Sumayya Tasneem Parapur, Nazim Husain*, Mohd Khalid, Saba Abdul Razzaq Mamdapur and Khan Ameer Kauser Khan

Evaluation of the efficacy of topical *Terminalia chebula* Retz. with vinegar in the treatment of tinea corporis: a non-inferiority randomized controlled trial

https://doi.org/10.1515/dmpt-2022-0188
Received November 11, 2022; accepted January 5, 2023;
published online April 4, 2023

Abstract

Objectives: Unani physicians have suggested a wide range of anti-dermatophytic remedies, although the scientific evidence is scarce. Thus, the efficacy and safety of *Terminalia chebula* Retz. fruit powder mixed with vinegar was compared with terbinafine hydrochloride 1% cream in the treatment of tinea corporis in order to establish the non-inferiority of test drugs.

Methods: The primary outcome measures were change in the presence or absence of hyphae on KOH mount test, change in pruritus severity assessed on 100 mm VAS and change in physician's global assessment. Secondary outcome measure was change in the dermatology life quality index (DLQI). Hemograms, serum creatinine, serum bilirubin, and random blood sugar levels were measured at the baseline and after treatment to ensure the safety of the interventions.

Results: A per-protocol analysis was done on 40 participants (21 in the test group and 19 in the control group). The observed differences in the primary and secondary outcomes between the test and control groups were greater than the non-inferiority margin, signifying that the test drugs were not inferior.

Conclusions: It may be inferred that the trial drug *Terminalia chebula* Retz. fruit powder mixed with vinegar is not inferior to terbinafine hydrochloride cream in the treatment of tinea corporis.

***Corresponding author: Nazim Husain**, Department of Moalajat (Medicine), Luqman Unani Medical College, Hospital and Research Center, Bijapur, Karnataka, 586101, India, Mobile: +919212143572, E-mail: nazimcrium@gmail.com. https://orcid.org/0000-0002-8933-3447
Sumayya Tasneem Parapur, Mohd Khalid, Saba Abdul Razzaq Mamdapur and Khan Ameer Kauser Khan, Department of Moalajat (Medicine), Luqman Unani Medical College, Hospital and Research Center, Bijapur, Karnataka, India. https://orcid.org/0000-0003-1928-3744 (M. Khalid)

Keywords: dermatophytosis; *Halela Zard*; Quba; tinea; Unani medicine.

Introduction

Dermatophytosis, also referred to as "tinea," is a very common clinical problem caused by superficial mycoses (dermatophytes) that infect the skin, hair, and nails [1, 2]. Dermatophytes are inoculated into the host skin through penetration followed by full-blown lesions mediated by proteases, serine-substilisins, and fungolysin which cause digestion of keratin network into oligopeptide or amino acid and act as potent immunogenic stimuli [3]. It is clinically manifested by well demarcated, annular, pruritic, and scaly lesions with central clearing [4]. According to WHO, the reported worldwide prevalence is about 20–25%, whereas approximately 30–70% adults suffer from asymptomatic superficial mycosis [5, 6]. The incidence of this disease increases with the passage of age [5].

Clinically, dermatophytoses are categorized by the names of the body parts affected, i.e., tinea capitis (head); tinea corporis (body); tinea cruris (groin); tinea unguium (nail), and tinea pedis (feet) [4]. Among these subtypes, tinea corporis is the commonest type characterized by dermatophytosis of glaborous skin except palms, soles, and groin area [6, 7]. It is treated by both the topical and oral antifungal agents in the conventional medicine [4, 6, 7]. Systemic antifungals include terbinafine; griseofluvin; itraconazole, and fluconazole [1, 4, 7], but failure reports of systemic therapy and associated resistance is the most alarming concern; especially mutation in the sequalene peroxidise enzyme that leads to the drug resistance [8]. High recurrence rate was also reported if these therapies are discontinued [9]. Thus, it creates a potential space for further exploration of alternative treatment modality, and Unani medicine may play an important role in its management.

In Unani system of medicine, *Qūbā* clinically resembles with tinea [10, 11] and has extensively been described in various Unani classical textbooks with special focus on its

classification, pathogenesis, prevention, and treatment [12]. It is defined as annular, dry, and pruritic eruptions [11] caused by amalgamation of *Mirra Sawda*' (bilious melancholhe) into blood or *Ruṭūbat-i Ghalīẓ* and *Balgham-i Shor* (saline phlegm) [10] which is diverted towards the skin by *Quwwat-i Ṭabī'yya* (natural faculty) resulting in the pruritic skin lesion [13]. The line of treatment of *Qūbā* is based on *Teḥlīl* (resolution), *Tanqiya-i Mawād* (elimination of morbid material from the body) and *Talṭīf-i Mawād* (rarefaction of morbid matter) [12]. Based on these therapeutic principles, various single and compound formulations are used as systemic and topical agents in the treatment of *Qūbā* by Unani physicians. Accordingly, a combination of two Unani drugs were selected for this study as *Halela Zard* (*Terminalia chebula* Retz.) fruit powder mixed with *Sirka* (vinegar) is recommended for the treatment of *Qūbā* [11, 13] which possesses *Teḥlīl* and *Talṭīf* properties. Moreover, *Halela Zard* (*T. chebula* Retz.) exerts *Jālī* (cleansing), anti-inflammatory, and antipruritic activities [14]. The hypotheses for the study were H_0: $\varepsilon \leq \delta$ vs. H_a: $\varepsilon > \delta$, where ε is the mean or proportion difference between test and control group and δ is the noninferiority margin (δ<0). The rejection of the null hypothesis indicates the noninferiority of the test drug against the control.

