

RESEARCH

Open Access



Multidimensional analysis and clinical efficacy: evaluating the therapeutic and metabolic potential of Itrifal Ustukhudus in chronic rhinosinusitis management with four-month surveillance

Huma Rafiq¹, Arif Habib^{1*}, Shaista Urooj², Arjumand Shah¹, Kounser Shah¹, Arsheed Iqbal¹ and Sabia Rasool¹

Abstract

Background Chronic rhinosinusitis (CRS) is a common inflammatory disorder associated with persistent sinonasal symptoms and impaired quality of life. Despite available conventional therapies, many patients experience incomplete relief or adverse effects, highlighting the need for safe and sustainable alternative approaches.

Objective To evaluate Clinical and Radiological Outcomes of Itrifal Ustukhudus (*Itrifal Ustukhudus*, a classical Unani polyherbal formulation containing *Lavandula stoechas* along with *Triphala* components (*Terminalia chebula*, *Terminalia bellerica*, and *Phyllanthus emblica*)) in Chronic Rhinosinusitis in a prospective real-world surveillance.

Methods This prospective, open-label, single-arm surveillance study included 100 adults with chronic rhinosinusitis (CRS) (37 males, 63 females). Participants received Itrifal Ustukhudus for six weeks and were assessed at 15-day intervals during the treatment period. Clinical outcomes were evaluated using the Sino-Nasal Outcome Test-22 (SNOT-22), while radiological changes were assessed using standardized imaging criteria. Safety evaluation included haematological parameters, liver and kidney function tests, erythrocyte sedimentation rate (ESR), and serum uric acid levels. Longitudinal changes were analysed using linear mixed-effects models for repeated measures, with statistical significance set at $p < 0.05$.

Results Participants demonstrated substantial reductions in SNOT-22 scores from baseline to the end of treatment, indicating marked improvement in sinonasal symptom burden. Radiological improvement was observed in more than half of the participants, with the most notable changes seen in individuals with bilateral sinus involvement. Laboratory parameters, including haematological indices and liver and kidney function markers, remained stable throughout the study period, suggesting an acceptable safety profile. Reductions in ESR and serum uric acid levels were also observed, indicating a potential reduction in systemic inflammatory activity.

*Correspondence:
Arif Habib
dr.arifhabib@gmail.com

Full list of author information is available at the end of the article

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Conclusion Itrifal Ustukhudus was associated with clinically meaningful improvements in symptoms and favourable radiological trends, with a reassuring safety profile during the study period. However, given the open-label, single-arm design, these findings should be interpreted as preliminary and hypothesis-generating.

CTRI no CTRI/2018/10/016178.

Keywords Chronic rhinosinusitis, Unani medicine, Integrative otolaryngology, Real-world evidence, Surveillance study, SNOT-22

Introduction

Chronic rhinosinusitis (CRS) is a persistent inflammation of the nasal and paranasal sinus mucosa, lasting for at least 12 weeks [1]. It represents a significant global health burden, affecting over 10% of adults in Europe and the United States and contributing to substantial morbidity, healthcare utilization, and socioeconomic costs [1]. Key clinical manifestations include nasal obstruction, nasal discharge, facial pain or pressure, and, in advanced cases, hyposmia or anosmia, memory impairment, and reduced attention [2]. According to the EPOS 2012 criteria, CRS is diagnosed when symptoms persist for more than 12 weeks, with at least two or more cardinal symptoms, such as nasal obstruction or discharge, facial pain/pressure, or smell reduction [2]. Epidemiological studies indicate a prevalence ranging from 5% to 15% across age groups [3].

The chronic and recurrent nature of CRS substantially diminishes patients' quality of life (QoL) and contributes to high healthcare expenditures. It is reported as the fifth leading indication for antibiotic prescriptions [4]. Beyond symptomatic burden, CRS is associated with systemic comorbidities, including asthma exacerbation and sleep disturbance, and, in rare instances, severe complications such as meningitis, brain abscess, orbital cellulitis, or intracranial infections, which may result in visual or neurological deficits [5, 6]. This emphasizes the need for effective, sustainable management strategies.

The etiology of CRS is multifactorial and remains incompletely understood. Bacterial, viral, and fungal infections, environmental allergens, and toxins disrupt the delicate host-mucosa balance, perpetuating chronic inflammation [5, 7]. Polymicrobial colonization, particularly by *Staphylococcus aureus*, anaerobes, and resistant strains, complicates conventional antibiotic therapy and contributes to frequent relapses [4]. This microbial heterogeneity underlines the importance of exploring treatments that modulate host inflammatory responses in addition to targeting pathogens.

