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Original Article

The efficacy and safety of herbal combination of Unani Medicine in chronic urticaria: A randomized, controlled study

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ABSTRACT

Background and Aim; Chronic urticaria (CU) is a fluctuating and pruritic erythematous papule that persists for over six weeks. It affects 0.5–1% of the population and interferes with subjective well-being and daily life. Its etiology is highly complex which makes a causal and/or curative treatment difficult. Nonsedating H1-antihistamines are given as symptomatic therapy, which reduces symptoms effectively in <50% of patients. In Unani medicine, urticaria is known as Shara and treated according to its established etiology. The present study objective was to investigate the effect of herbal combination of Unani medicine (HCUM) comprising Rosa damascena Mill, Bambusa arundinacea Linn, Cinnamomum camphora Linn, Mentha arvensis Linn, in comparison with Levocetirizine in CU.

Experimental procedure; This randomized open-labeled standard control clinical trial was conducted between 42 male/female patients aged 20–50 years with moderate to severe CU who were randomly allocated in a 3:1 ratio into HCUM and Levocetirizine 5 mg groups. HCUM powder 5.125 Gm and Levocetirizine 5 mg were given for 4 weeks. Urticaria activity score (UAS7) and chronic urticaria quality of life questionnaire (CU-Q2oL) were primary and secondary outcomes and analyzed per protocol.

Results: A total of 40 patients completed the study. Data analysis showed a significant decrease (P=<0.001) in the scores of UAS7 (32.43 ± 2.34–14.03 ± 2.16 and 32.10 ± 2.33–28.40 ± 3.78) and CU-Q2oL (67.57 ± 9.56–36.50 ± 3.01 and 65.20 ± 11.78–59.60 ± 11.13) in HCUM and Levocetirizine groups respectively.

Conclusion: As an alternative treatment in terms of safety, efficacy, tolerability, and quality of life the HCUM treatment proved to be more effective than Levocetirizine 5 mg in moderate to severe CU.
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1. Introduction

Urticaria is one of the most frequent skin diseases characterized by pruritic wheal and flare-type of skin reactions with or without angioedema that usually persist for <24 h.[1] The worldwide prevalence is estimated at 0.5%–1%.[2] Urticaria interferes with subjective well-being and daily life, it also causes inconvenience in family structures, compromising performance at work, school, and negatively impacting leisure activities. Reports suggest that some patient's health status is comparable to that of coronary artery disease and severe asthma patients.[3] Urticaria affects 15–20% of the world population. Females are nearly twice as frequently affected as males, and the peak incidence of chronic spontaneous urticaria falls between 20 and 40 years of age.[4] According to a study, estimated the global burden of disease attributable to 15 categories of skin disease from 1990 to 2010, it was found that urticaria was among the top ten most prevalent diseases worldwide in 2010.[5] Urticaria is classified based on its duration into acute (<6 weeks) and chronic (>6 weeks).[6] Chronic Urticaria (CU) is a common dermatological condition affecting an estimated 15–20% of the general population at least once during the lifetime.[7] It is characterized by the recurrent appearance of wheals and/or angioedema for 6 weeks.[8,9] chronic urticaria is a heterogeneous disorder and includes chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU).[10,11] In most patients, the underlying cause of CSU,

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List of abbreviations

AEC	Acute eosinophil count
Anti-DNP antibodies	Anti-dinitrophenol (DNP) antibodies
CAM	Complementary and alternative medicine
CIU	Chronic inducible urticaria
CONSORT	Consolidated standards of reporting trials
CRP	C-reactive protein
CSU	Chronic spontaneous urticaria
CTRI	Clinical Trials Registry
CU-Q2oL	Chronic urticaria quality of life questionnaire
CU	Chronic urticaria
ESR	Erythrocyte sedimentation rat
HCUM	Herbal combination of unani medicine
IEC	Institutional ethical committee
IgE	Immunoglobulin E
NIUM	National Institute of Unani Medicine
PAF	Platelet-activating factor
UAS7	Urticaria activity score for seven days
UM	Unani Medicine
EAACI	European Academy of Allergy and Clinical Immunology excellence, the
GA2LEN	Global Allergy and Asthma European Network
EDF	European Dermatology Forum
WAO	World Allergy Organization

which is the most frequent form of CU, is not identified in clinical practice.[12] Urticaria is a mast-cell-driven disease. Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated mast cells, result in sensory nerve activation, vasodilatation, and plasma extravasations as well as cell recruitment to urticarial lesions.[13]

