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Ketoconalzole-An Aquatic Pollutant: Sources, Impact, And Regulatory Aspects

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Abstract
Ketoconazole is a common imidazole antifungal medication used in both human and veterinary medicine to remedy for a range of fungal infections.
It exhibits fungicidal and fungistatic activities against fungi such as dermatophytes, yeasts, and eumycetes. Its primary mechanism involves inhibiting cytochrome P450 enzymes, crucial for ergosterol synthesis, thereby disrupting fungal cell membranes and leading to fungal death or growth inhibition. It has been used commonly in pharmaceutical and healthcare products that can leave residual amounts of certain compounds, which may result in adverse ecological health issues. Research on ketoconazole (KTZ) underscores its environmental impact and regulatory concerns, particularly regarding toxicity in aquatic ecosystems. Key findings include:
Toxicity: KTZ, along with other azole fungicides, shows significant toxicity to aquatic plants like Lemna minor and heightened sensitivity in Daphnia similis. Synergistic Effects: KTZ can amplify toxicity when combined with substances like erythromycin, leading to greater bioaccumulation in fish and adverse biochemical effects. Endocrine Disruption: KTZ disrupts reproductive and metabolic functions in aquatic organisms, with potential negative outcomes from co-exposure to estrogens. Environmental Persistence: KTZ has a long half-life and high water solubility, posing risks of groundwater contamination and effects on non-target species. Human Health Risks: Its impact on aquatic ecosystems, including potential links to increased fungal resistance, raises concerns for human health via environmental exposure. These findings highlight the need for further research on KTZ and azole compounds to assess their ecological effects.
KTZ faces regulatory challenges due to safety concerns, primarily its ability to elevate plasma levels of other drugs, leading to adverse effects like QT prolongation. The FDA has restricted its use, recommending against it as a first-line treatment for fungal infections but allowing it for life-threatening systemic mycoses when alternatives are unavailable. In contrast, the European Medicines Agency (EMA) has approved KTZ in the EU, citing its benefits for treating Cushing's syndrome as outweighing risks, while the CHMP believes liver-related risks can be managed. In Australia, the TGA has deregistered KTZ's oral form due to liver injury concerns, though topical formulations remain available. Overall, KTZ's therapeutic potential is recognized, but its regulatory status reflects ongoing safety concerns.
Despite this, it remains approved for specific conditions with safety managed through risk minimization measures.
Key words: *ecotoxicological impacts, detoxified ketoconazole, bioconcentration of ketoconazole, metal-organic framework*

INTRODUCTION

Water Pollutants: Sources and Impact

Lakes and tanks in the metropolitan area are reservoirs for rainwater harvesting. The need for creating and sustaining these man-made blockaded freshwater reservoirs were created due to lack of a major water source such as rivers, basins, sea nearby coupled with a growing settlement that demands excess utility of water (Chinnaiyan et al., 2018; Van De Steene et al., 2010). Agricultural lands were gradually rendered as non-agricultural lands due to urbanization. The impact of urbanization reduced the inflow of rain water reaching the lakes to recharge it. The development also resulted in letting in untreated sewage water from housing societies and using the lake surrounding area to dump solid waste. Industries also started dumping their waste into the lakes. (Alsbaiee et al., 2016).

Significant sources contributing to the rise of contaminants, particularly from pharmaceuticals, are referred to as Contaminants of Emerging Concern (CECs) (Campos-Mañas et al., 2017). These CECs can arise from various origins, such as medications, food additives, personal care items (PCPs), plasticizers, pesticides, and other industrial, construction, or manufacturing activities (Botero-Coy et al., 2018; Rizzo et al., 2019). The majority of these contaminants flow from municipal wastewater, with treatment plants acting as the main collectors of these pollutants. Such emerging contaminants can potentially harm human health as well as non-target organisms, highlighting their role as significant pollution contributors. The release of large quantities of chemicals into water bodies—including pharmaceutical compounds, polycyclic aromatic

hydrocarbons (PAHs), and estrogenic hormones—intensifies environmental issues. This complicated blend of pollutants can disrupt ecosystems, compromise water quality, and pose health risks to aquatic life, and possibly to humans via exposure routes like drinking water.

It is crucial to ensure that the pollutants designated for removal from treated waters do not merely transfer from effluent to sludge, which can then leach into the soil as a possible contaminant. Currently, Contaminants of Emerging Concern (CECs) are not regulated by existing environmental laws. Nonetheless, there is an increasing awareness of the necessity to track and reduce the effects of these emerging substances on water ecosystems. To support this awareness, it is vital to collect information regarding the prevalence and impacts of CECs to guide future regulatory actions and lessen their harmful effects on aquatic environments. Creating regulatory guidelines for the management of CECs is essential for the practices of the future. These guidelines should specify methodologies for monitoring, evaluating, and controlling the presence of emerging contaminants in water bodies. Furthermore, regulatory frameworks can provide criteria for wastewater treatment facilities and other organizations responsible for releasing potentially harmful substances into the environment, ensuring necessary measures are implemented to limit CECs.

One such CEC being discussed is Ketoconazole (KTZ) that presents specific issues as a pollutant primarily due to its environmental persistence, potential for bioaccumulation, and toxicity to aquatic organisms. Key aspects of its significance as a pollutant have been identified as Environmental Persistence thereby leading to other concerns such as Toxicity to Aquatic Life, Endocrine Disruption and Bioaccumulation.

KTZ has a long half-life and is resistant to degradation, leading to accumulation in water bodies. Its high solubility in water increases the risk of contaminating aquatic ecosystems. It is highly toxic to various aquatic organisms, including algae, invertebrates, and fish. It can disrupt reproductive and metabolic functions, posing risks to biodiversity and ecosystem health. KTZ has been shown to exhibit endocrine-disrupting properties, which can affect the reproductive systems of aquatic organisms, leading to potential long-term ecological impacts. KTZ can accumulate in the tissues of aquatic animals, leading to increased concentrations up the food chain and posing risks to predator species, including humans.

In addition, regulatory guidelines can stimulate research and development focused on finding alternative approaches to managing and treating CECs, including advanced treatment methods or environmentally friendly production techniques for pharmaceuticals. By promoting innovation and the adoption of best practices, regulatory frameworks can assist in reducing the environmental effects of CECs while protecting public health and ecological stability.

Due to its environmental risks, KTZ has drawn attention from regulatory agencies, prompting guidelines to limit its use and manage its presence in the environment. Overall, KTZ's persistence, toxicity, and potential for bioaccumulation underscore its significance as a pollutant, highlighting the importance of monitoring and regulating its environmental impact.

