Power of Drug Repurposing. Drug Repurposing. 2024;1(1):1–5. https://doi.org/10.58647/drugrepo.24.1.0013
7. Rahmat M, Sklavenitis Pistofidis R, Ghobrial IM. Repositioning the Repurposed Drug, a Structural Study of Thalidomide Analogs. Hematol. 2019;16(3):1–4. https://doi.org/10.1182/hem.v16.3.9556
8. Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep. 2014;4:10–1. https://doi.org/10.1038/srep04874
9. Yoonbee Kim and Young-Rae Cho. Predicting Drug–Gene–Disease Associations by Tensor Decomposition for Network-Based Computational Drug Repositioning . Biomedicines 2023, 11, 1998

10. Jarada TN, Rokne JG, Alhajj R. A review of computational drug repositioning: Strategies, approaches, opportunities, challenges, and directions. J Cheminform. 2020;12(1):1–23. Available from: https://doi.org/10.1186/s13321-020-00450-7.
11. Li J, Zheng S, Chen B, Butte AJ, Swamidass SJ, Lu Z. A survey of current trends in computational drug repositioning. Brief Bioinform. 2016;17(1):2–12. https://doi.org/10.1093/bib/bbv020
12. Amiri R, Razmara J, Parvizpour S, Izadkhah H. A novel efficient drug repurposing framework through drug-disease association data integration using convolutional neural networks. BMC Bioinformatics. 2023;24(1):1–17. https://doi.org/10.1186/s12859-023-05572-x
13. Hosseini K, Ahangari H, Chapeland-Leclerc F, Ruprich-Robert G, Tarhriz V, Dilmaghani A. Role of Fungal Infections in Carcinogenesis and Cancer Development: A Literature Review. Adv Pharm Bull. 2022;12(4):747–56. https://doi.org/10.34172/apb.2022.076
14. Huët MAL, Lee CZ, Rahman S. A review on association of fungi with the development and progression of carcinogenesis in the human body. Curr Res Microb Sci. 2022;3.https://doi.org/10.1016/j.crmicr.2021.100090
15. Deshmukh SK, Prakash V, Ranjan N. Marine fungi: A source of potential anticancer compounds. Front Microbiol. 2018;8(JAN):1–24. https://doi.org/10.3389/fmicb.2017.02536
16. Kousar R, Naeem M, Jamaludin MI, Arshad A, Shamsuri AN, Ansari N, et al. Exploring the anticancer activities of novel bioactive compounds derived from endophytic fungi: mechanisms of action, current challenges and future perspectives. Am J Cancer Res. 2022;12(7):2897–919. http://www.ncbi.nlm.nih.gov/pubmed/35968347%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC9360238
17. Padyana AK, Gross S, Jin L, Cianchetta G, Narayanaswamy R, Wang F, et al. Structure and inhibition mechanism of the catalytic domain of human squalene epoxidase. Nat Commun. 2019;10(1):1–10. http://dx.doi.org/10.1038/s41467-018-07928-x
18. Nakamura H, Sugino Y. Metabolism of Deoxyribonucleotides II. Enzymatic Phosphorylation of Deoxycytidylic Acid in Normal Rat Liver and Rat Ascites Hepatoma Cells. Cancer Res. 1966;26:1425–9.
19. Kielley, R. K. Particle-bound thymidylate kinase in mouse liver, a possible factor in the control of DNA synthesis.Biochem. Biophys. Res. Commun. 10 (1963) 249.