Materials and methods

Trial design and setting

This prospective, non-inferiority, randomized, open-label, active-controlled, parallel-group clinical trial was conducted from January 2021 to February 2022 at department of Moalajat, Luqman Unani Medical College, Hospital and Research Centre, Vijayapura (Bijapur), Karnataka India.

Participants

Male or female participants aged 18–65 years diagnosed with tinea corporis clinically as well as by KOH mount test without nail or scalp involvement and body surface area BSA ≤20% were included in this study. Although, patients already on topical and/or systemic antifungal treatment (1 week of topical therapy and/or 4 weeks of systemic antifungal therapy before baseline visit), patient with diabetes mellitus, immunosuppressive disease or on immunosuppressant, super-imposed cases of tinea corporis, non-compliance with the trial protocol; pregnant and lactating mothers were excluded from the clinical trial.

Selection of the participants

To recruit trial participants, they underwent a thorough screening process that included complete medical history, general physical examination, and systemic examination. The trial enrolled participants who met the inclusion and exclusion criteria and conducted routine investigation. The demographic profile of the participants, a detailed history of the disease, and a physical and systemic examination were all recorded in the IEC-approved Case Report Form.

Interventions

Participants were randomly assigned to receive either topical application of *Halela Zard* and Sirka (sugar cane vinegar) in sufficient quantity to cover the lesion in the Unani group or topical terbinafine 1% cream in the control group. Concomitant use of any medication was not allowed during the study. Participants in both groups were followed up on every 10th day for a period of 40 days.

Herbal medicine product: The trial drug combination *Halela Zard* and Sirka was chosen from authentic Unani textbook *Dhakhīra Khwārizm Shāhi* [13].

Dosage regimen and quantitative description: Participants in the Unani group were advised to apply *Halela Zard* fruit powder mixed with *Sirka* to the affected sites twice daily in an amount sufficient to cover skin lesion for 40 days. The control group was instructed to apply terbinafine hydrochloride 1% cream topically twice daily in an amount sufficient to cover the lesions for 40 days [15].

Qualitative testing and preparation of Safūf (powder): *Halela Zard* (*T. chebula* Retz.) fruit and sugarcane vinegar were procured from a registered herbalist "Bhagvati Herbal & Healthcare Pvt. Ltd.", Gujrat, India. *T. chebula* was subjected to taxonomical identification and authentication by Miss Vidyashree Suryavanshi (Botanist). The identified drugs were also deposited in the Museum of author's institute, bearing herbarium file No. 04/HERB/LUMC/19 and voucher specimen numbers as *T. chebula* Retz. (DBARSI-BJP1902). Additionally, online database "World Flora Online" was used to verify the botanical name of the plant. *Safūf* (powder) was prepared by grinding *Halela Zard* fruits and sieving through sieve no. 80. The fine powder was then mixed with vinegar in 1:1 ratio and a homogenous paste was made. The formulation was then placed in plastic containers and given to patients for local application on lesions twice daily for 20 minutes. The patients were also trained on how to apply the paste.

Rationale for the type of control used: Terbinafine hydrochloride 1% is a well-established treatment option for dermatophyte infections, such as tinea corporis/cruris and tinea pedis, achieving a high rate of mycological cure [16]. It works by inhibiting squalene epoxidase, a precursor enzyme that fungi use to synthesise ergosterol, a critical component of fungal cell membrane, that impairs the fungal membrane function and cell wall synthesis [17].

Outcomes

Primary outcome measures: The primary outcome measures were the presence or absence of hyphae on the KOH mount test at baseline and at the conclusion of the trial, change in pruritus severity measured by the 100 mm visual analogue scale (VAS), and change in physician's global assessment (PGA) assessed on a 5-point scale at each follow-up.

Secondary outcome measure: Secondary outcome included change in the DLQI evaluated at baseline and at end of trial.

Safety and adverse event monitoring

To ascertain the safety of interventions, local dermal tolerability, changes in vital signs at each follow-up visit, and routine laboratory investigations such as hemograms, serum creatinine, serum bilirubin, and random blood sugar were performed prior to and after the trial. Adverse event, if any, occurred during the study was duly monitored and documented in the adverse event monitoring form.

Withdrawal criteria

Participants were withdrawn from the study if they developed any adverse effect necessitating the additional therapy or missed more than two consecutive treatment sessions.

Sample size

The sample size was determined to be 40 (20 in each group) based on data from a previous study that indicated a 74.3 % mycological cure (clearance of hyphae on KOH mount) [18]. To establish the non-inferiority of the test drug we assumed α=0.05, power=80%, ratio of sample size, treat/control=1, expected proportion in the treatment group=0.860, expected proportion in the control group=0.743, and noninferiority margin= −0.2 [19]. The required sample size was increased by 10% to account for projected dropouts. Thus, the intended sample size for this study was 44 participants in total (22 in each group). Although, the total number of participants who completed the trial were 21 in test group and 19 in control group.