In the Unani system of medicine, CRS is closely associated with *Nazla*, derived from the term *Nuzool*, which describes the downward movement of phlegm from the brain to the nasal passages [8]. Classical scholars, including Ibn Sina (Avicenna) ⁸, Zakariya Razi (Rhazes) [9], and Ali Ibn Majoosi (Haly Abbas) [10], described intrinsic factors such as weak cerebral metabolism and brain

temperament imbalances, and extrinsic factors like exposure to cold and environmental irritants, as contributing to excessive phlegm production. The qualitative nature of nasal secretions—whether watery, thick, hot, or cold—is interpreted within Unani principles to reflect the underlying temperament and causative factors [11, 12].

Modern therapeutic strategies, including decongestants, antihistamines, corticosteroids, and antibiotics, offer symptomatic relief but are often limited by adverse effects, incomplete resolution, and increasing microbial resistance. Surgical approaches, such as functional endoscopic sinus surgery or antral puncture, may provide temporary improvement but rarely achieve permanent cure. The World Health Organization (WHO) reports that more than half of the population in developing countries relies on traditional medicine for primary healthcare needs [13]. This underscores the global relevance of integrating evidence-based traditional interventions.

Given the anti-inflammatory, immunomodulatory, and mucolytic properties of various Unani herbs—such as *Ustukhuddus* (*Lavandula stoechas*) [10], *Banafsha* (*Viola odorata*) [12], *Amla* (*Embllica officinalis*) [10], *Aftimoon* (*Cassia fistula*) [11], *Balela* (*Terminalia bellerica*) [14], and *Halela* (*Terminalia chebula*)¹⁷—there is a strong rationale to investigate their clinical efficacy in CRS. This study aims to evaluate the therapeutic potential of these multi-herbal formulations using objective radiological parameters, validated patient-reported outcomes, and biochemical markers, thereby providing a bridge between classical Unani knowledge and contemporary evidence-based medicine.

Material and methods

Study rationale and justification

Randomized comparative controlled trials (RCTs) are widely regarded as the gold standard for establishing therapeutic efficacy in clinical research. However, before conducting large-scale controlled trials, exploratory clinical investigations are often necessary to generate preliminary evidence regarding safety, feasibility, and potential clinical outcomes, particularly for traditional formulations that have long-standing historical use but limited evaluation through contemporary research methodologies. In such contexts, observational or single-arm clinical designs serve as an important initial step in the

evidence-generation pathway, helping to document treatment patterns, patient responses, and the feasibility of standardized outcome assessment prior to undertaking more resource-intensive controlled trials.

Itrifal Ustukhudus has been traditionally used for the management of upper respiratory disorders, including Nazla-e-Muzmin (chronic rhinosinusitis); however, systematic clinical documentation using validated contemporary outcome measures remains limited. The present investigation was therefore undertaken to systematically document clinical outcomes using the SNOT-22 (Sino-nasal Outcome Test-22), a widely accepted instrument for assessing symptom burden in chronic rhinosinusitis, while also monitoring the safety profile of the formulation during the treatment period. The primary objective of the study was to generate preliminary observational clinical evidence that may guide the design of future controlled trials evaluating this traditional formulation.

Intervention and standardization

The intervention consisted of Itrifal Ustukhudus, a classical Unani pharmacopoeial formulation described in authoritative Unani medical texts and standardized in the National Formulary of Unani Medicine (NFUM) [15], administered in a semisolid oral dosage form.

Participants received 7 g twice daily with lukewarm water for a total duration of six weeks. The formulation was prepared according to standardized pharmacopoeial procedures and comprised multiple herbal ingredients, including *Terminalia chebula* (three varieties), *Terminalia bellerica*, *Emblica officinalis*, *Lavandula stoechas*, *Rosa damascena*, *Polypodium vulgare*, *Cuscuta reflexa*, and *Vitis vinifera*, along with excipients such as clarified butter and sugar.

To ensure quality, consistency, and reproducibility, the formulation underwent multidimensional standardization, including qualitative phytochemical screening (for glycosides, tannins, phenols, terpenes/steroids, and amino acids), physicochemical evaluation (moisture content, ash values, pH, and extractive values), and thin-layer chromatography (TLC) profiling across multiple solvent systems. These analytical parameters are summarized in Fig. 2 and detailed in Table 1, confirming the compositional integrity and batch consistency of the study drug.