20. ZHOU J, HE E, SKOG S. The proliferation marker thymidine kinase 1 in clinical use. Mol Clin Oncol. 2013;1(1):18–28. https://doi.org/10.3892/mco.2012.19
21. Doulabi EM, Dubois L, Löf L, Sinha TK, Harinck GM, Stålhandske P, et al. Increased levels of thymidine kinase 1 in malignant cell-derived extracellular vesicles. Biochem Biophys Reports. 2024;39:1–25.https://doi.org/10.1016/j.bbrep.2024.101761
22. Ferreira EDS, Cordeiro L V., Silva DDF, Souza HDS, DE ATHAYDE-FILHO PF, Barbosa-Filho JM, et al. Antifungal activity and mechanism of action of 2-chloro-n-phenylacetamide: A new molecule with activity against strains of aspergillus flavus. An Acad Bras Cienc. 2021;93:1–15. https://doi.org/10.1590/0001-3765202120200997
23. Huang CY, Chen YC, Wu-Hsieh BA, Fang JM, Chang ZF. The Ca-loop in thymidylate kinase is critical for growth and contributes to pyrimidine drug sensitivity of Candida albicans. J Biol Chem. 2019;294(27):10686–97. https://doi.org/10.1074/jbc.RA118.006798

24. Greenberg JW, Kim H, Moustafa AA, Datta A, Barata PC, Boulares AH, et al. Repurposing ketoconazole as an exosome directed adjunct to sunitinib in treating renal cell carcinoma. Sci Rep. 2021;11(1):1–12. Available from: https://doi.org/10.1038/s41598-021-89655-w
25. Marcondes MC, Fernandes ACS, Itabaiana I, De Souza ROMA, Sola-Penna M, Zancan P. Nanomicellar formulation of clotrimazole improves its antitumor action toward human breast cancer cells. PLoS One. 2015;10(6):1–20. https://doi.org/10.1371/journal.pone.0130555
26. Liu R, Li Q, Qin S, Qiao L, Yang M, Liu S, et al. Sertaconazole-repurposed nanoplatform enhances lung cancer therapy via CD44-targeted drug delivery. J Exp Clin Cancer Res. 2023;42(1):1–13. https://doi.org/10.1186/s13046-023-02766-2
27. Amado J, Pires PC, Veiga F, Santos AC. Miconazole Nanoemulsions to Treat Melanoma: A Study of Formulation Development, Droplet Size and Solubility.Medicines Science Forum. 2023;119. https://doi.org/10.3390/ecmc2022-13416
28. Wang S, Miao J, Zhu P, Xu L. Co-delivery of Liposomal Ketoconazole and Bevacizumab for Synergistical Inhibition of Angiogenesis Against Endometrial Cancer. Mol Biotechnol. 2024;(0123456789). https://doi.org/10.1007/s12033-024-01227-1
29. Rybarczyk-pirek AJ, Dominikowska J, Stryjska K, Zyro D. Silver Complexes of Miconazole and Metronidazole : Potential Candidates for Melanoma Treatment. International Journal of Molecular Sciences.2024; 25, 5081. https://doi.org/10.3390/ ijms25105081
30. Alyami MH, Musallam AA, Ibrahim TM, Mahdy MA, Elnahas HM, Aldeeb RA. The Exploitation of pH-Responsive Eudragit-Coated Mesoporous Silica Nanostructures in the Repurposing of Terbinafine Hydrochloride for Targeted Colon Cancer Inhibition: Design Optimization, In Vitro Characterization, and Cytotoxicity Assessment. Pharmaceutics. 2023;15(12). https://doi.org/10.3390/pharmaceutics15122677
31. Adesunloye BA, Karzai FH, Dahut WL. Angiogenesis inhibitors in the treatment of prostate cancer. Chem Immunol Allergy. 2014;99(2):197–215. https://doi.org/10.1159/000353255
32. Waheed A, Mohamed M, Dalia E, Elkhodary A, Ahmed M. The effect of itraconazole on the clinical outcomes of patients with advanced non small cell lung cancer receiving platinum based chemotherapy : a randomized controlled study. Med Oncol. 2021;38(3):1–9. https://doi.org/10.1007/s12032-021-01475-0
33. Pace JR, Deberardinis AM, Sail V, Tacheva-Grigorova SK, Chan KA, Tran R, et al. Repurposing the Clinically Efficacious Antifungal Agent Itraconazole as an Anticancer Chemotherapeutic. J Med Chem. 2016;59(8):3635–49. https://doi.org/10.1021/acs.jmedchem.5b01718.