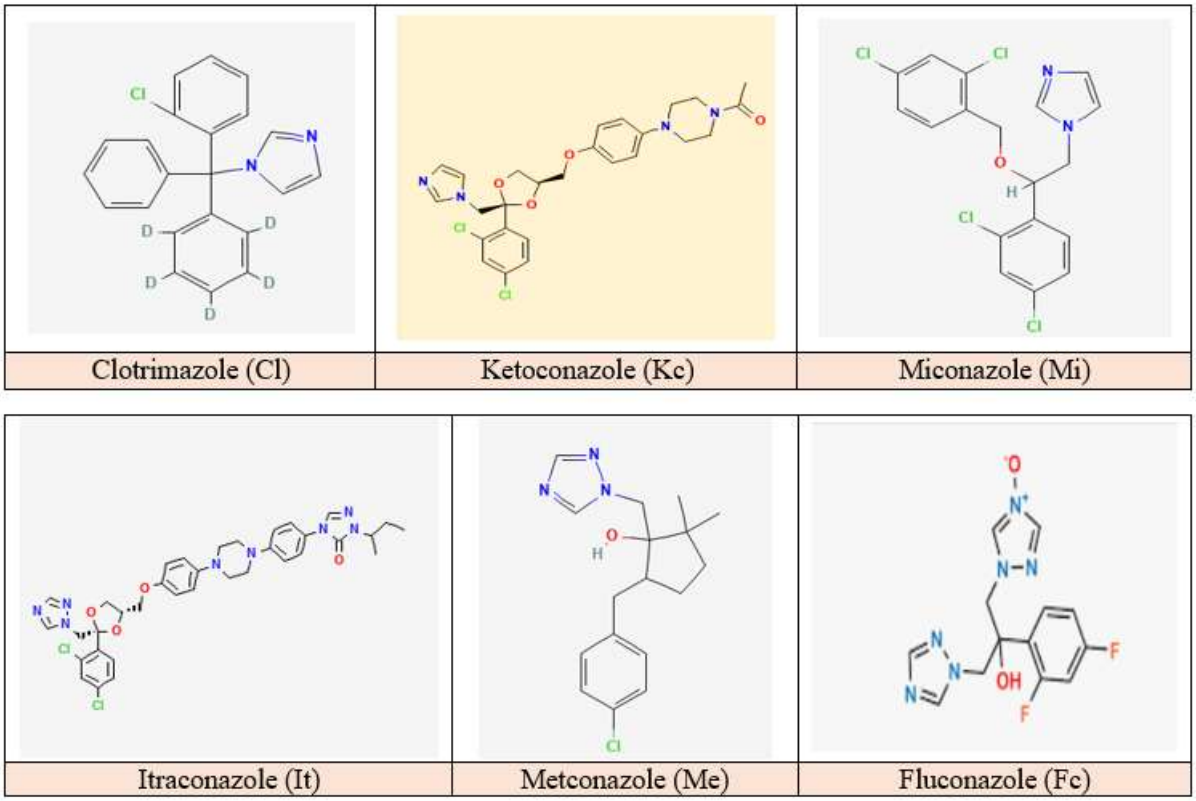
In conclusion, while existing environmental laws may not directly address CECs, the creation of regulatory guidelines for monitoring and managing these emerging contaminants is vital for safeguarding water bodies and encouraging sustainable environmental practices in the future.

Azoles as Environmental Contaminants

Azoles represent a category of five-membered heterocyclic compounds that include a nitrogen atom along with at least one additional non-carbon atom, which can be nitrogen, sulfur, or oxygen, in the ring structure. Widely utilized azole fungicides include imidazoles, such as clotrimazole (Cl), ketoconazole (KTZ), and miconazole (Mi), as well as triazoles like itraconazole (It), metconazole (Me), and fluconazole (Fc). These fungicides are favored primarily because they have relatively low skin absorption and a high emission rate of 90-95% in rinse-off products (Letzel et al., 2009).

In a study analyzing eight commonly used azole antifungal drugs. In South Africa, water samples collected from three wastewater treatment plants (WWTPs) and a drinking water treatment plant (DWTP) were analysed. Six of the drugs were detected at least once. Detection rates ranged from 11% for (It) to 96% for (Fc), with average concentrations between 0.2 ng/L (Cl) and 9959.0 ng/L (Fc) (Hailemariam et al., 2019).

In the study as explored by (Amanda Pacholak et al., 2022), the biological and chemical degradation of four azole antifungals and their transformation products (TPs), it was found that Climbazole (Cb) was partially biodegraded, while the others were resistant. Clotrimazole (Cl) and Epoxiconazole (Ep) were adsorbed onto sludge, but Fluconazole (Fc) was found to resist both sorption and biodegradation. Photolysis, particularly with the Fenton process and UV irradiation, effectively degraded Cl, Cb, and Ep. Certain TPs, particularly those from Ep and Fc, exhibited heightened cytotoxic effects, underscoring the necessity for effective cleanup technologies and more stringent controls on the release of azole fungicides into the environment.



Chemical Structure of some important antifungal Azoles

Fluconazole is the most prevalent antifungal medication found wastewater treatment facilities, surface waters, and groundwater (Mzimkhulu et al., 2021). Over the past thirty years, azole compounds have been identified as environmental pollutants that pose potential risks to both human health and ecosystems. These substances are utilized in various pharmaceutical applications to treat cancer and hyperthyroidism. These drugs are even used as antifungal agents in agricultural products (Matthiessen and Weltje, 2015). Additionally, azole antifungal medications are components of personal care products and are employed in treating fungal infections in humans and animals (ANTIFUNGALS et al., 2017).

Proactive strategies can reduce the environmental effects of azole antifungals, helping maintain their clinical effectiveness and the health of ecosystems. Studies indicate that wastewater treatment plants (WWTPs) are major contributors to the emergence of antifungal-resistant fungi, creating risks through the discharge of effluents. In South Africa, azole resistance has been identified in 41 fungal isolates, which include species such as Aspergillus, Fusarium, and Candida, as determined by the CLSI microdilution method. While A. fumigatus displayed sensitivity to some azoles, resistance to fluconazole was noted. Examination of the Cyp51A gene revealed an absence of mutations associated with drug resistance, suggesting that alternative mechanisms could be at play. Further investigation with a range of fungal isolates is vital for understanding the activity of WWTPs in the enhancement of azole resistance and for informing strategies to protect public health.

Once azole fungicides are released into the environment, they have the potential to affect non-target aquatic animals negatively, including algae and fish (Corcoran et al. 2014; González-Ortegón et al. 2013). The widespread application of azole antifungals raises serious concerns regarding their environmental footprint, as they can contaminate ecosystems through wastewater, agricultural runoff, and improper waste disposal, threatening non-target organisms and overall ecosystem health. The rise of azole-resistant fungal strains highlights the urgency of tackling this challenge.

According to Mzimkhulu et al. (2021), continued exposure of pathogenic yeasts to antifungal agents contributes to the development of antifungal resistance, diminishing treatment efficacy. This resistance, combined with the presence of antifungal agents and resistant yeasts, can infiltrate drinking water supplies due to ineffective treatment processes and inappropriate disposal methods, posing notable health risks for humans. To slow the advance of antifungal resistance, it is crucial to enforce stricter regulations regarding the use, management, and disposal of antifungal agents.

To increase our understanding of resistance mechanisms and reduce ecological concerns, it is crucial to do in-depth study on the distribution and prevalence of azole antifungals in the environment as well as azole-

resistant fungi. Future initiatives should focus on reducing both ecological and human health threats posed by azoles by instituting stricter regulations, promoting environmentally friendly alternatives, and improving surveillance for resistance in both environmental and clinical contexts.

Influence of Ketoconazole as a Contaminant in Water

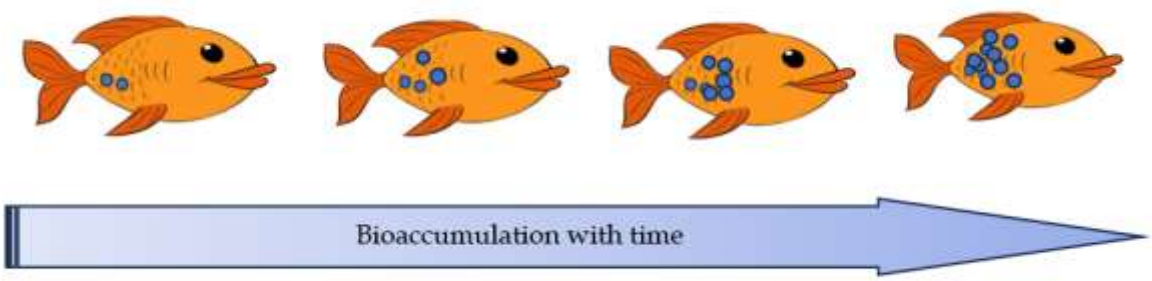
Azole antifungal medications have greatly broadened the options available for treating systemic fungal infections. These medications are divided into two main groups for systemic application: triazoles, which encompass fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole, and imidazoles, which include ketoconazole, miconazole, and clotrimazole.

