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Efficacy of Isotretinoin in Treating Fungal Infections: A Systematic Review

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Abstract **Objective:** This systematic review evaluates the effectiveness of oral isotretinoin, either as monotherapy or in combination with antifungal agents, in treating fungal skin infections. **Methods:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) standards were adhered to in drafting the systematic review. An extensive search was performed in the following databases covering the last decade from January 2015 to December 2024: PubMed, Scopus, Web of Science and Google Scholar. The selection of eligible studies adhered to the PICOS criteria (Population, Intervention, Comparator, Outcome and Study design). Due to substantial heterogeneity in study designs, interventions and outcome measures, a quantitative meta-analysis was not feasible and findings were synthesized narratively. **Results:** Two hundred forty-nine articles concerning the use of isotretinoin for fungal infections were identified. Titles and abstracts of 152 studies were evaluated, resulting in 54 studies deemed eligible for full-text evaluation. Finally, this review considered 16 studies evaluating isotretinoin regimens ranging from low-dose schedules (10-20 mg/day) to weight-based dosing up to 0.5 mg/kg/day. Four studies were on dermatophytosis, three on seborrhoeic dermatitis and two on pityriasis versicolor and tinea, with isolated reports on chromoblastomycosis and mycosis fungoides. The most consistent evidence of clinical benefit was observed in recurrent dermatophytosis and seborrhoeic dermatitis, especially when isotretinoin was used as an adjunct to the standard therapy. Out of the six studies evaluated using the ROBINS-I tool, three studies exhibited a low RoB and three other studies demonstrated a serious RoB. The RoB 2.0 tool revealed that all the assessed RCTs exhibited high RoB, except for one study that raised some concerns. **Conclusion:** Isotretinoin has potential in the adjuvant treatment of fungal infections especially recurrent dermatophytosis but is more of a supportive than a standalone therapy. **Clinical Relevance:** Isotretinoin may be a promising adjunctive therapy, especially in recurrent dermatophytosis and should be further investigated as a way to improve treatment outcomes and reduce disease recurrence.

Key Words Antifungal Drugs, Fungal Diseases, Isotretinoin, Mycosis, Tinea

INTRODUCTION

Infections caused by superficial fungi are among the most prevalent diseases in humans. They impact approximately 20-25% of the worldwide population. In humans, dermatophytes are the predominant factor causing superficial fungal diseases [1]. In recent years, there has been an increase in incidence particularly in tropical countries with a concomitant increase in chronic and recurrent dermatophytosis [2]. A significant disparity exists between the treatment needed in the current situation and the established treatment guidelines [3]. The cornerstone of therapy consists of topical and systemic antifungal agents. In the current context, topical antifungal agents have a restricted impact on adults. In contrast, systemic antifungals have been linked with reduced cure rates, increased adverse effects, several drug interactions and the development of drug resistance in various regions of the country [4]. Conversely, contemporary antifungals such as itraconazole,

which formerly exhibited elevated cure rates, are now failing to achieve an acceptable clinical cure. Various strategies have been employed to overcome this problem including prolonging the period of treatment, increasing normal antifungal doses, using multiple antifungals concurrently and using penetration-enhancing agents [3]. Isotretinoin (13-cis-retinoic acid) has been suggested in several studies to contribute to the management of fungal infections through mechanisms that are primarily indirect rather than directly fungicidal. Its keratolytic properties enhance epidermal turnover and desquamation of the stratum corneum, thereby reducing fungal burden and potentially improving the efficacy of concomitant antifungal agents such as itraconazole. In addition, isotretinoin reduces sebum production and modifies the cutaneous microenvironment, factors that may limit fungal persistence in certain conditions [4,5].

Isotretinoin has gained extensive application in clinical practice and current attention has turned to its potential antifungal properties. Although isotretinoin was first created and widely used to treat acne vulgaris, its effects on microbial colonization, sebaceous gland activity and epidermal differentiation have sparked interest in its potential uses outside of acne. Given that keratinization irregularities, sebum production and biofilm formation impact a number of superficial fungal illnesses, these documented pharmacological actions offer a convincing justification for examining isotretinoin as an adjuvant therapy approach [6,7].

Fungal biofilms are integral to the pathogenesis of superficial mucosal and potentially fatal systemic mycosis [6]. Fungal cells embedded in biofilms exhibit greater resistance to antifungal agents and host immunological defences compared to their planktonic equivalents. Consequently, fungal proliferating in biofilms can endure within the host, resulting in severe infections [8]. Consequently, there is an immediate necessity to devise innovative therapeutic approaches to inhibit biofilm formation and dismantle established biofilms. Retinoids may offer a new strategy to inhibit and diminish the growth of biofilm in this scenario. Currently, while it has been demonstrated that these compounds possess antibacterial and anti-biofilm properties in bacterial cultures, there is a lack of data about their potential application against biofilm-associated fungal infections [9]. The combined administration of oral isotretinoin and oral itraconazole is proved to be effective in treating chronic persistent and recurrent dermatophytosis. Isotretinoin was believed to aid in eradicating the organisms by enhancing the proliferation of the epidermis, resulting in the desquamation of keratinocytes [10].

The evidence for isotretinoin as an adjuvant treatment for fungal infections is still dispersed across various fungal illnesses, study designs and treatment approaches, despite the drug's increasing popularity. To the best of our knowledge, no prior systematic review has thoroughly compiled the clinical data pertaining to the use of isotretinoin, either alone or in conjunction with antifungal medications, throughout the range of fungal infections and fungal-associated dermatoses. Thus, the purpose of this systematic review is to identify existing data gaps and future research goals while critically assessing the clinical applicability, safety and efficacy of isotretinoin in fungal infections.

