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REVIEW PAPER

Exploring the versatility of ciclopirox – from anti-fungal to anticancer agent and beyond

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ABSTRACT

Introduction and aim. Ciclopirox has been treating fungal infections for decades. Recent studies suggest ciclopirox may be repurposed to treat cancer, viral infections, and neurological disorders. Ciclopirox exerts anticancer by inhibiting multiple pathways of cancer cell growth and survival and anti-viral actions by reducing viral replication and altering the host immunological response to viral infection. Recent research suggests that ciclopirox may protect against neurodegenerative illnesses including Alzheimer's and Parkinson's. This narrative review shows ciclopirox's potential to treat cancer, viral infections, and neurological diseases.

Material and methods. Current relevant research publications focused on ciclopirox and its repurposing medicinal potential, therefore a well-designed technique was used to find them. „Ciclopirox", „Anti-fungal", „Anti-cancer", „Repurposing", and „Therapeutic potential" were used to search PubMed, Web of Science, EMBASE, and Google Scholar.

Analysis of literature. Ciclopirox may reduce oxidative stress and inflammation, which may cause several illnesses. Overall, the repurposing of ciclopirox for the treatment of cancer, viral infections, and neurodegenerative disorders represents a promising avenue of research that warrants further investigation.

Conclusion. It was concluded that CPX and olamine derivatives as outstanding antifungal medications, as well as provide information on ongoing research to use them for other illnesses.

Keywords. AIDS, anti-fungal, cancer, cardiovascular diseases, ciclopirox

The list of abbreviations:

CPX – ciclopirox, **CPO** – ciclopirox olamine, **CPX-POM** – fosciclopirox, **HPCH** – hydroxypropyl chitosan, **VVC** – vulvovaginal candidiasis, **BBB** – blood–brain barrier, **AKT** – protein kinase B, PKB/AKT, **GSK3** – glycogen synthase kinase 3, **RR** – ribonucleotide reductase, **AML** – acute myeloid leukaemia, **DOHH** – deoxyhypusine hydroxylase, **HIF–1α** – hypoxia inducible factor–1α, **eIF5A** – eukaryotic translation initiation factor 5A

Introduction

In the current period of serious dermatological disorders, there is a demand for effective medications that can treat a variety of conditions. Ciclopirox (CPX) is

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a promising therapy choice for a number of dermatological conditions due to its broad-spectrum antifungal activity, capacity to target various stages of the fungal life cycle, and minimal toxicity. CPX is a unique formulation with an array of uses (Table 1 and Fig. 1). While it is primarily used as an antifungal drug, it can also be utilized as an anti-inflammatory medication. This antifungal drug unlike others belongs neither to the azole nor the imidazole class of chemical agents but is uniquely from the hydropyridone class, one which has been proven incredible to be incredibly effective against a wide spectrum of dermatological disorders. These include dermatophytes and those caused by microorganisms including yeast, fungi, bacteria, etc.[1]

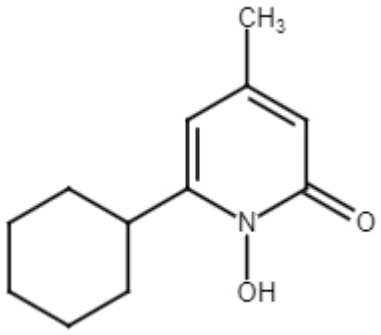

Fig. 1. Chemical structure of ciclopirox

Table 1. Chemical properties and names of ciclopirox

IUPAC	6-cyclohexyl-1-hydroxy-4-methyl pyridin-2-one
Generic	Ciclopirox
Synonyms	Batrafen, ciclopiroxolamine, cyclopirox, ciclopiroxium, HOE-296, Loprox, Penlac.
Molecular weight	207.27
Molecular formula	$C_{12}H_{17}NO_2$
Half-life	1.7 hours
Melting point	143°C-144°C

CPX antifungal topical drug therapy has a unique and different mechanism of action. This drug acts by penetrating the nails and other sites if administration and counters the ill effects of infection like brittle nails, scaly patches and many more by acting on the infection causing microbes. In minimal concentration, CPX acts by blocking the transportation of amino acids across the cell membrane.[2] Studies that have been undertaken on CPX prove that its sole use may not be restricted to its isolated antifungal action only but it can act for a variety of other purposes too. One of the many involve its action as an antibacterial. It's antibacterial action includes targeting both gram-positive (*Staphylococcus aureus, Enterococcus faecalis*) as well as gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumoniae*).[3] Another of its many functions is as an HIV-1 inhibitor.[4] In this inhibitory action, the novel drug is believed to inhibit deoxyhypusine hydrolyse an inhibitor of the cell cycle through inhibition of DNA polymerase alpha. Research has also proved that CPX besides the above-mentioned uses, can also be efficacious in treating malignant leukaemia and a variety of cancers. These include myeloma, colorectal cancers and various types of tumours. CPX, a unique formulation of hydroxypirdone is an antifungal therapy that has been used for over three decades for various skin-related purposes as well as a nail lacquer. This Distinctive cream-based antifungal therapy gained USFDA approval in June 2004 and has been used Ever since for an array of functions.[5] CPX has been developed using unique drug innovation technology, which is rational drug designing. Researchers identified a specific enzyme (squalene epoxidase) that is essential for the growth of fungi and yeast. They then used this knowledge to design a molecule (CPX) that would bind to the enzyme and inhibit its function, thereby stopping the growth of the fungi. Onychomycosis is a typical infectious disease caused by fungi and may be incredibly painful and uncomfortable. Barring degradation of the patient's quality of life it may also cause immense physical impairment. CPX formulations are also used for the treatment and management of the disease.[6] Generally, an 8 % CPX hydroxypropyl chitosan (HPCH) formulation is considered most suitable and is used to treat mild to moderate fungal infections.[7]

The current scenario of dermatophytes is extensively alarming and calls for careful attention. Innumerable studies have been undertaken to look into the same and management still seems to be a challenging aspect to deal with. Whilst studies on different topical antifungals was being considered it was majorly concluded that CPX is not only a safe and efficacious option for antifungal therapy but also proves to be useful to patients who do not respond to other antifungal. Therefore, the considerations of this versatile antifungal in dermatological diseases is proving to be highly beneficial.[8] Furthermore, beyond its established use as an antifungal agent, CPX has shown potential in a number of different fields. Its possibility for use in the treatment of autoimmune diseases, cancer, and neurodegenerative disorders is currently being studied in researches that are ongoing.

Aim

It is a narrative review that reveals the repurposing potential of ciclopirox to cure cancer, viral infections, and neurodegenerative disorders.

Material and methods

Current relevant research publications focused on ciclopirox and its repurposing medicinal potential, therefore a well-designed technique was used to find them. „Ciclopirox", „Anti-fungal", „Anti-cancer", „Repurpos-

ing", and „Therapeutic potential" were used to search PubMed, Web of Science, EMBASE, and Google Scholar. The search method included applicable keywords, The search phrases, which were adapted to the study's specific goals, included „Ciclopirox," „Anti-fungal," „Anti-cancer," „Repurposing," and „Therapeutic potential," among other terms. After the initial search, retrieved articles were screened based on predetermined inclusion and exclusion criteria. The inclusion criteria encompassed includes up-to-date and pertinent information sources that are mostly vetted based on articles written during the last five years, Articles that helped provide information on drug repurposing based on clinical and preclinical trials conducted on ciclopirox were primarily screened using the titles of the subsections to be covered from research websites. Relevant and reliable information sources from reputable Journals were also used while the exclusion criteria were designed to exclude articles that did not meet the specific research focus.

