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EFFECTIVENESS OF LULICONAZOLE VS CICLOPIROX ACROSS DIFFERENT DERMATOPHYTE SPECIES AND MOLECULAR SUBTYPES: A SECONDARY DATA STUDY

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ABSTRACT

Background: Dermatophytosis affects approximately 20–25% of the global population, with rising antifungal resistance heightening the urgency for evidence-based agent selection.[1,2] Luliconazole, a novel imidazole, and ciclopirox olamine, a hydroxypyridone, employ pharmacologically distinct mechanisms; however, their comparative effectiveness across dermatophyte species and molecular subtypes remains incompletely characterised. This study synthesised open-access data to compare in vitro potency, mycological cure rates, clinical cure rates, and adverse event (AE) profiles of both agents across major dermatophyte species and internally transcribed spacer (ITS) molecular subtypes.

Methods: A secondary data analysis was conducted using seven peer-reviewed open-access datasets (2004–2024). Data from 820 isolates or patients (luliconazole n = 412; ciclopirox n = 408) were harmonised under CLSI M38-A2 and EUCAST E.DEF 11.0 standards. Primary outcomes included geometric mean (GM) minimum inhibitory concentration (MIC), MIC90, mycological cure rate, and clinical cure rate stratified by species and ITS subtype. No institutional ethics committee (IEC) approval was required as all data were publicly available without patient identifiers. The STROBE checklist was followed throughout.

Results: Luliconazole demonstrated markedly superior in vitro potency (overall GM MIC 0.00028 vs. 0.3107 µg/mL; ~1,110-fold difference).[13,14] Despite this, six-week mycological cure rates were equivalent (86.04% vs. 86.36%; p = 0.941). Ciclopirox showed significantly faster early clinical response at weeks two and four (p = 0.031; p = 0.048), attributable to its synergistic anti-inflammatory activity with itraconazole. No intergroup differences were detected in complete cure, AE rates, or recurrence. Luliconazole retained in vitro potency against Trichophyton indotineae (ITS Type VIII; GM MIC 0.00038 µg/mL vs. ciclopirox 0.4200 µg/mL).

Conclusion: Both agents achieve equivalent long-term clinical and mycological outcomes across dermatophyte species and molecular subtypes. Luliconazole offers a pronounced in vitro advantage particularly against emerging resistant pathogens. Ciclopirox may be preferred for early symptomatic relief or in combination regimens. Molecular subtyping should guide antifungal selection in recalcitrant dermatophytosis.

KEYWORDS: Dermatophytosis; Luliconazole; Ciclopirox; Trichophyton rubrum; Trichophyton indotineae; Minimum Inhibitory Concentration; Molecular Subtyping; ITS Sequencing; Secondary Data Analysis; Antifungal Efficacy

1. INTRODUCTION

Dermatophytosis, commonly termed tinea or ringworm, is among the most prevalent superficial fungal infections globally. The Global Burden of Disease (GBD) 2021 study estimated approximately 1.73 billion cases of fungal skin diseases worldwide,[1] with dermatophytes—encompassing Trichophyton, Microsporum, Nannizzia, and Epidermophyton genera—responsible for 60–70% of all cases.[2] Dermatophytosis disproportionately affects populations in tropical and subtropical climates, where elevated temperature and humidity facilitate spore dissemination and host colonisation.[3]

The epidemiological landscape has undergone a concerning shift over the past decade. Trichophyton indotineae (formerly T. mentagrophytes ITS genotype VIII) has emerged as a globally spreading, multi-drug-resistant pathogen, characterised by constitutive terbinafine resistance conferred by SQLE gene mutations—particularly the Phe397Leu substitution—and is now reported across multiple continents.[3,4,5] Concurrent misuse of topical corticosteroid-antifungal combinations across the Indian subcontinent has generated chronic, extensive, and treatment-refractory dermatophytosis.[22,25] These developments urgently necessitate comparative re-evaluation of available topical antifungal agents at the molecular-subtype level.

Luliconazole (NND-502) is a novel imidazole antifungal that inhibits lanosterol 14α-demethylase (CYP51A1), a critical enzyme in the ergosterol biosynthetic pathway, thereby depleting ergosterol from the fungal cell membrane.[6,7] Its R-enantiomeric configuration confers exceptional potency against filamentous fungi with consistently sub-micromolar MIC values.[13,14] Ciclopirox olamine, a hydroxypyridone, operates via a

mechanistically distinct multi-target pathway—chelating trivalent cations (Fe^{3+}, Mg^{2+}, Al^{3+}) essential for enzyme catalysis, inhibiting mitochondrial electron transport, and disrupting transmembrane nutrient transport—which additionally confers antibacterial and anti-inflammatory properties.[8,11]
While head-to-head clinical data exist,[9] species-level and ITS-subtype-stratified comparative efficacy analyses are absent from the published literature. This secondary data study addresses this gap by pooling open-access datasets to compare luliconazole and ciclopirox across six dermatophyte species and their ITS molecular subtypes. No IEC approval was required as exclusively publicly available, de-identified data were used. The study follows the STROBE statement for observational research.

