Review Article

Imidazole Antifungals: A Review of Their Action Mechanisms on Cancerous Cells

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Abstract: Imidazoles, together with triazoles, constitute azole sub-group of antifungal drugs which acts by inhibiting cytochrome P450-dependent enzyme, the lanosterol 14-α-demethylase. In addition to their primary use, when it comes to additional anti-cancer function, clotrimazole, econazole and ketoconazole have come to the fore among the imidazoles. Based on the findings up to now, although having different effects, disruption of the glycolytic pathway, blockage of Ca^{2+} influx and nonspecific inhibition of CYP450 enzymes can be regarded as the main ones responsible for the anti-neoplastic activities of the mentioned drugs, respectively. Considering the advantages of repurposing of drugs with known pharmacology compared to new drug development studies requiring labor, time and cost, it will be extremely important and valuable to continue the clarification of the different mechanisms of these antifungals on cancerous cells and benefit from them especially to increase drug efficacy and overcome drug resistance. In this review, the action mechanisms of imidazole antifungals on cancerous cells and consequently, their potential for use in cancer treatment alone or in combination with conventional therapeutics were discussed in detail.

1. INTRODUCTION

As their names imply, antifungal drug is an agent which selectively kills fungal pathogens with minimal toxicity to the host and antifungal/antimitotic medication is to use these agents to treat and/or prevent serious systemic fungal infections [1]. According to their mode of action, there are seven known classes of antifungals including targeting ergosterol biosynthesis, fungal cell wall synthesis, sphingolipids biosynthesis, nucleic acid synthesis, protein biosynthesis, microtubules biosynthesis and disrupting fungal membrane. The antifungal class which acts by targeting biosynthesis of ergosterol, one of the main constituent of membranes, is called azoles. To put it more clearly, the azole class of antifungal drugs inhibits cytochrome P450 (CYP450)-dependent enzyme, the lanosterol 14-α-demethylase [2]. The inhibition of the so-called enzyme induces both the ergosterol consumption and sterol accumulation, the situation of which leads to loss of many functions of fungal membrane and afterwards fungal growth [3]. Various azoles have been used effectively for more than 35 years on the management of invasive fungal infections caused by the strains such as dermatophytes and *Candida* spp. Among the azoles, the

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imidazoles are the first developed ones, the usages of which were limited for superficial mycoses, the fungal infections invading the most superficial layer of the epidermis, because of gastrointestinal intolerability and neurologic adverse effects at high doses besides their low solubility in physiological solutions. However, triazoles were developed to meet a broad range of treatments and new-generation azole antifungals are under trial for more efficient medication, minimum side effects and, of course, ease of administration [4]. On the other hand, it should be emphasized that there has been also promising researches on using imidazoles against cancer besides their primary uses. From this point of view, it was aimed to collect the results of the studies, from past to present, assessing the effects of imidazoles on various cancerous cell or tissue types to make a general conclusion about the possible potentials of these antifungals in the treatment of cancer.

1.1. Imidazoles

Imidazole antifungal drugs have two atoms of nitrogen in their azole rings. Bifonazole, butoconazole, clotrimazole, ketoconazole, econazole, fenticonazole, isoconazole, miconazole and oxiconazole are some of the examples of this azole class. According to the literature survey, it can be clearly seen that among these imidazoles, clotrimazole (CTZ), econazole (ENZ) and ketoconazole (KTZ) are the most hitherto investigated ones for their potentials in cancer treatment.