Analysis of literature

History of ciclopirox

The German pharmaceutical company Merz Pharmaceuticals GmbH first developed the drug in the 1970s (Fig. 2). The development of CPX began with the screening of a large number of compounds for their antifungal properties. One of the compounds, named CPX-772, showed promising activity against a variety of fungi.[9] Further studies showed that CPX-772 had a unique mechanism of action, disrupting the function of the fungal cell membrane.[10] In 1985, Merz Pharmaceuticals obtained a patent for the use of CPX as an antifungal agent. The drug was subsequently approved for use in Europe and Japan in 1987, and in the United States in 1990. CPX is now available as a topical cream, lotion, or nail lacquer for the treatment of various fungal infections, including onychomycosis (fungal nail infection), pityriasis versicolor (a fungal infection of the skin), and seborrheic dermatitis (a skin condition characterized by red, scaly patches).[10,11] CPX has also been studied for its potential use in the treatment of other conditions, such as cancer and Alzheimer's disease. Some studies have shown that CPX may have anti-tumor and neuroprotective effects, although more research is needed in these areas.[11] CPX is generally well-tolerated, with mild and transient side effects such as burning or itching at the site of application. However, in rare cases, more severe allergic reactions or skin irritation may occur. Today, CPX is manufactured and marketed by several pharmaceutical companies around the world, and is widely used as a safe and effective treatment for fungal infections of the skin and nails.[12]

Structure activity relationship of ciclopirox

CPX is called 1-hydroxypyridin-2(1H), which has methyl and cyclohexyl groups at meta and para respectively as substitutes for hydrogen (Fig. 3). It is a cyclic hydroxamic acid.[13] The sixth position is set aside for a lipophilic substitution, which allows you to swap out the hexyl ring with another type of ring, such as phenol. The medicine becomes less oily as a result, but the strength remains unaffected. The medication loses between 10 and 30 times its potency when the hexyl ring is moved from position 6 to positions 5 or 4. This demonstrates that what you put on the carbon as well as being greasy is what makes it strong. The medicine might eventually be strengthened by adding a methyl group at position 4 along with another component, as removing the methyl group has no effect on the drug's potency. The hexyl ring can be lengthened by adding more components to the sixth position, or a benzyl group or ring can take its place. Even if the benzyl ring is modified with a 4-chloro or methoxy group, the drug's effectiveness is unaffected.[14-16]

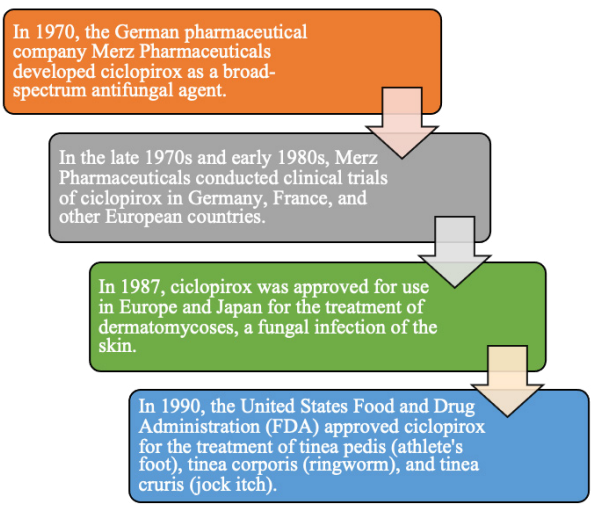

Fig. 2. Timeline of ciclopirox development starting from 1970 to recent uses

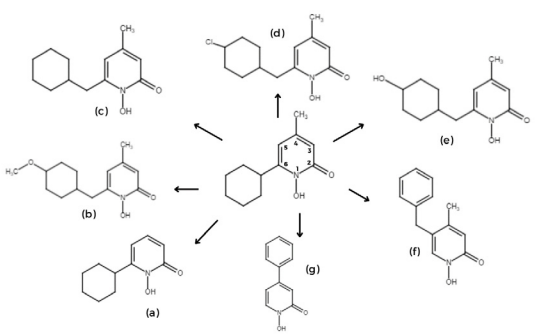

Fig. 3. Different substitution and modification to ciclopirox structure. (a) Desmethyl ciclopirox, cyclohexyl connected via methyl bridge replacement to (b) 4-methoxy phenyl, (c) phenyl, (d) 4- chlorine substituted phenyl, (e) phenol, (f) substitution on fifth position of benzyl connected by methyl bridge, (g) removal of side chain and substitution of methyl to benzene

General mechanism of ciclopirox

CPX acts by different mechanisms compared to normal antifungals like azoles, imidazoles, etc. CPX acts as a chelating agent for metal ions and inhibits metal-dependent enzymes confirmed by the genomic approach. Instead of intruding sterol biosynthesis of organisms like other agents it possesses a high affinity to trivalent metal cations like Fe^{3+} thus affecting cytochromes.[17] Not only cations but also radicals i.e., hydroxyl radicals are entrapped and provide relief from inflammation of the skin. These radicals are formed by superoxide anion which goes under dismutation by NADPH oxidase which also has an action against microbes.[18,19] Enzymes are degraded and electron transportation to mitochondria is hindered. creates an environment where it is hard for growing cells to take up amino acids that are essential for their growth.[17] Peroxides damage proteins, lipids, and nucleic acids, these peroxides degrading enzymes are inhibited by CPX as they chelate Al^{3+} and Fe^{3+} cations which affect the working of enzymes in low concentration.[3,18] It inhibits respiration in Candida albicans and at high concentrations, oxidation of NADH through mitochondria in yeast that are sensitive to inhibition that isolation of mitochondria.[3] CPX also acts on ferritin which is an iron complex involved in the activity of cysts in polycystic kidney disease. CPX inhibits the accumulation of ferritin in cysts via ferritinophagy. Ferritinophagy is ferritin degradation that results from its binding to nuclear receptor coactivator 4 present on autophagolysosome.[20] The anti-inflammatory action of CPX is likely due to the inhibition of cyclooxygenase and 5-lipooxygenase.

Pharmacokinetics and pharmacodynamics of ciclopirox

Pharmacokinetics

Absorption

Ciclopirox (CPX) absorption varies based on the formulation and route of administration (Table 2). Topical cream 1 % is equivalent to 0.77 % CPX as the olamine group has no activity.[5] In recent studies, CPX only partially penetrates deeper skin layers while maintaining larger concentrations on the skin's outermost layers. Peak blood levels of CPX are attained after a particular amount of time following topical application. For instance, peak serum levels of up to 0.01 mg/L are attained after 6 hours following the application of roughly 36 mg of the active component (CPX cream 1%). when studied using cadaverous skin, a horny layer showed the presence of more than the required inhibition concentration which is valued around 2300–2400 mg/cm^3.[21] To address specific medical needs, CPX is offered in a number of formulations. These compositions include shampoos, creams, gels, suspensions, and lacquers. Different amounts of CPX content and absorption properties are provided by each formulation. One recent development in pharmaceutical research is mucoadhesive films that contain CPX. These films stick to mucosal surfaces, enabling targeted drug delivery, increased local concentrations, and prolonged drug release. This advancement shows potential for boosting CPX's effectiveness in many therapeutic applications and promoting patient compliance.[22-24]

Radiolabelling CPX has shown that on the skin surface the most concentrated areas are the hair follicle and the upper dermis layer. It is safe to say that the absorption into the systemic region, the sebaceous gland, and the dermis which takes place through the hair follicles. Peak serum concentration is around 1.7 hours. Over 6 hours from administration, an average of 1.3 % of CPX (1%) was absorbed when applied on a 750 cm^3 area of skin.[25] Absorption is rapid when oral doses are administered. The penetration of CPX is dependent on how is the structure of the nail. The more damaged, the rougher, and the more fissured the nail is by myocyte the better and deep was the absorption of CPX.[17] Vaginal dosage gives 7 to 9 % absorption as 2 % douche for 6 days or 100 mg vaginal pessaries once daily for 3 days.[26]

Distribution

The concentration of CPX achieved in the nail bed exceeds the minimum inhibitory concentration required for onychomycosis compared to other fungal applications used (Table 2). The nail lacquer of CPX, after 24 hours of application, has shown a concentration ranging from eight μg/mg in the uppermost layer to 0.03 μg/mg in the deepest layer.[27] An open labelled study was carried out where five healthy subjects were asked to apply 8% nail lacquer for 24 to 26 weeks, once daily that is before bed on their toe nails and another group of 5 healthy individuals were asked to apply it on finger nails. CPX is highly keratinophilic and shows penetration into the nail bed through keratin like materials. CPX is distributed to all tissues but the highest concentrations are found in the kidney, liver, and smooth muscles of the stomach when given orally. The placental transfer is almost negligible.[28]

Metabolism

Protein binding is 94 to 97% by administration of CPX topically.[29,30] The main pathway of metabolism of the drug is through glucuronidation. Specifically, UGT1A1 and UGT1A9 are the main isoforms responsible for the glucuronidation of CPX. Other metabolic pathways of CPX include oxidative metabolism by cytochrome P450 enzymes, which leads to the formation of hydroxylated metabolites. CPX was extensively glucuronidated, consistent with substantial first-pass metabolism of the drug. The $t_{1/2}$ of CPX glucuronide was similar to that of the parent compound, ranging from 1.3 to 6.2 h.[31]

Excretion

The urine primarily containing 80% of the dose, which is converted into glucuronide metabolite, excretes CPX (Table 2). Bile juice excretion does not happen. These findings suggest that CPX has a low potential for drug interactions and is generally well-tolerated.