KTZ, prevalent in medical use among both imidazole and triazole agents, has the potential to disrupt endocrine functions in living organisms by serving as a competitive inhibitor for a variety of CYP enzyme expressions. This inhibits fungal growth through blocking a cytochrome P450 (CYP)-mediated step in ergosterol biosynthesis.

Due to its relatively high persistence and potential for bioaccumulation (log Kow > 3), KTZ has been detected in wastewater and groundwater samples at concentrations ranging from nanograms to micrograms per liter (Chen and Ying 2015). These results emphasise the need to consider ecotoxicity of pharmaceutical residues such as KTZ that share potential persistent and bioaccumulative properties. It is available in various forms such as tablets, creams, solutions, and shampoos, is commonly used in treatment of cutaneal fungal infections. It is a potential antidandruff component (Olga et al. 2013). It usually has modest absorption rates of 5–10% via the skin when applied topically or dermally (Letzel et al. 2009). However, in aquatic conditions, rinse-off products can leave significant residues of 90–95%.

Because of its higher solubility, KTZ is more likely to contaminate important aquatic ecosystems by penetrating groundwater through soil particles. In China, KTZ, along with other antifungal medications, was detected in wastewater at concentrations ranging from 1 to 1834 ng/L in two wastewater treatment plants (WWTPs). Treated sewage effluents contained low levels (2-8 ng/L) of KTZ, miconazole and clotrimazole. This is in turn found to be similar to levels as evaluated in the sample sources from Pearl River Delta (Huang et al. 2010).

Guanghua Lu et al.'s study from 2023 looked into influence of polystyrene microplastics (PSMPs) and KTZ on Limnodrilus hoffmeistteri. It found that KTZ accumulation increased over time, particularly with MPs. Both KTZ and PSMPs, individually and combined, reduced parent and offspring weight, triggered inflammatory responses, and caused sediment avoidance behavior. They also activated antioxidant and detoxifying enzymes and altered stress-related gene expression. MPs intensified KTZ bioaccumulation, worsening sediment avoidance and inflammation, highlighting the combined toxic effects of MPs and pollutants on benthic organisms.



Research conducted in various wastewater treatment plants has explored the removal of azoles. It has been consistently found that traditional treatments could not adequately clear such compounds as has been confirmed across numerous studies.

History of Ketoconazole

The development of azole compounds marked a significant milestone in medical research for treating fungal infections. The antimycotic properties of benzimidazole were first identified by Woolley in 1944, leading to further discoveries. A key moment came in 1958 with cloruremys, which demonstrated the therapeutic potential of azoles. The late 1960s saw the introduction of important antifungals like clotrimazole and miconazole, followed by econazole in the early 1970s, rejuvenating interest in azole compounds and establishing them as essential tools against invasive fungal infections.

The FDA, in 1981, approved ketoconazole (KTZ), an imidazole derivative developed by Janssen Pharmaceutica, making it the first orally active azole antifungal. KTZ was effective against a wide range of fungal infections and set the standard for systemic triazole therapy. However, its drawbacks included limited effectiveness against certain conditions like aspergillosis, mucormycosis, and central nervous system infections, as well as gastrointestinal side effects and the risk of drug-induced hepatitis, which could lead to severe liver dysfunction. These challenges prompted the development of alternative antifungal treatments, such as intravenous triazoles like itraconazole and voriconazole, which provide more adaptable and effective options for patients.

Structural features and Properties of Ketoconazole

KTZ is a racemic mixture consisting of cis-(2S, 4R)-(−) and cis-(2R, 4S)-(+) enantiomers.

Ketoconazole (KTZ), (cis-1-acetyl-4-{4-[cis-2-(2,4-dichlorphenyl)-2-(1-imidazolylmethyl)-1,3-dioxolan-4-ylmethoxy] phenyl}piperazin) a model pharmaceutical representing imidazole and triazole, is used in the clinic, horticulture and agriculture for the treatment of fungal infections.

With a chemical formula of $C_{26}H_{28}C_{l2}N_4O_4$, and Molecular Weight of 531.4 g/mol, the KTZ molecule contains a total of 68 bond(s). There are 40 non-H bond(s), 18 multiple bond(s), 7 rotatable bond(s), 1 double bond(s), 17 aromatic bond(s), 2 five-membered ring(s), 3 six-membered ring(s), 1 tertiary amide(s) (aliphatic), 1 tertiary amine(s) (aromatic), 2 ether(s) (aliphatic), 1 ether(s) (aromatic), and 1 Imidazole(s)

IUPAC name: cis-1-acetyl-4-(4-{[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazine, (Staub, Letícia Flores et al. 2010).

The first crystal data for DAK as a dihydrochloride salt was presented, highlighting its significance as a hepatotoxic impurity and hydrolysis product of KTZ. The conformation and crystal packing were elucidated, providing essential information for quality control in KTZ batches, with powder X-ray diffraction profiles and unit cell metrics. Additionally, the occurrence of KTZ hydrolysis was confirmed using quantitative 1H NMR, Patricia da Cruz et.al 2020)

As per Xin Chen et.al, 2020), KTZ, an imidazole derivative with low aqueous solubility, was co-crystallized with five phenolic acids to enhance therapeutic effects and reduce hepatotoxicity risk. Structural information on these cocrystals was disclosed through single-crystal X-ray diffraction, revealing hydroxyl···imidazole N hydrogen bonding as a key interaction. quick sturdy hydrogen bonds have been noted in two structures, and 15N solid-country NMR furnished insights into molecular states. Dissolution assessments indicated extensively improved solubility for the new cocrystals as compared to KTZ.

Kanika Sarpal et al, (2019), throws light on how Amorphous strong dispersions (ASDs) have been formulated the usage of KTZ with hydroxypropyl methyl cellulose (HPMC) and poly(acrylic acid) (PAA) as companies. Characterization through DSC, FTIR, SSNMR, and PXRD revealed that binary KET dispersions confirmed no particular interactions, while KET and KET: PAA dispersions exhibited ionic and hydrogen bonding. The binary KET system confirmed a higher incidence of interactions in comparison to the ternary device, and all ASDs had been homogeneous at a nanometric level. stronger interactions in these structures contributed to advanced physical balance below numerous garage conditions, highlighting the want for in addition research into the outcomes of dual polymer use in ASDs.

Mechanism of action

KTZ's robust in vivo interest is basically attributed to its effective oral absorption and minimum inactivation after absorption. these residences permit the drug to maintain therapeutic levels in the body, making it an powerful treatment for diverse fungal infections whilst administered orally. This bioavailability contributes to its potency and reliability as an antifungal agent.

In vitro, KTZ demonstrates superior pastime in opposition to the invasive form of Candida albicans, which explains its effectiveness in vivo. Even at low concentrations, KTZ can save you the development of pathogenic types of the fungus. in contrast to other imidazoles, its inhibition of morphogenesis isn't suffering from serum, permitting it to maintain its antifungal interest. furthermore, KTZ works synergistically with host protection cells to eradicate systemic fungal infections, as shown in way of life research. those specific houses, located via numerous microscopy strategies, set KTZ apart from different imidazole derivatives.