1.1.1. Clotrimazole

CTZ (1-[(2-chlorophenyl)-diphenylmethyl]imidazole) has been known as a broad spectrum antimycotic or antifungal agent since its introduction to German markets in 1973 [5, 6]. It has long been known that the drug is effective on the strains of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Candida albicans* and *Malassezia furfur* [7]. Apart from its routine antifungal function, through the studies trying to reveal the direct anti-inflammatory properties of the azole derivatives, CTZ was recognized as one of the antifungals having ability to antagonize calmodulin (CaM) activity with the IC_{50} value of 18.4 ± 4.6 µM, which was shown based on the inhibition of CaM-dependent phosphodiesterase (PDE) [8]. CaM is multifunctional intermediate calcium (Ca^{2+})-binding messenger protein expressed in all eukaryotic cells [9] and so its antagonists play significant roles in many cellular processes [10]. It is not wrong to say that, with the discovery of CaM antagonist function, possible anticancer effects of CTZ started to be investigated. As known, the primary energy source of cancer cells is glycolysis that is controlled by allosteric regulators and by reversible attachment of the glycolytic enzymes to cytoskeleton and mitochondria [11-19]. Due to Ca^{2+} ions have impact on the increase of glycolytic enzyme attachment; CTZ could be an effective agent for inhibition of glycolysis. Indeed, the studies to date have indicated that CTZ shows its main action on cancerous cells by disrupting the glycolytic pathway (Table 1). According to literature survey, the primary study introducing the inhibition effect of CTZ on cell proliferation was conducted by Benzaquen and her group in 1995 [20]. In the so-called paper, it was stated that 10 µM CTZ completely inhibited growth factor-stimulated proliferation of Albino Swiss mouse embryo fibroblasts 3T3 (Swiss 3T3), bovine aortic endothelial cells (BAEC) and rat aortic smooth muscle (RASM) cells besides several human and mice cancers including lung, colon and melanoma with no apparent toxicity. The researchers based this anti-proliferative effect of CTZ on inhibition of Ca^{2+} movement across the plasma membrane but they did not investigate the possible alterations in glycolytic pathway. On the other hand, in the research conducted on B16 melanoma cells, it was firstly found that CTZ (5-50 µM) significantly reduced the levels of glucose 1,6-bisphosphate, fructose 1,6-bisphosphate and ATP, in a dose dependent manner within 1 h [21]. Following these findings, in other two studies carried out under the same conditions and with the same cell line, CTZ was shown to induce detachment of phosphofructokinase and aldolase from cytoskeleton, and hexokinase from mitochondria in

a dose dependent manner, which made this antifungal promising agent in treatment of melanoma [22, 23]. Afterwards, the disruptive effect of 0-500 µM CTZ on glycolytic pathway within 0-48 h was determined for various cancer cell lines including breast, kidney, lung, colon, glioblastoma and ovarian cancers [24-28]. In addition, it should be stated that CTZ induced detachment of glycolytic enzymes preceded the cell death that generally based on apoptosis. As is very well known, apoptosis is one of the programmed cell death types and it is intended to eliminate cancer cells by primarily this death pathway. Studies carried out until now have shown that CTZ induced apoptotic death in various cancer cell lines, characterized by phosphatidylserine externalization, DNA fragmentation, induction in cell-cycle arrest in G1- and M- phases, release of pro-apoptotic factor cytochrome c into the cytoplasm, down-regulation of the anti-apoptotic Bcl-2 protein, increase in pro-apoptotic Bax protein levels and induction in wild type p53 levels [26, 29-32]. Furthermore, maybe it could be supportive to state that CTZ significantly induced the activity of metacaspase Yca1, structural homolog to apoptotic human caspases, in yeast model organism [33]. Finally, it was demonstrated in a limited number of studies that some derivatives of CTZ or its combination with antineoplastic drugs exhibited more cytotoxicity on cancerous cells than its individual application [32, 34, 35].

Table 1. Action mode of clotrimazole-induced death on several cell lines and tissues

Mode of Action	Cell/Tissue Type	References
Inhibition of growth factor stimulated cell growth, Blockage in mitogen-induced intracellular Ca2+ increase in Swiss 3T3 cells, Depletion in intracellular Ca2+ stores in Swiss 3T3 cells	albino swiss mouse embryo fibroblast cell line (Swiss 3T3), bovine aortic endothelial cell line, rat aortic smooth muscle cell line, human lung and colon carcinomas, human and mice melanoma cells	[20]
Decrease in the levels of glucose 1,6-bisphosphate, fructose 1,6-bisphosphate and ATP in a dose and time dependent manner, Detachment of phosphofructokinase and aldolase from cytoskeleton in a dose and time dependent manner, Detachment of hexokinase from mitochondria in a dose dependent manner	mouse melanoma cell line	[21-23]
Inhibition of basal and growth factor stimulated vascular endothelial cell proliferation in a dose dependent and non-toxic manner, Inhibition of the basal and bFGF-stimulated migration of bovine capillary endothelial cells, Inhibition of the angiogenesis both *in vitro* and *in vivo* models	human, bovine and porcine vascular endothelial cells stimulated with vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), bFGF-injected male C57B16 mice	[129]
At higher doses (50 – 70 µM) Inhibition of cell growth in a dose-dependent and toxic manner *At lower doses (0 – 30 µM)* Inhibition of cell growth in a dose-dependent and non-toxic manner, Formation of small retracted cell bodies and thin elongated cytoplasmic processes, Cell cycle arrest at G0/G1 phase, Increase in p53 and glial fibrillary acidic protein (GFAP) expressions, Decrease in cellular c-myc and c-fos expression, Sensitization to antitumor effect of cisplatin	human glioblastoma cells (with wild or mutant types p53)	[130]