Table 2. Summary of ciclopirox pharmacokinetics

Aspect	Summary	Reference
Absorption	- topical: limited deep, high surface - rapid oral and hair follicle absorption - vaginal: 7–9% absorption	5,21-26
Distribution	- effective in nails, high in kidney, liver, smooth muscles of stomach when given orally.	27
Metabolism	- mostly glucuronidation, CYP450 metabolism	31
Excretion	- mostly in urine, minimal interaction risk	1

Pharmacodynamics

CPX works by inhibiting the fungal cell membrane synthesis, disrupting the function of membrane-bound enzymes and transporters, and reducing the synthesis of ergosterol. It also exhibits antibacterial and anti-inflammatory properties, which make it useful in the treatment of skin infections and inflammatory conditions.[32] CPX binds to the fungal cell membrane and disrupts its function, causing a loss of membrane integrity and leading to leakage of cellular contents.[33] This leads to the inhibition of fungal growth and ultimately results in the death of the fungal cell. The anti-inflammatory activity of CPX is thought to be due to its ability to inhibit the production of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumour necrosis factor-alpha.[34]

Pharmacological actions of ciclopirox

The diverse inhibitory activities of CPX and its derivatives allow for a wide range of pharmacological applications (Table 3). Due to the chelating effect of trivalent and other ions, these compounds have been used for their action as antifungal, antibacterial, anti-inflammatory, and many other purposes. It's fascinating because CPX has lately been discovered to have a significant amount of potential to act against many other diseases, such as cancer, diabetes, AIDS, cardiovascular issues, inflammation, and bacterial infection. These results suggest that CPX is a highly promising drug for the treatment and prevention of a variety of disorders.

Ciclopirox as an anti-fungal

The possibility of CPX olamine as an antifungal drug was originally raised in 1973. It has a very a broad spectrum of action that inhibits practically all clinically relevant dermatophytes, yeasts, and moulds, including the azole-resistant *Candida* species *Candida glabrata, Candida krusei,* and *Candida guilliermondii*.[11] Depending upon its contact time it could be fungistatic or fungicidal. After a week, CPX olamine starts to have fungicidal effects. Fungicidal tests with a chosen strain of *T. mentagrophytes* revealed that fungicidal concentrations of CPX olamine against non-proliferating and proliferating fungal cells were approximately 30 times the minimum inhibitory concentration after 1 day of exposure of the organism to graded concentrations of the drug.[24] On the other hand, fungicidal and inhibitory concentrations were comparable after a week of CPX olamine exposure.[35] The reduction in CPX's antifungal activity could be due to the presence of iron salts in some media, which can combine with CPX to create complexes that are microbiologically inactive. The growth medium has an impact on the MIC of CPX olamine for common strains of *C. albicans* and *Trichophyton mentagrophytes*. Selected fungi were inhibited by CPX olamine at a dosage of 1.95 mg/L in the medium employed by scientists to test the drug's *in vitro* activity, whereas in thioglycolate medium, the same strains required a concentration of 31 to 62 mg/L to be inhibited.[1,36] Using a widely available agar diffusion technique, the *in vitro* antifungal activity of CPO was compared to that of clotrimazole, econazole, ketoconazole, miconazole, tioconazole, fluconazole, itraconazole, and nystatin. (NeoSensitabsTM, RoscoTM, Taastrup, Denmark), which had previously been described and assessed in collaborative works by Casals (1979). In order to treat candidiasis, antifungal medications were employed as 9 mm diameter tablets (NeoSensitabs, Rosco, Taastrup, Denmark). These tablets were made and supplied by the manufacturer. Only one yeast strain (0.4 %) and four (1.8 %) were deemed moderately susceptible to CPX, while 220 strains were susceptible (97.3 %) out of 225 yeast strains.[37,38] Some of the strains and their susceptible "n" in percentage are *C. albicans* (n=75), *C. parapsilosis* (n=21), *C. glabrata* (n=25), *C. tropicalis* (n=25); "n" represents the number of strains of the yeast species used in the experiment. Total 225.[39]

Ciclopirox as anti-inflammatory

An antifungal drug that simultaneously has intrinsic anti-inflammatory effect would be highly desired since superficial fungal infections may be accompanied by significant inflammation. The anti-inflammatory properties of CPX and its derivatives have been examined in *in vitro* and *in vivo* studies. Since ciclopirox is non-toxic and unlikely to irritate skin, it has a number of advantages. In both biochemical and pharmacological settings, it also has weak anti-inflammatory capabilities, demonstrating excellent tolerance and a noticeable absence of serious side effects. *In vitro* studies have demonstrated that CPX inhibits the formation of 5-lipoxygenase metabolites (5-HETE and leukotriene LTB4) as well as prostaglandin E2 (PGE2) cellular release.[40] The test for arachidonic acid-induced ear edema can be used to

measure topical anti-inflammatory activity. According to the percentage difference from inflamed control ears, CPX effectively lowers arachidonic acid-induced ear edema. In comparison to the anti-inflammatory medicines indomethacin and desoximetasone, this occurred at a rate that was about two times greater than what was observed with naftifine, ketoconazole, fluconazole, or miconazole.[25] Significant inflammation might be brought on by cutaneous candidiasis. In a double-blind, randomised comparative investigation, 96 patients with cutaneous candidiasis were enrolled and randomly allocated to receive either CPX olamine cream 1% or clotrimazole cream l%. Both treatments were successful; at the final evaluation two weeks following the end of active therapy, the final clinical cure rates for those receiving CPX olamine and clotrimazole were 76 and 63%, respectively; mycologic cure rates were likewise equal. However, those receiving CPX olamine showed earlier clinical improvement; in comparison to those getting clotrimazole, a considerably higher proportion of these patients were evaluated as clinically cured at weeks 1, 2, and 3.[41] In a different comparison study, 1% CPX olamine cream was shown to be just as effective as 1% clotrimazole cream for treating *tinea corporis* and *tinea cruris*. In this experiment, both treatment groups saw a similar time course of recovery throughout the duration of 4 weeks of therapy. In a multicenter, double-blind trial of patients receiving therapy for 4 weeks, it was discovered that the inflammatory signs and symptoms of tinea pedis responded preferentially to CPX olamine cream 1% as opposed to clotrimazole cream 1%. Early on in the experiment, there were particularly noticeable disparities between the therapy groups. At week 1, the CPX olamine group's clinical response rate (improvement and cure) was noticeably greater than the clotrimazole group's (93% versus 71 %, $p<0.01$). Only 2 % of the 43 patients who received clotrimazole obtained a clinical cure, compared to 26 % of those who received CPX olamine. For the CPX group, clinical cure rates and combined clinical and mycologic cure rates were greater in weeks two and three after therapy and at weeks five and six after treatment ($p<0.05$). The two groups' final cure rates did not significantly differ from one another.[3]

Ciclopirox as anti-bacterial

Secondary bacterial infections can make superficial mycotic illnesses more difficult. Although other antifungal substances also possess antibacterial capabilities, CPX stands out from the competition due to its larger scope and more consistent activity, particularly its ability to combat Gram-negative bacteria. *Trichomonas vaginalis* and *Mycoplasma* species have both been shown to be sensitive to CPX.[40] Numerous Gram-positive and Gram-negative bacteria are susceptible to CPX *in vitro*. It is advantageous for CPX to be active against Gram-negative germs rather to certain azoles, which are more effective against Gram-positive bacteria. It is advantageous to treat macerated *tinea pedis* because CPX has a broad range of action that encompasses both gram-negative infections and fungal pathogens.[25] Recent research using a standardised microdilution method revealed that CPX was active against both Gram-positive and Gram-negative bacteria, with a MIC range of 0.06-2 mg/mL against B-haemolytic *Streptococcus* group A, *Proteus mirabilis, Escherichia coli, K. pneumoniae, S. aureus*, and Micrococci. MICs of 16-32 mg/mL for Gardnerella vaginalis and greater than 128 mg/mL for Lactobacillus species were found in more recent tests utilising bacteria isolated from clinical samples of vaginal swabs.[40] Minimal inhibitory concentrations (MIC) for bacterial isolates (n=45) were established using a standardised microdilution technique. The MIC range for CPX is 0.06-2 g/mL, and it shown action against every isolate tested, including Gram-positive and Gram-negative.[9]