KTZ's antifungal motion entails no longer handiest the inhibition of ergosterol synthesis however also the accumulation of the metabolite 14α-methyl-3,6-diol that is toxic. This buildup further disrupts fungal cell membrane integrity by increasing membrane fluidity, which interferes with the organization and function of membrane-bound enzyme systems. The reduced packing density of these components impairs critical cellular processes, leading to either cell death or the inhibition of fungal growth. This dual mechanism enhances KTZ's effectiveness in treating fungal infections (Bernd Rupp et al., 2005).

Rehab M Abd El-Baky et al, (2019), concluded that KTZ was shown to decrease the MIC of tested antibiotics by 8 to 1024-fold, confirming synergistic activity through increased inhibition zone diameters. It enhanced the accumulation of EtBr by over 2-fold and significantly improved the killing activity of levofloxacin after 24 hours compared to levofloxacin alone. KTZ decreased NorA expression by 75–87% and inhibited efflux pump activity, while docking studies indicated effective binding at the active site of 1PW4. Overall, KTZ was found to potentiate fluoroquinolone potent against multi-drug resistant S. aureus by dual mechanism of efflux pump inhibition and disruption of biofilm in vitro. KTZ is implicated with apoptosis in various cells and shown to cause hepatocellular toxicity by impairing mitochondrial function, leading to superoxide accumulation. Treatment of L. (L.) amazonensis promastigotes with KTZ indicated a trend toward apoptosis and increased autophagic vacuoles, with evidence suggesting susceptibility linked to mitochondrial dysfunction. High drug concentrations led to rapid cell loss of life via necrosis. for this reason, the have a look at investigated by way of Débora Cristina et al (2022), confirmed KTZ's consequences on mitochondrial characteristic, mobile cycle, and dying in L. (L.) amazonensis promastigotes, highlighting the drug's ability effect on parasite viability and susceptibility to remedy.

Ketoconazole (KTZ) acts as an antifungal by inhibiting lanosterol 14α-demethylase, crucial for ergosterol biosynthesis in fungi. Understanding this mechanism helps predict potential off-target effects in humans and informs risks related to drug interactions, particularly with CYP3A4. Additionally, insights into KTZ's interactions with biological systems can guide the development of new antifungal agents and inform regulatory measures regarding its environmental impact. Understanding its mechanism of action sheds light on how it can inhibit the metabolism of other drugs, leading to increased plasma concentrations and potential toxicity.

Toxicology of Ketoconazole

KTZ shows both fungicidal and fungistatic activity in opposition to quite a number of fungi, together with dermatophytes, yeast fungi, dimorphic fungi, and eumycetes. Its number one mechanism of movement involves inhibiting cytochrome P-450 enzymes, that are crucial for the synthesis of ergosterol, a key element of fungal mobile membranes. by means of disrupting ergosterol manufacturing, KTZ weakens the fungal mobile membrane, main to both cell death or inhibition of fungal increase. This dual activity makes KTZ effective in treating various fungal infections.

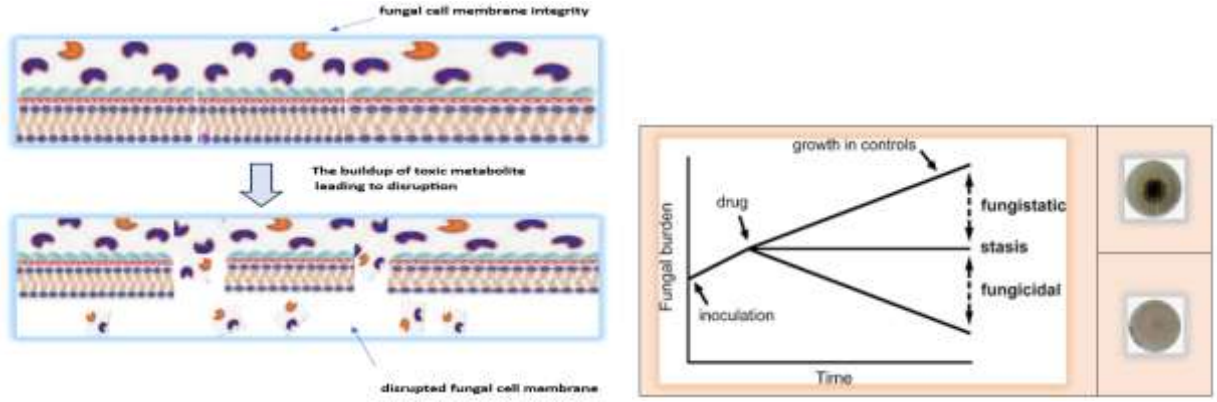


Illustration of fungicidal and fungistatic activity of Ketoconazole

KTZ's selective toxicity against yeasts and fungi is because of its inhibition of ergosterol biosynthesis, which disrupts the integrity of fungal cellular membranes. moreover, KTZ influences different membrane lipids, further compromising membrane shape and function. This selective focused on helps to minimize damage to human cells, which use cholesterol in preference to ergosterol of their membranes, making KTZ effective in treating fungal infections even as sparing human cells.

Orally administered KTZ is utilized to treat systemic fungal infections, which includes blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis, in addition to tinea infections affecting the pores and skin and nails. Its mechanism of action includes inhibiting ergosterol synthesis, a critical thing of fungal mobile membranes, by way of concentrated on the enzyme CYP51. This disruption of ergosterol production weakens the fungal cellular membrane, contributing to its antifungal effectiveness (Hegelund et al., 2004; Marty et al., 2001).

It has been established that KTZ extensively will increase oxidative harm and morphological deformities within the larval level of C. sancticaroli. Even at sub-lethal doses, KTZ demonstrates toxicological ability for non-goal aquatic organisms, together with C. sancticaroli. This highlights the significance of the use of biochemical biomarkers to advantage a more detailed understanding of the ecotoxicological consequences of

KTZ on aquatic ecosystems. In addition, KTZ has validated activity towards positive microorganism, consisting of staphylococci and streptococci. This vast-spectrum marginal similarly underscores KTZ 's versatility, even though its primary use remains as an antifungal agent.

Certainly, studies have concluded that KTZ may also have capacity antitumor ability. A few research have explored its ability to inhibit the growth of certain cancer cells. However, more studies are required to completely recognize its efficacy and the mechanisms at the back of its capacity antitumor effects. The ability of this dual role of KTZ in each antimicrobial and antitumor contexts highlights its versatility, however further research is important to establish its effectiveness and protection in most cancers remedy.

KTZ is a non-unique inhibitor of cytochrome P450 (CYP) enzymes, affecting drug metabolism and steroid hormone biosynthesis in vertebrates. This may result in drug interactions and hormonal imbalances, requiring cautious monitoring throughout therapy. KTZ has been proven to inhibit numerous drug oxidations with an extensive range of Ki values for human CYP enzymes. In vitro studies also affirm its effective inhibition of CYP1A and CYP3A enzyme sports in fish species like rainbow trout and killifish.

KTZ has been related to hepatotoxicity, making it critical to display liver characteristic tests all through treatment. Further to its effects at the liver, KTZ can purpose unfavourable results in humans, together with gynecomastia (enlargement of breast tissue) and impotence, due to its effect on steroid hormone synthesis. Thus, capability facet emphasizes the need for cautious tracking and a thorough evaluation of the dangers versus advantages whilst prescribing KTZ, ensuring that it is used competently and efficaciously.