Randomization

Participants were assigned to two parallel treatment groups using block randomization. The medical records department (MRD) of the institute created four-person randomization blocks and delivered them to the investigator in sequentially numbered, sealed, opaque envelopes.

Statistical methods

The data were entered into spreadsheet software, Microsoft Excel, and analyzed using statistical software, IBM SPSSS Statistics v26 (IBM corporation). The proportion, mean, and standard deviation (SD) of the data were appropriately represented. Chi-square test, independent samples t-tests, paired sample t-tests, and Mann-Whitney U tests were applied to draw the conclusions; $p<0.05$ was deemed significant in this study.

Results

Participant flow

A total of 56 patients were evaluated for eligibility with 50 people meeting the study requirements and being enrolled into the study. Of the remaining, 6 participants were excluded from the study due to not meeting inclusion criteria. Out of the 50 patients that were enrolled, 40 completed the course of treatment; 4 in test group and 6 in control group lost to follow-up. The statistical analysis was conducted on 40 participants who had completed the trial regimen (Figure 1).

Clinicodemographic profile

The mean (SD) age of participants in the Unani group was 33.10 (9.69) years, with 11 (52.4%) males and 10 (47.6%) females while in control group it was 39.79 (15.17) years, with 11 (57.9%) males and 8 (42.1%) females. Out of 40 participants, the majority 25 (62.5%) belonged to lower class followed by middle class 14 (35.0%) and upper class 1 (2.5%) participant. Diet-wise, the majority of participants 37 (92.5%) followed a mixed diet pattern, while 3 (7.5%) followed a vegetarian diet. Furthermore, 31 (77.5%) are married and 9 (22.5%) are unmarried. Temperament-wise maximum participants 16 (40.0%) had *Sawdāwī Mizāj*, followed by *Ṣafrāwī* Mizāj 13 (32.5%), *Damwī Mizāj* 8 (20.0%), and *Balghamī Mizāj* 3 (7.5%). In terms of demographic and clinical characteristics, the baseline distribution of individuals in the Unani and control groups was comparable, with statistically insignificant ($p>0.05$) differences between them (Table 1).

Change in the presence of hyphae on KOH mount test

At baseline, all participants, regardless of test or control group, had hyphae on their lesion. Following the trial's conclusion, hyphae were cleared in 15 (71.4%) of the test group's patients and 14 (73.7%) of the control group's patients. The remaining 6 (28.6 %) and 5 (26.3 %) participants in the test and control groups, respectively, retained lesion with hyphae. The odds ratio for presence vs. absence of hyphae on KOH mount was 0.89 (95%CI: 0.22, 3.59) with $p=1.000$ indicating that the difference between the efficacy of test and control interventions was not statistically significant (Table 2).

Change in severity of pruritus measured on VAS

The mean (SD) VAS score at baseline was 69.29 (14.86) in the test group and 67.63 (11.35) in the control group. The observed mean differences at the 1st, 2nd, 3rd, and final follow-up were 2.32 (95% CI: −6.26, 10.9, $p=0.587$), 2.29 (95%