METHODS

Study Protocol and Focussed Research Question

The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) standards [11], were adhered to in the systematic review selection of studies, synthesis and subsequent research findings. The research question was: "What is the comparative effectiveness of isotretinoin and antifungal therapies in treating skin fungal infections?" This would allow for the assessment of scientific documentation, the identification of specific clinical challenges, the recognition of gaps in the current literature and the evaluation of the need for additional research.

Information Sources and Search Strategy

An extensive search was performed in the PubMed, Scopus, Web of Science and Google Scholar databases, covering the last decade from January 2015 to December 2024. Only articles in the English language were incorporated into the searches. The lists of references of the original research and review articles were also screened for forward citations. After reviewing the literature, the following Medical Subject Headings (MeSH) phrase combination was used: (“Isotretinoin” OR “13-cis-Retinoic Acid” OR “Retinoids” OR “Retinoic Acid”) AND (“Fungal infections” OR “Fungal Diseases” OR “Mycoses” OR “Fungal biofilm” OR “Mucor” OR “Fonsecaea” OR “Dermatophytosis” OR “Candidiasis” OR “Seborrheic Dermatitis” OR “Pityriasis versicolor” OR “Tinea” OR “Mycosis fungoides”) AND (“Therapeutic effect” OR “Adverse effects” OR “Side effects” OR “Treatment outcome” OR “Efficacy” OR “Clinical cure” OR “Mycological cure” OR “Remission” OR “Recurrence”). The reference lists of the chosen studies were carefully examined to find any articles that were missing from internet databases.

Eligibility Criteria

The selection of eligible studies adhered to the PICOS criteria (Population, Intervention, Comparator, Outcome and Study design).

Inclusion Criteria

- **Population:** Individuals of any age, sex or ethnicity who had fungal infections were included
- **Intervention:** Research utilizing isotretinoin as a specific treatment for fungal infections
- **Comparator:** Any antifungal medicine or treatment for fungal infections other than isotretinoin. Nonetheless, the review also incorporated studies that did not employ a comparator

- **Outcome:** Research examining the direct and indirect effects of isotretinoin on fungal infections
- **Study Design:** All case reports, case series and clinical studies that discussed the application of isotretinoin in fungal illnesses were included

Exclusion Criteria

Non-English-language publications and studies on other diseases not associated with fungal pathogens were not included in this review. Studies performed in ambulatory environments or rehabilitation facilities were excluded. Systematic and narrative reviews, animal studies, editorial comments and expert opinions were also excluded.

Study Selection and Data Extraction Process

Two reviewers conducted a thorough search and screened according to the predetermined qualifying criteria of the review using online screening tool (Rayyan.ai). The titles and abstracts of the research studies were assessed and publications not meeting the criteria were excluded. Experts independently assessed the selected full-text articles. The reviewers arrived at a unanimous conclusion after a third reviewer had been invited in to mediate the conflicts between the two. The first author, journal, study title, year of publication, geographic area, study design, isotretinoin intervention regimen, employed antifungal therapies and study outcomes were gathered using a predefined data collection framework.

Data Synthesis

A quantitative meta-analysis was not possible due to the variability of trial designs, illness conditions, isotretinoin regimens, comparator therapies and outcome measures. As a result, the results were narratively summarized. Randomized controlled trials and comparative clinical studies were regarded as greater levels of evidence than case reports and case series, depending on the study design. To make it easier to compare the therapeutic benefits across research, results were categorized by type of fungal disease whenever possible.

Quality Appraisal

Risk of Bias (RoB) was appraised using the Cochrane Collaboration method ROBINS-I [12], which classifies bias as low, moderate, serious, critical or no information. The tool includes confounding bias, participant selection bias, intervention categorization bias, deviation from intended intervention bias, missing data bias, outcome assessment bias and selective reporting bias. Overall RoB for each study was categorized: Low RoB was given when all requirements were met. A moderate RoB was assigned to studies that did not meet any domains. When at least one domain had significant issues in any of the domains, it was considered a serious RoB. Critical concerns in at least one area indicate a critical RoB for the investigation. A study with no information and no evident evidence of serious or critical RoB was awarded no information.

Based on study quality according to the Cochrane Handbook for Systematic Reviews of Interventions, the RoB 2.0 tool was utilized to evaluate the RoB of RCTs as low, with some concerns or high [13]. These include randomization bias, departures from intended interventions, missing outcome data, measurement bias and reported result selection bias. Low RoB in all categories indicates low bias in the study. The overall RoB of the study is considered to have some concerns when the trial is determined to raise some issues in at least one domain. A study has a high RoB if it is regarded to be at high RoB in at least one area for this result or to have some issues for many domains that impair confidence in the result.

RESULTS

Two hundred forty-nine articles concerning the use of isotretinoin for fungal infections were identified. Titles and abstracts of 152 studies were evaluated, resulting in 54 studies deemed eligible for full-text evaluation. Thirty-eight studies were removed due to a lack of focus on fungal infections and inadequate target interventions. Finally, this review considered 16 studies [14-29] (Figure 1). Among them, three were case reports [14,19,28]. The findings of our investigation are encapsulated in Table 1. Four research [15,17,21,24,25] focused on dermatophytosis, three [16,26,27,29] on seborrhoeic dermatitis and two each on pityriasis versicolor [14,28] and tinea [18,20,23] and one each on chromoblastomycosis [19] and mycosis fungoides [22]. There were four studies from India [15,21,23,25], three from Brazil [14,26,29], two each from China [16,19], Turkey [22,28] and Iraq [17,27] one each from Pakistan [20], Egypt [18] and Bangladesh [24].