34. Liang G, Liu M, Wang Q, Shen Y, Mei H, Li D, et al. Itraconazole exerts its anti-melanoma effect by suppressing Hedgehog, Wnt, and PI3K/mTOR signaling pathways. Oncotarget. 2017;8(17):28510–25. https://doi.org/10.18632/oncotarget.15324
35. Lee JH, Park C, Weon KY, Kang CY, Lee BJ, Park JB. Improved bioavailability of poorly water-soluble drug by targeting increased absorption through solubility enhancement and precipitation inhibition. Pharmaceuticals. 2021;14(12). https://doi.org/10.3390/ph14121255
36. Willems L, Van Der Geest R, De Beule K. Itraconazole oral solution and intravenous formulations: A review of pharmacokinetics and pharmacodynamics. J Clin Pharm Ther. 2001;26(3):159–69.

https://doi.org/10.1046/j.1365-2710.2001.00338.x

37. Carbone C, Martins-Gomes C, Pepe V, Silva AM, Musumeci T, Puglisi G, et al. Repurposing itraconazole to the benefit of skin cancer treatment: A combined azole-DDAB nanoencapsulation strategy. Colloids Surfaces B Biointerfaces . 2018;167:337–44. https://doi.org/10.1016/j.colsurfb.2018.04.031
38. El-Sheridy NA, El-Moslemany RM, Ramadan AA, Helmy MW, El-Khordagui LK. Enhancing the in vitro and in vivo activity of itraconazole against breast cancer using miltefosine-modified lipid nanocapsules. Drug Deliv. 2021;28(1):906–19. Available from: https://doi.org/10.1080/10717544.2021.1917728
39. Jin M, Zeng B, Liu Y, Jin L, Hou Y, Liu C, et al. Co-Delivery of Repurposing Itraconazole and VEGF siRNA by Composite Nanoparticulate System for Collaborative Anti-Angiogenesis and Anti-Tumor Efficacy against Breast Cancer. Pharmaceutics. 2022;14(7). https://doi.org/10.3390/pharmaceutics14071369
40. Saraf S, Kumar Gupta M. Itraconazole loaded ethosomal gel system for efficient treatment of skin cancer. Int J Drug Deliv. 2018;10(1):12–9. https://doi.org/10.5138/09750215.2246.
41. El-Sheridy NA, El-Moslemany RM, Ramadan AA, Helmy MW, El-Khordagui LK. Itraconazole for Topical Treatment of Skin Carcinogenesis: Efficacy Enhancement by Lipid Nanocapsule Formulations. J Biomed Nanotechnol. 2022;18(1):97–111. https://doi.org/10.1166/jbn.2022.3217
42. Okeke CI, Eltahan AS, Zhang T, Chen J, Wang Y, Xu MQ, et al. Co-delivery of itraconazole and docetaxel by core/shell lipid nanocells for systemic antiangiogenesis and tumor growth inhibition. J Biomed Nanotechnol. 2017;13(11):1398–412. https://doi.org/10.1166/jbn.2017.2428
43. Alhakamy NA. Repurposing Itraconazole Loaded PLGA Nanoparticles for Improved Antitumor Efficacy in Non-Small Cell Lung Cancers. 2019; 11, 685. doi:10.3390/pharmaceutics11120685
44. Lin Y, He X, Zhou D, Li L, Sun J, Jiang X. Co-delivery of doxorubicin and itraconazole by Pluronic® P123 coated liposomes to enhance the anticancer effect in breast cancers. RSC Adv. 2018;8(42):23768–79. https://doi.org/10.1039/c8ra03787f
45. Nacev BA, Grassi P, Dell A, Haslam SM, Liu JO. The antifungal drug itraconazole inhibits Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) glycosylation, trafficking, and signaling in endothelial cells. J Biol Chem. 2011;286(51):44045–56. https://doi.org/10.1074/jbc.M111.278754