It's known to inhibit UGT2B7, slowing the metabolism of medicine like zidovudine and lorazepam, that may lead to higher drug tiers and multiplied threat of facet effects. The effect on UGT1A substrates is much less clear, however proof indicates that KTZ will increase the ranges of SN-38, the active metabolite of irinotecan, through inhibiting its glucuronidation. This may enhance drug efficacy, however, also raises the threat of toxicity, highlighting the importance of know-how drug-drug interactions with KTZ.

In cases of KTZ overdose, signs can also encompass liver injury, with symptoms including jaundice, fatigue, nausea, and anorexia. immediate treatment might involve gastric lavage with activated charcoal if within an hour of ingestion; in any other case, supportive care is essential. high doses of KTZ (over 400 mg daily) can inhibit hormone synthesis, probably causing endocrine issues like reduced testosterone and cortisol stages, and in uncommon cases, adrenal insufficiency. This threat highlights the need for cautious tracking and the usage of the bottom effective dose for the shortest time.

The observation by means of Caio César et al (2021), on daphnids verified the ecotoxicological consequences of KTZ revealing oxidative strain harm and its position as a robust endocrine disruptor. Changes in antioxidant biomarkers indicated that KTZ triggered oxidative pressure through peroxidative and superoxide radicals. Low doses of KTZ inspired reproduction in D. similis, suggesting it having an effect on parthenogenic aquatic organisms. The findings underscore the want for similar studies on KTZ's oxidative mechanisms and the improvement of strategies to enhance the antioxidant device in affected organisms.

In a study, evaluated by means of Caio César et al (2023), the effects indicated that KTZ extensively contributes to oxidative harm in the larval stage of C. sancticaroli, primerily to growth in morphological deformities. Toxicological capacity was determined even at sub-lethal doses, highlighting C. sancticaroli's effectiveness in ecotoxicological studies. The utility of biochemical biomarkers improved the translation of KTZ's ecotoxicological responses. Similarly, research is needed to explain the mechanisms underlying KTZ-triggered oxidative pressure in aquatic organisms.

Toxic Interaction of Ketoconazole with aquatic organisms

As in step with investigation carried out by Feng-Ling Huang et al (2023), Azole fungicides can pose potential poisonous risks in the surroundings, but their combined toxicity interactions remain doubtful. This study evaluated the toxic effects of 225 binary and 126 multi-component mixtures on *Chlorella pyrenoidosa*, revealing that the pEC50 values of the individual fungicides ranged from 4.23 to 7.22. Of the 351 mixtures tested, 69.23% exhibited additive effects at a 10% effect concentration, while higher concentrations showed a mix of synergistic and antagonistic interactions. Epoxiconazole was identified as a key component inducing synergistic effects, whereas clotrimazole contributed to antagonistic mixtures.

Three azole antifungal agents—climbazole, ketoconazole, and fluconazole—alongside a quaternary ammonium compound (benzyldimethyldodecylammonium chloride, BDDA), which are frequently detected in municipal sewage sludge and/or treated wastewater, were evaluated for their toxic effects on terrestrial (Brassica napus) and aquatic (Lemna minor) plant species. The results indicated that KTZ, fluconazole, and BDDA demonstrated significant toxicity to Lemna minor, with median effective concentrations ranging between 55.7 mg/L and 969 mg/L.

The study examined how erythromycin and KTZ, both individually and in combination, affect crucian carp (Carassius auratus) to better understand their impact on aquatic ecosystems. The focus was on bioaccumulation and the role of the antioxidant enzyme Superoxide dismutase (SOD) and biotransformation enzymes like 7-ethoxyresorufin-O-deethylase (EROD) and glutathione-S-transferase (GST) were investigated. Interestingly, erythromycin buildup in the fish's bile was significantly increased by KTZ at doses of 0.2, 2, and 20 μg/L. The combined presence of the two drugs led to notable disruptions in the biochemical responses of the fish.

Research has explored the effects of estradiol (E2) and KTZ, both individually and in combination, on various endocrine functions in male goldfish (Carassius auratus). These studies evaluated changes in vitellogenin (VTG) levels in the blood and liver, liver enzyme activity (specifically CYP1A-mediated EROD activity), circulating serum E2 levels, and gene transcription related to these processes. KTZ has been shown to inhibit the glucuronidation of UGT2B7 substrates like zidovudine and lorazepam, as well as UGT1A1-mediated glucuronidation of estradiol.

Most research has focused on individual contaminants, often neglecting the effects of mixtures, which better reflect real-world exposure scenarios for fish. Research investigating the combined effects of chemicals such as benzo(a)pyrene (BaP) and KTZ on estrogenic responses induced by estradiol (E2) has demonstrated that concurrent administration of KTZ markedly inhibited the expression of enzymes modulated by E2, resulting in heightened bioaccumulation of E2. These findings suggest that the combined exposure to BaP and KTZ alters E2 bioaccumulation, impacting biotransformation and steroidogenesis in male goldfish.

The presence of azole compounds in aquatic ecosystems may impact non-target organisms, including algae, daphnia, and fish, by inhibiting the enzymatic function of cytochrome P-45014α-demethylase. (Chen and Ying 2015). Existence of azole compounds in aquatic environments can affect non-target organisms such as algae, daphnia, and fish through inhibition of enzymatic activity of the cytochrome P-45014α-demethylase (Chen and Ying 2015). KTZ, an endocrine disruptor, induces oxidative stress in aquatic organisms like daphnids by decreasing GST and APX biomarkers and increasing CAT activity, driven by oxidative radicals. Even at low doses (0.36 μg/L), KTZ stimulates reproduction in *Daphnia similis* , highlighting its influence on endocrine systems. Environmental exposure to azole antifungals, such as KTZ, is linked to toxic effects like inhibited algal growth, endocrine disruption in fish, altered sex differentiation in frogs, and reduced larval growth. Additionally, the rise of azole-resistant fungi like *Aspergillus fumigatus* ties environmental contamination to human health concerns.

Research by Imaoka et al. (2004), Jaleel et al. (2007), Liu et al. (2017), and Wan et al. (2018) found that KTZ induces cellular stress in the redox system, resulting in a decreased production of hydroxyl radicals (OH•). The organism *Daphnia similis* exhibited greater toxicological sensitivity to KTZ, with an EC50 of 4.33 ± 0.1 μg·L−1.

Another study on KTZ in fathead minnows found decreased egg production at low concentrations, but no impact on sex steroid levels. males exhibited adaptive responses to KTC exposure, emphasizing the need for knowledge such responses in ecological chance assessment. KTZ is thought for good sized drug interactions, mainly with cyclosporine, because of its inhibition of CYP3A4 enzymes, which metabolize many tablets. Co-management with cyclosporine can enhance cyclosporine levels, risking toxicity. these interactions are unpredictable and vary based on person elements, necessitating cautious tracking and dosage adjustments while KTZ is blended with other medicinal drugs.

KTZ inhibits glucuronidation of UGT2B7 substrates like zidovudine and lorazepam and has been proven to protect in opposition to carbon tetrachloride-caused acute liver harm in rats. Its shielding consequences stem from suppressing inflammation and oxidative strain, decreasing tissue damage, and scavenging reactive oxygen species. these findings propose KTZ's capability as a therapeutic agent for treating liver accidents due to poisonous substances, highlighting its promise for brand new liver sickness treatments.

studies on KTZ has often centered on its endocrine-disrupting effects in mammals, with constrained research on fish. In aquatic environments, KTZ and estrogens might also coexist, doubtlessly affecting vertebrates thru shared pathways involving steroidogenic and metabolic enzymes. Co-exposure to those chemical substances could bring about synergistic or adverse results, leading to varied negative effects. similarly studies is wanted to recognize those interactions in aquatic organisms and their implications for environmental and human health.