Khattab *et al.* [18] administered treatment to patients with chronic recurrent/recalcitrant tinea utilizing the combined administration of oral itraconazole and isotretinoin, itraconazole monotherapy and voriconazole monotherapy, revealing cure (clinical) rates of 53.3% for the itraconazole group, 70% for the itraconazole/isotretinoin group and 83.3% for the voriconazole group. Mycological cure observed in the itraconazole, itraconazole/isotretinoin and voriconazole cohorts were 56.7, 83.3 and 86.7%, respectively. A statistically significant difference was observed across the three cohorts, favouring voriconazole against the combination group. A comparable study by Alhamdi and Alhamdi indicated a clinical cure rate of 97.5% for the combined administration of isotretinoin and itraconazole, accompanied by a notably low recurrence rate of 12.8%. In contrast, patients receiving itraconazole alone exhibited a cure rate of 53.7% and a relapse rate of 68.1%, with insignificant adverse effects disclosed. Rahman [24] performed a clinical trial to determine the efficacy of an oral

Table 1: Summary Characteristics of the Reviewed Studies

Author-Year, place of study	Study design	Disease condition	Characteristics of the study sample	Intervention (isotretinoin)	Comparator	Cure rate/clinical findings	Recurrence rate	Adverse effects	Study outcome
Veasey *et al.* [14] (Brazil)	Case report	Chronic PV	40 year old male	Oral isotretinoin 20 mg/week for 8 weeks	NA	Significant improvement	NR	NR	Low-dose isotretinoin may serve as an effective therapy alternative for recurring and chronic PV
Priyadarshi *et al.* [15] (India)	RCT	Superficial dermatophytosis	Isotretinoin: 34.04±10.02 Itraconazole: 35.35±11.27 (n = 90 in each group)	Oral itraconazole 200 mg plus oral isotretinoin 20 mg daily	Oral itraconazole 200 mg daily,	Isotretinoin: 97.5% Itraconazole: 89.2%	Isotretinoin: 2.6% Itraconazole: 13.5%	Gastritis, hepatic and lipid derangements, lip cheilitis, Skin dryness, photosensitivity	Oral isotretinoin causes early recovery with a reduced recurrence rate, making it a useful supplementary treatment for superficial dermatophytosis
Yanfei *et al.* [16] (China)	Clinical study	Seborrheic dermatitis	Isotretinoin 20 mg/day: N = 26 Isotretinoin 10 mg/day: N = 22	Oral isotretinoin (20 mg/day and 10 mg/day)	NA	Symptom Scale of Seborrheic Dermatitis: Isotretinoin 20 mg/day: 10.95±1.15 Isotretinoin 10 mg/day: 10.30±1.11	NR	NR	Moderate to severe seborrhoeic dermatitis can be treated with oral isotretinoin
Alhamdi *et al.* [17] (Iraq)	Open labelled RCT	Chronic Recurrent Dermatophytosis	With isotretinoin: Age: 39.647±1.988 M/F: 23/17 Without isotretinoin: Age: 38.969±1.956 M/F: 23/18	Low-dose isotretinoin every other day for 2 months along with itraconazole	Itraconazole for 7 days per month for 2 consecutive months	97.5% (isotretinoin); 53.7% (comparator)	12.8% (isotretinoin); 68.1% (comparator)	NR	The combination of low-dose isotretinoin and itraconazole is a viable treatment for persistent recurrent dermatophytosis
Khattab *et al.* [18] (Egypt)	RCT	Recalcitrant or recurrent Tinea	Itraconazole monotherapy: n = 30 Combined itraconazole/ isotretinoin therapy: n = 30 Voriconazole monotherapy: n = 30	Oral isotretinoin 20 mg daily for six weeks	Oral itraconazole 200 mg daily for six weeks	Itraconazole monotherapy: 53.3% Combined itraconazole/isotretinoin therapy: 70% Voriconazole monotherapy: 83.3%	Isotretinoin: 28%	Lip cheilitis and skin dryness	For intractable dermatophytosis, voriconazole may be an option
Lan *et al.* [19] (China)	Case report	Hyperkeratotic chromoblastomycosis	66 year-old male	Oral isotretinoin: 20 mg/day	Oral terbinafine: 250 mg/day Itraconazole: 400 mg/day carbon dioxide laser, ALA-PDT	Significant imporvement noted	NR	NR	For recalcitrant chromoblastomycosis, retinoid, CO2 laser and ALA-PDT may be an innovative adjuvant treatment
Naseemullah *et al.* [20] (Pakistan)	Clinical study	Chronic Tinea	Isotretinoin: 32.11±4.23 (n = 40) Itraconazole: 33.72±6.11 (n = 40)	Oral itraconazole (100 mg/day) combined with oral isotretinoin (20 mg daily dose) while	Oral itraconazole (200mg/day) alone.	Isotretinoin: 100% Itraconazole: 50%	Isotretinoin: 0% Itraconazole: 50%	Cheilitis and dryness of lips	Chronic tinea is effectively and safely treated with oral itraconazole and isotretinoin
Verma *et al.* [21] (India)	Open-label RCT	Recurrent dermatophytosis	Isotretinoin: 29.85±9.18 (n = 48) Terbinafine group: 28.65±9.35 (n = 52)	Oral isotretinoin 0.5 mg/kg/day and oral terbinafine 250 mg twice/day for four weeks	Oral terbinafine 250 mg twice/day for four weeks	Isotretinoin: 43.18% Terbinafine: 42.55%	Isotretinoin: 63.1% Terbinafine: 65%	Cheilitis and dryness of the lips	Isotretinoin combined with terbinafine does not improve the therapeutic results
Taslidere *et al.* [22] (Turkey)	RCT	Early-stage mycosis fungoides	Narrow-band UVB+isotretinoin: 46.81±12.99 years (n = 11) UVB: 50±12.15 years (n = 10)	Narrow-band UVB alongside 0.5 mg/kg/day oral isotretinoin	Narrow-band ultraviolet B (UVB: 0.005 joule/cm^2 three days/week for 30 sessions, increasing the dose by 30% in every third session)	Symptom severity score after treatment: UVB+isotretinoin: 5.18±4.42 UVB: 5.4±4.97	NR	NR	Narrow-band UVB+ isotretinoin fails to enhance clinical outcomes or induce apoptosis better than narrow-band UVB alone. The isotretinoin and narrow-band UVB group recovered faster