Repurposing the forgotten anti-fungal CPX

An anticancer therapeutic

In terms of how it affects dermatophytes, yeast, filamentous fungus, and bacteria, CPX has a very broad range of activity. The methods by which CPX exerts these effects appear to be varied, involve altering membrane function in fungi or focusing on various metabolic (respiratory) and energy-producing activities in bacteria. CPX may also have an impact on the yeast *Saccharomyces cerevisiae* by interfering with intracellular transport, mitotic spindles, cell division signals, and DNA repair. In addition to its antibacterial and antimycotic properties, CPX also causes cell cycle arrest in the G1 phase in human cells and the G_2/M phase in yeast *S. cerevisiae*.[42-44] According to the most current research, CPX-induced cell death was linked to the chelation of intracellular iron and the suppression of the iron-dependent enzyme ribonucleotide reductase. Without causing severe organ damage or weight loss in NOD/SCID mice models, it appeared that CPX hindered the engraftment of primary acute myeloid leukaemia (AML) cells and appeared to cause cell death in primary human AML cells. Studying the *in vivo* impact of CPX on the growth of the human breast cancer MDAMB231 tumour in a mouse xenograft model was done in order to give more preclinical support for the development of CPX as an anticancer treatment. Results demonstrate that CPX potently reduced tumour development by preventing tumour cell proliferation and causing apoptosis *in vivo*. The preclinical anticancer potential of CPX against solid tumours such as rhabdomyosarcoma, breast cancer, prostate cancer, and colon cancer is still being evaluated.[45] According to research, there are two substances that reversibly halt the lymphocyte cell cycle. In late G_1, 1-2 h before the GUS boundary, which is determined by APH, the

compound mimosine (MIMO) reversibly stops the progression of B cells. Another substance, [2-(4-hydroxytoluene-3-yl)-4,5-dihydro-4carboxythiazole] (HTDCT; Hoechst 768159), inhibits T lymphocyte activation after the stimulation of cell surface transferrin receptors, suggesting that HTDCT may also operate in late G_1 phase.[46] The chemical CPX, which blocks the HL-60 promyeloid leukaemia cells' cell cycle reversibly at the same location close to the G_1/S phase boundary, produces the same results. After performing the flow cyclometer methodology, it was determined that, in contrast to the exponentially growing control, all arrest cell growth in the G_0/G_1 phase of the cell cycle. A batch of synchronously developing cells has advanced through the S phase around halfway after a 5 hours release.[47] CPX and HTDCT arrest HL-60 cells in late G_1 as determined by a series of drug release and readdition tests. Aphidicolin (APH), an inhibitor of DNA polymerase α activity, was also intended to show this. APH stops G_1 phase cells from entering the S phase just beyond the G_1/S barrier. It has been shown in the past using this strategy. The two chemicals CPX and HTDCT have an effect on HL-60 cells just before the early S phase arrest detected by APH, which takes place close to the G_1/S phase boundary. With no delay or a 1 h delay, cells discharged from CPX and HTDCT into APH do not reach the S phase.[46]

Additionally, by suppressing the production of vascular endothelial growth factor, CPX can prevent human umbilical vein endothelial cells from proliferating and forming new blood vessels.[48] Recent research indicates that CPX also prevents lymphatic endothelial cells from forming tubes, which may prevent lymphangiogenesis. These discoveries further underline the potential of CPX for the treatment and prevention of cancer since angiogenesis and lymphangiogenesis are essential for carcinogenesis and metastasis.[49] According to research, CPX prevents deoxyhypusine hydroxylase from working (DOHH). DOHH is an iron-dependent enzyme, just the same as RR.[50] Deoxyhypusine is transformed to hypusine via DOHH, which is necessary for the development of eukaryotic translation initiation factor 5A (eIF5A), an integral to maintaining translation elongation.[51,52] Deoxyhypusine hydroxylation was inhibited in a concentration-dependent manner when CPX and [3H]-spermidine were treated with exponentially developing HUVECs for 20 hours. Only [3H]-hypusine, not [3H]-deoxyhypusine, was found in the cellular protein hydrolysates of control HUVECs and HUVECs that had received 2.5 μM or less of CPX. At larger dosages (5-100 M), CPX inhibited deoxyhypusine hydroxylase, resulting in the formation of the intermediate [3H]-deoxyhypusine and a corresponding drop in [3H]-hypusine. Based on the fact that the IC_{50} for this inhibition was around 5 M and no [3H]-hypusine was identified at >10 M, the deoxyhypusine hydroxylase was totally inhibited. We compared the effects of CPX and the other test chemicals on DNA synthesis in HUVECs since deoxyhypusine hydroxylation and eIF5A have been connected to cell proliferation. All substances induced concentration-dependent suppression of DNA synthesis 18 hours into the therapy. A 10 μM IC_{50} for CPX demonstrated the highest inhibition.[53]

Cells were transfected with cDNA matching to the ribonucleotide reductase M2 subunit of ribonucleotide reductase (RRM2) or vector control in order to ascertain if inhibiting ribonucleotide reductase was functionally significant for CPX-induced mortality. Ribonucleotide reductase is the enzyme in charge of converting nucleoside diphosphates into deoxynucleoside diphosphates, so providing a consistent supply of deoxyribonucleotides for DNA synthesis. Because the ribonucleotide reductase M2 subunit of this enzyme contains an iron core that is necessary for the complex's enzymatic activity, it is iron-dependent.[54] After that, cells were exposed to CPX at progressively higher doses, and the MTS test was used to gauge cell viability. RRM2 overexpression prevented CPX-induced cell death, proving that ribonucleotide reductase inhibition is crucial for CPX's cytotoxic effects. Notably, CPX was more than 200 times more effective than hydroxyurea, a ribonucleotide reductase inhibitor that functions in a different way than CPX. As a result, CPX has an anticancer impact through at least one mechanism, which is the suppression of ribonucleotide reductase activity.[55]

Diabetes management

Diabetes causes endoplasmic reticulum (ER) stress to be induced on pancreatic β-cells, which is associated with pancreatic dysfunction. Because cells are unable to meet the increasing demands for insulin generation and secretion, endoplasmic reticulum (ER) stress is fundamental to the pathophysiology of diabetes. This loss of cell mass occurs over time. When treating diabetic mice with nutlin-3a, the proapoptotic effects of p53 are still present without p21, which decreases islet survival and function. Studies through experimentation reveal that the drug CPX, which promotes p21 expression, has an impact on insulin release in cultured pancreatic islets and glucose homeostasis in diabetic animals. Wild type mice's pancreas expressed p21 when CPX was administered at doses as low as 5 mg/kg. Inducing a decrease in blood glucose levels, CPX at 25 mg/kg once day significantly improved glucose homeostasis. A diabetic animal with blood sugar levels of 180 mg/dl is noteworthy since CPX treatment had a similar impact on p21, albeit at greater doses. Following CPX therapy, ferritin levels considerably reduced ($P<0.05$) from their high state in the diabetic mice's serum. Due to CPX injection having no effect on glucose levels in wild type non-diabetic mice, the effects of CPX on glucose homeostasis were

only seen in diabetic mice. CPX provides protection for pancreatic islets in the presence of p21/p53 expressions at glucotoxic levels.[56-59] The hypo-insulin condition results from islet cells, which are in charge of secreting insulin, malfunctioning or even dying. As a result of the pro-inflammatory cytokine's activation of inducible nitric oxide synthase expression and subsequent generation of nitric oxide, ATP synthesis is blocked, insulin secretion is inhibited, and cell death is induced.[60] According to one theory, eIF5A moves *Nos2* mRNA from the nucleus to the cytoplasm to encourage translation of the *Nos2* gene, which codes for inducible nitric oxide synthase. For eIF5A-mediated *Nos2* mRNA trafficking and the pathogenesis of islet cells, eIF5A must be hypusinated. Since CPX olamine has an IC_{50} of roughly 5 M and can inhibit DOHH, an essential enzyme for hypusination of eIF5A, it is promising to use CPX olamine for treating Type I diabetes.[61]

For acquired immune deficiency syndrome (AIDS)

CPX suppresses HIV replication in human peripheral blood mononuclear cells. In host cells, eIF5A is expressed and is implicated in the nucleocytoplasmic trafficking of viral mRNA and HIV replication. HIV replication is impeded by DOHH suppression, which interferes with hypusine formation on eIF5A. CPX olamine has been suggested to have a significant potential for the treatment and prevention of AIDS due to its powerful inhibitory action on the DOHH-eIF5A axis. Drugs hindered the maturation of eIF5A and inhibited substrate binding to DOHH.[61] At the RNA level, viral gene expression from HIV-1 molecular clones was inhibited independently of all viral genes. The inhibition took place at the stage of HIV-1 transcription beginning and was specific to the viral promoter. The suppression of HIV-1 gene expression caused by partial eIF5A-1 knockdown by siRNA was non-additive to medication activity.[62] Acute infection is suppressed and infected cells are preferentially eliminated when using the antifungal drug CPX, which inhibits retroviral gene expression in persistently infected T cells while concurrently activating the intrinsic route of death.[4] The 5'-untranslated region of HIV, which is not only necessary for HIV replication but also for the most conserved area of the HIV genome, is the focus of CPX's unique mechanism of blocking HIV gene expression. As a result, CPX could be able to counteract treatment resistance caused by HIV's variable nature.[63]