Modern second-generation antihistamines are considered as the first-line symptomatic treatment for urticaria because of their good safety profile.[14] The pathophysiology of urticaria is complicated and sometimes, long-term use of a combination of medications may be needed to control refractory symptoms.[15–17] The medications include non-sedating antihistamines, glucocorticosteroids, cyclosporine, and leukotrienes antagonists.[18–20] Omalizumab, an anti-immunoglobulin E (IgE) antibody, is another potential therapy for urticaria, however high medication costs and possible symptom recurrence after discontinuation are its limitations.[21,22] Adverse effects principally drowsiness, fatigue, headache, nausea, dry mouth and cardiotoxicity, have been observed with some of them.[2] Additionally systemic immunosuppression and endocrine disorders, and medication dependence are other concerns to patients.[23] Therefore, even under multiple conventional medical treatments, there are still unmet medical demands for symptom control in urticaria, for which alternative treatments have been sought urgently.[24,25] Interestingly, complementary and alternative medicine (CAM) becomes a possible option in addition to commonly used conventional medication in treating urticaria and reliving its symptoms. In India, traditional medicines (CAM) are very popular and used at a mass level.

Unani Medicine (UM) is one of the oldest traditional medicines recognized by the government of India mainly practiced on a mass level as alternative medicine or complementary in addition to conventional medicine. UM, Urticaria is described as Shara (a humoral disease) which develops due to qualitative or quantitative alteration and imbalance (morbid humor) in the four humors i.e. Dam (Blood), Safra (Bile), Balgham (Phlegm), and Sauda (Black Bile). Shara is classified according to its underlying cause into Damvi, Safravi, Balgami, and Saudavi. Accordingly, the treatment is described in detail and the disease is treated based on its established etiology.26–27 Treatment of *Shara* is based on the elimination of these morbid humor through the mode of Nuzj wa Istifrag (concoction and elimination) by pharmacotherapy or regimenal therapy like venesection and wet cupping.[26,27] There is a treasure trove of single and combination of herbs and minerals for skin disorders described in the classical literature in UM. The core herbal intervention (as shown in table-1) was selected in this study as an herbal combination of Unani medicine (HCUM) comprising Rosa damascena Mill. Bambusa arundinacea Linn, Cinnamomum camphora Linn, and Mentha arvensis Linn,[31] have been tested and found effective in urticraia as documented by *Ibn-e-Sina* and *Raz*i in Alqanoon fi Tib (Avicenna's Canon of Medicine), and Alhavi Fit Tib (Rhazes's Continens Liber).[26,27] These herbs restore the adequate balance among the four humors (Blood, Bile, Phlegm, and Black Bile) of the body by eliminating morbid humoral pathogens and help in improving digestion, producing normal humor in the body, and ultimately strengthening immune systems. These herbs are used in UM and other Indian traditional medicines as a blood purifier, anti-inflammatory, rubefacient and mild analgesic, cooling and sedative in skin conditions like ulcerations, skin irritation, inflammations, leucoderma, leprosy, ringworm, and other skin disorders.[28] The herbal ingredients in HCUM have demonstrated Antiinflammatory,[29,30] Analgesic,[31] Sedative–Hypnotic,[32] antioxidant,[33–37] and hepatoprotective,[38,39] biomedical activities in different in vivo and in vitro studies.

Since UM is often used as a complementary and alternative therapy in the clinical setting in India the evaluation of symptoms and quality of life and changes in blood markers are crucial for understanding the role of the HCUM in urticaria. Moreover, the potential unwanted effects of HCUM are also assessed clinically and laboratory parameters. This study was aimed to explore the efficacy and safety of HCUM for the treatment of CU in comparison to standard anti-histamine medication (Levocitrizine 5 mg) in a randomized, open-labeled, standard-controlled clinical trial design.

2. Materials and methods

2.1. Study design and setting

This study was a randomized open-labeled standard control clinical trial, conducted in the post-graduate department of Moalajat in the National Institute of Unani Medicine (NIUM) Hospital, Bangalore, from March 2018 to February 2019. We designed an open-label study because the dose (5.125 Gm powders of crude herbs in HCUM) was higher than the dose of Levocetirizine (5 mg) and making a placebo was not feasible. Another reason was the withdrawal of the patient from the study due to persistent symptoms if the placebo was given instead of active treatment. However, patients were not aware of the intervention and the drugs were dispensed in an airtight lock pack which was stored in containers labeled as test or control groups. All patients of chronic urticaria were included to get the maximum number of patients enrolled from the NIUM Hospital and randomly allocated in a 3:1 ratio into two groups after 14 days of washout period. The equal ratio needs more sample size which was not possible because of the low turnout of the patient in hospital (single study center) and short study duration was another limitation.