Azole fungicides, with half-lives of weeks to a month, have high water solubility, increasing the risk of groundwater and aquatic ecosystem contamination. In vitro studies show that KTZ competitively inhibits the glucuronidation of SN-38, particularly affecting UGT1A1 and UGT1A9, with Ki values of 3.3 μmol/L and

32 μmol/L, respectively. This inhibition explains the increased exposure to SN-38 when KTZ is co-administered with irinotecan, highlighting a significant drug interaction.

The preceding discussions indicate that KTZ, fluconazole, and BDDA demonstrated considerable toxicity to Lemna minor, with median effective concentrations varying between 55.7 mg/L and 969 mg/L. In contrast, *Daphnia similis* exhibited a markedly higher sensitivity to KTZ, evidenced by an EC50 value of 4.33 ± 0.1 μg/L. Additionally, erythromycin buildup in fish bile was significantly increased upon exposure to KTZ at doses of 0.2, 2, and 20 μg/L. Consequently, it is imperative to investigate the sensitivity and detection methods for KTZ.

According to Delphine Franssen et al. (2023), female rats' GnRH secretion and hypothalamus transcriptome were impacted by perinatal exposure to diethyl stilbestrol (DES) and KTZ. Both compounds produced similar transcriptional changes, with KTZ significantly altering gene expression before puberty and having lasting effects into adulthood. Enriched pathways and differentially expressed genes at postnatal day (PND) 22 remained altered at PND 90, indicating their potential as biomarkers for endocrine disruptor testing and risk assessment.

Understanding the toxic interactions of ketoconazole with aquatic organisms is essential for developing effective sensing methods to monitor its environmental presence and mitigate potential ecological risks.

Sensing of Ketoconazole

This substance has been detected in numerous aquatic environments and its concentrations variety from ng to g/L (Lindberg et al., 2010; Van De Steene and Lambert, 2008). The evaluation of the responses obtained from the water and fish tissue samples was performed using ultra-performance liquid chromatography tandem triple quadrupole mass spectrometry (UPLC/MS/MS). The qualitative analysis of metabolites was executed through UPLC/MS/MS by employing full-scan mode, product-ion scan mode, and multiple reaction monitoring mode.

The characterized nanostructure was analyzed using a range of techniques, including energy-dispersive X-ray spectroscopy (EDX), X-ray diffraction (XRD), and field emission scanning electron microscopy (FE-SEM). The evaluation of the electrocatalytic performance of the constructed electrode was carried out using several techniques, including cyclic voltammetry (CV), differential pulse voltammetry (DPV), linear sweep voltammetry (LSV), and chronoamperometry. The limit of detection (LOD) for the developed sensor regarding KTZ was established at 0.04 μM. The reaction was observed to occur within a dynamic concentration range of 0.1–110.0 μM in a phosphate buffer solution. The developed electrode exhibited significant electrocatalytic activity for the oxidation of KTZ, showing a high sensitivity of 0.1342 μA·μM−1. The sensor's ability to detect KTZ in actual aqueous samples was validated through standard addition experiments.

Modifications to the surface of the carbon paste electrode were made using Ce-BTC MOF NS and an ionic liquid, facilitating the electrochemical detection of KTZ. The modified electrode demonstrated remarkable sensitivity and selectivity for the target analyte, exhibiting a low limit of detection. The linear dynamic range extended from 0.1 to 110.0 μM (R^2 = 0.9906), with a limit of detection as low as 0.04 μM in the optimized conditions. Additionally, the diffusion coefficient was calculated to be 5×10^{-6} cm^2/s, while the electron transfer coefficient was determined to be 0.49. The realistic applicability of the as-fabricated changed electrode changed into showed via efficaciously sensing KTZ in actual prescription drugs and urine specimens, reaching pleasant recuperation quotes.

The fabrication and analytical programs of varieties of potentiometric sensors for the willpower of KTZ are outlined. these sensors utilize KET-molybdophosphoric acid (MPA) ion pairs as electroactive substances. The constructed sensors comprise polymer membrane and carbon paste electrodes. Both types of sensors demonstrated linear, robust, and nearly Nernstian responses, with slopes measuring 57.8 mV/decade for the polymer membrane sensors and 55.2 mV/decade for the carbon paste sensors. These responses were observed across a significantly broad range of KET concentrations, specifically from 1 × 10−2 to 5 × 10−5 for the polymer membrane and from 1 × 10−2 to 1 × 10−6 for the carbon paste sensors. The sensors verified speedy response times of much less than 30 seconds and 45 seconds for the % membrane and carbon paste sensors, respectively. each variety of sensors exhibited a useful pH variety of 3–6. The % membrane sensor executed a detection restrict of 2.96 × 10−5 M, while the carbon paste sensor displayed a lower detection restriction of 691 × 10−6 M. moreover, The proposed sensors exhibited excellent selectivity for KTZ when compared to a wide variety of ions. Successful applications of these sensors have been demonstrated for the quantification of KET in pharmaceutical formulations, yielding results that were in strong alignment with those obtained through conventional methods.

In this study, a new modified glassy carbon electrode (GCE) has been developed, which integrates carbon black (CB) and gold nanoparticles (AuNPs) within a crosslinked chitosan (CTS) matrix. The electroanalytical capabilities of the CB-CTS-AuNPs/GCE were assessed for the voltammetric detection of KTZ, a widely utilized antifungal drug. Characterization of the nanocomposite was performed using scanning electron microscopy (SEM), X-ray diffraction (XRD), and a range of electrochemical methods. The electrochemical behaviour of KTZ at the modified electrode was explored, revealing an irreversible oxidation reaction occurring at a potential of +0.65 V (vs. Ag/AgCl (3.0 mol L−1 KCl)). This redox reaction was utilized for the detection of KTO via square-wave voltammetry. The resulting calibration curve demonstrated linearity across the KTO concentration range of 0.10 to 2.9 μmol L−1, with a limit of detection (LOD) of 4.4 nmol L−1 and a sensitivity of 3.6 μA L μmol−1. The modified electrode was effectively employed for the quantification of KTO in pharmaceutical products and biological fluid samples.

An advanced voltametric sensor characterized by high sensitivity and selectivity has been developed for the detection of KTZ in real samples. This sensor employs a specially modified carbon paste electrode that features a distinctive sheaf-like Ce-BTC metal-organic framework (MOF) nanostructure combined with an ionic liquid. The synthesized nanostructure underwent comprehensive characterization through various methods, including field emission scanning electron microscopy (FE-SEM), energy-dispersive X-ray spectroscopy (EDX) and X-ray diffraction (XRD). The electrocatalytic properties of the modified electrode were evaluated using techniques such as linear sweep voltammetry (LSV), cyclic voltammetry (CV), differential pulse voltammetry (DPV) and chronoamperometry. The sensor demonstrated a limit of detection (LOD) for KTZ at 0.04 μM, with a detection range spanning from 0.1 to 110.0 μM in a phosphate buffer solution. The proposed electrode demonstrated significant electrocatalytic activity for the oxidation of KTC, achieving a high sensitivity of 0.1342 μA·μM−1. Additionally, the sensor successfully detected KTC in real aqueous samples, as confirmed by
standard addition experiments.