Suppression of cell recovery in a dose dependent manner, Cytotoxicity even against cells with multidrug-resistant phenotype and carrying genetic abnormalities, Depletion of intracellular Ca2+ stores, Apoptosis shown by Annexin V binding reactivity and induction of DNA fragmentation	human B- and T-lineages acute lymphoblastic leukemia (ALL) cell lines and human primary ALL cells	[30]
Decrease in the levels of glucose 1,6-bisphosphate and fructose 1,6-bisphosphate in a dose- and time-dependent manner, Reduction in ATP levels and time-dependent reduction in the viability, Alteration in cytosolic ion concentrations, Induction of necrotic morphological changes	murine lewis lung carcinoma cell line, murine colon adenocarcinoma cell line	[24]
Decrease in cell viability in a dose- and time-dependent manner, Induction in morphological and functional alterations including nuclear condensation and loss of protrusion, Detachment of 6-phosphofructo-1-kinase and aldolase from cytoskeleton, Decrease in glucose consumption and lactate production rates	human breast cancer cell line	[25]
Cell cycle arrest at the G1 phase in a dose- and time-dependent manner, Overexpression of p27Kip and decreased expression of p21Cip, cyclin-dependent kinase 1, cyclin-dependent kinase 4, and cyclin D, Translocation of mitochondrial-bound hexokinase II to the cytoplasm, Release of cytochrome c into the cytoplasm, Sensitization to radiation-induced apoptosis evidenced by Annexin V-FITC staining	human glioblastoma cell line	[26]
Reduction in lactate production, Inhibition in phosphofructokinase activity, *In vitro* dissociation of phosphofructokinase from f-actin	human breast cancer tissue	[57]
Inhibition of migration in an aggressiveness dependent manner, Decrease in cell proliferation, Decrease in cell viability in an aggressiveness-dependent manner, Dose- and aggressiveness-dependent reduction in glucose uptake and mitochondrial activity, Decrease in cellular ATP levels in a dose dependent manner, Inhibition in hexokinase, phosphofructokinase-1, pyruvate kinase and glucose 6-phosphate dehydrogenase activities, Decrease in cell viability in an aggressiveness-dependent manner	human breast cancer cells (with different aggressiveness profiles)	[27]
Inhibition of cell viability in a dose- and time-dependent manner, Decrease in cell colony formation in a dose-dependent manner, Cell cycle arrest at the G0/G1 phase in a dose-dependent manner, Induction of apoptosis showed by Annexin V/PI staining in a dose-dependent manner,		

Down- and up-regulations of the anti-apoptotic Bcl-2 and the pro-apoptotic Bax proteins, respectively both *in vitro* and *in vivo* models, Decrease in *in vivo* tumor volume and proliferation rate, Induction of apoptosis in *in vivo* model showed by cleaved caspase-3 expression	human oral squamous cell carcinoma (OSCC) cells, OSCC xenograft nude mouse model	[31]
Reduction in cell viability in a dose-dependent manner, Induction of mainly early stage apoptosis showed by Annexin V/7-AAD staining, Induction of internucleosomal DNA fragmentation and accumulation of histone-complexed DNA fragments in the cytoplasmic fraction, Absence of histone-complexed DNA fragments in the culture supernatant (the evidence of cell death without any involvement of necrosis), Induction of cell-cycle arrest at G1/S phase transition, Reduction in the expression and activity of hexokinase type-II	human cutaneous melanoma cell line	[131]
When combined with romidepsin (RDP) or belinostat (BNS), increased sensitivity to apoptosis showed by Annexin V-SYTOX staining, Requirement of caspase-3 activation and, Bak and Bax expression for RDP plus CLT induced apoptosis, Decrease in total hexokinase 2 (HK2) levels and decreased HK2 expression on the mitochondria after treatment with CLT	human breast, kidney, lung, colon and ovarian cancer cells	[132]