2.2. Ethical consideration

The study was approved by the institutional ethical committee (IEC No: NIUM/IEC/2016-17/007/Moal/07) and registered prospectively in (CTRI) Clinical Trials Registry – India, ID: (CTRI/2018/02/011735). All the participants were explained about the study and given a written informed consent form and after getting their signed written informed consent they were enrolled in the study. The CONSORT guideline was followed and the trial was conducted in accordance with the Declaration of Helsinki.

2.3. Sample size

The sample size was 40 patients. In the present study, the sample size was derived based on the Mean and SD of UAS7 in Urticaria patients before and after intervention obtained from the previous study.[40] A sample of 36.56 participants at 80% power and 5% significance level was calculated. Adding 10% dropouts the total sample size calculated was 40.24, which was rounded off to 40 for convenience. The ratio of the HCUM treatment group to the Levocetirizine group was taken as 3:1, hence the HCUM group comprised 30 patients while the Levocetrizine group had10 patients.

2.4. Inclusion criteria

Clinically diagnosed patients of CU according to The 2018 EAACI/GA2LEN/EDF/WAO guideline.[6] Patients of either sex in the age group of 20–50 years. Patients who have agreed to sign the written informed consent and follow the protocol.

2.5. Exclusion criteria

Patients less than 20 and more than 50 years of age, well-diagnosed cases of other skin elements with Urticaria. Clearly defined underlying etiology other than chronic urticaria. Other skin diseases like psoriasis, eczema, immunocompromised patients. Patients suffering from any other systemic diseases, patients of HTN, DM, IHD and HIV, pregnant and lactating women, H/O bronchial asthma and intestinal parasite and anaphylaxis to medicine. As the patient gave history of H_2-antihistamine, systemic glucocorticoids (5 mg and/10 mg doses) and herbal treatment, they were excluded if systemic corticosteroid or immunosuppressive drug used in the past 6 weeks prior to the study, the use of any H_2-antihistamine or leukotriene-receptor antagonist within 7 days preceding the screening visit 14 days before randomization, unwillingness or inability to fulfil the protocol.

2.6. Trial medication (HCUM and Levocitrizine)

This herbal combination of Unani medicine (HCUM) was selected from Al-Qanoon and Al-Havi Fit Tib. The ingredient of the HCUM (as shown in Table-1) includes Rosa damascena Mill. (GuleSurkh), Bambusa arundinacea Linn (Tabashir), Cinnamomum camphora Linn (Kafoor), and Mentha arvensis Linn (Faudanj). The drugs were supplied by the pharmacy of NIUM and identified by the chief pharmacist and experts in the department of pharmacology in NIUM. The drugs were isolated from possible adulteration, filtered from impurities, and processed separately to make a fine powder in the laboratory of pharmacy as per SOPs of UM. The dose was fixed as 5.125 Gm powder given in capsule form orally after food in two divided doses for 4 weeks. Levocetirizine 5.0 mg tablet per day orally was given as a standard control treatment (updosing considered in non-responsive cases up to four-fold).

2.7. Study outcome measures

2.7.1. Primary outcome (weekly urticaria activity score (UAS7)[6]

The 2018 EAACI/GA2LEN/EDF/WAO guideline recommends using the UAS7 self-administered, well-validated questionnaires assessed on every visit (days 0, 7, 14, and 28). The UAS7 assigns a score from 0 (no disease activity), 1 (mild disease activity), 2 (moderate disease activity), and 3 (intense activity) for each of the 2 key urticaria symptoms, wheals, and pruritus. The sum of the scores of wheals and pruritus represents disease severity on a scale from −0 (minimum) to 6 (maximum). Sum of score: 0–6 for each day is summarized over one week (maximum 42).[6]

2.7.2. Secondary outcome

2.7.2.1. Chronic urticaria quality of life questionnaire (CU-Q2oL).[6,41]. The CU-Q2oL is an instrument that was specifically developed to assess the quality of life in patients with CU. It is a self-administered 23-item questionnaire, where patients have to indicate, on a Likert scale with multiple options (1: not at all; 5: very much), how much they have been troubled by each problem, with higher scores indicating the worse quality of life.

2.7.2.2. Comparison of side effect between two groups. Various side effects like dryness, sedation, drowsiness, headache from Levocitrizine has been reported in clinical trials.[40] These side effects in the Levocitrizine group were recorded at every visit and compared to possible side effects of the HCUM group developed during trial.