Table 1: Continue

Author-Year, place of study	Study design	Disease condition	Characteristics of the study sample	Intervention (isotretinoin)	Comparator	Cure rate/clinical findings	Recurrence rate	Adverse effects	Study outcome
Kaushik *et al.* [23] (India)	RCT	Tinea corporis and Tinea cruris	Isotretinoin: 29.5±5.4 (n = 35) Salicylic acid: 30±5.2 (n = 35)	Oral isotretinoin 20 mg plus oral itraconazole 200 mg daily for one month	Salicylic 30% chemical peeling once per week for one month	Isotretinoin: 91% Salicylic acid: 74%	NR	NR	The oral drug combination of itraconazole and isotretinoin eliminates microbes better than salicylic acid 30% chemical peel
Rahman *et al.* [24] (Bangladesh)	Clinical study	Recurrent and recalcitrant superficial dermatophytosis	Age: 21-50 years N = 40	Daily low dose of isotretinoin (20 mg)	Oral monthly pulse (200 mg twice daily for 7 days each month) dose of Itraconazole for 3 months	Clinical cure: 90% Mycological cure: 95%	15%	NR	Itraconazole Pulse treatment with daily isotretinoin may alleviate relapsing superficial dermatophytosis
Arora and Solanki [25] (India)	RCT	Recalcitrant superficial dermatophytosis	Isotretinoin: 41.7±12.3 Itraconazole: 43.4+14.9 (n = 38 in each group)	Oral isotretinoin 0.3-0.4 mg/kg/day	Oral itraconazole 100 mg twice a day along with clotrimazole	Isotretinoin: 86.8% Itraconazole: 76.3%	Isotretinoin: 7.9% Itraconazole: 26.3%	Mild abdominal discomfort and cheilitis	Adding 2 weeks of isotretinoin to oral antifungals can help cure recalcitrant superficial dermatophytosis
Kamamoto *et al.* [26] (Brazil)	RCT	Seborrheic dermatitis	M. globosa: 28.5±5.6 (n = 24; [isotretinoin: n = 13]) M. restricta: 28.3±7.2 (n = 10; [isotretinoin: n = 7])	Oral isotretinoin, 10 mg, every other day over six months	Anti-seborrheic shampoo (piroctone olamine), over six months	NR	NR	NR	Following both treatments, Malassezia spp. remained in the scalp and controlled seborrhea/seborrheic dermatitis equally well
Meran and Saeed [27] (Iraq)	RCT	Seborrheic dermatitis	Mean age: 31.26±14.15 Isotretinoin: n = 37 Comparator group: n = 31	oral isotretinoin 20 mg twice weekly for three months	200 mg/day oral itraconazole for one week of the first month, followed by 200 mg for the first two days of the next two months	Isotretinoin showed a significantly greater decrease in SDASI score than that of the itraconazole group	NR	Cheilitis, mucocutaneous dryness and epistaxis were reported in isotretinoin group	Low-dose oral isotretinoin treats seborrhoea dermatitis better than oral itraconazole
Yazici *et al.* [28] (Turkey)	Case report	Recurrent PV	33 year-old male	Isotretinoin therapy (20 mg/day)	NA	100% cure rate	NR	NR	Isotretinoin at low doses and for brief periods can ameliorate recurrent and chronic PV
Kamamoto *et al.* [29] (Brazil)	RCT	Seborrhea and seborrheic dermatitis	Isotretinoin group: 28.7±5.8 years (n = 28) Comparator group: 29.8±6.5 years (n = 21)	Isotretinoin 10 mg every other day	Antiseborrheic topical treatment	The mean total DLQI scores diminished significantly after both treatments with no difference between the groups	Cheilitis, Body and face skin fragility, Headache, Eczema, Nose fragility, Diarrhea, Abnormal serum lipids were commonly reported	NR	Oral isotretinoin at low doses can treat moderate to severe seborrhoea and dermatitis