Study design considerations

The study employed an open-label, single-arm design without a comparator group, which represents an inherent methodological limitation. Single-arm exploratory studies are widely recognized as an important

Table 1 Mechanism of action of ingredients in chronic rhinosinusitis (CRS) with supporting evidence

Ingredient	Mechanism of Action (Evidence / Rationale)	Relevance to Chronic Rhinosinusitis (CRS)	Reference Number
Post-e-Halela Zard / Kabuli / Halela Siyah (<i>Terminalia chebula</i>)	Anti-inflammatory via NF-κB, STAT1/3, and MAPK inhibition; reduces ROS, NO, TNF-α, IL-6, IL-8 in macrophage and murine models [1, 2]	Reduces mucosal inflammation, oxidative stress, and cytokine-driven tissue injury in sinus mucosa	[15]
Post-e-Balela (<i>Terminalia bellerica</i>)	Suppresses COX-2, 5-LOX, NO, ROS; downregulates NF-κB signalling; reduces pro-inflammatory cytokines in LPS-stimulated macrophages [3, 4]	May reduce sinus mucosal edema and inflammation through modulation of eicosanoid pathways	[16, 17]
Aamla (<i>Emblica officinalis</i>)	Anti-inflammatory and antioxidant; inhibits NF-κB, iNOS, COX-2, reduces ROS; increases endogenous antioxidants (GSH, SOD, catalase); contains gallic acid, quercetin, ellagic acid [5, 8]	Protects sinus epithelium from oxidative stress and chronic inflammatory injury; may restore mucosal barrier integrity	[18, 19, 20]
Gul-e-surkh (<i>Rosa damascena</i>)	Reduces pro-inflammatory cytokines via NF-κB inhibition; antioxidant activity from polyphenols and flavonoids [11]	Dampens mucosal inflammatory response; protects sinus epithelium from oxidative stress	[21]
Ustukhuddus (<i>Lavandula stoechas</i>)	Reduces NO production, COX-2, iNOS, IL-1β, IL-6, TNF-α, MMP-9; antioxidant activity; 1,8-cineole component may modulate mucosal inflammation [9, 10]	Anti-inflammatory and antioxidant effect may reduce sinus edema, cytokine infiltration, and tissue remodelling	[22, 23]
Bisfayej (<i>Polypodium vulgare</i>)	Limited recent mechanistic studies; traditionally considered anti-inflammatory and mucolytic; contains polyphenols and saponins with antioxidant activity	May reduce mucosal congestion and oxidative stress; supportive in symptom relief	[24]
Aftmoon (<i>Cuscuta reflexa</i>)	Sparse mechanistic data; traditional use: immunomodulatory, anti-inflammatory; contains flavonoids, alkaloids, lignans [13]	Could modulate immune response in CRS; exact mechanisms need further research	[25]
Kishmish (<i>Vitis vinifera</i>)	Polyphenols (resveratrol, proanthocyanidins) exert antioxidant and anti-inflammatory effects; inhibit NF-κB and COX-2 in vitro [15]	Antioxidant effect may protect sinus mucosa; anti-inflammatory effect may reduce cytokine-induced tissue damage	[26]
Roghan-e-zard (Clarified butter / Ghee)	Traditionally considered anti-inflammatory and demulcent in Unani medicine; may support absorption of lipid-soluble phytochemicals [27, 28]	May enhance bioavailability of lipophilic compounds and soothe mucosa; no direct CRS evidence	--
Qand safaid (Sugar)	Acts as excipient and carrier; can have soothing effect in syrups; no direct anti-inflammatory effect [17]	Supports palatability and delivery of herbal formulations; no direct CRS mechanistic role	--

preliminary step in the clinical evidence pathway, particularly for traditional or historically used therapies where systematic clinical documentation is limited and where initial data are required to inform the design of subsequent randomized controlled trials. While this design allowed documentation of symptom changes following administration of the formulation in a real-world clinical setting, it does not allow definitive causal inference regarding treatment efficacy.

Therefore, the findings of the present study should be interpreted as associations observed during the treatment period rather than definitive proof of therapeutic efficacy. Nevertheless, the systematic documentation of clinical outcomes using validated symptom scores provides important preliminary data regarding the potential clinical utility and safety profile of this traditional formulation. These findings may serve as a foundation for designing future randomized controlled trials with appropriate comparator groups to more rigorously evaluate the efficacy and long-term effectiveness of Itrifal Ustukhudus in the management of chronic rhinosinusitis.

Participant flow and attrition

This open-label, single-arm, longitudinal study evaluated the safety and efficacy of the Unani pharmacopoeial formulation Itrifal Ustukhudus in adults with chronic rhinosinusitis (CRS), diagnosed according to Nazla-e-Muzmin criteria. Historical outpatient footfall over the preceding three years averaged 82 patients per year.

A formal power analysis determined that a minimum of 82 evaluable participants was required to detect a

clinically significant change ($\text{MCID} \geq 8.9$ points) in SNOT-22 scores with 80% power and a 5% significance level. To account for anticipated attrition in this longitudinal study, a total of 261 participants were consecutively enrolled to ensure that the final analytical cohort met or exceeded this requirement.