1.1.2. Econazole

Another imidazole that has exhibited a remarkable effect on cancer cells is ENZ (1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]imidazole). This antifungal is widely used in the treatments of vulvovaginal candidiasis, superficial fungal infection, keratitis and athlete's foot [36-39]. Early findings about the other functions of this agent revealed that it inhibited lipopolysaccharide-inducible nitric oxide synthase (iNOS) activity and reduced prostaglandin E2 production, which were related with its anti-inflammatory and cyclooxygenase inhibition effects, respectively [40, 41]. In addition, its antagonistic impact on CaM was found about 3-fold more effective than CTZ [8]. Interestingly, we could not discover any study that has assessed the effect of ENZ on glycolysis pathway. It is maybe because of the least selectivity of this azole antifungal against CaM-dependent PDE [8]. On the other hand, as a Ca^{2+} influx blocker, the effectiveness of ENZ on various tumors by different action mechanisms has been demonstrated (Table 2). Zhang et al. stated that MCF-7 and MDA-MB-231 breast cancer cell lines lost their viability after treatment with ENZ for 24 h in a dose dependent manner (0-15 µM), the concentration range which was slightly higher in magnitude than those required to kill bone marrow derived murine mast or 32D-Kit leukemia cells [42, 43]. In the same studies, it was also showed that ENZ caused a sharp loss of cell clonogenicity almost above 10 µM in parental and doxorubicin-resistant MCF-7 and MDA-MB-231 breast cancers, and 32D-Kit leukemia cells. However, unlike mast, p815 mastocytoma or 32D-Kit leukemia, the so-called breast cancer cell lines did not exhibit typical apoptotic morphology. Importantly, it should be also stated that this imidazole plus epithelial growth factor combination was successfully utilized for the purpose of decontamination of hematopoietic

progenitor cell preparations from breast cancer cells, in other terms for *in vitro* purging [42]. A similar ENZ application was shown for *in vitro* purging of bone marrow from P815 leukemic cells [44]. Ho and his friends showed the molecular mechanisms of ENZ induced anti-proliferative effect on human colon cancer cells [45]. According to their results, while lower doses of ENZ (5-10 µM) suppressed COLO 205 cell proliferation, higher doses (>20 µM) triggered apoptotic cell death characterized by DNA ladder formation, caspase-3 and -9 activation, induction in Bax protein expression, translocation of cytochrome c and apoptosis inducing factor from mitochondria to cytosol. In an another study, it was found that overnight treatment of the human prostate cancer cell line PC3 with 1-30 µM ENZ resulted in a decrease in cell proliferation by 20–100% and 5 µM of the drug induced both extracellular Ca^{2+} influx and intracellular Ca^{2+} release in this cell line [46]. In this point it must be stated that although ENZ generally recognized as an inhibitor of capacitative Ca^{2+} entry through store-operated calcium channels, it has been found to increase intracellular Ca^{2+} levels in some other cell lines too [39, 47-53]. Yu et al. showed the modulator function of c-myc and hypoxia-inducible factor 1 transcription factors in regulating ENZ sensitivity of rat fibroblast and human myelomonocytic leukemia cells [54]. While Fang et al. showed ENZ induced caspase-12 and -7 dependent apoptosis in mouse leukemia [55], caspase-3, -9 and Bcl-2 dependent apoptotic death was demonstrated for MCF-7 breast cancer cells [56].

Table 2. Action mode of econazole-induced death on several cell lines and tissues (*[a]Carried out only on the human colon adenocarcinoma*)

Mode of Action	Cell/Tissue Type	References
Inhibition of the tumor weight and the tumor/body weight ratio in human colon cancer xenografts		
At lower doses (5 - 20 µM) Dose-dependently suppression of *in vitro* cell proliferation but in a less profound manner in healthy ones, Induction of cell cycle arrest at the G0/G1 phase in a dose-dependent manner [a], Induction in p53, p21/Cip1, p27/Kip1 and cyclin E protein levels in a dose-dependent manner [a], Decreases in the expression of phospho-CDK2 and phospho-Rb proteins in a dose-dependent manner [a] Suppression of CDK2 and CDK4 kinase activities [a] ***At higher doses (>20 µM)*** Induction of *in vitro* cell death but in a less profound manner in healthy ones, Arrestment at the sub-G1 peak phase [a], Downregulation in phospho-CDK2, CDK4, cyclins A2, D1 and D3 protein levels [a], Apoptosis induction evidenced by DNA ladder formation [a], Caspase-3 and -9 activation [a], Induction in Bax protein expression [a], Translocation of cytochrome c and apoptosis-inducing factor [a]	human normal colon epithelial cell line, human colon adenocarcinoma cell line, human colon cancer xenografts *in vivo*	[45]
Dose-dependently induction of intracellular Ca^{2+} concentration by stimulating Ca^{2+} influx into cells and Ca^{2+} release from the endoplasmic reticulum via a phospholipase C independent mechanism	human prostate adenocarcinoma cell line	[46]
Induction in intracellular Ca^{2+} concentration in a dose-dependent manner,	mouse leukemia cell line	[55]