An extraordinarily sensitive anti-KCZ monoclonal antibody (mAb) became evolved by way of Yuan Cheng et al (2022), accomplishing an IC50 of 0.7 ng/mL and a detection variety of 0.20–2.55 ng/mL the use of IC-ELISA. primarily based in this mAb, a competitive gold immunochromatographic assay (CGIA) for KCZ residue detection in chicken samples turned into set up. beneath most beneficial situations, the tested limit of detection (vLOD) and CGIA reduce-off values had been 0.5 ng/g and 20 ng/g, respectively, confirmed by IC-ELISA and LC-MS/MS methods. The CGIA is suitable for speedy detection of KCZ residues in fowl.

A fairly sensitive voltammetric approach for the electrochemical oxidation of KTZ has been evolved through Sandeep R. Kurundawade et al (2024), the use of a TiO2-HNC/glassy carbon electrode. Characterization of the electrode become performed with XRD and SEM–EDS analyses. top-quality oxidation occurred at pH 7.0, revealing an irreversible, diffusion-managed system with a linear detection variety of 1.0 to 10.0 μM. The detection restrict changed into observed to be 1.67 nM, surpassing preceding findings. The sensor demonstrated stability and sensitivity, making it appropriate for detecting KTZ in organic and pharmaceutical samples, with potential packages in pharmacokinetics and best manage.

A modified glassy carbon electrode incorporating carbon black (CB) and gold nanoparticles (AuNPs) within a crosslinked chitosan (CTS) matrix was developed by Fernando Cruz Moraes et al. (2024) for the voltammetric detection of KTZ. Characterization techniques adopted to verify an irreversible oxidation process occurring at +0.65 V by using scanning electron microscopy and X-ray diffraction. A linear analytical method was developed to achieve a limit of detection (LOD) of 4.4 nmol L−1 and a sensitivity of 3.6 μA L μmol−1 for KTO concentrations between 0.10 and 2.9 μmol L−1. The electrode demonstrated effective detection of KTO in both biological and pharmaceutical matrices.

The effective sensing of ketoconazole is a crucial first step that enables accurate quantification, ensuring reliable assessments of its concentration in various environments and applications.

Quantification of Ketoconazole

The concentrations of KTZ in both water and fish tissues were utilized to calculate tissue-specific bioconcentration factors (BCFs) for various tissues. The BCF values in various tissues demonstrated an inverse correlation with the exposure concentrations in the fish. The BCF values obtained in this study were found to be lower than those predicted by the model, attributable to several factors: (1) KTZ was more readily bioconverted in fish, resulting in reduced accumulation in tissues; (2) The 14-day exposure duration was insufficient for attaining full saturation of the tissues with KTZ.; and (3) The exposure concentrations significantly influenced the bioconcentration of KTZ, likely leading to lower accumulation levels in fish tissues than those anticipated.

KTZ demonstrated significant uptake by crucian carp from the ambient water at different nominal concentrations (0.2, 2, and 20 mg/L) over a period of 14 days. There was a steady rise in the levels of KTZ in the liver, brain, and muscle tissues during the exposure period; however, the bioconcentration factor (BCF) values were found to be lower than expected. The efficient metabolism of KTZ led to the discovery of seven metabolites in the fish tissues, with N-deacetyl KTZ identified as the primary metabolite present in the liver. Alterations in biological responses, such as increased activity of superoxide dismutase (SOD) and the suppression of acetylcholinesterase (AChE), 7-ethoxyresorufin-O-deethylase (EROD), and glutathione S-transferase (GST) activities, seemed to be associated with the absorption and metabolism of KTZ within the tissues of the fish. These results underscore the importance of combining physiological and biochemical biomarker responses with measures of tissue bioaccumulation in fish, positioning them as potential "bioindicator" species for assessing pharmaceutical contamination in aquatic ecosystems. (3) The Ag3PO4/GO composite was effectively synthesized using the in situ growth technique. Characterization analyses indicated that the Ag3PO4 nanoparticles were adequately encapsulated within the GO sheets leading to the formation of The nanocatalysts exhibited a narrow band gap, enabling activation under visible light. Central composite design (CCD) was employed for the modeling and optimization of the photocatalytic degradation of KTZ. The experimental data were analyzed using second-order regression models. Under optimal conditions (1.62 g catalyst dosage, 5.87 mg/L KTZ concentration at pH 8 after 93.34 minutes of contact time), a removal efficiency of 96.53% for KTZ was achieved with the Ag3PO4/GO nanocomposite. When compared to pure Ag3PO4, the Ag3PO4/GO photocatalyst exhibited a 2.3-fold enhancement in photocatalytic activity. The enhanced performance can be ascribed to a direct Z-scheme mechanism that optimizes redox processes and improves the stability of the nanocomposite. As a result, the Z-scheme Ag3PO4/GO photocatalyst exhibits significant promise for the elimination of other comparable persistent organic pollutants at low concentrations in the environment. (4) Laccase effectively detoxified KTZ when optimized for enzyme activity, pH, and temperature. Additionally, the impact of HBT, a laccase mediator, at varying concentrations was explored in eliminating the substrate. This system holds promise for the biotransformation of non-phenolic pollutants and the mitigation of their toxicities. However, its efficacy in true wastewater containing KTZ needs verification through further studies. (5) An RQ (Risk Quotient) based method was employed to assess the potential human health and ecological risks associated with the presence of azole antifungal drugs in treated wastewater and/or drinking water. This approach serves as a rapid screening tool for evaluating large groups of emerging pollutants, facilitating further assessment and monitoring. The results of the risk assessment indicated that concentrations of azole antifungals detected in effluent wastewater are unlikely to cause significant detrimental effects on algae, daphnia, and fish populations. (6) he bioconcentration of ERY in fish brains appeared to increase with the addition of KCZ, indicating a potential bioconcentration risk for fish in scenarios of co-exposure to complex pharmaceutical mixtures. Reduced AChE activity induced by both ERY and KCZ, either alone or combined, at the end of the exposure period raises concerns about potential neurotoxicity with continual life-cycle exposure in natural waters. Additionally, observed behavioural changes suggest modifications in wild fish behaviour due to pharmaceutical exposure, likely impacting ecosystems. Furthermore, significant correlations between biochemical responses (AChE activity) and behavioural alterations (swimming activity and shoaling) imply that neurological and behavioural responses may result from ERY and KCZ accumulation in the brain and subsequent biochemical effects.

Understanding the quantification of ketoconazole not only provides insight into its presence and concentration but also serves as a foundational element for conducting comprehensive degradation studies on its stability and environmental behaviour.

Degradation studies of Ketoconazole

KTZ experiences degradation when exposed to ultraviolet (UV) and visible light, particularly in the presence of a photocatalyst derived from the residual materials of a Ziegler-Natta catalyst used in petrochemical processes. The most significant rates of drug degradation were recorded at 48.6% under UV radiation and 45.2% under visible light.

The Ag3PO4/GO nanocomposite demonstrated significantly improved photocatalytic efficiency in the degradation of KTZ, achieving a performance level 2.4 times higher than that of pure Ag3PO4. This enhancement in activity is ascribed to the operation of a direct Z-scheme mechanism. These results highlight the potential of the Ag3PO4/GO nanocomposite as an effective nano photocatalyst for the degradation of azole contaminants, demonstrating high activity, satisfactory reusability, and strong stability in aqueous environments.