For anti-hepatitis B virus

HBV replication in cells and mice by blocking assembly of the HBV capsid. The crystal structure of the HBV core protein and the ciclopirox complex revealed a novel binding mode at dimer-dimer interfaces. It is also found that ciclopirox synergized with NAs to prevent HBV replication in cells and in a humanized liver mouse model. Orally administered ciclopirox may block HBV capsid assembly effectively and thus provide a novel opportunity to combat chronic HBV infection.[64] In an article written by Kang et al.[65] they performed experiments on mice using 978 FDA approved drugs using Cp149-Y132A as marker for core protein inhibition in HBV, it was discovered that ciclopirox showed inhibition of HBV capsid assembly and secretion of HBV DNA in infected cells in vitro and in mice. Due to particular residue and loop

Table 3. Summary of ciclopirox pharmacodynamics

Medical condition	Pharmacodynamic properties of ciclopirox and mechanism	References
Anti-fungal	Ciclopirox exhibits broad-spectrum antifungal activity by inhibiting fungal growth through interference with cell membrane integrity and transport processes. It targets various fungi, including dermatophytes, yeasts, and molds. Mechanism is various like reducing oxidating NADPH, inhibiting ferritin accumulation and chelating metal ions, etc	3,1
Anti-inflammatory	The anti-inflammatory action of CPX is likely due to the inhibition of cyclooxygenase and 5-lipooxygenase	40
Anti-bacterial	Ciclopirox demonstrates antibacterial properties by disrupting bacterial cell membranes and interfering with essential metabolic pathways. It has shown effectiveness against some gram-positive and gram-negative bacteria. Mechanism is quite similar to how it acts as an anti-fungal drug i.e., through ferritin and other metal ions chelation and inhibition. This affects cytochrome activities	3,20
Anti-cancer	Ciclopirox has been investigated for its potential anti-cancer effects due to its ability to inhibit cell proliferation and induce apoptosis in certain cancer cell lines. It may interfere with multiple signalling pathways involved in cancer growth and survival. It shows many mechanisms but suppression of ribonucleotide reductase activity is ultimate result	55,83,84
Anti-HIV	Studies suggest that ciclopirox may possess anti-HIV activity by blocking viral entry, replication, and maturation stages. It could inhibit enzymes and viral interactions required for HIV replication within host cells. Hinders the maturation of eIF5A and inhibited substrate binding to DOHH	62
Anti-HBV	Ciclopirox has been explored for its anti-hepatitis B virus (HBV) activity. It may inhibit HBV replication by interfering with viral polymerase activity and affecting viral protein synthesis, thereby suppressing viral load. It inhibits HBV capsid assembly and secretion of HBV DNA in infected cells. Also synergizes with NAs to prevent HBV replication in cells	65, 81
Anti-diabetic	Ciclopirox has shown potential in reducing insulin resistance by modulating cellular pathways involved in glucose metabolism. It may enhance insulin sensitivity and offer benefits in managing type 2 diabetes. CPX which promotes p21 expression which is vital for survival of pancreatic islet	56-59
Neurological disease	Emerging research suggests that ciclopirox might have neuroprotective effects by modulating signalling pathways involved in neurodegeneration. It could potentially offer therapeutic benefits in neurological disorders. Decreases the cell cycle and nitric oxide (NO) release in lipopolysaccharide (LPS)-induced BV-2 cells by phosphorylation of AKT and GSK3	67
Cardiovascular disease	Ciclopirox's impact on cardiovascular diseases is less studied. Some evidence indicates its potential to affect pathways relevant to cardiovascular health, but further research is needed to establish its direct effects in this area. CPX-induced HIF-1 promotes the increased production of urocortin 2, which has been shown to improve cardiac output and myocardial contractility	68,82

Table 4. List of documented preclinical studies of ciclopirox as a potential therapeutic molecule

Drug administered	Model	Dose	Duration of study	Study design	Results	Ref
Ciclopirox	Dermatophytes (110 strains; 98 from *Trichophyton* spp.), *Candida* spp. (14 strains)	0.003–2 µg /mL	7 days	Microbroth dilution *in vitro* susceptibility test as per National Committee for Clinical Laboratory Standards (NCCLS) M27-A proposed standard	Minimum inhibitory concentration 100% growth inhibition. MIC values) (µg/mL) for dermatophyte: (0.03–0.25), yeast: (0.001–0.25)	[9]
Ciclopirox	Non-dermatophyte moulds (nine strains)	0.003–4 µg /mL	72 h	Checkerboard microdilution method	The non-dermatophyte fungi MIC values (microg mL-1) (mean±SEM) were: ciclopirox (1.04±2.62)	[69]
Fulcare [ciclopirox hydroxypropyl chitosan nail lacquer]	Bovine hoof slices	75 µl	30 h	Transungal permeations of bovine hooves	Amount permeated (3.29±0.67%, wt/wt) in the slices. Works not only on nail plates but also on nail beds	[72]
Ciclopirox	*Escherichia coli*	Varied concentrations of ciclopirox	Not specified	*In vitro* study	- Ciclopirox inhibited the growth of *E. coli* in a dose-dependent manner. -The antibacterial effect was enhanced when ciclopirox was combined with low levels of iron	[73]
Ciclopirox Olamine	Murine myeloma model	Not specified	Not specified	*In vivo* experimental study	- It suppressed tumor growth and prolonged survival in the mice. - The drug reduced the expression of Wnt pathway-related proteins and inhibited myeloma cell proliferation	[74]

Table 5. Documented clinical trials of ciclopirox as an antifungal agent

Indication	Study type	Sample size	Treatment	Duration	Results	Refs
Onychomycosis	Randomized, double-blind, placebo-controlled	131	Ciclopirox cream	48 weeks	Significantly improved nail appearance and mycological cure compared to placebo	[75]
Onychomycosis	Randomized, double-blind, vehicle-controlled	131	Ciclopirox nail lacquer	48 weeks	Significantly greater complete cure of the target toenail compared to vehicle	[76]
Seborrheic dermatitis	Randomized, double-blind, placebo-controlled	43	Ciclopirox shampoo	4 weeks	Significantly reduced severity of seborrheic dermatitis compared to placebo	[77]
Tinea pedis	Randomized, double-blind, placebo-controlled	87	Ciclopirox cream	4 weeks	Significantly improved signs and symptoms of tinea pedis compared to placebo	[78]
Vulvovaginal candidiasis	Randomized, double-blind, placebo-controlled	297	Ciclopirox cream	7 days	Significantly improved clinical and mycological cure compared to placebo	[79]
Diaper dermatitis	Randomized, double-blind, placebo-controlled	90	Ciclopirox cream	14 days	Significantly improved diaper dermatitis compared to placebo	[80]

modifications, ciclopirox binds to three out of the hydrophobic pocket's six binding sites in the HBV core protein when it is complexed with it. Additionally, ciclopirox demonstrates synergistic actions that prevent HBV replication when coupled with TDF and ETV. This implies ciclopirox may be thought of as a supplement to TDF or ETV therapy for HBV-infected individuals. When cells were treated with 1 M ETV or TDF with varied doses of ciclopirox (0.1–10 µM), HBV DNA secretion was synergistically inhibited. Many other studies show a potential of ciclopirox to be used as an adjunct therapy with HBV medications.[66]

Neural diseases and cardiovascular

Acute cerebral thrombosis causes the serious disease known as an ischemic stroke. In a traditional rat model of ischemic stroke, CPX post-ischemic therapy reduced brain infarction, neurological impairments, and brain edema. A single dosage of CPX administered after an ischemic stroke had occurred had a long-lasting neuroprotective effect that might be strengthened by administering further doses. Additionally, CPX successfully repaired the blood-brain barrier (BBB) damage, glial activation, and neuronal loss brought on by ischemia. In oxygen glucose deprivation (OGD) exposed SH-SY5Y cells, CPX significantly increased the phosphorylation of AKT (protein kinase B, PKB/AKT) and GSK3 (glycogen synthase kinase kinase 3), and it significantly decreased the cell cycle and nitric oxide (NO) release in lipopolysaccharide (LPS)-induced BV-2 cells, which may help.[67] Through the activation of Hypoxia-inducible factor-1α, CPX is able to mitigate the lowered responsiveness to inotropic stimulation in aged myocytes (HIF-1). Additionally, CPX-induced HIF-1 promotes the increased production of urocortin 2, which has been shown to improve cardiac output and myocardial contractility, lessen peripheral resistance, and lessen the effects of ischemia.[68]