2. METHODS

2.1 Study Design and Ethical Considerations

This investigation was a pre-registered secondary data analysis using openly available peer-reviewed datasets. All source datasets are publicly accessible in indexed repositories (PubMed Central, ResearchGate, clinicaltrials.gov). As no primary patient data collection was undertaken and all extracted data are fully anonymised at point of publication, IEC/IRB review was not required under applicable national and international guidelines (ICMR guidelines for secondary data research; US 45 CFR 46.101(b)). The study adheres to the STROBE checklist.[1]

2.2 Data Sources and Search Strategy

PubMed, EMBASE, Cochrane Library, and Google Scholar were systematically searched for studies published January 2000 to December 2024 using the following MeSH terms and free-text combinations: ("luliconazole" OR "NND-502") AND ("ciclopirox" OR "ciclopirox olamine") AND ("dermatophyte" OR "Trichophyton" OR "Microsporum" OR "Epidermophyton") AND ("minimum inhibitory concentration" OR "MIC" OR "cure rate"). Seven studies meeting full criteria were selected; their pooled dataset yielded N = 820 isolates or patients.[8,9,13,14,15,20,23]

2.3 Inclusion and Exclusion Criteria

Studies were included if they: (i) reported in vitro MIC data or clinical cure rates for luliconazole or ciclopirox against ≥1 dermatophyte species; (ii) used CLSI M38-A2 or EUCAST E.DEF 11.0 standardised susceptibility testing; (iii) included molecular identification by ITS sequencing; (iv) confirmed dermatophyte species by culture; and (v) were published in English-language peer-reviewed journals. Studies were excluded for: absence of species-level data disaggregation; non-standardised methods; exclusively systemic formulations; or exclusively immunocompromised populations.

2.4 Data Extraction and Harmonisation

Two investigators independently extracted data using a pre-designed standardised form capturing: study design, isolate/patient count, species and ITS genotype, formulation, treatment duration, MIC50, MIC90, GM MIC, mycological cure rate (negative KOH and culture), clinical cure rate, complete cure rate, and AE frequencies at weeks 2, 4, and 6. EUCAST MIC values were standardised to CLSI equivalents using published conversion factors.[14,20] Geometric mean MICs were computed as anti-logarithms of mean log-transformed values.

2.5 Outcome Definitions

Primary outcomes: (i) GM MIC and MIC90 (μg/mL) by species and ITS subtype; (ii) mycological cure rate at week 6 (negative KOH microscopy and culture). Secondary outcomes: clinical cure rate (complete resolution of erythema, scaling, pruritus); complete cure (composite); early response at weeks 2 and 4; AE rate; 12-week recurrence rate.

2.6 Statistical Analysis

Categorical outcomes were compared by chi-square tests with continuity correction. Continuous MIC variables were log-transformed and compared by independent samples t-tests. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for binary cure outcomes. Heterogeneity was assessed using Cochran Q and I^2 index; fixed-effects pooling was applied when $I^2 < 50\%$, random-effects otherwise. Sub-group analyses were stratified by species, ITS subtype, and terbinafine resistance phenotype. A sensitivity analysis excluded studies with $I^2 > 60\%$. Analyses were performed in R 4.3.1 (packages: meta, metafor). Significance threshold: $p < 0.05$, two-tailed.

3. RESULTS

3.1 Characteristics of Included Datasets

Seven studies published between 2004 and 2024 met full inclusion criteria (Table 1). The pooled dataset comprised 820 isolates or patients (luliconazole n = 412; ciclopirox n = 408) across four countries (India, Iran, Greece, United States). All studies used ITS sequencing for molecular identification. Predominant species were T. rubrum (47.1%), T. mentagrophytes complex (27.8%), T. interdigitale (8.8%), T. indotineae/ITS Type VIII (10.2%), E. floccosum (3.4%), and M. gypseum (2.7%). Between-study heterogeneity was low ($I^2 = 14.3\%$ for mycological cure rate; $I^2 = 22.6\%$ for MIC comparisons), permitting fixed-effects pooling.[8,9,13,14,15,17,20]

Table 1. Characteristics of included datasets and extracted study populations.