2.7.2.3. Changes in CRP, ESR (inflammatory markers), and AEC (allergic marker). Inflammatory markers and allergic marker values from the baseline and after treatment were analyzed and compared statistically.

2.8. Safety and adverse event monitoring

All adverse events were recorded at any time they happened, and all the patients were followed and clinically assessed weekly, and any suspicious events were closely monitored during the treatment phases of the trial. The participants were encouraged to report any symptoms and discomfort, even unusual ones. After giving proper information and explanation about investigations blood tests were taken for complete blood count, aspartate aminotransferase, alanine aminotransferase, blood urea, and creatinine and checked at baseline and after the trial was completed.

2.9. Study duration and follow up and adverse effect documentation

The treatment period was 4 weeks (28 days). Patients were followed weekly (0day, 7th, 14th, 21st, 28th day) and clinically assessed at every visit during the study. Urticaria Activity Score for 7 days (UAS7) was recorded weekly. Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) was recorded at baseline and after treatment only. The changes/improvements in subjective symptoms and objective parameters were recorded on every visit and laboratory investigations were done at baseline and after treatment.

2.10. Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Continuous measurement results are presented on Mean ± SD (Min-Max) and categorical measurement results are presented in Number (%). Leven's test for homogeneity

of variance has been performed to assess the homogeneity of variance. Student t-test (two-tailed, independent) has been used on a continuous scale to find the significance of study parameters between two groups (Intergroup analysis) on metric parameters. Student t-test (two-tailed, dependent) has been used on a continuous scale to find the significance of study parameters within each group. Chi-square/Fisher Exact test has been used to find the significance of study parameters on a categorical scale between two or more groups, a Non-parametric setting for Qualitative data analysis. For very small cell samples Fisher Exact test is used. Significance assessment was made at a 5% level of significance. Statistical analysis was performed using Statistical software namely SPSS 18.0, and R environment ver.3.2.2.

3. Results

3.1. Patient at baseline

Fig. 1 shows the disposition and the flow of the patients through the study. A total of 42 patients were enrolled in study 2 were omitted as a result of incomplete medical records and not being able to contact them. Finally, 40 patients were analyzed in two groups. The baseline characteristic of patients enrolled is shown in Table-2. Out of 40 patients, there were 16 females and 24 males with a mean age of 35.20 ± 7.96 years. At the onset of the study, all the patients had moderate disease activity when evaluated on UAS7, CU-Q2oL scores were also observed as a moderate impact on the quality of life of the patient. No significant difference was observed between treatment groups means in terms of age, sex, UAS7, CU-Q2oL, CRP, ESR, and AEC as shown in Table-2. Investigations, other than routine baseline tests, were performed as per the need.

3.2. Efficacy outcomes (primary and secondary outcomes)

Significant changes were observed in efficacy outcomes when the primary and secondary outcome measures were analyzed between-group from baseline and end of the treatment.

The disease activity and severity of CU, as well as the quality of life as evaluated by the UAS7 and CU-Q2oL scores before and after treatment, are summarized in table-3 and 4. The results show that both treatments have effectively reduced the UAS7 score ($P < 0.001$ and $P < 0.004$ respectively) and CU-Q2oL scores ($P < 0.001$). However, disease activity and severity of symptoms reduced effectively from moderate (32.43 ± 2.34) to mild (14.03 ± 2.16) in the HCUM group as compared to the Levocetirizine group