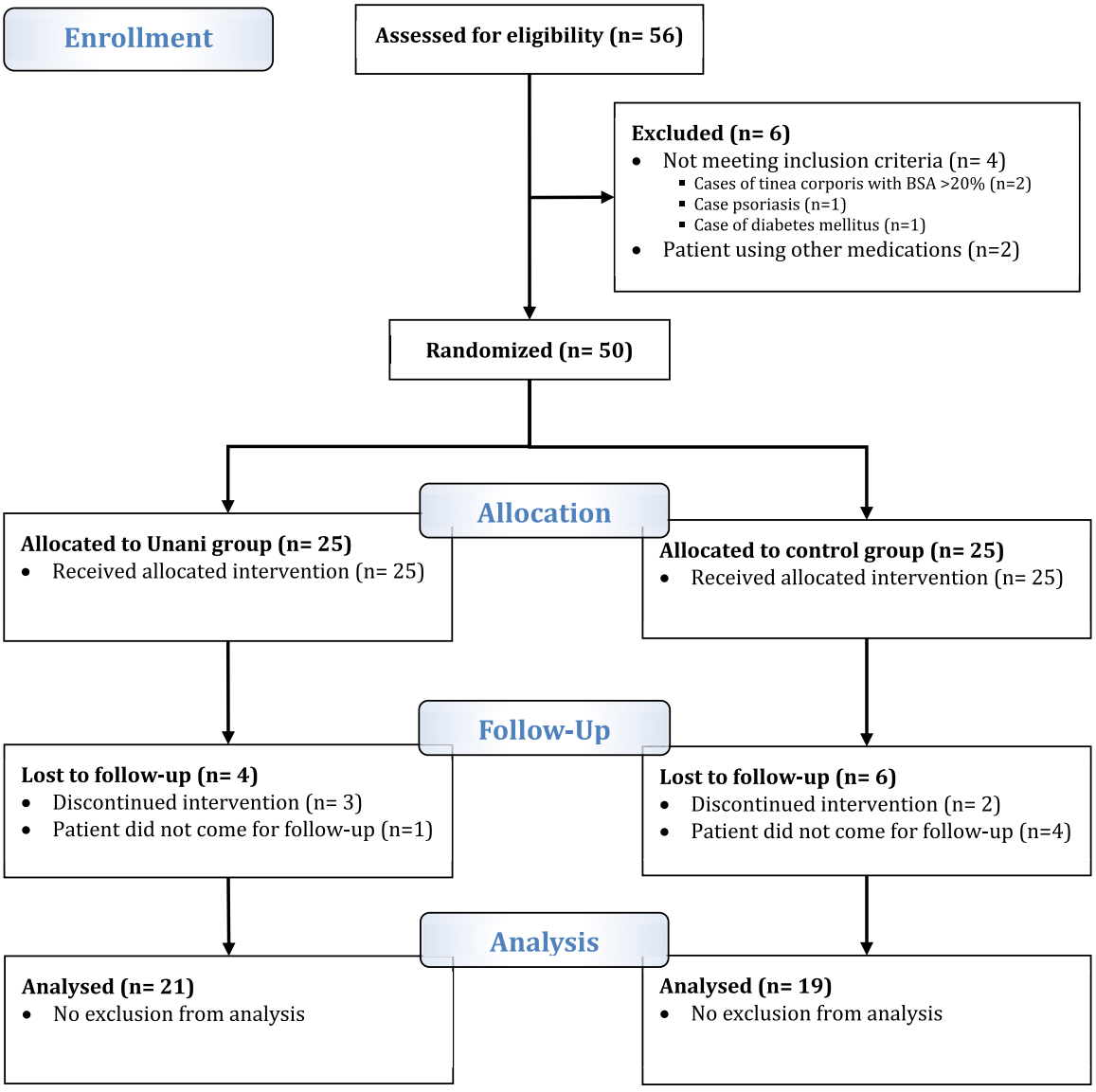

Figure 1: CONSORT flow chart of the participants.

CI: −6.87, 11.46, p=0.615), 2.26 (95% CI: −8.4, 12.91, p=0.671), and 3.3 (95% CI: −6.13, 12.72, p=0.483), respectively (Figures 2 and 3). The differences at each follow-up were more than non-inferiority margin (δ) suggesting that the test drug is non-inferior to control drug in reducing pruritus. Though pre- and post-treatment differences in pruritus reduction on the VAS were within the clinically significant range (>30%) for both groups [20].

Change in PGA

The PGA was assessed on a 5-point scale. In the test group, 11 (52.4%) cases had moderate lesions, whereas 10 (47.6%) had severe lesions at baseline. The severity of the lesions was significantly reduced at each follow-up (p<0.0001). At the first follow-up, one case (4.8%) had almost completely cleared lesions, 2 (9.5%) cases had mild lesions, 14 (66.7%) cases had moderate lesions, and 4 (19.0%) case had severe lesions. On second follow-up, three (14.3%) cases had nearly cleared lesions, nine (42.9%) cases had mild lesions, and nine (42.9%) cases had moderate lesions. At the third follow-up, 1 (4.8%) case had no lesions, 6 (28.6%) had nearly cleared lesions, 11 (52.4%) had mild lesions, and 3 (14.3%) had moderated lesions. At the final follow-up, six cases (28.6%) were completely free of lesions, nine (42.9%) had nearly cleared lesions, and only six (28.6%) had mild lesions (Table 3).

Table 1: Baseline demographic and clinical profiles of the participants.

Characteristics		Unani group (n=21)	Control group (n=19)	p-Value
Age, mean (SD), years		33.10 (9.69)	39.79 (15.17)	0.226[a]
Male, n, %		11 (52.4%)	11 (57.9%)	0.761[b]
Female, n, %		10 (47.6%)	8 (42.1%)	
Socio-economic status	Upper class, n, %	1 (4.8%)	0 (0.0%)	1.000[b]
	Middle class, n, %	7 (33.3%)	7 (36.8%)	
	Lower class, n, %	13 (61.9%)	12 (63.2%)	
Diet	Vegetarian diet, n, %	1 (4.8%)	2 (10.5%)	0.596[b]
	Mixed diet, n, %	20 (95.2%)	17 (89.5%)	
Marital status	Married, n, %	16 (76.2%)	15 (78.9%)	1.000[b]
	Unmarried, n, %	5 (23.8%)	4 (21.1%)	
Temperament	Damawī (sanguine), n, %	4 (50.0%)	4 (50.0%)	0.830[b]
	Balghamī (phlegmatic), n, %	1 (33.3%)	2 (66.7%)	
	Ṣafrāwī (bilious), n, %	6 (46.2%)	7 (53.8%)	
	Sawdāwī (melancholic), n, %	10 (62.5%)	6 (37.5%)	
KOH test positives		21 (100.0%)	19 (100.0%)	1.000[b]
Pruritus severity on VAS, mean (SD)		69.29 (14.86)	67.63 (11.35)	0.697[a]
Overall disease severity on PGA	Mild, n, %	0 (0.0%)	1 (5.3%)	0.630[b]
	Moderate, n, %	11 (52.4%)	11 (57.9%)	
	Severe, n, %	10 (47.6%)	7 (36.8%)	
DLQI, mean (SD)		14.76 (3.59)	14.32 (3.90)	0.709[a]

[a]Independent samples t-test, [b]Chi-square test.

Table 2: Change in the presence or absence of hyphae on KOH test after treatment.

Hyphae on KOH mount	Test (n=21)	Control (n=19)	OR (95% CI)[a]	p-Value[b]
Absent	15 (71.4%)	14 (73.7%)	0.89 (0.22, 3.59)	1.000
Present	6 (28.6%)	5 (26.3%)		

[a]OR, odds ratio for absence/presence of hyphae on KOH mount test with lower and upper bound confidence intervals; [b]Chi-square test.