An interim methodological review was conducted after approximately 50% of the target sample had been enrolled to reassess the assumptions underlying the initial sample size estimation and to evaluate participant retention patterns. This review was performed using aggregated and de-identified data, without formal hypothesis testing. No modifications were made to the sample size, study design, or statistical analysis plan based on this review.

During the six-week treatment period, 161 participants were lost to follow-up. This attrition was primarily attributed to perceived symptomatic improvement reported by participants, logistical constraints, or personal circumstances rather than adverse events. This resulted in a final analytical cohort of $n=100$ complete cases, which exceeded the original power requirement of 82 participants.

To assess whether attrition introduced systematic bias, baseline demographic characteristics and SNOT-22 scores were compared between the 100 completers and the 161 participants lost to follow-up. No statistically significant differences were observed ($p > 0.05$), supporting the assumption that the missing data were Missing at Random (MAR).

Attrition of this magnitude is not uncommon in longitudinal studies conducted in routine clinical practice, particularly for chronic symptomatic conditions where participants may discontinue follow-up after perceived clinical improvement or due to logistical constraints.

A structured CONSORT flow diagram illustrating participant enrolment, follow-up, and analysis is provided in Figure A. Although a notable level of attrition occurred during the study period, most losses to follow-up were attributable to personal circumstances, symptomatic improvement, non-compliance with study procedures, or lack of continued contact after intervention completion, rather than adverse events related to the intervention. Nevertheless, the possibility of attrition bias cannot be completely excluded, and this limitation should be considered when interpreting the findings.

Inclusion, exclusion, and study schedule

Eligible participants were adults aged 18–65 years with CRS symptoms persisting for more than 12 weeks and a SNOT-22 score > 7 . Exclusion criteria included acute rhinosinusitis, structural or local nasal pathologies (deviated septum, nasal polyps, mucocele, cysts), history of facial trauma, systemic illnesses requiring long-term therapy, and pregnancy or lactation. The study was conducted

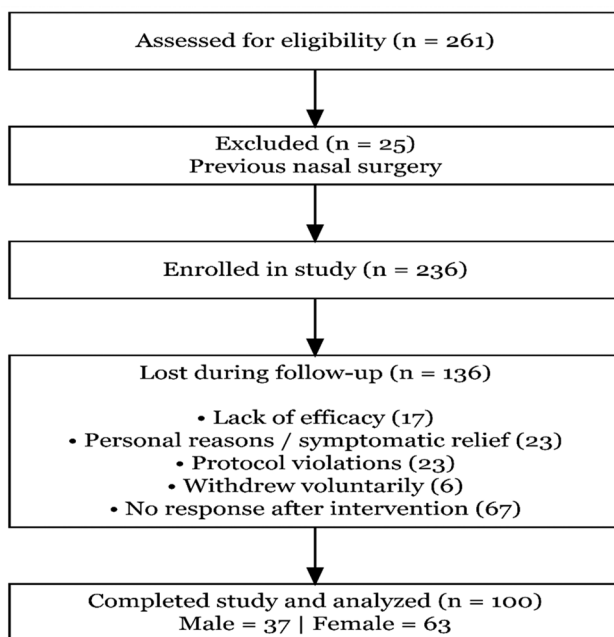


Fig. A CONSORT flow diagram of participant recruitment, enrolment, follow-up, and analysis

over two years, with a six-week treatment period. Participants were clinically assessed every 15 days during treatment. To evaluate disease surveillance and recurrence risk, a single post-treatment follow-up assessment was conducted at four months (approximately 16 weeks) after completion of therapy using the SNOT-22 assessment.

Concomitant medications that could influence CRS outcomes, including antibiotics, corticosteroids, antihistamines, or other nasal therapies, were not routinely permitted during the study period to minimize confounding effects. Participants were counselled at enrolment and at each follow-up visit regarding adherence to the study protocol. However, in accordance with ethical clinical practice, rescue medication was allowed if clinically indicated, and such instances were documented. Compliance was monitored through participant self-reporting and clinical assessment during scheduled visits.

Therapeutic rationale

The therapeutic rationale of Itrifal Ustukhudus in CRS is based on its multifaceted pharmacological action: it exhibits anti-inflammatory, mucolytic, and immunomodulatory effects that help reduce mucosal edema, enhance mucociliary clearance, and restore nasal sinus homeostasis. Its ingredients are known in the Unani pharmacopoeia to counter chronic congestion, facilitate drainage, and improve local immune responses, addressing both the symptoms and underlying pathophysiology of CRS (Table 1).