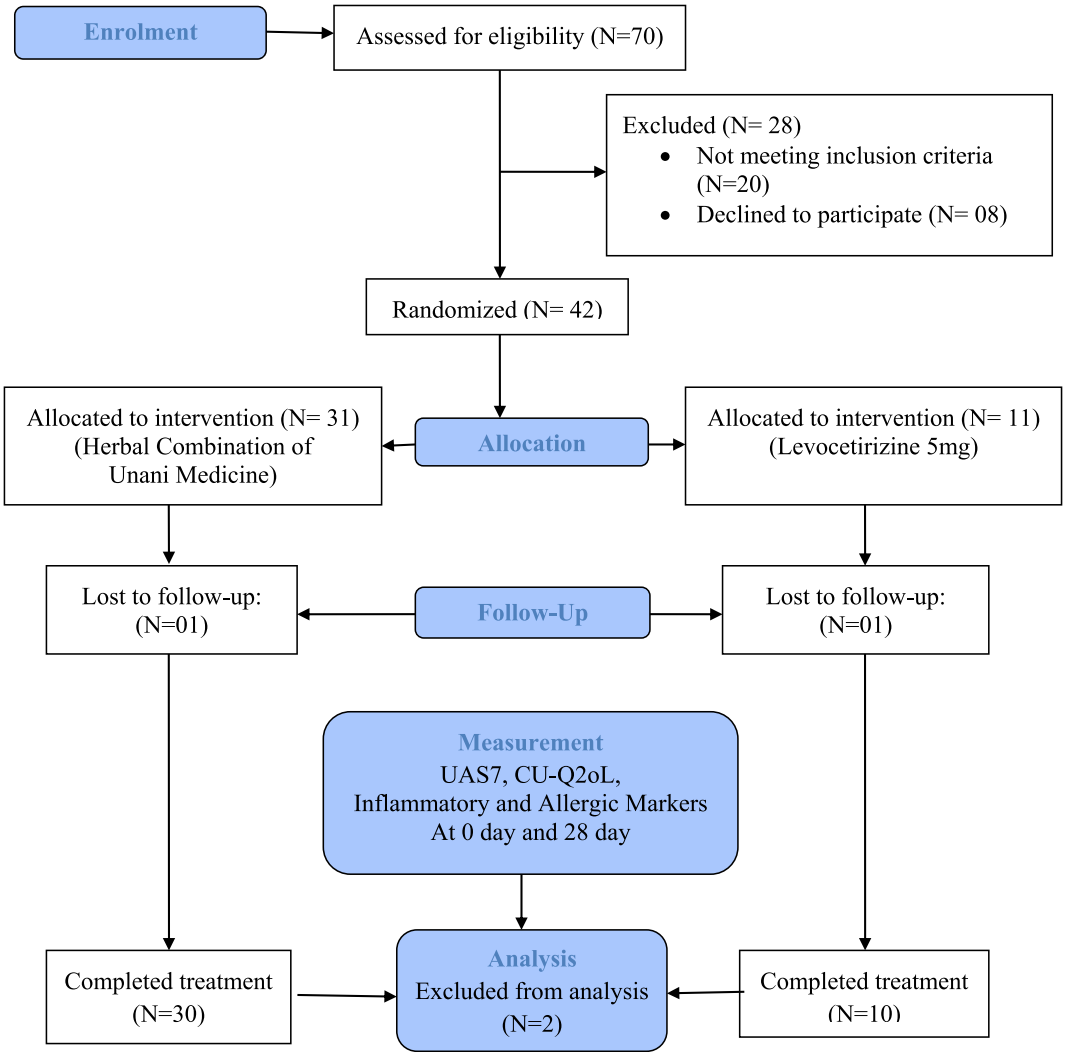

Fig. 1. CONSORT Diagram showing patient flow.

Table 1
The composition of HCUM used in this trial.

Name	Scientific Name	Family	Part used	Weight
Faudanj	*Mentha arvensis* Linn	*Labiatae;Lamiaceae*	Leave	4 gm
Tabashir	*Bambusa arundinacea* Linn	*Gramineae;Poaceae*	Bamboomana	4 gm
Gule Surkh	*Rosa damascena* Mill	*Rosaceae*	Petals	2 gm
Kafoor	*Cinnamomum camphora* Linn	*Lauraceae*	Camphor	125 mg

Table 2
Comparison of the baseline characteristics between two groups.

Characteristic HCUM			Levocetirizine	Total P value
Age (year)[a]		36.60 ± 7.95	31.00 ± 6.72	35.20 ± 7.96 0.100
Gender (F/M)[b]	12/18(40/60)		4/6(40/60)	16/24(40/60) 1.000
UAS7[a]	32.43 ± 2.34		32.10 ± 2.33	32.35 ± 2.32 0.699
CU-Q2oL[a]	67.57 ± 9.56		65.20 ± 11.78	66.98 ± 10.05 0.526
CRP (positive)[b]	17(56.7%)		6(60%)	23(57.5%) 1.000
ESR[a]	33.67 ± 20.98		27.60 ± 13.15	32.15 ± 19.35 0.398
AEC[a]	349.13 ± 144.42		380.00 ± 126.58	356.85 ± 139.25 0.551

CRP=C-reactive protein, ESR = erythrocyte sedimentation rat, AEC = Acute eosinophil count.
[a] Mean ± SD.
[b] Number (Percentage).

Table 3
Urticaria Activity Score (UAS 7) analyzed (Mean ± SD) in two groups at baseline and after 28 days.