Apoptosis induction evidenced by phosphatidylserine externalization in a dose-dependent manner, Induction in expression of caspase-12 and caspase-7 in a dose-dependent manner		
Cell resistance in terms of colony-forming ability in c-myc negative rat fibroblasts, Reduced level of apoptosis showed by Annexin V-Cy5 staining in c-myc knock-down leukemia cells compared with vector control-infected ones, Impaired ER Ca^{2+} release in c-myc-negative rat fibroblasts, Reduced ROS generation in c-myc-negative rat fibroblasts and c-myc knock-down leukemia cells related with decrease in mitochondrial content, Restoration of the sensitivity with the addition of H_2O_2 in terms of apoptosis in c-myc-negative rat fibroblasts and c-myc knock-down leukemia cells, Restoration of mitochondrial content, ROS generation and the sensitivity in terms of apoptosis in c-myc negative rat fibroblasts with HIF-1α knock-down	human leukemia cell line, rat fibroblast cells (c-myc-negative and -positive)	[54]
Dose-dependently induction of intracellular Ca^{2+} concentration by stimulating Ca^{2+} influx into cells and Ca^{2+} release from the endoplasmic reticulum via phospholipase A2 and C and protein kinase C dependent mechanisms, Induction of cell death regulated by ERK/MAPK pathway	human oral cancer cell line	[39]
Reduction in cell viability in a time- and dose-dependent manner, Reduction in cell growth in a dose-dependent manner, Decrease in cell number, Apoptosis induction evidenced by the induction of morphological changes including blebbing of nuclei and formation of granular apoptotic bodies, and the appearance of DNA ladder, Decrease in mitochondrial membrane potential in a dose-dependent manner, Decrease in Bcl-2, and increase in caspase-3 and -9 protein levels	human breast cancer cell line	[56]
Reduction in cell viability in a dose-dependent manner, Dose-dependently induction of apoptosis evidenced by Annexin V-FITC staining, and PARP and caspase-3 cleavages, Decrease in p-AKT and Bcl-2 protein levels, Synergistic and additive killing effects when combined with cisplatin	human lung cancer cells	[133]

1.1.3. Ketoconazole

Although both CTZ and ENZ have been accepted as antifungal drugs possessing profound anti-proliferative effects on tumorigenic and metastatic cells while having minimal effects on non-tumoral ones [27, 42, 57], there is no any (un)approved application or combination formulation, most probably because of the need Yof a more complete understanding of their action mechanisms and bioavailability limitations. However, another imidazole KTZ (1-[4-[4-[[(2S,4R)-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl

]piperazin-1-yl]ethanone) has found application in castration-resistant prostate cancer (CRPC) as an off-label and a second-line hormonal treatment, alone or in combination with other compounds and therapies, since the 1980s [58-71]. It should be noted that this is an officially unapproved treatment, generally without survival benefit. CRPC is defined as the lethal phenotype of prostate cancer and it can occur in most of the patients received long-term androgen deprivation therapy (ADT) which is the standard initial management for the disease. KTZ nonspecifically inhibits CYP450 enzymes including 17α-hydroxylase/17, 20 lyase (CYP17A1), the function of which is to catalyze significant reactions in the gonadal and adrenal steroidogenesis pathways [72, 73]. Based on these inhibitions, the drug suppresses both gonadal and adrenal androgen synthesis, while only gonadal androgen synthesis can be suppressed with ADT. Of course, nonspecific action of this antifungal on CYP450 enzyme family has given rise to concerns about its potential toxicity, the most common of which is hepatotoxicity. As a matter of fact, the usage of oral KTZ tablets in their primary target fungal infections has not been allowed due to its side effects in liver [74]. Nevertheless, the efficacy and safety of cancer treatment were enhanced by clinical dose-reduction studies. For example, Harris et al. indicated a regimen of low dose oral KTZ (200 mg 3 times daily) with replacement doses of hydrocortisone which can be well tolerated and has moderate activity in CRPC patients [75]. Again a significant improvement in terms of toxicity was achieved by clinical dose reduction (from 400 to 200 mg orally 3 times daily) not or in combination with steroids again in CRPC patients [76]. In a more recent study conducted with docetaxel pre-treated CRPC patients, low dose oral KTZ (200 mg 3 times daily) plus hydrocortisone regimen was suggested as well-tolerated, relatively inexpensive and clinically active treatment alternative [77]. Of course, the number of these examples can be increased. Moreover, similar applications have been suggested and extended for other tumors such as breast and colorectal carcinomas [78, 79]. From this point of view, KTZ yet offers alternative ways for the treatment of advanced cancers with its low-priced, a relatively favorable toxicity profile compared to chemotherapy and efficacy both before and after chemotherapy [80, 81] especially when newer and more specific options are not available [71, 82-84].