Pre-clinical and clinical trials of ciclopirox

Preclinical and clinical studies have been conducted to evaluate its efficacy and safety profile (Table 4 and 5). A study published by Gupta investigated the *in vitro* antifun-

gal activity of CPX against 51 strains of dermatophytes, which are fungi that cause skin infections. The study found that CPX was effective against all tested strains, suggesting its potential for the treatment of dermatophyte infections.[69] Another preclinical study published by Gupta A.K evaluated the efficacy of CPX in treating nail infections caused by dermatophytes. The study found that CPX penetrated the nail plate and reached therapeutic levels in the nail bed, indicating its potential as a topical treatment for onychomycosis.[70] In addition, CPX has been studied for its potential to treat other conditions, such as psoriasis and cancer. For instance, a study found that CPX could inhibit the growth of cancer cells and induce cell death *in vitro* and *in vivo*.[71]

Conclusion

An efficient anti-fungal medication called CPX has fallen out of favour over time. Because of its distinct mechanism of action, *in vitro* and *in vivo* effectiveness, broad-spectrum antimycotic coverage, additional antibacterial and anti-inflammatory activity, well-established safety, excellent tolerance, lack of drug resistance currently, with an extremely low likelihood of developing resistance in the future, and accessibility, CPO 1% cream may be the best topical antifungal for superficial cutaneous mycoses. RR, DOHH/eIF5A, Wnt/-catenin, HIF-1/VEGF, VEGFR-3/Erk1/2, mTOR, and CDKs are just a few of the enzymes or signalling pathways that CPX has the power to influence. The majority of these actions are associated with its chelation of iron. As a result, CPX has been discovered to have novel potentials, such as inhibiting the growth of tumours, reducing diabetes and its consequences, preventing HIV infection, and enhancing age-related cardiovascular abnormalities. Acute and latent nervous system infection, blepharitis development, and HSV-1 multiplication in the cornea are all decreased by topical therapy with CPX olamine. It is uncertain if CPX prevents infection of the neurological system only due to its effect on corneal replication, however this is doubtful given that low dosage CPX appeared to have a disproportionally high effect on accumulation of latent genomes. It is available worldwide in various formulations for the treatment of superficial fungal infections, including tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis, and tinea versicolor. Excellent bioavailability of CPX was seen after subcutaneous injection, showing the viability of this mode of administration should CPX-POM therapy prove effective in an outpatient or ambulatory cancer treatment context. For the treatment of both muscle-invasive and non-muscle-invasive bladder cancer, CPX-POM is currently being developed. Acute myelogenous leukaemia in humans, breast cancer, rhabdomyosarcoma, and colon carcinomas are among the illnesses for which CPX has recently been repositioned as a viable treatment drug. It is also used to combat viruses that cause HIV, HPV and other infections, as well as cyst formation in polycystic kidney disease. Its diversity is still underappreciated, particularly in light of the pharmaceutical industry's emphasis on creating and promoting „newer azoles". Most notably, CPX can help control treatment-resistant dermatophytic infections, tinea incognito, mixed infections, and recurrent VVC as well as the threat of steroid misuse. Ciclopirox's multi-faceted mechanisms of action make it an intriguing candidate for repurposing in the treatment of cancer, diabetes, HBV, neural degradation, and HIV. While preliminary evidence is encouraging. With continued research and exploration, CPX has the potential to bring significant benefits to patients suffering from various diseases and become a valuable addition to the pharmacological armamentarium.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Not applicable.

References

1. Jue SG, Dawson GW, Brogden RN. Ciclopirox Olamine 1% Cream A Preliminary Review of its Antimicrobial Activity and Therapeutic Use. *Drugs*. 1985;29(4):330-341. doi: 10.2165/00003495-198529040-00002
2. Sigle HC, Thewes S, Niewerth M, Korting HC, Schäfer-Korting M, Hube B. Oxygen accessibility and iron levels are critical factors for the antifungal action of ciclopirox against Candida albicans. *J Antimicrob Chemother*. 2005;55(5):663-673. doi: 10.1093/jac/dki089
3. Abrams BB. Ciclopirox Olaminer A Hydroxypyridone Antifungal Agent. *Clin Dermatol*. 1991;9(4):471-417. doi: 10.1016/0738-081x(91)90075-v
4. Hoque M, Hanauske-Abel HM, Palumbo P, et al. Inhibition of HIV-1 gene expression by Ciclopirox and Deferiprone, drugs that prevent hypusination of eukaryotic initiation factor 5A. *Retrovirology*. 2009;6:90. doi: 10.1186/1742-4690-6-90
5. Sonthalia S, Agrawal M, Sehgal VN. Topical Ciclopirox Olamine 1%: Revisiting a Unique Antifungal. *Indian Der-*

matol Online J. 2019;10(4):481-485. doi: 10.4103/idoj.IDOJ_29_19

6. Piraccini BM, Iorizzo M, Lencastre A, Nenoff P, Rigopoulos D. Ciclopirox Hydroxypropyl Chitosan (HPCH) Nail Lacquer: A Review of Its Use in Onychomycosis. *Dermatol Ther (Heidelb)*. 2020;10(5):917-929. doi: 10.1007/s13555-020-00420-9
7. Iorizzo M, Hartmane I, Derveniece A, Mikazans I. Ciclopirox 8% HPCH Nail Lacquer in the Treatment of Mild-to-Moderate Onychomycosis: A Randomized, Double-Blind Amorolfine Controlled Study Using a Blinded Evaluator. *Skin Appendage Disord*. 2016;1(3):134-140. doi: 10.1159/000441569
8. Saraf V, Mahajan S, Deshmukh G, Dhoot D, Barkate H. Effectiveness and safety of ciclopirox olamine in patients with dermatophytosis: a retrospective cohort analysis. *International Journal of Research in Dermatology*. 2020;7:38. doi: 10.18203/issn.2455-4529.IntJResDermatol20205592
9. Kokjohn K, Bradley M, Griffiths B, Ghannoum M. Evaluation of in vitro activity of ciclopirox olamine, butenafine HCl and econazole nitrate against dermatophytes, yeasts and bacteria. *Int J Dermatol*. 2003;42(1):11-17. doi: 10.1046/j.1365-4362.42.s1.4.x
10. Niewerth M, Kunze D, Seibold M, Schaller M, Korting HC, Hube B. Ciclopirox Olamine Treatment Affects the Expression Pattern of Candida albicans Genes Encoding Virulence Factors, Iron Metabolism Proteins, and Drug Resistance Factors. *Antimicrob Agents Chemother*. 2003;47(6):1805-1817. doi: 10.1128/AAC.47.6.1805-1817.2003
11. Chen L, Chen D, Li J, et al. Ciclopirox drives growth arrest and autophagic cell death through STAT3 in gastric cancer cells. *Cell Death Dis*. 2022;13(11):1-13. doi: 10.1038/s41419-022-05456-7
12. Belenky P, Camacho D, Collins JJ. Fungicidal Drugs Induce a Common Oxidative Damage Cellular Death Pathway. *Cell Rep*. 2013;3(2):350-358. doi: 10.1016/j.celrep.2012.12.021
13. ciclopirox (CHEBI:453011). https://www.ebi.ac.uk/chebi/searchId.do?chebiId=453011. Accessed November 18, 2022.
14. Hu L, Feng H, Zhang H, et al. Development of Novel N-hydroxypyridone Derivatives as Potential Anti-Ischemic Stroke Agents. *J Med Chem*. 2020;63(3):1051-1067. doi: 10.1021/acs.jmedchem.9b01338
15. Lin J, Zangi M, Kumar TVNH, et al. Synthetic Derivatives of Ciclopirox are Effective Inhibitors of Cryptococcus neoformans. *ACS Omega*. 2021;6(12):8477-8487. doi: 10.1021/acsomega.1c00273
16. Liu Z, Yao Y, Kogiso M, et al. Inhibition of Cancer-Associated Mutant Isocitrate Dehydrogenases: Synthesis, Structure–Activity Relationship, and Selective Antitumor Activity. *J Med Chem*. 2014;57(20):8307-8318. doi: 10.1021/jm500660f
17. Bohn M, Kraemer KTh. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. *J Am Acad Dermatol*. 2000;43(4):57-69. doi: 10.1067/mjd.2000.109072
18. Sato E, Kohno M, Nakashima T, Niwano Y. Ciclopirox olamine directly scavenges hydroxyl radical: A hydroxyl radical scavenger, ciclopirox olamine. *Int J Dermatol*. 2007;47(1):15-18. doi: 10.1111/j.1365-4632.2007.03359.x
19. Nakashima T, Sato E, Niwano Y, Kohno M, Muraoka W, Oda T. Inhibitory or scavenging action of ketoconazole and ciclopiroxolamine against reactive oxygen species released by primed inflammatory cells. *Br J Dermatol*. 2007;156(4):720-727. doi: 10.1111/j.1365-2133.2006.07655.x
20. Radadiya PS, Thornton MM, Puri RV, et al. Ciclopirox olamine induces ferritinophagy and reduces cyst burden in polycystic kidney disease. *JCI Insight*. 2021;6(8):e141299. doi: 10.1172/jci.insight.141299
21. Kellner HM, Arnold C, Christ OE, et al. Pharmacokinetics and biotransformation of the antimycotic drug ciclopiroxolamine in animals and man after topical and systemic administration. *Arzneimittelforschung*. 1981;31(8A):1337-1353.
22. Gajdošová M, Vetchý D, Muselík J, et al. Bilayer mucoadhesive buccal films with prolonged release of ciclopirox olamine for the treatment of oral candidiasis: In vitro development, ex vivo permeation testing, pharmacokinetic and efficacy study in rabbits. *Int J Pharm*. 2021;592:120086. doi: 10.1016/j.ijpharm.2020.120086
23. Rachh MR, Barot BS, Parejiya PB, Shelat PK, Deshpande SS. Development and characterization of ciclopirox olamine loaded buccoadhesive film for treatment of oral candidiasis. 2013;3(1):360-365.
24. Dhamoon RK, Popli H, Gupta M. Novel Drug Delivery Strategies for the Treatment of Onychomycosis. *PNT*. 2019;7(1):24-38. doi: 10.2174/2211738507666190228104031
25. Gupta AK, FRCP(C). Ciclopirox: an overview. *Int J Dermatol*. 2001;40(5):305-310. doi: 10.1046/j.1365-4362.2001.01156.x
26. Farr A, Effendy I, Frey Tirri B, et al. Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k). *Mycoses*. 2021;64(6):583-602. doi: 10.1111/myc.13248
27. Subissi A, Monti D, Togni G, Mailland F. Ciclopirox: Recent Nonclinical and Clinical Data Relevant to its Use as a Topical Antimycotic Agent. *Drugs*. 2010;70(16):2133-2152. doi: 10.2165/11538110-000000000-00000
28. Nair AB, Singh K, Al-Dhubiab BE, Attimarad M, Harsha S, Alhaider IA. Skin uptake and clearance of ciclopirox following topical application. *Biopharmaceutics & Drug Disposition*. 2013;34(9):540-549. doi: 10.1002/bdd.1866
29. Ciclopirox. https://go.drugbank.com/drugs/DB01188. Accessed November 18, 2022.
30. Pfaller MA. Antifungal Drug Resistance: Mechanisms, Epidemiology, and Consequences for Treatment. *Am J Med*. 2012;125(1):3-13. doi: 10.1016/j.amjmed.2011.11.001
31. Minden MD, Hogge DE, Weir SJ, et al. Oral ciclopirox olamine displays biological activity in a phase I study in patients with advanced hematologic malignancies. *Am J Hematol*. 2014;89(4):363-368. doi: 10.1002/ajh.23640

32. Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia*. 2008;166(5-6):353-367. doi: 10.1007/s11046-008-9109-0
33. Gupta AK, Nicol KA. Ciclopirox 1% shampoo for the treatment of seborrheic dermatitis. *Int J Dermatol*. 2006;45(1):66-69. doi: 10.1111/j.1365-4632.2004.02331.x
34. Nenoff P, Krüger C, Schaller J, Ginter-Hanselmayer G, Schulte-Beerbühl R, Tietz HJ. Mycology - an update part 2: dermatomycoses: clinical picture and diagnostics. *J Dtsch Dermatol Ges*. 2014;12(9):749-777. doi: 10.1111/ddg.12420
35. Dittmar W, Lohaus G. HOE 296, a new antimycotic compound with a broad antimicrobial spectrum. Laboratory results. *Arzneimittelforschung*. 1973;23(5):670-674.
36. Danielli LJ, Pippi B, Duarte JA, et al. Antifungal mechanism of action of *Schinus lentiscifolius* Marchand essential oil and its synergistic effect *in vitro* with terbinafine and ciclopirox against dermatophytes. *Journal of Pharmacy and Pharmacology*. 2018;70(9):1216-1227. doi: 10.1111/jphp.12949
37. Carrillo-Muñoz AJ, Brió S, Alonso R, del Valle O, Santos P, Quindós G. Ciclopiroxolamine: in vitro antifungal activity against clinical yeast isolates. *Int J Antimicrob Agents*. 2002;20(5):375-379. doi: 10.1016/S0924-8579(02)00206-6
38. Carrilo-Muñoz AJ, Tur C, Torres J, Seymour AC. In-vitro antifungal activity of sertaconazole, bifonazole, ketoconazole, and miconazole against yeasts of the Candida genus. *J Antimicrob Chemother.* 1996;37(4):815-819. doi: 10.1093/jac/37.4.815
39. Harada I, Mitsui K, Uchida K, Yamaguchi H. [The in vitro properties of a new hydroxypyridone antimycotic rilopirox, with special reference to its anti-Candida activity]. *Jpn J Antibiot*. 1999;52(2):146-152.
40. Gupta AK, Plott T. Ciclopirox: a broad-spectrum antifungal with antibacterial and anti-inflammatory properties. *Int J Dermatol*. 2004;43(1):3-8. doi: 10.1111/j.1461--1244.2004.02380.x
41. Lee REB, Liu TT, Barker KS, Lee RE, Rogers PD. Genome-wide expression profiling of the response to ciclopirox olamine in Candida albicans. *J Antimicrob Chemother*. 2005;55(5):655-662. doi: 10.1093/jac/dki105
42. Leem SH, Park JE, Kim IS, Chae JY, Sugino A, Sunwoo Y. The possible mechanism of action of ciclopirox olamine in the yeast Saccharomyces cerevisiae. *Mol Cells*. 2003;15(1):55-61.
43. Farinelli S, Greene L. Cell cycle blockers mimosine, ciclopirox, and deferoxamine prevent the death of PC12 cells and postmitotic sympathetic neurons after removal of trophic support. *J Neurosci*. 1996;16(3):1150-1162. doi: 10.1523/JNEUROSCI.16-03-01150.1996
44. Almeida B, Sampaio-Marques B, Carvalho J, et al. An atypical active cell death process underlies the fungicidal activity of ciclopirox olamine against the yeast Saccharomyces cerevisiae. *FEMS Yeast Research*. 2007;7(3):404-412. doi: 10.1111/j.1567-1364.2006.00188.x
45. Zhou H, Shen T, Luo Y, et al. The antitumor activity of the fungicide ciclopirox. *Int J Cancer*. 2010;127(10):2467-2477. doi: 10.1002/ijc.25255
46. Hoffman BD, Hanauske-Abel HM, Flint A, Lalande M. A new class of reversible cell cycle inhibitors. *Cytometry*. 1991;12(1):26-32. doi: 10.1002/cyto.990120105
47. Lalande M. A reversible arrest point in the late G1 phase of the mammalian cell cycle. *Exp Cell Res*. 1990;186(2):332-339. doi: 10.1016/0014-4827(90)90313-y
48. Luo Y, Zhou H, Liu L, et al. The fungicide ciclopirox inhibits lymphatic endothelial cell tube formation by suppressing VEGFR-3-mediated ERK signaling pathway. *Oncogene*. 2011;30(18):2098-2107. doi: 10.1038/onc.2010.590
49. Sundar SS, Ganesan TS. Role of lymphangiogenesis in cancer. *J Clin Oncol*. 2007;25(27):4298-4307. doi: 10.1200/JCO.2006.07.1092
50. Wolff EC, Kang KR, Kim YS, Park MH. Posttranslational synthesis of hypusine: evolutionary progression and specificity of the hypusine modification. *Amino Acids*. 2007;33(2):341-350. doi: 10.1007/s00726-007-0525-0
51. Kaiser A. Translational control of eIF5A in various diseases. *Amino Acids*. 2012;42(2):679-684. doi: 10.1007/s00726-011-1042-8
52. Kim YS, Kang KR, Wolff EC, Bell JK, McPhie P, Park MH. Deoxyhypusine hydroxylase is a Fe(II)-dependent, heat-repeat enzyme: identification of amino acid residues critical for Fe(II) binding and catalysis. *J Biol Chem*. 2006;281(19):13217-13225. doi: 10.1074/jbc.M601081200
53. Clement PMJ, Hanauske-Abel HM, Wolff EC, Kleinman HK, Park MH. The antifungal drug ciclopirox inhibits deoxyhypusine and proline hydroxylation, endothelial cell growth and angiogenesis in vitro. *Int J Can*. 2002;100(4):491-498. doi: 10.1002/ijc.10515
54. Furukawa T, Naitoh Y, Kohno H, Tokunaga R, Taketani S. Iron deprivation decreases ribonucleotide reductase activity and DNA synthesis. *Life Sciences*. 1992;50(26):2059-2065. doi: 10.1016/0024-3205(92)90572-7
55. Eberhard Y, McDermott SP, Wang X, et al. Chelation of intracellular iron with the antifungal agent ciclopirox olamine induces cell death in leukemia and myeloma cells. *Blood*. 2009;114(14):3064-3073. doi: 10.1182/blood-2009-03-209965
56. Simcox JA, McClain DA. Iron and Diabetes Risk. *Cell Metab*. 2013;17(3):329-341. doi: 10.1016/j.cmet.2013.02.007
57. Papa FR. Endoplasmic Reticulum Stress, Pancreatic β-Cell Degeneration, and Diabetes. *Cold Spring Harb Perspect Med*. 2012;2(9):a007666. doi: 10.1101/cshperspect.a007666
58. Mihailidou C, Chatzistamou I, Papavassiliou AG, Kiaris H. Ciclopirox enhances pancreatic islet health by modulating the unfolded protein response in diabetes. *Pflugers Arch*. 2016;468(11-12):1957-1968. doi: 10.1007/s00424-016-1887-5
59. Mihailidou C, Chatzistamou I, Papavassiliou AG, Kiaris H. Modulation of Pancreatic Islets' Function and Survival During Aging Involves the Differential Regulation of Endoplasmic Reticulum Stress by p21 and CHOP. *Antioxid Redox Signal*. 2017;27(4):185-200. doi: 10.1089/ars.2016.6671