NR – Not reported; NA – Not applicable; SDASI - Seborrheic dermatitis area severity index; PV - Pityriasis versicolor; RCT – Randomized comparative trial; ALA-PDT - 5-aminolevulinic acid-based photodynamic therapy; DLQI - Dermatology Life Quality Index; IQR –Interquartile range

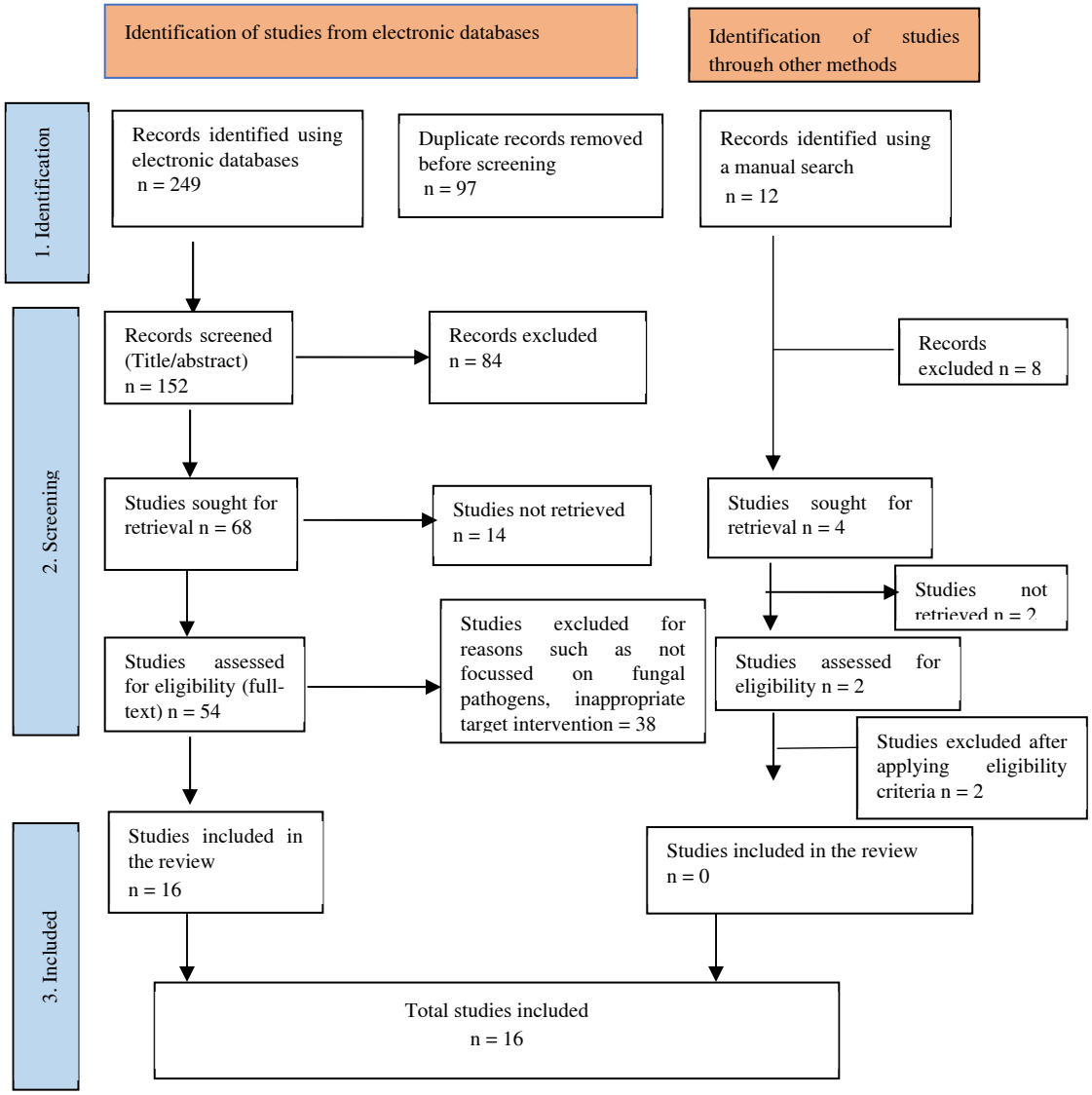

Figure 1: PRISMA (2020) Flow Chart of the Reviewed Studies

monthly pulse regimen of itraconazole (200 mg twice/day for 7 days every month) that was combined with an everyday low dose of isotretinoin (20 mg) for the management of persistent superficial dermatophytosis. The treatment resulted in a 90% clinical cure rate and a 95% mycological cure rate, with no hematologic or biochemical variations seen.

A retrospective study [16] revealed that patients with moderate-to-severe seborrhoeic dermatitis who were administered either 20 mg or 10 mg of oral isotretinoin daily for 2-6 months, had a substantial decrease in the seborrhoeic dermatitis symptom scale in comparison with baseline measurements. Furthermore, there was no notable disparity in the results of these two groups. Kamamoto *et al.* [29] conducted an RCT among patients with moderate-to-severe seborrhoeic dermatitis contrasted isotretinoin 10 mg administered every other day to topical therapy, demonstrating that isotretinoin considerably reduced scalp pruritus and sebum production while enhancing quality of life relative to topical application. Taslidere *et al.* [22] observed that the combined use of narrow-band UVB and isotretinoin was not beneficial to narrow-band UVB therapy alone in terms of improved clinical outcomes and apoptotic induction. Nevertheless, recovery commenced sooner in the isotretinoin combined with the narrow-band UVB group. Verma *et al.* [21] also asserted that incorporating isotretinoin with terbinafine offers no further advantage in the management of those with recurrent dermatophytosis. The mycological cure rate in the isotretinoin and itraconazole cohort in the clinical trial by Priyadarshi *et al.* [15] was 97.5%. The cure rate was significantly higher than that stated in prior studies by various researchers [17,18,24,25] indicating that daily administration of 20 mg oral isotretinoin for two months provides additional advantages in the treatment of superficial dermatophytic infections. Furthermore, the relapse rate found by