Formulation quality assessment and mechanistic profiling

To ensure rigorous quality assessment and mechanistic understanding, the formulation underwent multidimensional analytical profiling. Quantitative analysis

determined the contribution of each ingredient in grams, while qualitative screening identified the presence or absence of key phytoconstituents, including alkaloids, amino acids, flavonoids, glycosides, phenols, resins, starch, terpenes/steroids, and tannins. Physicochemical profiling evaluated parameters such as loss on drying, moisture content, total ash, pH, specific gravity, and solvent extractive values, represented in a radar plot for a multidimensional overview. Thin-layer chromatography (TLC) with multiple detection methods (daylight, UV, and spray) was employed to determine R_f values for alcohol, methanol, and aqueous extracts. This comprehensive approach ensured a robust understanding of the formulation's composition, quality, and potential mechanisms of action Figs. 1 and 2.

Outcome measures

The primary outcome was the change in SNOT-22 scores from baseline to the end of the six-week treatment period. The SNOT-22 score was also the sole measure for the post-treatment follow-up assessment at four months to evaluate long-term disease surveillance. Secondary outcomes included resolution of radiological findings of paranasal sinuses. Radiological severity was quantified using the Lund-Mackay (LM) Scoring System. Each sinus group (Maxillary, Anterior Ethmoid, Posterior Ethmoid, Sphenoid, and Frontal) was graded 0, 1, or 2, with the osteomeatal complex graded as either 0 or 2. To facilitate clinical analysis, patients were categorized into four mutually exclusive diagnostic groups based on their LM distribution:

- Normal: An aggregate LM score of 0 across all sinus groups.

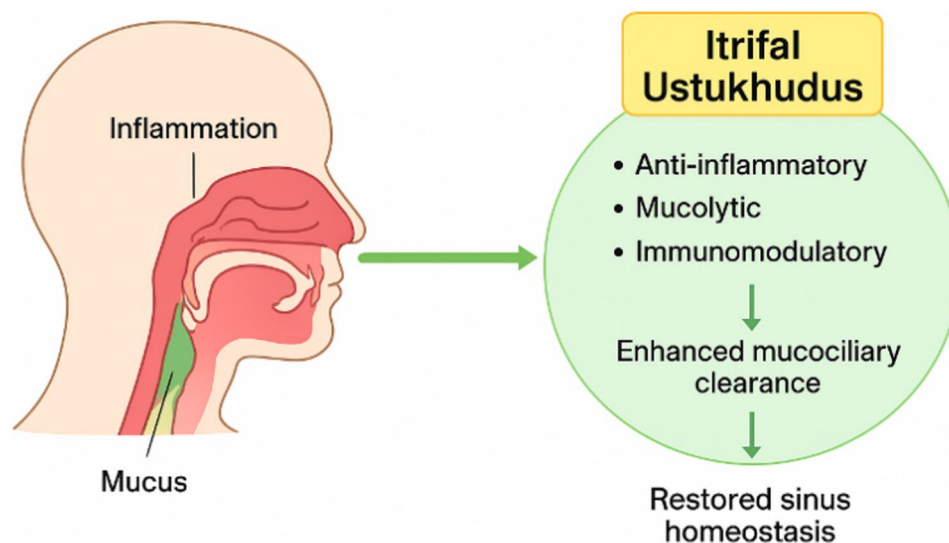


Fig. 1 Mechanistic model depicting the pharmacological actions of Itrifal-e-Ustukhuddus in the pathogenesis and management of chronic rhinosinusitis (CRS)