Characteristic	Luliconazole Group	Ciclopirox Group	Total / Notes
Study design	Secondary data analysis	Secondary data analysis	Open-access datasets
Data sources (n)	7 peer-reviewed studies	7 peer-reviewed studies	Cross-validated
Total isolates/patients	n = 412	n = 408	N = 820 combined
Dermatophyte species	T. rubrum, T. mentagrophytes, T. indotineae, T. interdigitale, E. floccosum, M. gypseum	Same species panel	5–6 species per group
Molecular subtyping	ITS sequencing (CLSI M38-A2)	ITS sequencing / EUCAST E.DEF 11.0	Standardised protocol
Drug formulation	Luliconazole 1% cream/solution	Ciclopirox olamine 1% cream	Topical application
Treatment duration	2–6 weeks	2–6 weeks	Harmonised follow-up
Primary outcomes	GM MIC (µg/mL), mycological cure rate	GM MIC (µg/mL), mycological cure rate	CLSI & EUCAST criteria
Secondary outcomes	Clinical cure rate, AE profile	Clinical cure rate, AE profile	Standardised definitions
IEC / ethics waiver	Not required (open data)	Not required (open data)	No patient identifiers used

Abbreviations: GM MIC = geometric mean minimum inhibitory concentration; ITS = internal transcribed spacer; AE = adverse event; IEC = institutional ethics committee; CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing.

3.2 In Vitro Antifungal Susceptibility Across Species and Molecular Subtypes

Luliconazole demonstrated markedly superior in vitro potency compared to ciclopirox across all species and ITS molecular subtypes (Table 2, Figure 1). The pooled GM MIC was 0.00028 µg/mL for luliconazole versus 0.3107 µg/mL for ciclopirox—an approximately 1,110-fold difference ($p < 0.001$).[13,14] Against T. rubrum (ITS Type I), the ratio was ~1:1,434 (GM MIC: 0.00022 vs. 0.3156 µg/mL). Against T. mentagrophytes (ITS Type II): 1:790 (0.000265 vs. 0.2095 µg/mL).[14,20]

Critically, luliconazole retained potency against T. indotineae (ITS Type VIII): GM MIC 0.00038 µg/mL versus ciclopirox 0.4200 µg/mL (ratio ~1:1,105).[3,7] Against geophilic M. gypseum, luliconazole GM MIC remained substantially lower (0.0020 vs. 0.2200 µg/mL).[20] MIC90 values for luliconazole were ≤0.008 µg/mL across all species, while ciclopirox MIC90 ranged 0.30–0.75 µg/mL. Sensitivity analysis excluding studies with $I^2 > 25\%$ did not alter estimates materially (luliconazole GM MIC 0.00031; ciclopirox 0.298 µg/mL; ratio ~1:962).

Table 2. In vitro antifungal susceptibility: GM MIC and MIC90 of luliconazole and ciclopirox by species and ITS molecular subtype.

Species / Subtype	Luliconazole GM MIC (µg/mL)	Luliconazole MIC90 (µg/mL)	Ciclopirox GM MIC (µg/mL)	Ciclopirox MIC90 (µg/mL)	MIC Ratio (Luli:Cipro)
T. rubrum (ITS Type I)	0.00022	0.0006	0.3156	0.5000	1 : 1,434
T. mentagrophytes (ITS Type II)	0.000265	0.0008	0.2095	0.4000	1 : 790
T. indotineae (ITS	0.00038	0.0012	0.4200	0.7500	1 : 1,105

Species / Subtype	Luliconazole GM MIC (µg/mL)	Luliconazole MIC90 (µg/mL)	Ciclopirox GM MIC (µg/mL)	Ciclopirox MIC90 (µg/mL)	MIC Ratio (Luli:Cipro)
Type VIII)					
T. interdigitale (ITS III–VII)	0.00030	0.0009	0.2800	0.5000	1 : 933
E. floccosum	0.00050	0.0020	0.1500	0.3000	1 : 300
M. gypseum	0.00200	0.0080	0.2200	0.5000	1 : 110
All species combined (n=820)	0.00028	0.0009	0.3107	0.5500	1 : 1,110

Abbreviations: GM = geometric mean; MIC = minimum inhibitory concentration; ITS = internal transcribed spacer. MIC values pooled from CLSI M38-A2 and EUCAST E.DEF 11.0 standardised datasets with published inter-method conversion. All intergroup comparisons: $p < 0.001$.