In the control group, 11 (57.9%) cases had moderate lesions, 7 (36.8%) had severe lesions and 1 (5.3%) case had mild lesions at baseline. The severity of the lesions was significantly reduced at each follow-up (p<0.0001). Thus, 7 (36.8%) cases had mild lesions, 8 (42.1%) cases had moderate lesions, and 4 (21.1%) cases had severe lesions. On second follow-up, 6 (31.6%) cases had nearly cleared lesions, 8 (42.5%) cases had mild lesions, and 5 (26.3%) cases had moderate lesions. At the third follow-up, 4 (21.5%) cases had no lesions, 7 (36.8%) had nearly cleared lesions, 6 (31.6%) had mild lesions, and 2 (10.5%) had moderated lesions. At the final follow-up, 10 (52.6%) cases were completely free of lesions, 6 (31.6%) had mild lesions, 2 (10.5%) had moderate lesions, and 1 (5.3%) had severe lesions (Table 3). Intergroup analysis revealed no statistically significant difference between the two groups at each follow-up.

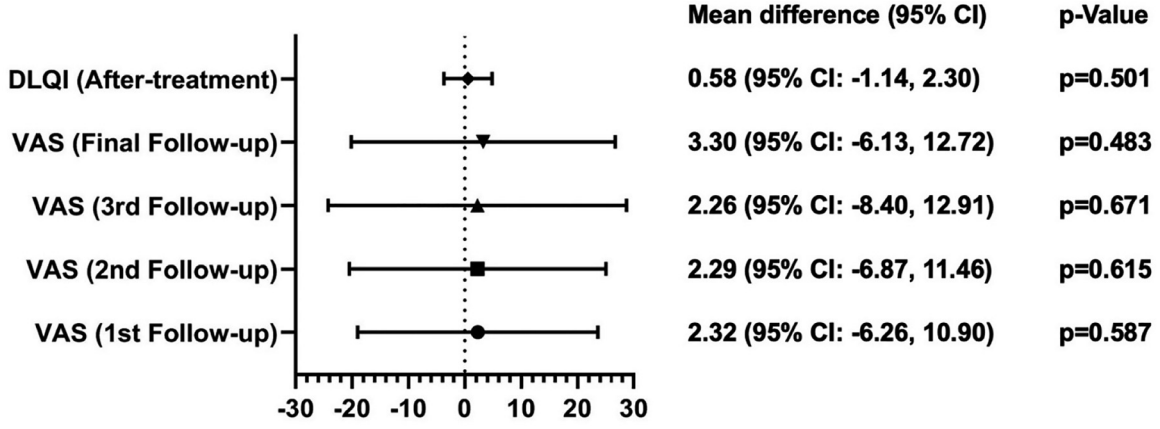

Figure 2: Effect estimates of VAS and DLQI.

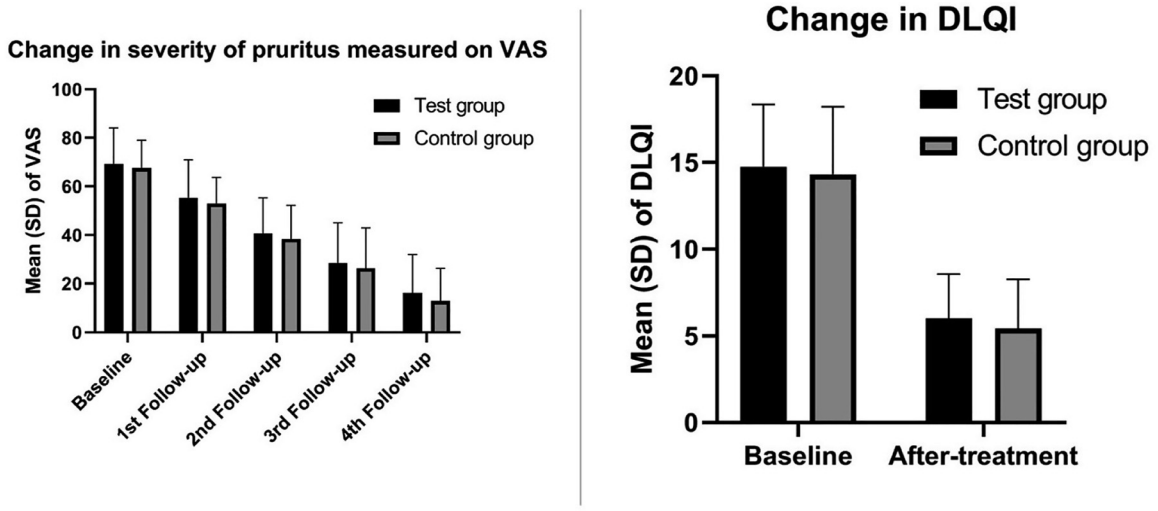

Figure 3: Change in severity of pruritus measured on VAS and DLQI.

Table 3: Change in physician global assessment for overall disease severity at each follow-up visit.