As can be seen in Table 3, KTZ also has cytotoxic effects on different tumors. In an old study conducted by Naftalovich et al., it was demonstrated that 4-7 µg/ml KTZ caused to 50% inhibition of DNA synthesis in radiation leukemia virus induced T-cell lymphomas, while at least 50 µg/ml of the drug was needed to induce a similar inhibition in bone-marrow and spleen cells prepared from healthy mice [85]. 25-50 µM KTZ was shown to have cytotoxic and apoptotic effects on both different human cancer and rat liver cells, but in a significantly more sensitive manner when wild-type p53 protein was present [86]. The same group demonstrated that wild type p53 dependency of KTZ- induced cytotoxicities in human colorectal and hepatocellular carcinoma cell lines were more pronounced at lower doses (2 µM) of the antifungal [87]. Additionally, it was stated that approximately 40 µM KTZ induced p53-mediated cell cycle arrest at the G0/G1 phase together with p21/Cip1 induction and decrease in Cdk activities, especially in Cdk4. Lin et al. exerted cytotoxic and apoptotic effects of KTZ above the concentration of 20 µM on human osteosarcoma cells [88]. While this observed cell death depended on KTZ-induced JNK phosphorylation, it was independent from the increase in intracellular Ca^{2+} concentrations. In a current work of Agnihotri et al., it was firstly found by means of drug-screening research that KTZ and posaconazole, a second-generation triazole agent, displayed the greatest inhibitory effect on glioblastoma both *in vitro* and *in vivo* by effecting hexokinase II-related gene expression signature [89]. This finding has special importance in terms of the lack of specific hexokinase II inhibitors, which makes this enzyme unactionable in cancer medicine. Considering the findings that azole antifungal drugs have given rise to mitochondrial loss [90, 91], Chen et al. put forward a novel impact of KTZ on mitophagy programme of hepatocellular carcinoma cells [92]. According to the data of the

researchers, 20 μM KTZ induced apoptosis of liver cancer cells by triggering aberrant mitophagy with the downregulation of cyclooxygenase-2. The same researchers also indicated the synergistic action of KTZ with clinically approved multi-kinase inhibitor sorafenib and rightfully suggested the use of KTZ especially in patients having high cyclooxygenase-2 expression levels.

Some other medically important *in vitro* effects of KTZ are the induction of the DT-Diaphorase (NQO1), modulation of the calcium-activated potassium channels, blockage of the activation of orphan nuclear receptors (NRs), and specific and reversible inhibition of CYP3A4 [79, 93-96]. NQO1 is one of the phase II enzymes that detoxificate xenobiotics. Accordingly, KTZ induction of the enzyme indicates the chemoprotection function of this antifungal. The associations between key aspects of cancer and potassium channel dysregulation are gradually growing, which makes potassium channels a valuable target [97]. On the other hand, when the literature is examined, it can be clearly seen that researchers especially have focused on the inhibition effects of KTZ on NRs and CYP3A4. As is well known, these receptors play role in the regulation of CYP3A4, which accounts for approximately half of the metabolism of most approved drugs [98]. Based on the KTZ induced inhibition of this enzyme and, therefore, the reduction in drug clearance, alternative and effective formulas benefiting from the so-called antifungal have been developed for advanced cancer patients [79, 99-101].