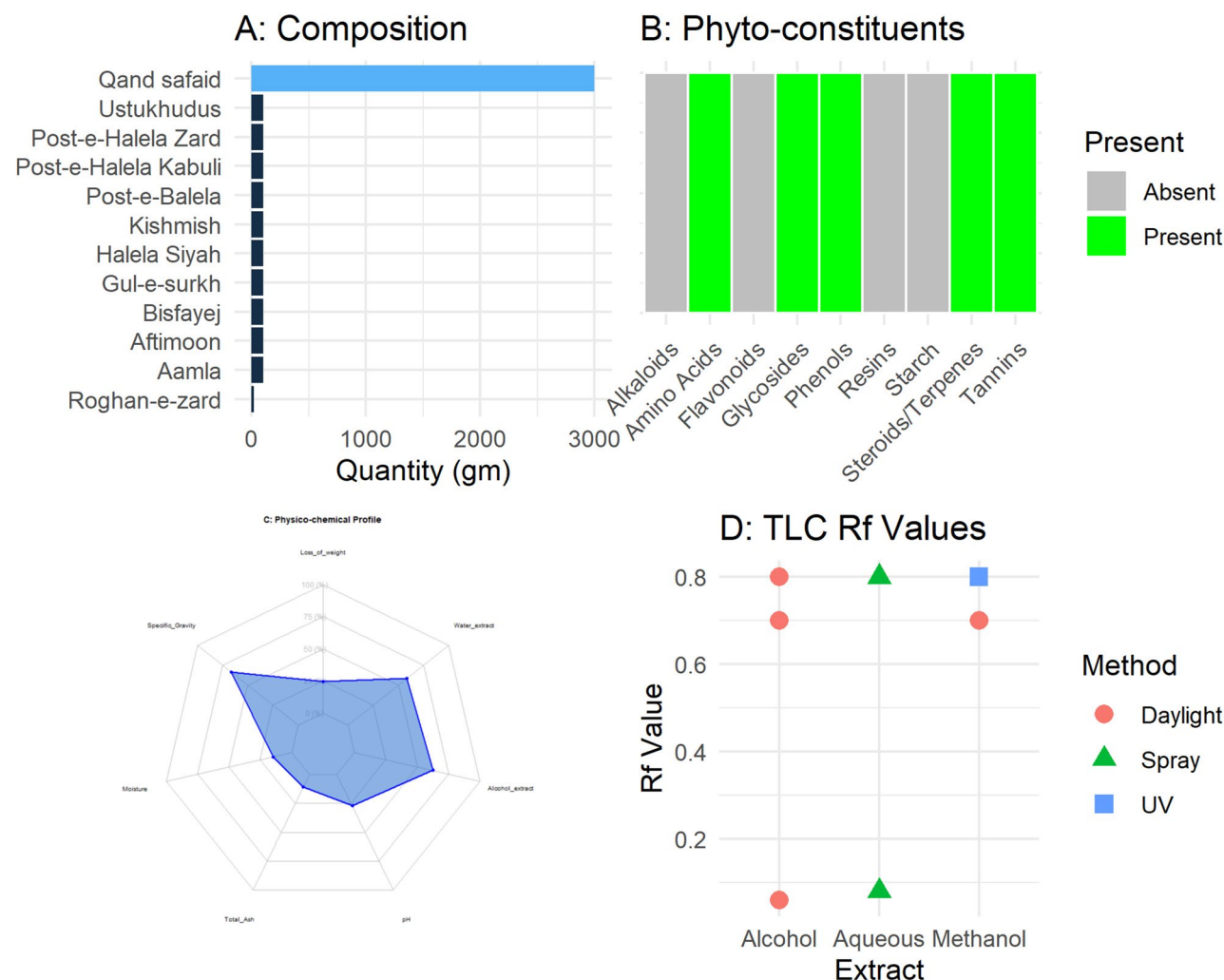


Fig. 2 Multidimensional analytical profile of the Unani compound formulation. Figure 2 Presents a multidimensional characterization of the study formulation. Panel **A** illustrates the quantitative composition of the formulation, demonstrating a standardized distribution of herbal constituents with *Qand Safaid* serving as the primary excipient. Panel **B** summarizes qualitative phytochemical screening, indicating the presence of key bioactive constituents including glycosides, tannins, phenols, steroids/terpenes, and amino acids, while alkaloids, flavonoids, starch, and resins were absent. Panel **C** depicts the physicochemical profile, including moisture content, ash values, pH, and extractive values, confirming formulation stability and quality. Panel **D** shows thin-layer chromatography (TLC) profiles across different solvent systems, demonstrating distinct Rf values under daylight, UV, and spray detection, supporting chemical consistency and batch standardization

- One-Sided Sinusitis: Opacification (LM score ≥ 1) restricted to one or more sinus groups on a single hemisphere only.
- B/L (Bilateral) Maxillary Sinusitis: Opacification (LM score ≥ 1) present in both the left and right maxillary sinuses, with or without involvement of the ethmoid or sphenoid cells, but excluding the frontal sinuses.
- Frontal Sinusitis: Any opacification (LM score ≥ 1) involving one or both frontal sinuses, regardless of involvement in other sinus groups.

All images were evaluated by two independent radiologists blinded to the treatment phase. Discrepancies were resolved by consensus or by a third senior radiologist."

Statistical analysis and sensitivity

The primary results are presented for the $n=100$ complete cases to evaluate the intervention's efficacy in those who adhered to the full protocol. To validate these findings, a Mixed Model for Repeated Measures (MMRM) with an unstructured covariance matrix was employed as a sensitivity analysis. By utilizing all available longitudinal data from the original 261 participants, the MMRM provided unbiased estimates that confirmed the trends observed in the complete-case cohort, adjusting for baseline covariates such as allergy status and disease duration. Statistical analyses were performed using R (version 4.4), with significance set at $p<0.05$. All statistical assumptions underlying the applied models were assessed prior

to analysis, and model diagnostics were performed to confirm the stability and robustness of the estimates.