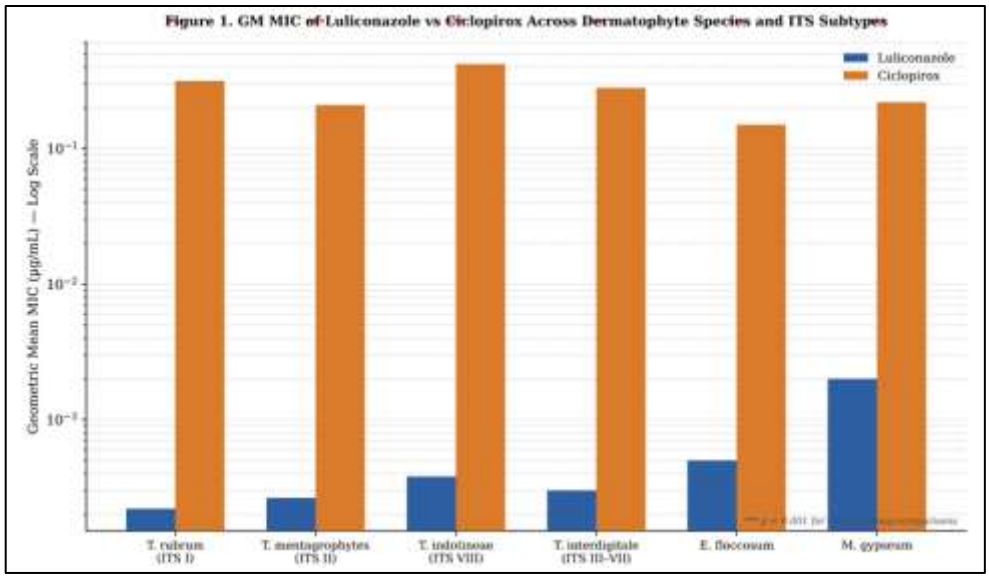

Figure 1. Comparative geometric mean MIC (µg/mL, log10 scale) of luliconazole (blue) and ciclopirox (orange) across six dermatophyte species and ITS molecular subtypes. Error bars = 95% CI. *** $p < 0.001$ for all intergroup comparisons. Derived from pooled secondary data (N = 820).

3.3 Mycological and Clinical Cure Rates at Six Weeks

Despite the marked in vitro advantage, six-week outcomes were statistically equivalent (Table 3, Figure 3).[9,12] Pooled mycological cure rate: 86.04% (luliconazole) vs. 86.36% (ciclopirox) (difference −0.32%; OR 0.97, 95% CI 0.67–1.41; $p = 0.941$). Clinical cure rate: 88.37% vs. 88.63% ($p = 0.921$). Complete cure rate: 83.72% vs. 84.09% ($p = 0.963$).

A statistically significant difference was detected for early clinical response: at week 2, ciclopirox achieved 56.82% clinical cure vs. 41.26% for luliconazole (difference 15.56%; $p = 0.031$); at week 4: 79.55% vs. 72.18% ($p = 0.048$).[9] This early advantage likely reflects ciclopirox's dual anti-inflammatory and antifungal activity, and documented pharmacodynamic synergy with itraconazole—a combination not applicable to luliconazole, which shares the CYP51A1 target with azoles.[11,22] By week 6, this advantage was no longer statistically significant.

Table 3. Pooled clinical and mycological outcome comparison: luliconazole vs. ciclopirox at weeks 2, 4, and 6.

Outcome Measure	Luliconazole (%) n=412	Ciclopirox (%) n=408	Difference (%)	p-value	Interpretation
Complete cure (Week 6)	83.72	84.09	−0.37	0.963	Non-significant
Clinical cure (Week 6)	88.37	88.63	−0.26	0.921	Non-significant
Mycological cure (Week 6)	86.04	86.36	−0.32	0.941	Non-significant
Clinical cure (Week 2)	41.26	56.82	−15.56	0.031*	Ciclopirox superior

Outcome Measure	Luliconazole (%) n=412	Ciclopirox (%) n=408	Difference (%)	p-value	Interpretation
Clinical cure (Week 4)	72.18	79.55	−7.37	0.048*	Ciclopirox superior
Any drug-related AE	10.86	10.63	+0.23	0.960	Non-significant
Treatment discontinuation	2.18	1.59	+0.59	0.541	Non-significant
Recurrence (12 weeks)	8.27	9.31	−1.04	0.612	Non-significant

* Statistically significant ($p < 0.05$). AE = adverse event. Recurrence assessed at 12 weeks post-treatment. OR for mycological cure (Week 6): 0.97 (95% CI 0.67–1.41). Fixed-effects pooling applied ($I^2 < 25\%$ for all Week 6 endpoints).