60. Ashcroft FM, Rorsman P. Diabetes mellitus and the β-cell: the Last Ten Years. *Cell*. 2012;148(6):1160-1171. doi: 10.1016/j.cell.2012.02.010
61. Maier B, Ogihara T, Trace AP, et al. The unique hypusine modification of eIF5A promotes islet β cell inflammation and dysfunction in mice. *J Clin Invest*. 2010;120(6):2156-2170. doi: 10.1172/JCI38924
62. Hanauske-Abel HM, Saxena D, Palumbo PE, et al. Drug--Induced Reactivation of Apoptosis Abrogates HIV-1 Infection. *PLoS One*. 2013;8(9):e74414. doi: 10.1371/journal.pone.0074414
63. Berkhout B, Arts K, Abbink TEM. Ribosomal scanning on the 5′-untranslated region of the human immunodeficiency virus RNA genome. *Nucleic Acids Res*. 2011;39(12):5232-5244. doi: 10.1093/nar/gkr113
64. Kim SW, Yoon JS, Lee M, Cho Y. Toward a complete cure for chronic hepatitis B: Novel therapeutic targets for hepatitis B virus. *Clin Mol Hepatol*. 2022;28(1):17-30. doi: 10.3350/cmh.2021.0093
65. Kang JA, Kim S, Park M, et al. Ciclopirox inhibits Hepatitis B Virus secretion by blocking capsid assembly. *Nat Commun*. 2019;10(1):2184. doi: 10.1038/s41467-019-10200-5
66. Mohebbi A, Ghorbanzadeh T, Naderifar S, Khalaj F, Askari FS, Sammak AS. A fragment-based drug discovery developed on ciclopirox for inhibition of Hepatitis B virus core protein: An in silico study. *PLOS ONE*. 2023;18(5):e0285941. doi: 10.1371/journal.pone.0285941
67. Feng H, Hu L, Zhu H, et al. Repurposing antimycotic ciclopirox olamine as a promising anti-ischemic stroke agent. *Acta Pharmaceutica Sinica B*. 2020;10(3):434-446. doi: 10.1016/j.apsb.2019.08.002
68. Tan T, Marín-García J, Damle S, Weiss HR. Hypoxia-inducible factor-1 improves inotropic responses of cardiac myocytes in ageing heart without affecting mitochondrial activity. *Exp Physiol*. 2010;95(6):712-722. doi: 10.1113/expphysiol.2009.051649
69. Gupta AK, Kohli Y. In vitro susceptibility testing of ciclopirox, terbinafine, ketoconazole and itraconazole against dermatophytes and nondermatophytes, and in vitro evaluation of combination antifungal activity. *Br J Dermatol*. 2003;149(2):296-305. doi: 10.1046/j.1365-2133.2003.05418.x
70. Gupta AK, Joseph WS. Ciclopirox 8% nail lacquer in the treatment of onychomycosis of the toenails in the United States. *J Am Podiatr Med Assoc*. 2000;90(10):495-501. doi: 10.7547/87507315-90-10-495
71. Zhou H, Shen T, Shang C, et al. Ciclopirox induces autophagy through reactive oxygen species-mediated activation of JNK signaling pathway. *Oncotarget*. 2014;5(20):10140-10150.
72. Monti D, Mazzantini D, Tampucci S, et al. Ciclopirox and Efinaconazole Transungual Permeation, Antifungal Activity, and Proficiency To Induce Resistance in Trichophyton rubrum. *Antimicrob Agents Chemother*. 2019;63(10):e00442-e00519. doi: 10.1128/AAC.00442-19
73. Conley ZC, Carlson-Banning KM, Carter AG, de la Cova A, Song Y, Zechiedrich L. Sugar and iron: Toward understanding the antibacterial effect of ciclopirox in Escherichia coli. *PLoS One*. 2019;14(1):e0210547. doi: 10.1371/journal.pone.0210547
74. Kim Y, Schmidt M, Endo T, Lu D, Carson D, Schmidt--Wolf IGH. Targeting the Wnt/beta-catenin pathway with the antifungal agent ciclopirox olamine in a murine myeloma model. *In Vivo*. 2011;25(6):887-893.
75. Rey JB, Osgood AT, Anvari AA. Topical and Device-Based Treatment of Toenail Onychomycosis. *Am Fam Physician*. 2021;103(3):145-146.
76. Krasaeath R, Elizondo J. Topical Antifungals for Treatment of Onychomycosis. *Am Fam Physician*. 2016;94(9):734-734.
77. Abeck D, Loprox Shampoo Dosing Study Group. Rationale of frequency of use of ciclopirox 1% shampoo in the treatment of seborrheic dermatitis: results of a double--blind, placebo-controlled study comparing the efficacy of once, twice, and three times weekly usage. *Int J Dermatol*. 2004;43(1):13-16. doi: 10.1111/j.1461-1244.2004.02382.x
78. Aly R, Maibach HI, Bagatell FK, et al. Ciclopirox olamine lotion 1%: bioequivalence to ciclopirox olamine cream 1% and clinical efficacy in tinea pedis. *Clin Ther*. 1989;11(3):290-303.
79. Wajnberg M, Wajnberg A. Doppelblind-Vergleichsstudie mit Ciclopiroxolamin- und Miconazol-Vaginalcreme bei uilvovaginaler Candidose. *Mycoses*. 1981;24(12):721-730. doi: 10.1111/j.1439-0507.1981.tb01827.x
80. Gallup E, Plott T, Ciclopirox TS Investigators. A multicenter, open-label study to assess the safety and efficacy of ciclopirox topical suspension 0.77% in the treatment of diaper dermatitis due to Candida albicans. *J Drugs Dermatol*. 2005;4(1):29-34.
81. Bernier KM, Morrison LA. Antifungal drug ciclopirox olamine reduces HSV-1 replication and disease in mice. *Antiviral Research*. 2018;156:102-106. doi: 10.1016/j.antiviral.2018.06.010
82. Shen T, Huang S. Repositioning the Old Fungicide Ciclopirox for New Medical Uses. *CPD*. 2016;22(28):4443-4450. doi: 10.2174/1381612822666160530151209
83. Weir SJ, Wood R, Schorno K, et al. Preclinical Pharmacokinetics of Fosciclopirox, a Novel Treatment of Urothelial Cancers, in Rats and Dogs. *J Pharmacol Exp Ther*. 2019;370(2):148-159. doi: 10.1124/jpet.119.257972
84. Shaikh KS. Repurposing ciclopirox for treating multiple forms of cancer: New reports and approaches. *JMPAS*. 2022;11(2):4727-4733. doi: 10.55522/jmpas.V11I2.2545