Safety was assessed through adverse event monitoring and laboratory investigations. Sample size was initially estimated and refined after a blinded interim analysis. Safety analysis included all participants receiving at least one dose, while efficacy analysis included participants with baseline SNOT-22 scores and at least one follow-up. The primary radiological endpoint was the transition between these diagnostic categories from baseline to week six. Discrepancies between the two blinded readers were resolved by consensus or by a third senior radiologist where necessary. Improvements were defined as a shift from a more complex category (e.g., Frontal) to a simpler one (e.g., One-Sided) or to Normal status.

All study data were initially entered and managed using Microsoft Excel. The clinical significance of the observed changes in the $n=100$ cohort was evaluated against the Minimal Clinically Important Difference (MCID) for SNOT-22. Following Hopkins et al. (2009), a reduction of ≥ 8.9 points was the threshold for success. Our findings are reported with 95% Confidence Intervals to demonstrate that the treatment effect consistently exceeded this threshold.

Symptom changes were analysed using a mixed model for repeated measures (MMRM) with unstructured covariance, adjusting for baseline scores, prior history, disease duration, and allergy status. To ensure that this attrition did not introduce systematic bias, a Mixed Model for Repeated Measures (MMRM) was employed using an unstructured covariance matrix. This model utilized all available longitudinal data from the original 261 participants. Because the MMRM estimates are unbiased under the Missing at Random (MAR) assumption, it served as a sensitivity analysis to validate the findings of the complete-case cohort. Furthermore, a comparison of baseline SNOT-22 scores and demographics showed no significant differences between completers ($n=100$) and those lost to follow-up ($n=161$), suggesting that the observed 'substantial improvement' is representative of the broader study population.

The study methodology was described in sufficient detail to facilitate reproducibility in comparable clinical settings.

Results

A total of 100 patients with chronic rhinosinusitis were enrolled in the study, including 37 males and 63 females. The mean age of male participants was 38.4 ± 13.7 years, whereas the mean age of female participants was 33.2 ± 12.6 years. The baseline demographic and clinical characteristics of the study population are presented in Fig. 3. The mean age differed between sexes, with male participants showing a higher mean age compared with

female participants (Fig. 3A). The duration of chronic rhinosinusitis varied across predefined categories, with patients distributed across all duration groups, including less than 6 months, 6–12 months, 12–18 months, 18–24 months, and more than 24 months, for both males and females (Fig. 3B). Categorical baseline characteristics demonstrated sex-wise distributions for allergy status, dietary pattern, family history, and smoking status, as illustrated in Fig. 3C.

All Participants exhibited a steady and clinically meaningful improvement in sinonasal symptoms throughout the treatment period. Baseline SNOT scores were high (mean ≈ 42), indicating a substantial symptom burden. Symptom relief began early, with clinically relevant reductions evident by the second follow-up (mean ≈ 33), and continued to progress across subsequent assessments. By the later treatment stages, scores had declined to near-mild levels (≈ 20 at Follow-up-5), and by the Post-Study evaluation most patients achieved minimal or near-resolved symptoms, with final mean scores approximately 4–6 Fig. 4.

The patient-level trajectories showed a uniformly downward trend, demonstrating consistency of improvement across the cohort. Baseline characteristics were compared between the study completers ($n=100$) and those lost to follow-up ($n=161$); no statistically significant differences were found in age, gender, or baseline SNOT-22 severity ($p>0.05$).

The overall reduction—exceeding 30 points on average—far surpasses established thresholds for clinically meaningful change in chronic rhinosinusitis. Additionally, the narrowing variability and progressively tighter confidence intervals suggest a reliable and sustained therapeutic response.

Linear mixed-effects model confirmed a significant time-dependent improvement in SNOT scores. Compared with baseline, each follow-up point showed a statistically significant reduction, beginning at Follow-up-1 ($\beta = -2.75$, $p=0.036$) and strengthening thereafter. The magnitude of improvement continued to increase over time: Follow-up-4 ($\beta = -14.74$, $p<0.001$), Follow-up-5 ($\beta = -19.81$, $p<0.001$), Follow-up-6 ($\beta = -31.34$, $p<0.001$), with the largest effect observed at the Post-Study assessment ($\beta = -37.82$, $p<0.001$).

Random-effects estimates indicated notable between-patient variability at baseline ($SD \approx 6.48$), while residual variance decreased over time, reflecting convergence of patient responses with continued treatment. Collectively, these findings support a strong, statistically robust, and clinically meaningful reduction in symptom severity attributable to the intervention.