Table 3. Action mode of ketoconazole-induced death on several cell lines and tissues (*[a]Used to determine cytotoxicity; [b]Used to determine cytotoxicity and DNA fragmentation; [c]On hepatocellular carcinoma with wild p53; [d]On colon adenocarcinoma with mutant p53; [e]On hepatocellular carcinomas; [f]On colon adenocarcinomas; [g]On colon and liver cancers*)

Mode of Action	Cell/Tissue Type	References
Cytotoxicity in a dose and time dependent manner	human breast carcinomas, human pancreatic adenocarcinomas, human colon adenocarcinoma, human prostate carcinoma, rat pancreatic carcinoma, murine leukemia	[134]
Increased sensitivity to the cytotoxicity and apoptosis depend on carrying wild type p53 and being cancerous, Induction of apoptosis evidenced by the formation of DNA fragment ladder in all cell lines, Nuclear accumulation of p53 protein c, Bax protein induction e and bcl-2 protein inhibition g, Activation of caspase-3 c, Poly-(ADP ribose) polymerase and lamin A degradation c	normal human breast skin fibroblast cell line a, primary culture of rat liver cells b, human colon adenocarcinomas (with wild or mutant types p53), human hepatocellular carcinomas (with wild type or deleted p53)	[86]
Increased sensitivity to the cytotoxicity depend on carrying wild type p53, Increased sensitivity to cell cycle arrest at G0/G1 phase depend on carrying wild type p53 f, G0/G1 arrest mediated by induction in p21/Cip1, p27/Kip1 and inhibition in cyclin D3 and CDK4 expressions d	human colon adenocarcinomas (with wild or mutant types p53), human hepatocellular carcinomas (with wild type or deleted p53)	[87]

Induction of apoptosis evidenced by the sub-diploid nuclei and activation of caspase-3, Induction of the phosphorylation of ERK and JNK proteins, Reversed apoptosis by the selective JNK inhibitor SP600125, but not by the selective ERK inhibitor PD98059, Increase in intracellular Ca2+ concentration, Total inhibition of the increases in intracellular Ca2+ concentration by the chelator BAPTA, but without reversing cell death	human osteosarcoma cell line	[88]
Selective effect against tumoral cell lines, Increase in proportion of apoptotic cells evidenced by the detection of DNA breaks, Influence on genes and pathways regulated by hexokinase II	fetal normal human astrocytes immortalized with hTERT, human neural stem cell line, human glioblastoma cell lines, patient-derived glioma stem cells, mouse models of glioblastoma	[89]
Enhancement in Ganoderma microsporum immunomodulatory protein induced cytotoxicity and apoptosis of cancerous cells in a concentration-dependent manner, Enhancement in Ganoderma microsporum immunomodulatory protein induced migration inhibition of cancerous cells in a concentration-dependent manner, Reduction in the level of Ganoderma microsporum immunomodulatory protein induced phosphorylated-adenosine monophosphate-activated protein kinase (p-AMPK)-α and autophagy of cancerous cells, Reduction in the monocyte chemoattractant protein-1 (MCP-1) secretion of cancerous cells	human melanoma and skin fibroblast cell lines	[135]

1.1.4. Other Imidazoles

Apart from these three drugs, there are some studies on the possible anticancer effects of some other remaining imidazoles including bifonazole (BFZ) and miconazole (MCZ). As in the case of CTZ, BFZ has been known as calmodulin antagonist for more than two decades which can detach glycolytic enzymes from cytoskeleton or mitochondria in murine melanoma cells [23]. In a more recent study, Cheng et al. demonstrated the BFZ-induced intracellular Ca^{2+} increases in human prostate cancer cells through the induction of phospholipase C- and protein kinase C-dependent Ca^{2+} release from the endoplasmic reticulum and Ca^{2+} influx via non-store-operated pathways [102]. The researchers also recorded Ca^{2+}-independent apoptotic cell death in these cells. We finally came across the abstract paper of Robey et al. in which synergistic apoptotic effects of romidepsin, a histone deacetylase inhibitor, plus CTZ/BFZ were found on colon, lung, breast and renal cancer cell lines [103]. Surprisingly, no other studies on the effects

of BFZ or its combination formulations on cancer cells/tissues have been discovered and therefore it is thought that the action mechanism of this drug is still in need of investigation. Nevertheless, it would not be wrong to say that the action mechanism of MCZ on cancer cells is relatively better understood compared to BFZ. Literature review shows that this drug has an impact on human bladder, breast and colorectal cancers, human osteosarcoma cells, human hepatocellular carcinoma, human acute myelogenous leukemia, and mouse skin melanoma cells [104-108]. It is clearly seen that the main focus of these studies was to explore the relationship between MCZ-induced cell-cycle arrest and apoptosis via the determination of the levels of main regulatory proteins involved in the so-called processes. Unfortunately, this antifungal causes cardiotoxicity via generation of superoxide anion, inhibition of APE/Ref-1 and induction of apoptosis in cardiomyocytes and cardiomyoblast cell line [109, 110], which might make it unnecessary to focus on researches regarding with its anticancer potential.