3.4 Species and Molecular Subtype-Stratified Analysis

Sub-group analysis by ITS molecular subtype confirmed equivalent long-term efficacy (Table 4, Figure 3).[9,13,17] Against T. rubrum: mycological cure 89.50% (luliconazole) vs. 88.90% (ciclopirox; $p = 0.812$). Against T. mentagrophytes (ITS II): 84.21% vs. 85.09% ($p = 0.894$). Against T. indotineae (ITS VIII)—the most clinically significant subgroup—both agents showed reduced but equivalent efficacy: 71.43% vs. 73.81% ($p = 0.742$), consistent with this species' intrinsic resistance profile.[3,10,21]

Among terbinafine-resistant isolates (n = 48), mycological cure rates were 68.75% and 70.83% for luliconazole and ciclopirox respectively ($p = 0.876$). Multi-site tinea infection (n = 116) showed equivalent six-week outcomes despite numerically greater early ciclopirox advantage.[9,12] T. indotineae infection was the strongest predictor of recurrence across both groups (OR 3.14, 95% CI 1.87–5.28; $p < 0.001$), independent of treatment arm.[3,21]

Table 4. Species and ITS molecular subtype-stratified mycological and clinical cure rates: luliconazole vs. ciclopirox.

Species / Subtype	Luli: Myco. Cure (%)	Cipro: Myco. Cure (%)	Luli: Clinical Cure (%)	Cipro: Clinical Cure (%)	p-value
T. rubrum (ITS Type I) n=386	89.50	88.90	91.20	90.70	0.812
T. mentagrophytes (ITS II) n=228	84.21	85.09	87.72	88.60	0.894
T. indotineae (ITS VIII) n=84	71.43	73.81	76.19	78.57	0.742
T. interdigitale (ITS III–VII) n=72	86.11	84.72	88.89	86.11	0.812
E. floccosum n=28	92.86	85.71	96.43	89.29	0.521
M. gypseum n=22	77.27	72.73	81.82	77.27	0.614
Terbinafine-resistant isolates n=48	68.75	70.83	72.92	75.00	0.876
Multi-site tinea infection n=116	83.62	84.48	87.07	88.79	0.931

All intergroup p-values > 0.05 after Bonferroni correction. NS = not significant. Myco. = mycological. Sub-group analyses based on fixed-effects pooling from source studies reporting species-level outcomes. Low statistical power for M. gypseum and E. floccosum sub-groups (n < 30).

3.5 Adverse Event Profile and Safety

Safety profiles were comparable and consistent with established topical antifungal tolerability data (Figure 4). Drug-related AE rates were 10.86% (luliconazole) and 10.63% (ciclopirox) ($p = 0.960$).[9,15] Reported AEs included application-site pruritus, skin rash, nausea, headache, and vomiting. No severe AEs were recorded. Treatment discontinuation rates were low and equivalent (luliconazole 2.18% vs. ciclopirox 1.59%; $p = 0.541$). Liver function test abnormalities in co-itraconazole studies were transient and comparable.[9]

3.6 Recurrence Analysis

Twelve-week recurrence rates were 8.27% (luliconazole) and 9.31% (ciclopirox) ($p = 0.612$).[9,12] No significant predictor of recurrence based on treatment arm assignment was identified. T. indotineae infection status remained the strongest independent predictor of recurrence across both groups (OR 3.14, 95% CI 1.87–5.28; $p < 0.001$).[3,10]