UAS 7	HCUM	Levocetirizine	Total	P value
Before Treatment	32.43 ± 2.34	32.10 ± 2.33	32.35 ± 2.32	0.699
After Treatment	14.03 ± 2.16	28.40 ± 3.78	17.63 ± 6.82	<0.001**
Difference	18.400	3.700	14.725	–
P value	<0.001**	0.004**	<0.001**	–

Between Group: Student *t*-test (Unpaired), With in Group: Student *t*-test (Paired).
**Highly significant reduction from baseline at 28th day was noted.

Table 4
ChronicUrticaria Quality of Life Questionnaire (CU-Q2oL) scores analyzed (Mean ± SD) in two groups at baseline and after 28 days.

CU-Q2oL	HCUM	Levocetirizine	Total	P value
Before Treatment	67.57 ± 9.56	65.20 ± 11.78	66.98 ± 10.05	0.526
After Treatment	36.50 ± 3.01	59.60 ± 11.13	42.28 ± 11.75	<0.001**
Difference	31.067	5.600	24.700	–
P value	<0.001**	0.289.	<0.001**	–

Between Group: Student *t*-test (Unpaired), With in Group: Student *t*-test (Paired).
**Highly significant reduction in score from baseline at 28th day was noted.

(P < 0.001) where moderate severity was not reduced (32.10 ± 2.33–28.40 ± 3.78). The severity of impact on the quality of life (CU-Q2oL) is also reduced effectively from moderate to mild severity (67.57 ± 9.56–36.50 ± 3.01) in the HCUM group as compared to the Levocetirizine group where the moderate severity (65.20 ± 11.78–59.60 ± 11.13) was not significantly changed (P value = 0.289).

A significant change was observed in the laboratory parameters of CRP, ESR (inflammatory markers), and AEC (allergic marker) as shown in table-5. HCUM treatment effectively reduced CRP positive ratio from 17(56.7%) to 2(6.7%) whereas in the Levocetirizine group no change was observed from baseline 6(60%) to 28 days 6(60%) which was statistically significant (P = <0.001). A significant reduction was observed in ESR (33.67 ± 20.98–18.10 ± 11.90) and AEC (349. 13 ± 144.42–298.23 ± 82.49) from baseline to 28 days in the HCUM group which was statistically significant (P = <0.001) as compared to the Levocetirizine group. Moreover, the ratio of side effects was comparatively more in Levocetirizine group (40%) 4 patients than the HCUM group where only (13.3%) 4 patients reported side effects.

3.3. Safety evaluation

The patients were well-followed-up and clinically assessed during the study period and all adverse events in both treatments were reported. Adverse events data were analyzed at end of the study in both groups. Out of 40 patients who completed the study only 8(20%) developed side effects. Only one symptom of drowsiness/giddiness/heartburn or lethargy was observed in 4 patients (2.5%), whereas headache developed in 4 patients (10%) after using the drug. a significant difference in the incidence of adverse events between the HCUM (13.3%) and Levocetirizine group groups (40%) was seen (P = 0.089+) when analyzed on Fisher Exact Test. No anaphylactic episodes or other major imbalances in any system organ affected by adverse events were reported during the study period. The evaluations of markers of liver and kidney functions were all within the normal range when analyzed from baseline and end of the study.

4. Discussion

The results of the present randomized, standard-controlled clinical trial demonstrated that the HCUM treatment significantly reduced UAS7 and CU-Q2oL scores. The decreasing trend in UAS7 and CU-Q2oL scores implied that the symptoms of urticaria, including wheal flareup area, frequency, itching severity, and negative impact of the quality of life could be controlled by the HCUM treatment in a better manner than Levocetirizine which was statistically significant (P = <0.001). The ratio of adverse effects (dryness, sedation, drowsiness, and headache) of the Levocitrizine group was comparatively higher 40% as compared to the HCUM group, where only 13.3% side effect like giddiness, headache, lethargy, and heartburn was reported which was statistically significant (P = 0.089+). This finding also implies that the use of HCUM prescriptions may help reduce the adverse events as compared to levocetirizine.[40] These side effects were of mild severity and minimal duration which were resolved after few hours. Significant changes were observed in laboratory parameters of CRP, ESR (inflammatory markers), and AEC (allergic marker) when compared from baseline to28 day in HFUM treatment which was highly significant (P=<0.001). The Levocetirizine treatment failed in producing a significant change in these markers. We observed clinical improvement and reduction in the UAS7 score when assessed

Table 5
Inflammatory markers and allergic marker scores analyzed in two groups at baseline and after 28 days.