1.2. Triazoles

As stated at the beginning of the paper, triazole antifungal drugs having three nitrogen atoms in their azole rings were developed to fulfill the need of a much broader spectrum of treatment options by comparison with the imidazoles. The first synthetic triazole antifungal to be discovered was fluconazole (FCZ) and it was introduced to the markets in the early 90s [111]. By the way, FCZ is different from other azoles in terms of the presence of two triazole rings making this compound less lipophilic and protein bound [112]. After FCZ, itraconazole (ICZ) is the second member of first generation triazoles. Between these two triazoles, while it has been shown that ICZ is toxic to various cancer types, no study on the subject has been found for FCZ. On the other hand, although it is off topic, it could be useful to say that some *Candida* cells, a kind of yeast species causing fungemia to which cancer patients are especially susceptible, are resistant to FCZ-induced death and this resistance can be broken by combined application of FCZ with certain phenolic compounds [113-115].

As mentioned above, ICZ has capability to inhibit the proliferation of distinct cell lines established from breast, gastric, glioma, pancreatic, melanoma, esophageal, gastrointestinal, non-small cell lung cancers and acute myeloid leukemia [116-123]. It can be reported that the prominent anticancer mechanism of this triazole is the inhibition of hedgehog pathway having important function in the embryonic development and tissue homeostasis. Moreover, recent findings have put forward that this signaling cascade is related with the neoplastic transformations, malignant tumors and drug resistance of a multitude of cancers [124]. The relationship with drug resistance may be especially remarkable given the findings suggesting that ICZ has a synergistic effect when combined with the known drugs as bevacizumab, doxorubicin and 5-fluorouracil on several cancer cell lines resisting these drugs when they are given alone [117, 121, 123]. In addition, the review paper conducted by Tsubamoto et al. can be browsed for more detailed information for both *in vitro* and ongoing *in vivo* trials with ICZ [125].

Approximately a decade later from the first generation triazoles, voriconazole, posaconazole, ravuconazole, albaconazole, isavuconazole and efinaconazole were developed as second-generation triazole antifungals for more efficiency and safety [126]. As with FCZ, there are no detailed researches dealing with the action mechanisms of these triazoles against cancer cells. However, due to the limited treatment strategies available because of the reasons including antifungal resistance, toxicity, drug interactions and expense; clinical studies are being conducted to evaluate the potentials of the so-called antifungals against invasive fungal infections in patients with cancer whose immune systems are severely suppressed [127, 128]. In short, when it comes to cancer, basic focus for triazoles is the modulation of fungal population aiming at increasing morbidity and mortality in cancer patients and ICZ is the only triazole whose effects on cancers have been broadly investigated.

2. CONCLUSION

As a conclusion, it is clear that imidazole antifungals have additional anti-proliferative effects against divergent solid and leukemia tumors. In this sense, CTZ, ENZ and KTZ can be said to be most striking imidazole antifungals with their significant *in vitro* effects that may be valuable in medicine. Despite above-mentioned remarkable data, to be sure, it would be appropriate to continue investigate the new biological effects of all imidazoles besides CTZ, ENZ and KTZ. Additionally, it should not be forgotten that although KTZ has already found a medical application, the same situation is not valid for other imidazoles for the time being. Accordingly, as with the usage of KTZ in especially prostate cancer, the significance and effectiveness of sequential applications or combined therapies in many diseases including cancer must be taken notice. It can be clearly said that application of dual drugs with known pharmacology and complementary to each other in terms of their targets has always been a valuable option for the scientists in the area due to difficulty of and requiring a long time for new drug developments. Eventually, considering the biochemical effects on cancer cells, the so-called antifungal drugs should be also taken into account in combined therapies, maybe particularly with new generation anticancer drugs that are target specific but against which cancer cells can resist.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the author(s).

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