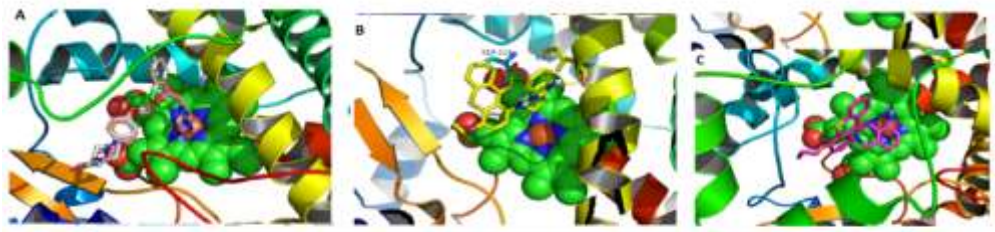
Extending the reaction time from 15 minutes to 120 minutes led to a notable improvement in photocatalytic efficiency. Specifically, the degradation of KTZ increased from 50.8% to 98.3% for Ag3PO4/GO, while for Ag3PO4, the degradation rose from 43.8% to 76.12%. This development changed into attributed to the technology of greater reactive oxygen species with extended touch time, leading to more desirable degradation. track et al. (2016) further found that the degradation of tetracycline the usage of BWO-cross elevated with irradiation time. ANOVA consequences indicated that contact time was the most critical aspect, with p-values < 0.0001. vital composite design (CCD) became hired to version and optimize the photocatalytic degradation procedure, with experimental information becoming second-order regression models. Under optimized conditions (1.62 g of catalyst, 5.87 mg/L of KTZ at pH 8 for 93.34 minutes), the Ag3PO4 nanocomposite achieved a KTZ removal efficiency of 96.53%. The Ag3PO4/go photocatalyst demonstrated a photocatalytic activity that was 2.3 times greater than that of pure Ag3PO4.

The insights gained from degradation studies of ketoconazole are essential for a docking approach, as they inform the potential metabolites and interactions that may influence the compound's toxicological profile.

Docking approach to understanding toxicity of Ketoconazole

An overview of molecular docking methods, their evolution, and applications in drug discovery can be evaluated. It covers fundamental theories such as sampling algorithms and scoring functions, and discusses the differences and performance of existing docking software. The challenges posed by flexible receptor docking, with a focus on the Local Move Monte Carlo (LMMC) approach as a potential solution, are also considered.

The study on automated docking simulations entailed the development of three-dimensional models for KTZ and 4′,5′-Odicaffeoylquinic acid (4′,5′-ODCQA). The validation of the structures and the formal charges of the atoms was conducted through two-dimensional representations. This was succeeded by a conformational search and energy minimization of all conformers, utilizing the Molecular Operating Environment (MOE) version 2014.09 at the Faculty of Pharmacy, Assuit University, in partnership with Chemical Computing Group Inc. based in Montreal, Canada.



Representation of the crystallographic ligand ketoconazole (grey) and best docking binding conformations of the same compound (orange) (A) in CYP3A4 binding pocket.

Overall, docking facilitates the discovery of novel compounds with therapeutic potential by predicting interactions between ligands and targets at a molecular level. It enables the exploration of ligand-target interactions and helps delineate structure-activity relationships (SAR) even when the chemical structure of other target modulators is not known beforehand.

The findings from the docking approach, which elucidate the toxicological mechanisms of ketoconazole, are crucial for informing the regulatory aspects surrounding its use, safety assessments, and potential health risks.

Regulatory aspects of Ketoconazole

With reference to FDA Drug Safety Communication, KTZ, a potent inhibitor of CYP3A4, can elevate plasma levels of co-administered drugs, increasing the risk of adverse reactions like QT prolongation. Its use is restricted in drug labels due to this. It's not recommended as a first-line treatment for any fungal infection, including candidiasis or superficial fungal infections. However, it may be considered in life-threatening systemic mycoses when alternate antifungal drugs are unavailable or intolerable.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has approved KTZ HRA for use in the EU, recognizing that its benefits outweigh its risks. The decision was based on the well-established use of KTZ HRA in treating Cushing's syndrome, supported by scientific literature. Given the rarity of the disease, additional treatment options are necessary, further justifying its approval. Regarding safety concerns, the CHMP believes that the risk of liver problems associated with KTZ HRA can be effectively managed through appropriate measures.

Following a TGA news alert, it's noted that liver injury is a recognized risk associated with oral KTZ treatment. Consequently, several risk minimization measures have been implemented over the years. Janssen-Cilag (Australia), in collaboration with the TGA, has deregistered oral KTZ (Nizoral) 200 mg tablets since December 1, 2013, and supplies have been discontinued. However, it's important to note that topical forms of KTZ, such as Nizoral cream and shampoo, remain available and unaffected by this change.

Future perspectives

Despite the implementation of labelling changes and market withdrawal for oral KTZ due to significant adverse effects, topical KTZ is widely regarded as both effective and safe for managing superficial fungal infections. Recent dermatological applications for topical KTZ have emerged, including its use in treating onychomycosis, blepharitis, and hair loss. This article seeks to review existing literature concerning the efficacy and adverse effects of topical KTZ, while also offering an overview of current understanding regarding its mechanism of action and future developments. Topical KTZ has demonstrated clinical effectiveness in treating Malassezia-related conditions, such as seborrheic dermatitis (SD) and pityriasis versicolor (PV), with reported efficacy rates ranging from 63% to 90% and 71% to 89%, respectively.

To mitigate the environmental risks of ketoconazole (KTZ), policymakers should establish stricter regulations on its manufacturing and disposal, and promote eco-friendly practices in the pharmaceutical industry. Comprehensive monitoring programs are essential for assessing KTZ levels in various environments, while public education campaigns can raise awareness about the importance of proper pharmaceutical disposal. Encouraging collaboration between pharmaceutical companies, environmental scientists, and regulatory bodies can lead to the development of safer alternatives. Finally, allocating funding for research into KTZ's ecological impacts and mitigation strategies will foster innovative solutions to address these environmental challenges effectively.

CONCLUSION:

Molecular docking methods play a crucial role in drug discovery by predicting ligand-target interactions and aiding in the exploration of structure-activity relationships. The study highlights the automated docking of KTZ showcasing the potential of docking to identify novel therapeutic compounds. it emphasizes the significance of those techniques in advancing drug improvement.

KTZ is a mighty CYP3A4 inhibitor with limited use due to risks like QT prolongation and liver injury. whilst the eu drug treatments agency has accredited KTZ HRA for treating Cushing's syndrome, oral forms have been deregistered in Australia because of safety concerns, despite the fact that topical formulations continue to be to be had.

Topical KTZ exhibits significant therapeutic effectiveness in conditions associated with Malassezia. Currently, there are additional highly effective treatments available for Tinea and Candida infections. Although topical KTZ is generally considered safe, healthcare providers should remain vigilant regarding the potential for allergic contact dermatitis to develop. Further research is warranted to explore the application of topical KTZ in the treatment of hair loss and inflammatory skin disorders.

Future research on ketoconazole (KTZ) as an environmental pollutant should prioritize several key areas. First, investigations into the long-term ecological effects of chronic exposure to KTZ in aquatic organisms are essential. This research should focus on life cycle impacts, reproductive toxicity, and population dynamics in sensitive habitats. Additionally, studies examining the transfer of KTZ through the food chain are critical, particularly regarding bioaccumulation and biomagnification across various trophic levels. Such insights will enhance our understanding of its ecological impact and the potential risks to human health from consuming contaminated wildlife.

Another important area of study involves assessing the environmental degradation of KTZ and its metabolites. By understanding how these transformation products impact ecological health and their toxicity profiles, researchers can gain valuable insights. Furthermore, developing mitigation strategies is vital, including improving wastewater treatment processes and creating biodegradable alternatives to help minimize ecological risks.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used [Grammarly] in order to [modulate a statement with least errors]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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