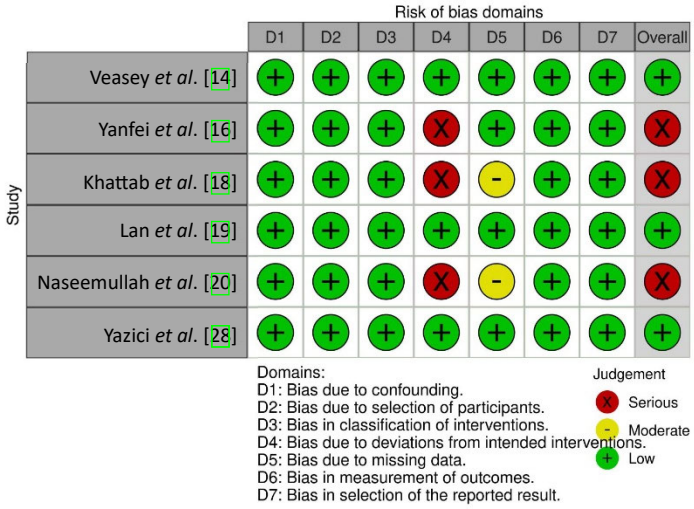

Figure 2: ROBINS-I Tool for Evaluating the Risk of Bias of the Reviewed Non-Randomized Studies

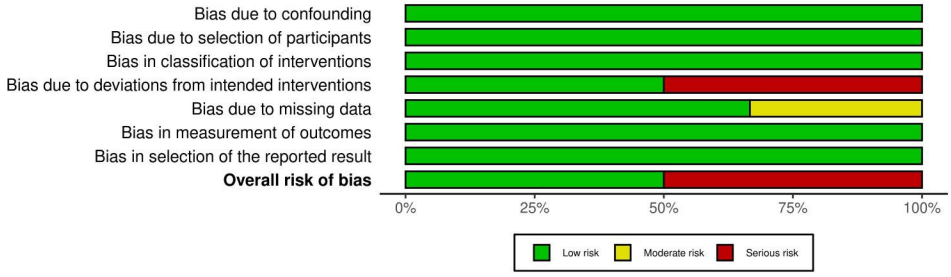

Figure 3: ROBINS-I Tool for Determining the Risk of bias across the Reviewed Non-Randomized Studies

Priyadarshi *et al.* [15] was substantially lower in the isotretinoin and itraconazole group (2.6%) than documented in many other studies [17,18,24,25], emphasizing the relevance of oral isotretinoin in the alleviation of relapse if administered for a prolonged period. According to Yazici *et al.* [28], a case was successfully managed with oral isotretinoin (20 mg/day) for two months and a year-long remission was attained.

Henceforth, isotretinoin, whether administered as monotherapy or alongside existing antifungal medications, may serve as an intriguing option for innovative therapeutic or preventative antifungal strategies; thereby addressing the significant clinical challenge of fungal drug resistance.

Although several studies reported favorable outcomes with isotretinoin, these findings should be interpreted cautiously, as a substantial proportion of the evidence was derived from small sample sizes, open-label studies, observational designs and case reports.

Quality Assessment of the Reviewed Studies

Out of the six studies appraised using the ROBINS-I tool, three studies [14,19,28] exhibited a low RoB and three other studies [16,18,20] demonstrated a serious RoB (Figure 2). Figure 3 illustrates the RoB across the non-randomized studies. The RoB 2.0 tool revealed that all the assessed studies [17,21-27,29] exhibited high RoB, except for one study [15] that raised some concerns (Figure 4). The RoB across the evaluated RCTs is depicted in Figure 5. The predominance of studies with high or serious risk of bias limits confidence in the reported efficacy outcomes and highlights the need for cautious interpretation of the available evidence.

DISCUSSION

The effectiveness of isotretinoin as a treatment for superficial mycoses is demonstrated by data from the reviewed clinical trials. Nevertheless, some of the reviewed studies [18,21,22] found isotretinoin ineffective in treating fungal infections than that of the comparison group. Further, Kamamoto *et al.* [26] documented equal effectiveness with isotretinoin and anti-seborrheic shampoo for the control of seborrhea/seborrheic dermatitis. Dermatophytic infections are rising globally, ascribed to a complicated interaction among host, fungus, medication and environment [30]. Additional significant causes comprise humid and elevated climatic conditions, the unregulated application of topical corticosteroid combinations, heightened utilization of broad-spectrum antibiotics, widespread usage of antifungal agents in agriculture and the rise of antifungal medication resistance [31]. Recurrences following an apparent resolution are also prevalent [32]. Multiple approaches have been employed to promote cure rates, including escalating the dosage of