PGA	Test group (n=21)					Control group (n=19)					p-Value[a]
	No lesion	Almost clear	Mild	Moderate	Severe	No lesion	Almost clear	Mild	Moderate	Severe	
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (52.4%)	10 (47.6%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	11 (57.9%)	7 (36.8%)	0.630
1st follow-up	0 (0.0%)	1 (4.8%)	2 (9.5%)	14 (66.7%)	4 (19.0%)	0 (0.0%)	0 (0.0%)	7 (36.8%)	8 (42.1%)	4 (21.1%)	0.133
2nd follow-up	0 (0.0%)	3 (14.3%)	9 (42.9%)	9 (42.9%)	0 (0.0%)	0 (0.0%)	6 (31.6%)	8 (42.5%)	5 (26.3%)	0 (0.0%)	0.210
3rd follow-up	1 (4.8%)	6 (28.6%)	11 (52.4%)	3 (14.3)	0 (0.0%)	4 (21.5%)	7 (36.8%)	6 (31.6%)	2 (10.5%)	0 (0.0%)	0.361
4th follow-up	6 (28.6%)	9 (42.9%)	6 (28.6%)	0 (0.0%)	0 (0.0%)	10 (52.6%)	6 (31.6%)	2 (10.5%)	1 (5.3%)	0 (0.0%)	0.195
p-Value[b]	p<0.0001 (within-group)					p<0.0001 (within-group)					–

[a]Chi-square test (intergroup analysis), [b]Wilcoxon signed ranks test (within-group analysis).

Change in DLQI

The mean (SD) of DLQI in the test group was, significantly reduced from baseline 14.76 (3.59) to 6.00 (2.55) after completion of the treatment (p<0.001). Also, in the control group, the mean (SD) of DLQI significantly reduced from baseline 14.32 (3.90) to 5.42 (2.84) at the conclusion of the trial (p<0.0001) (Figure 3). The observed mean difference after completion of the trial was 0.58 (95% CI: −1.14, 2.3, p=0.501) indicating statistically insignificant difference between both the groups. Moreover, the differences at each follow-up were more than non-inferiority margin (δ) suggesting that the test drug is non-inferior to control drug in improving the DLQI (Figure 2).

Change in safety parameters

The safety of both interventions was determined using a record of adverse events and changes in hemogram, as well as serum creatinine, serum bilirubin, and RBS levels. During the course of the trial, no adverse event was observed. Although statistically significant changes in random blood sugar was observed, it was clinically within normal limits (Table 4).

Discussion

The study was conducted to establish the non-inferiority of topical *Halela Zard* (*T. chebula* Retz.) fruit powder mixed with Sirka (acetic acid) vs. terbinafine 1% in management of Qūbā (tinea corporis). Based on the preliminary findings, it may be inferred that the efficacy and safety of test and control drugs were comparable and the test drug is non-inferior to control drug in the amelioration of the overall disease severity and clinical features.

The mean age of all the participants was 36 years which is concurrent with Banerjee et al. and Kim et al. who reported the peak age of incidence in the third decade of

Table 4: Change in the safety parameters after trial completion.

Parameters	Test group	Control group	p-Value[a]
Hemoglobin, g/dL, mean (SD)	12.85 (1.39)	13.21 (1.05)	0.375
Neutrophils, %, mean (SD)	53.90 (7.88)	55.47 (7.98)	0.536
Eosinophils, %, mean (SD)	1.57 (1.21)	1.68 (1.25)	0.773
Basophils, %, mean (SD)	0.00 (0.00)	0.00 (0.00)	–
RBC $\times 10^{-6}$/μL, mean (SD)	4.00 (0.53)	4.02 (0.50)	0.898
MCV, fL, mean (SD)	77.19 (6.01)	78.32 (78.32)	0.536
MCHC, g/dL, mean (SD)	33.29 (1.31)	33.05 (1.13)	0.552
Hematocrit (PCV), %, mean (SD)	45.29 (2.57)	45.16 (2.81)	0.881
Platelet count $\times 10^{-3}$/μL, mean (SD)	3.86 (0.44)	3.80 (0.48)	0.649
Serum creatinine, mg/dL, mean (SD)	0.65 (0.12)	0.665 (0.13)	0.346
Serum bilirubin, mg/dL mean (SD)	0.24 (0.12)	0.25 (0.13)	0.802
Random blood sugar, mg/dL, mean (SD)	80.00 (6.69)	72.50 (9.53)	0.006

[a]Independent samples t-test.

life [21, 22]. Moreover, Leung et al. observed the highest incidence in the post-pubertal children and young adults [23]. Gender-wise, majority of the cases were male which corroborates with the reports of Lauren et al. Neena et al. and Penmetcha et al. who concluded that males are more likely to develop tinea corporis than the females [4, 6, 24]. In contrast, Leung et al. discovered that this disease has no gender predominance [23]. Out of 40 cases, majority of the cases were married. The data is consistent with Aaliya et al. who also observed almost the same percentage of married participants in their study [25]. Diet-wise, maximum number of the participants had mixed dietary habit. The data is corroborated by Aaliya et al. who also discovered the higher proportion of participants with mixed dietary pattern [25]. Although, it is difficult to infer a link between mixed diet and tinea corporis as the majority of patients are members of the mixed diet community. Our study observed the highest incidence of lower class followed the middle class participants. The findings are in consistent with Mangala et al. Penmetcha et al. and Mohanty et al. who also reported the highest prevalence in the patients of low socioeconomic status [24, 26, 27]. Temperament-wise, majority of the study population *Sawdāwī*, followed by *Ṣafrāwī*, *Damawī*, and *Balghamī*. The distribution in both groups was equal as the difference was not statistically significant (p>0.05).