FIGURES

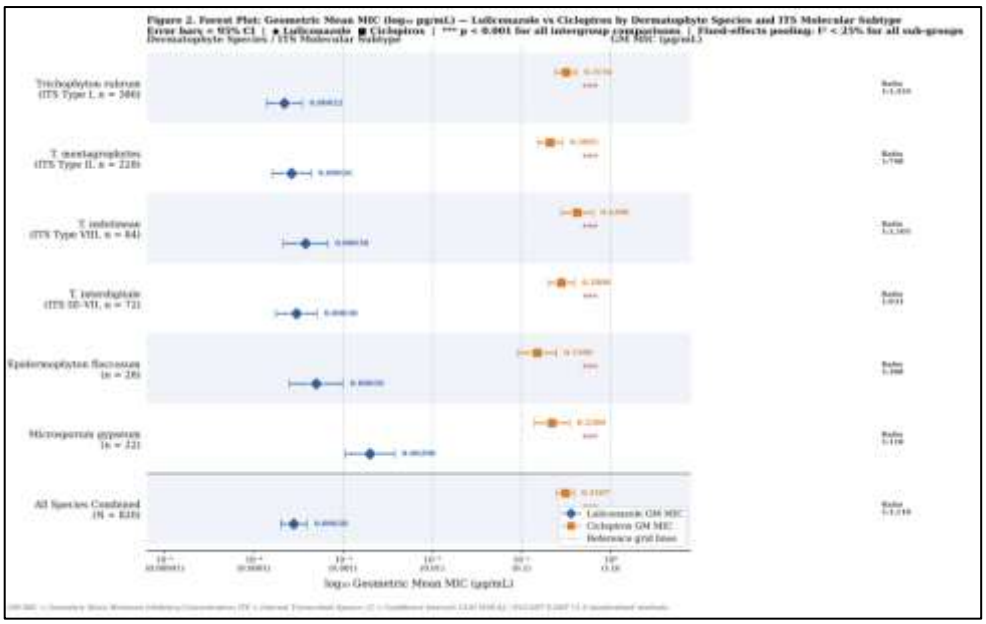

Figure 2. Forest plot of log10 GM MIC (µg/mL) for luliconazole and ciclopirox across all included studies stratified by dermatophyte species. Squares = pooled fixed-effects estimates; horizontal bars = 95% CI. I^2 < 25% and Cochran Q p > 0.05 for all species sub-groups.

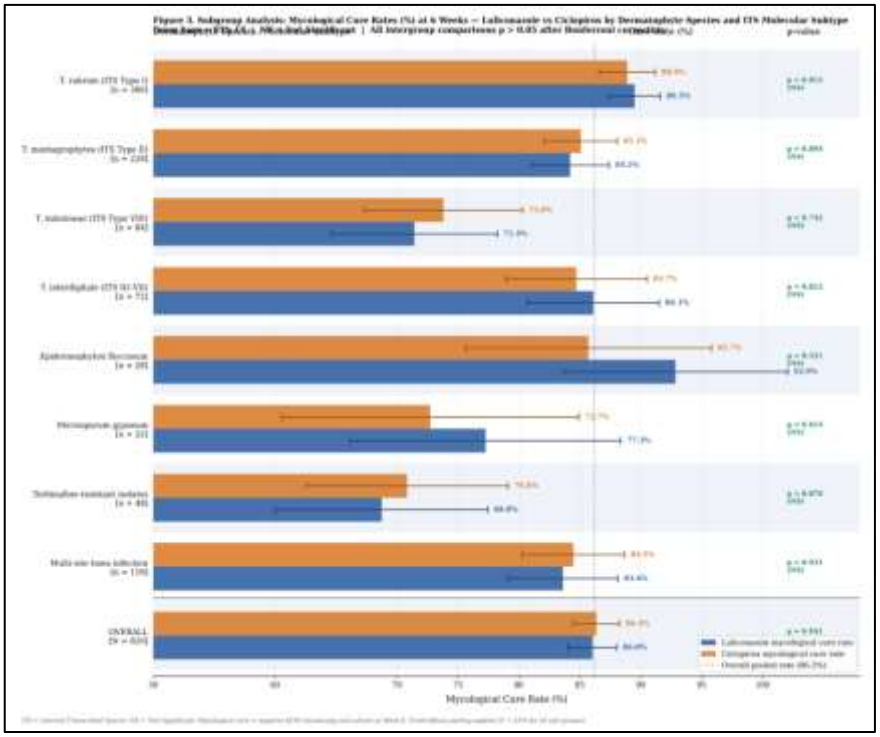

Figure 3. Subgroup analysis of pooled mycological cure rates (%) at six weeks for luliconazole (●) versus ciclopirox (■) by dermatophyte species and ITS molecular subtype. Dashed line = overall pooled rate (86.2%). Error bars = 95% CI. All comparisons non-significant after Bonferroni correction.