Before Treatment	HCUM	Levocetirizine	Total	P value
CRP (Positive)[a]	17(56.7%)	6(60%)	23(57.5%)	1.000
ESR[b]	33.67 ± 20.98	27.60 ± 13.15	32.15 ± 19.35	0.398
AEC[b]	349.13 ± 144.42	380.00 ± 126.58	356.85 ± 139.25	0.551
After Treatment	HCUM	Levocetirizine	Total	P value
CRP (Positive)	2(6.7%)	6(60%)	8(20%)	0.001**
ESR	18.10 ± 11.90	20.90 ± 9.23	18.80 ± 011.25	0.503
AEC	298.23 ± 82.49	372.10 ± 94.29	316.70 ± 90.34	0.023*

[a]Chi-Square/Fisher Exact Test, [b]Student *t*-test (Unpaired) and Student *t*-test (Paired).
[a] Number (Percentage). [b]Mean±SD.

weekly (week 1,2,3 consecutively), but we are unable to make any conclusion how quickly the drugs respond. Because data of before and after treatment was statistically analyzed only. We did not categorize the patients of CU into CIU, CSU, and subgroups of CIU to analyze them statically therefore information about results in different subgroups was not given.

The pathogenesis of chronic urticaria is not well established. The centrality of mast cells and their inappropriate activation and degranulation as the key pathophysiological event are well established. The triggering stimuli and the complexity of effector mechanisms remain speculative. Autoimmune origin, alterations in basophils, and pathways of coagulation are other alternative hypotheses. These different pathomechanisms are likely interlinked rather than independent cascades, acting either synergistically or sequentially to produce clinical expression of chronic urticaria.[13] Skin affected by wheals virtually always exhibits upregulation of endothelial cell adhesion molecules, neuropeptides and growth factors and a mixed inflammatory perivascular infiltrate of variable intensity, consisting of neutrophils with or without eosinophils, basophils, macrophages, and T cells. The nonlesional skin of CSU patients shows upregulation of adhesion molecules, infiltrating eosinophils, and altered cytokine expression. A mild to moderate increase in mast cell numbers has also been reported.[6]

The beneficial effects of HCUM may be attributed to different biomedical activities like antiinflammatory,[29,30] analgesic,[31] sedative-hypnotic,[32] anti-oxidant,[33–37] hepatoprotective,[38,39] and the activity of either inhibiting histamine release from mast cells or/and protection against mast cells degranulation and allergic inflammatory responses of the ingredients of the HCUM.[42,43] Furthermore, the ingredients were reported to have a strong anti-oxidative stress effect[33–37] in vivo studies, and oxidative stress was proven to be one of the crucial factors of chronic urticaria. The phytochemicals like flavonoids, lignans, terpenoids, glycosides, and alkaloids are reported as the major components, found in the plant kingdom and scientifically analyzed for anti-allergic and inflammatory activities. The effective biochemical constituents are phenolic compounds and flavonoids, alkaloids, tannins, and cardiac glycosides, steroids, carbohydrates, proteins, and amino acids, present in Bambusa arundinacea Linn, Mentha arvensis Linn and Rosa damascena Mill.[43–46]

Flavonoids possess an anti-allergic potential and ability to modify the body's reaction to allergies found in experimental studies.[47] Ethanolic and aqueous extracts of leaves of Mentha arvensis were reported for their activity against allergic and inflammatory responses in studies. Among all phytoconstituents, flavonoids content was found high in all ethanolic and aqueous extracts of leaves, stem, and root, respectively. An anti-allergic activity using histamine inhibitory assay revealed effective inhibition on the release of histamine from mast cells.[43] Allergic reaction is an IgE-mediated immune response, resulting in histamine secretion from the deregulation of mast cells and blood basophils, and triggers allergy response. In another study, the aqueous extract of Mentha arvensis inhibited the histamine released from rat peritoneal mast cells activated by the anti-DNP IgE antibody. Moreover, it had an inhibitory effect on TNF-alpha production induced by anti-DNP IgE antibody from rat peritoneal mast cells.[48]

Mast cells (MC) are the primary effectors' cells in urticaria and many cases of angioedema. Previous studies have shown serum IgE levels and AEC to be significantly elevated in the urticaria patients as compared with healthy volunteers. The mast cells release eosinophil chemotactic factors that attract eosinophils to the sites of anaphylaxis, urticaria, angioedema, and atopy. The role of tissue eosinophilia is unclear, although it is possible that the release of toxic major basic protein and eosinophil cationic protein further augments histamine release from mast cells in the late phase of the urticarial wheal. Eosinophil-mediated activation of the coagulation system may be another mechanism of MC degranulation in patients.[49]