The effect of the test interventions may be accredited to their pharmacological actions described in Unani system of medicine corroborated by the recent scientific studies. Thus, the reduction in pruritus and erythema may be due to the *Muṣaffi Dam* (blood purifier), *Dāfi-i Khārish* (antipruritic), *Mus'hil Sawdā'* (melanogogue), *Muḥallil* (anti-inflammatory), and *Jali* (skin cleansing) actions of *Halela Zard*. Pharmacologically, anti-inflammatory, carminative, digestive, laxative, purgative, and antiseptic actions with indications in wounds, ulcers, inflammation, skin diseases, neuropathy, and general debility are reported [28]. Dutta B K, et al. and Rubini B, et al. reported that the aqueous extract of *T. chebula* fruit has potent anti-fungal activity, especially against *Trichophyton rubrum* [29, 30]. Aqueous and ethanolic extracts of *T. chebula* were found to have antifungal activity and were nearly identical to that of the standard antifungal agents itraconazole, fluconazole, and ketoconazole against *T. mentagrophytes* and *T. rubrum* isolated from Tinea corporis patients [30]. Nigam, et al. discovered that methanol, ethyl acetate, and chloroform extracts are inhibitors of fungal mycelial growth [31]. Venkatachalam, et al. investigated the anticandidal and antifungal activity of *T. chebula* dried fruit extracts and discovered that methanol extracts of *T. chebula* dried fruit possessed the highest antifungal activity [32]. Furthermore, *Sirka* (acetic acid) was used as vehicle in this study due to its *Sarī al-Nufūz* (penetration enhancer) property. In addition, *Sirka* has *Mulaṭṭif* (demulcent) and *Muḥallil-i Waram* (anti-inflammatory) properties [33]. Samad, et al. reported that vinegar exhibits the antifungal activity due to its extremely low-pH [34].

Strength and limitations of the study: This study was conscientiously designed and implemented to reduce the possibility of bias and confounding variables, and reported following the CONSORT extension for herbal medicine interventions. To avoid information bias, the objective parameter PGA was also employed along with the subjective parameter VAS. The pathology departments independently submitted the laboratory investigation reports. To minimize the effect of confounding variables, a thorough randomization procedure was used to evenly distribute participants with known or unknown confounding variables.

Future recommendations

Considerable research has been conducted to better understand the biological systems through the use of computational approaches such as genomics, transcriptomics, proteomics, metabolomics, and metagenomics, which can be combined with further experimental work in this area. In addition, the cream formulation of the test formulation may improve patient compliance and efficacy. The dose/concentration may be determined using the extractive value of the test drug and the dose specified in the Unani text.

Conclusions

Based on the observed findings, it may be inferred that the efficacy of trial drug *Halela Zard* (*T. chebula* Retz.) fruit powder mixed with *Sirka* (vinegar) is not inferior to terbinafine hydrochloride in the treatment of tinea corporis. Additionally, no significant adverse events were observed in both the interventions during the course of the trial. Moreover, clinical trials with rigorous study design and adequate sample size may be conducted to bolster the scientific evidence.

Acknowledgments: The authors would like to express their heartfelt appreciation to Dr. Mohd. Aqil Quadri (Dean), Dr. Shehnaz Banu (Principal), Dr. Tasmiya Indikar (Vice-principal), and Dr. Nuzhat Patel, Dr. Meenu Doni, Dr. Mohammad Iliyas Patel and Dr. Aaftab M Nadaf of Luqman Unani Medical College Hospital and Research Center, Bijapur, Karnataka, as well as to all the patients who participated in this study for their cooperation in conducting the trial.
Research funding: None declared.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: This research complied with all the applicable national and institutional regulations, as well as the precepts of the Helsinki Declaration (as revised in 2013) and was approved by the Institutional Ethics Committee of Luqman Unani Medical College with the protocol number (BJP/LUMC/PG/IEC/04/2019-20/MOALIJAT/01) and prospectively registered on Clinical Trial Registry of India (CTRI) with CTRI number CTRI/2021/01/030404.