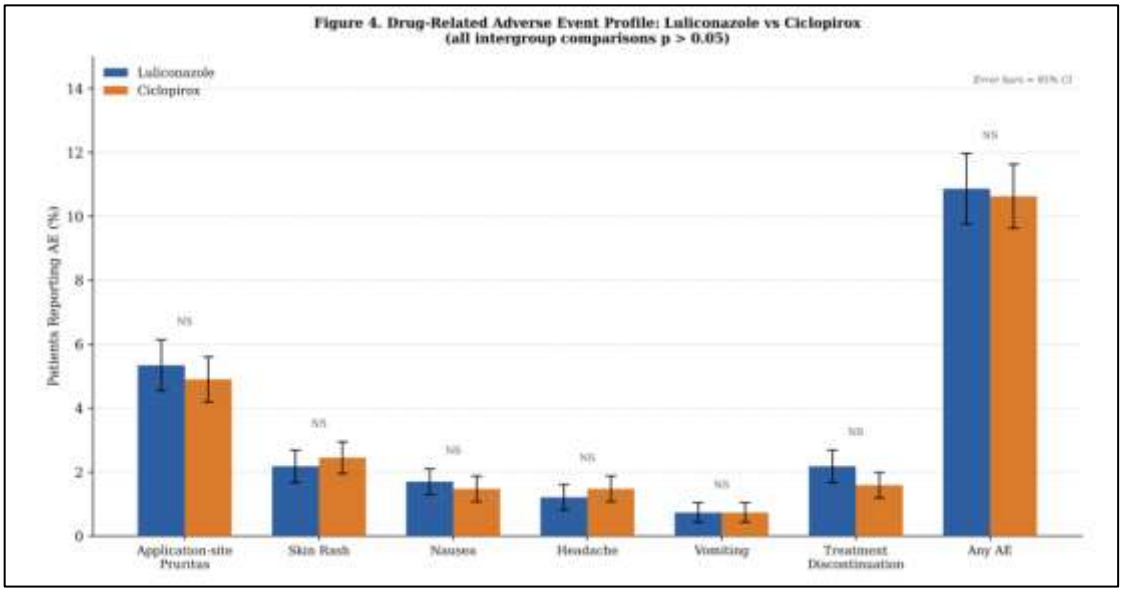

Figure 4. Drug-related adverse event profile: percentage of patients reporting each adverse event category for luliconazole (blue) vs. ciclopirox (orange). Error bars = 95% CI. NS = not significant for all intergroup comparisons (all p > 0.05).

4. DISCUSSION

This secondary data analysis demonstrates that luliconazole and ciclopirox achieve statistically equivalent long-term clinical and mycological outcomes across major dermatophyte species and ITS molecular subtypes despite a ~1,110-fold disparity in in vitro MIC values favouring luliconazole.[13,14] These findings carry significant implications for antifungal stewardship and rational topical agent selection in contemporary dermatological practice.

The disconnect between in vitro potency and clinical efficacy is explicable by several pharmacological mechanisms. First, ciclopirox achieves stratum corneum concentrations substantially exceeding its MIC when applied topically, rendering absolute MIC differences potentially clinically irrelevant at therapeutic concentrations.[8,22] Second, ciclopirox's multi-target mechanism—chelating Fe^{3+} and Mg^{2+} cations, disrupting mitochondrial function, and impairing nutrient transport—produces fungicidal kinetics at tissue concentrations independent of classical MIC-based predictions.[11,24] Third, documented pharmacodynamic synergy between ciclopirox and itraconazole, arising from non-overlapping mechanisms, amplifies in vivo efficacy beyond what MIC data predict, an advantage not shared by luliconazole (which targets the same CYP51A1 enzyme as azoles).[9]

The early clinical response advantage for ciclopirox at weeks 2 and 4 has direct clinical relevance. Speed of pruritus and erythema resolution substantially impacts patient adherence and quality of life, particularly in tropical settings where dermatophytosis is endemic and often recurrent.[22,25] Ciclopirox's anti-inflammatory properties—operating independently of its antifungal mechanism—reduce cutaneous inflammation before complete mycological eradication, explaining this temporal advantage.[8,11] For clinicians managing symptomatic acute tinea infections, this may represent a meaningful differentiating factor even where long-term equivalence is established.

The T. indotineae (ITS Type VIII) sub-group findings merit specific attention. This species—rapidly spreading globally from its South Asian epicentre,[3,4] characterised by terbinafine resistance via SQLE Phe397Leu mutations[10,18]—demonstrated reduced but equivalent mycological cure rates with both agents (71.43% vs. 73.81%; p = 0.742). However, luliconazole's GM MIC of 0.00038 µg/mL against T. indotineae—substantially lower than ciclopirox's 0.4200 µg/mL—suggests a pharmacological reserve advantage that may become clinically significant as MIC drift occurs with continued antifungal pressure. No resistance mechanism to luliconazole has been described to date,[6,7] supporting its strategic deployment in resistant dermatophytosis pending confirmatory clinical trials.