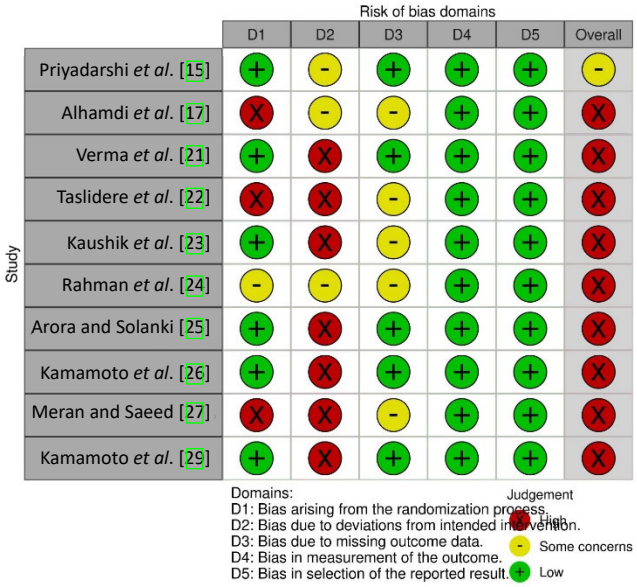

Figure 4: ROB 2.0 tool for determining the risk of bias of the reviewed randomized controlled trials

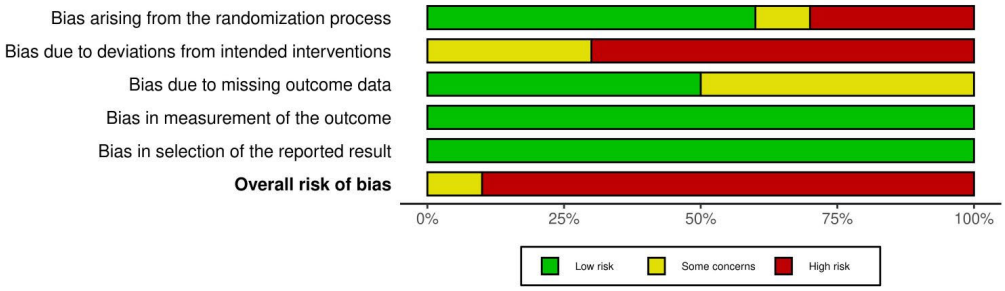

Figure 5: ROB 2.0 Tool for Determining the Risk of Bias Across the Reviewed Randomized Controlled Trials

antifungal medications, prolonging treatment time, utilizing an array of multiple oral antifungal agents and employing penetration promoters [3,21].

Dermatophytes inhibit keratinases and non-specific proteolytic enzymes, which are key virulence agents and exhibit their peak potency at acidic Ph [33]. Consequently, growth is contingent upon the skin pH, which, being acidic, provides an ideal setting for the fungus. Elevated transepidermal water loss and compromised skin barrier function are associated with increased skin Ph [34]. The elevation of skin pH due to treatment with retinoid compounds may limit the formation of dermatophytes. Ultimately, retinoids are widely regarded as stimulants of both humoral and cellular immunity and can augment antibody synthesis by activating T-helper cells. The cell surface antigens of T lymphocytes and natural killer cells were documented to be elevated following retinoid treatment *in vitro* [35]. Conversely, dermatophytes possess strategies that enable them to circumvent the host response such as a decrease in inflammation and phagocytosis [36,37]. Therefore, retinoids may mitigate certain immunosuppressive effects of the dermatophyte [5].

The medication causes atrophy of sebaceous glands and diminishes sebum production by up to 90%. Kraus *et al.* [38] documented that sebum production drops back to roughly 40% of the initial level within a month of therapy ending and it seldom regains its original levels. The concept may elucidate the sustained long-term remission achieved using isotretinoin medication. In the literature, isotretinoin has been successfully used to treat hidradenitis suppurativa, pityrosporum folliculitis, seborrhoeic dermatitis and persistent acne through the same approach [39,40]. Layton *et al.* [41] found that most patients exhibited long-term improvement in acne management following low-dose isotretinoin therapy, in addition to the well-established effectiveness of isotretinoin at doses of 0.5-1.0 mg/kg/day in the management of acne by Mandekou-Lefaki *et al.* [42]. Similarly, Geissler *et al.* [43] indicated that a minimal dosage of isotretinoin, specifically 2.5 mg administered three times/week, is beneficial in managing seborrhoea.

Ardeshna *et al.* [5] claimed superior outcomes for combination therapy utilizing isotretinoin and itraconazole in the management of recurrent dermatophytosis. Bartell *et al.* [44] also documented similar outcomes in the management of Tinea versicolor and were the first to see an incidental remission of a pre-existing skin infection lasting nine months following the administration of oral isotretinoin

(40 mg twice daily) for acne vulgaris. Abraham and Piguet [45] documented two instances of Malassezia dermatosis that were well managed with oral isotretinoin (20 mg/day) in conjunction with topical ketoconazole. A recent systematic review [46] demonstrated that isotretinoin is more efficacious than oral itraconazole, antifungal shampoo or salicylic acid-incorporated soap in alleviating seborrhoeic dermatitis symptoms, even at modest dosages. Isotretinoin is an efficacious treatment for moderate-to-severe seborrhoeic dermatitis and is typically well-tolerated and safe [46]. Conversely, a retrospective investigation [47] has indicated that five patients who received isotretinoin treatment for acne later experienced seborrhoeic dermatitis-like skin eruptions.