References

1. Kim BY, Thomas JL. Approach to the patient with a skin disorder. In: Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's principles internal medicine, 20th ed. New York: Mc-Grill Education; 2018:335–6 pp.
2. Henry WL. Eczemas, photodermatoses, papulosquamous (including fungal) diseases, and figurate erythemas. In: Lee G, Andrew S, editors. Goldman-cecil medicine, 24th ed. New York: Elsevier; 2012, vol II:2521 p.
3. Sahoo AK, Mahajan R. Management of tinea corporis, tinea cruris, and tinea pedis: a comprehensive review. Indian Dermatol Online J 2016;7:77.
4. Khanna N. Illustrated synopsis of dermatology and sexually transmitted diseases, 4th ed. Delhi: Elsevier; 2011:282–90 pp.
5. Carol AK. Mucormycosis. In: Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's principles of internal medicine, 20th ed. New York: Mc-Grill Education; 2018:1546 p.
6. Lauren NC, Stefan MS. Fungal diseases. In: Kang S, Amagai M, Bruckner AL, H. AE, Margolis DJ, McMichael AJ, et al. editors. Fitzpatrick's Dermatology, 9th ed. New York: McGraw Hill Education; 2019:2926–44 pp.
7. Hay RJ, Ashbee HR. Infections and infestation. In: Griffiths C, Barker J, Bleiker T, Robert C, Creamer D, editors. Rook's textbook of dermatology, 9th ed. United Kingdom: Blackwell, Wiley; 2016, vol I: 32.35–7 pp.
8. Shenoy M, Jayaraman J. Epidemic of difficult-to-treat tinea in India: current scenario, culprits, and curbing strategies. Arch Med Heal Sci 2019;7:112.
9. Varma SMR, Madhu R. The great indian epidemic of dematophytosis: an appraisal. Indian J Dermatol 2017;62:227–36.
10. Majusi AA. Kamil al-sana. New Delhi: Idara kitab al-shifa; 2010:432 p.
11. Arzani MA. Meezan al-tibb. New Delhi: Idara kitab al-shifa; 2002:249 p.
12. Sina I. Alqanoon, 2nd ed. New Delhi: Idara kitab al-shifa; 2014: 1431–2 pp.
13. Jurjani AH. Dhakhira khwarizm shahi. New Dehli: Idara kitab al-shifa; 2010: 24–6 pp.
14. Ghani N. Khazain al-adwiya. New Delhi: Idara kitab al shifa; 2007: 1352–4 pp.
15. Naseem S, Nawab M, Fatima SH, Minhajuddin A, Khan AA. Assessing the efficacy and safety of unani pharmacopoeial formulations in dermatophytosis (quba) – a randomized controlled trial. Drug Metab Pers Ther 2022. https://doi.org/10.1515/dmpt-2022-0125 [Epub ahead of print].
16. Balfour JA, Faulds D. Terbinafine. Drugs 1992;43:259–84.
17. Ryder NS. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol 1992;126:2–7.
18. Bhatia A, Kanish B, Badyal DK, Kate P, Choudhary S. Efficacy of oral terbinafine versus itraconazole in treatment of dermatophytic infection of skin – a prospective, randomized comparative study. Indian J Pharmacol 2019;51:116–9.
19. Chow SC, Shao J, Wang H, Lokhnygina Y. A CRC Title, Part of the Taylor & Francis Imprint, a member of the Taylor & Francis Group, the Academic Division of T&F Informa Plc. In: Sample size calculations in clinical research, Chapman & Hall/CRC biostatistics series, 3rd ed. Boca Raton: Taylor & Francis, Chapman and Hall/CRC; 2017, vol 10–11:77–80 pp.
20. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: immpact recommendations. J Pain 2008;9:105–21.

21. Kim ST, Jun JB, Suh SB. Clinical and mycological observations on tinea corporis. Korean J Dermatol 1982;20:703–12.
22. Banerjee M, Ghosh AK, Basak S, Das KD, Gangopadhyay DN. Comparative evaluation of effectivity and safety of topical amorolfine and clotrimazole in the treatment of tinea corporis. Indian J Dermatol 2011;56:657–62.
23. Leung AK, Lam JM, Leong KF, Hon KL. Tinea corporis: an updated review. Drugs Context 2020;9:1–12.
24. Penmetcha U, Myneni RB, Yarlagadda P, Simgamsetty S. A study of prevalence of dermatophytosis in and around guntur district, Andhra Pradesh, south India. Int J Curr Microbiol App Sci 2016;5:702–17.
25. Aaliya NM, Kazmi MH, Ayyub S. A randomized active controlled clinical trial to evaluate safety and efficacy of a topical unani formulation marham kharish jadeed in the management of qūbā (tinea corporis). Cell Med 2020;10:1–7.
26. Mangala GK, Chandrappa NR. Epidemiological study of dermatophytosis in and around davanagere. Indian J Public Heal Res Dev 2013;4:112.
27. Mohanty JC, Mohanty SK, Sahoo RC, Sahoo A, Praharaj CN. Incidence of dermatophytosis in Orissa. Indian J Med Microbiol 1998;16:78–80.
28. Prajapati ND, Purohit SS, Sharma SS, Kumar T. A handbook of medicinal plants (a complete source book). Jodhpur, India: Agrobios; 2003:508 p.
29. Dutta BK, Rahman I, Das T. Antifungal activity of indian plant extracts antimyzetische aktivität indischer pflanzenextrakte. Mycoses 1998;41: 535–6.
30. Rubini B, Shanthi G, Rajarajan S, Soundhari C. Antifungal activity of terminalia chebula and terminalia catappa on two dermatophytes. J Med Aromat Plants 2013;4:15–9.
31. Nigam M, Mishra AP, Adhikari-Devkota A, Dirar AI, Hassan MM, Adhikari A, et al. Fruits of terminalia chebula retz.: a review on traditional uses, bioactive chemical constituents and pharmacological activities. Phyther Res 2020;34:2518–33.
32. Venkatachalam P, Chittibabu CV. Antifungal activity of terminalia chebula fruit extracts. Curr Bot 2020;11:216–20.
33. Saleem MN, Idris M. Sirka (vinegar): from traditional use to the scientific approach. J Herb Med Res 2016;1:32–9.
34. Samad A, Azlan A, Ismail A. Therapeutic effects of vinegar: a review. Curr Opin Food Sci 2016;8:56–61.