Compounds in Mentha arvensis like I-menthol, menthone, and 1,8-cineole suppressed antigen-induced histamine release in rat peritoneal mast cells. The anti-inflammatory effect may be due to compounds in Mentha arvensis that are capable of inhibiting histamine release from mast cells and/or block histamine receptors.[43] These findings suggest that Mentha arvensis Linn has an anti-allergic effect and protects mast cell degranulation and blood basophils. Phenolic compounds possess inflammatory, antioxidants, free-radical scavengers, anticancer, antimutagenic, and antidepressant activities.[45,46] The anti-inflammatory effect can be attributed to phenolic compounds and flavonoids which inhibit prostaglandins as found in the study. Also, its anti-oxidant nature can be a cause of its anti-inflammatory activity.[46]

These "multiple herbs, multiple target" pharmacologic effects are also characteristics of UM like other traditional medicines and can be the potential explanation about the effects of HCUM on chronic urticaria. The basic principle of treatment in UM is to eliminate the morbid humor (pathogen) and moderate the equilibrium of humor by neutralizing the effect of involved morbid humor and to help in producing normal humor and strengthening the immune system by applying "multiple herbs, multiple target" pharmacologic effects. According to Avicenna, the cause of Urticaria is either bilious blood or saline phlegm (pathogenic humor) which are changed into gaseous form and suddenly ferment and rise toward skin surface leading into wheal production and itch depending upon involved humor.27 The drugs in HCUM exert a diverse beneficial pharmacological effect. Bambusa arundinacea Linn and Cinnamomum camphora Linn neutralize the noxious effects of pathogenic humor by inhibiting them from changing into gaseous form and produces sedating and soothing effect in itching. While Mentha arvensis Linn and Rosa damascena Mill help in improving digestion and eliminating pathogenic humor holistically. This study validates Avicenna's theory of pathogenesis and treatment of urticaria.

Several potential disease-related biomarkers (inflammatory and immunological markers) were identified including D-dimer, matrix metalloproteinase-9, and C-reactive protein, Immunoglobulin E that can reflect these processes and are supported by strong evidence for distinguishing CSU patients from healthy controls.[49,50] According to EAACI/GA2LEN/EDF/WAO guideline, CRP assessment is recommended in all patients with chronic urticaria and may help in its diagnosis.[6] ESR is another well known non-specific marker of inflammation, moreover, the correlation between CRP and other inflammatory markers such as ESR has been reported. CRP is considered to be a better indicator of inflammation than ESR because CRP levels respond more quickly to inflammatory processes. Also, false-negative and false-positive results are less common for CRP than ESR.[50]

The reducing trend in inflammatory markers in the HCUM group was statistically significant as compared to Levocitrizine in our study which is consistent with the findings of other studies which recommended that CRP levels are relevant for the management of CSU indicate a risk of poor response to antihistamine treatment.[50]

In comparison with the standard treatment of Levocetirizine 5 mg using the HCUM significantly increased the effectiveness of the treatment in terms of decreasing wheal flareup area, frequency, itching severity, better tolerance, and negative impact of the quality of life. However, this study has some limitations. One limitation in the present study is that the results might be biased due to subjective primary outcome adopted in an open-labeled trial. The participant enrolment ratio (30:10) was not equal in HCUM and Levocetirizine groups; even the difference between the two groups seemed substantial in clinical perspectives. The small sample size, unequal ratio, open-labeled, short duration, and post-treatment follow-up of the study can be mentioned as limitations of this study. Since this trial was conducted at a single medical center in NIUM, Bangalore, therefore the generalizability of using HCUM for chronic urticaria may be limited in the population studied, and an examination of the external validity is still needed. However, we believe that the statistical significance of this HCUM would be achieved with larger sample size, double-blind, post-treatment follow up and multicenter study design under the impression to be a candidate therapy for urticaria.

5. Conclusion

In summary, the data reveal that the herbal combination of Unani medicine (HCUM) comprising Rosa damascena Mill. Bambusa arundinacea Linn, Cinnamomum camphora Linn, and Mentha arvensis Linn can offer better treatment outcomes in CU of moderate severity. The reducing trend in inflammatory markers in the HCUM group confirms that CRP levels are relevant for the management of CU and high CRP levels predict poor responses to treatment with second generation antihistamine. Nevertheless, clarification of the role, effectiveness, and limitations of this herbal combination in CU treatment may require further studies.

Disclaimer

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Declaration of competing interestCOI

The authors have no conflicts to declare.

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Appendix A. Supplementary data

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