The prevalence of obstinate recurrent infections caused by dermatophytes is approaching endemic status [5]. Our observation offers up possibilities for more research to address the utility of oral isotretinoin in recurrent dermatophytosis, even though we do not advise its routine usage for treating dermatophytes. Isotretinoin is excreted from the body by the desquamation of the stratum corneum during epidermal regeneration. Given that isotretinoin influences epidermal cell dynamics and enhances cell turnover, the concurrent treatment of isotretinoin and itraconazole would probably lead to expedited elimination of itraconazole from the dermis [48]. Consequently, we propose that comprehensive studies examining the impact of isotretinoin on the drug metabolism of itraconazole, specifically the variance in drug concentrations within the stratum corneum and sebum with and without the concomitant use of isotretinoin, should be conducted to further validate the integration of oral retinoids into antifungal treatment.

While several studies suggested potential benefits of isotretinoin, the overall certainty of the evidence remains limited because many included studies were characterized by small sample sizes, methodological limitations and high or serious risk of bias. Consequently, the reported benefits should be regarded as preliminary rather than definitive. Evidence from randomized controlled trials and comparative clinical studies was considered more clinically informative, whereas findings from case reports and case series should be regarded as hypothesis-generating and require confirmation in larger controlled investigations.

Cheilitis is the predominant side effect of isotretinoin, succeeded by eczema, fatigue and mood alterations. Laboratory studies reveal an elevation in total cholesterol and serum triglyceride levels. Mild and well-tolerated side effects are common. Nonetheless, the well-established teratogenicity of isotretinoin is an important safety concern; therefore, it should not be used during pregnancy or lactation [49]. In addition, regular clinical and laboratory monitoring is necessary throughout treatment because of its potential effects on lipid profiles and liver function. These considerations may reduce the practicality of isotretinoin as an adjunctive therapy for fungal diseases, particularly when safer conventional antifungal alternatives are available.

The adverse effects associated with isotretinoin predominantly involved mucocutaneous ailments including dry skin, skin fragility, erythema, xerosis, rashes, cracked lips, dry and sore mouth, insatiable thirst, cheilitis and nasal dryness. However, all of them are transitory and not serious. Furthermore, isotretinoin treatment has an impact on liver function tests and lipid profiles with a higher likelihood of increasing lipid levels than liver enzymes. In almost all the studies reviewed, the abnormalities in liver markers and lipid profiles were normalized immediately after discontinuation of the medication, in line with the findings of a recent single-arm meta-analysis [50]. Retinoid-induced myositis must be acknowledged in the clinical setting, as it presents a diagnostic difficulty due to the various aetiologies linked to myopathic disorders [51]. These undesirable effects signify individual reactions to a medication [29]. Comprehending the adverse events spectrum and effectively communicating it to the patient enhances the probability of adherence to the prescribed dose regimen and the utilization of supplementary treatment, which may mitigate or eradicate undesirable consequences.

From a clinical perspective, isotretinoin should not currently be considered a routine treatment for superficial fungal infections. Conventional antifungal agents remain the standard of care because of their established efficacy, safety profile and broader evidence base. Based on the currently available evidence, isotretinoin may be considered only as a selective adjunctive option in carefully chosen cases, particularly recurrent or treatment-resistant conditions and only after careful evaluation of potential risks and benefits.

Future Recommendations

Traditional antifungal drugs still remain the first-line treatment due to the proven efficacy, safety profile and solid research background. Considering the current level of evidence, isotretinoin should be limited to a selective adjunctive treatment in well-selected cases, particularly recurrent and resistant to treatment and after a comprehensive evaluation of possible risks and benefits. Future Recommendations Future research should focus on specific fungal diseases, rather than combining several diseases in a single study design. In particular, recurrent dermatophytosis and moderate-to-severe seborrhoeic dermatitis seem to be the most promising areas for further research. Well-designed double-blind randomized controlled trials are needed to determine the optimal dosing schedules, duration of treatment, recurrence rates and long-term safety outcomes. Further studies investigating the mechanisms are also needed to determine whether the beneficial effects of isotretinoin are due to changes in the skin environment or rather direct effects on the fungus's ability to cause disease and form biofilms.

CONCLUSIONS

Despite its potential as an adjunctive treatment for selected fungal disorders, isotretinoin currently functions primarily as a supportive rather than a standalone therapy. The most

encouraging evidence has been observed in recurrent dermatophytosis and seborrhoeic dermatitis; however, the available literature remains limited by small sample sizes, clinical heterogeneity and methodological limitations. Conventional antifungal agents should therefore remain the cornerstone of treatment. Further disease-specific, adequately powered, double-blind randomized controlled trials are required to clarify the efficacy, safety and optimal clinical role of isotretinoin in fungal diseases.

Limitations

This review should be considered in the context of the literature available. The number of studies eligible for inclusion was relatively small, reflecting the early stage of research on isotretinoin in fungal diseases. Moreover, clinical and methodological heterogeneity was introduced due to variations in fungal diseases, study designs, treatment regimens, outcome measures and follow-up durations. A number of studies had incomplete reporting of outcomes, including recurrence rates, adverse effects and long-term follow-up data, which limited the ability to directly compare across studies. Consequently, a quantitative meta-analysis and formal certainty-of-evidence assessment were not feasible. Nevertheless, the systematic inclusion of diverse study designs enabled a comprehensive overview of the currently available evidence and helped identify recurring patterns, potential therapeutic applications and important areas for future investigation. Therefore, while the findings should be interpreted with appropriate caution, they provide a valuable foundation for the design of future well-controlled studies evaluating isotretinoin as an adjunctive antifungal therapy.

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