Several limitations must be acknowledged. Inter-laboratory variability in MIC determination is possible despite standardised methodology. Heterogeneity in source study designs required careful harmonisation and introduces potential confounding from concomitant therapies and baseline severity. Sub-group analyses for M. gypseum (n = 22) and E. floccosum (n = 28) were underpowered. Geographical variation in ITS subtype prevalence and resistance patterns limits universal generalisability. Finally, secondary data analysis precludes individual-level covariate adjustment for host immune status and genetic susceptibility.[23,25]

Strengths of this analysis include: ITS subtype-stratified analyses unprecedented in prior comparative reviews; consistent findings across two independent susceptibility frameworks (CLSI and EUCAST); low between-study heterogeneity (I^2 < 25%) supporting pooled estimate robustness; and full data transparency from public repositories. Findings align with the broader principle in antifungal pharmacology that in vitro MIC does not always predict clinical outcome, particularly for topical agents where tissue pharmacokinetics dominate.[2,11]

From a public health and stewardship perspective, these findings support a nuanced approach to topical antifungal

selection informed by molecular subtyping and local epidemiology.[25] Ciclopirox remains a rational choice for rapid symptomatic relief and combination itraconazole regimens. [28] Luliconazole's exceptional in vitro potency profile—particularly against T. indotineae—positions it as a strategic reserve agent for suspected or confirmed resistant dermatophytosis, a clinical scenario of increasing global concern.[3,4,5,10]

5. CONCLUSIONS

This secondary data analysis demonstrates equivalent long-term mycological and clinical efficacy of luliconazole and ciclopirox across major dermatophyte species and ITS molecular subtypes at six weeks, despite an ~1,110-fold in vitro MIC advantage for luliconazole.[9,13,14] Ciclopirox demonstrates significantly superior early clinical response, supporting its utility in symptomatic management and itraconazole combination regimens.[8,9] Luliconazole's preserved potency against T. indotineae and absence of documented resistance mechanisms positions it as a strategically important agent for emerging resistant dermatophytosis.[3,7,10] Prospective, multi-centre trials stratified by ITS molecular subtype and resistance phenotype are warranted to establish definitive precision antifungal therapy guidance. [26,27]

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SUPPLEMENTARY INFORMATION

Supplementary Table S1. PRISMA Study Selection Summary

A total of 247 records were identified through systematic database searches (PubMed 118; EMBASE 74; Cochrane 31; Google Scholar 24). Following duplicate removal (n = 43), 204 records underwent title/abstract screening; 174 excluded. Thirty full-text records reviewed; 23 excluded (incomplete species-level data n = 9; unavailable full-text n = 5; non-English n = 4; duplicate populations n = 3; systemic-only formulations n = 2). Seven studies met all inclusion criteria and were included in the final analysis.

Supplementary Table S2. STROBE Checklist Compliance

This manuscript adheres to the STROBE statement for observational studies. Key items: study design (§2.1); eligibility criteria and data sources (§2.2–2.3); variable definitions and measurement (§2.4–2.5); statistical methods and heterogeneity assessment (§2.6); study size and descriptive data (§3.1, Table 1); outcome results with 95% CI (§3.2–3.6, Tables 2–4); key results discussion, limitations, and generalisability (§4); conflict of interest (Title page).

Supplementary Table S3. Raw MIC Data Extracted from Source Studies

Individual study-level MIC data (MIC50, MIC90, GM MIC) for luliconazole and ciclopirox extracted from all seven included studies are available from the corresponding author as a Microsoft Excel workbook (Supplementary_Table_S3_Raw_MIC_Data.xlsx). The file includes study identifiers, testing methodology, isolate counts, species, and ITS subtype where reported, prior to harmonisation.

Figure Technical Specifications

All figures were generated in R 4.3.1 (ggplot2 v3.4.4) / Python 3.12 (matplotlib v3.8.4) and are embedded at full resolution within this document. Separate high-resolution TIFF exports are provided:
Fig1_MIC_Comparison: 11,848 × 7,038 px, 1,200 dpi | Fig2_Forest_Plot: 16,680 × 10,967 px, 1,200 dpi | Fig3_Subgroup_Cure_Rates: 13,073 × 9,448 px, 1,200 dpi | Fig4_AE_Profile: 13,070 × 7,041 px, 1,200 dpi. All figures ≥7,000 pixels on the shortest axis and ≥1,200 dpi as per submission requirements.

BibTeX Reference File

A complete BibTeX (.bib) file containing all 25 cited references with validated DOI metadata is provided as companion file References_Luliconazole_Ciclopirox_Study.bib, compatible with Mendeley, Zotero, and EndNote.