Radiological assessment of the study cohort demonstrated substantial improvement across diagnostic categories. The proportion of patients with Normal

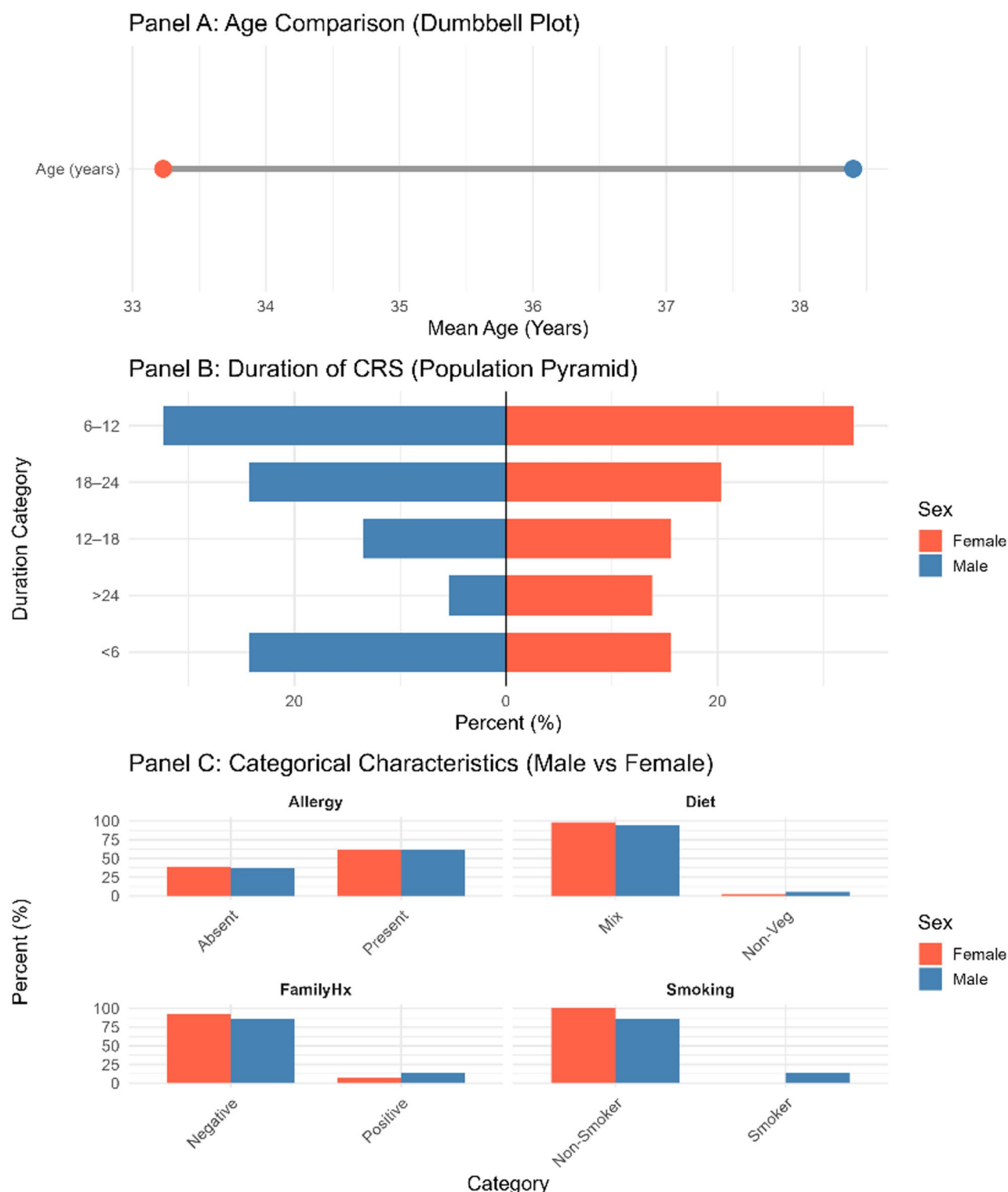


Fig. 3 Characteristics of the base line population and Clinical Information of the studied subjects. Panel **A** illustrates the comparison of mean age between male and female participants using a dumbbell plot. Panel **B** depicts the distribution of chronic rhinosinusitis (CRS) duration across predefined time categories in a population-pyramid format, allowing visual assessment of proportional differences between sexes. Panel **C** presents the percentage distribution of key categorical variables—including allergy status, diet pattern, family history, and smoking habit—stratified by sex. Collectively, these panels summarise the demographic and clinical baseline profile of the study cohort

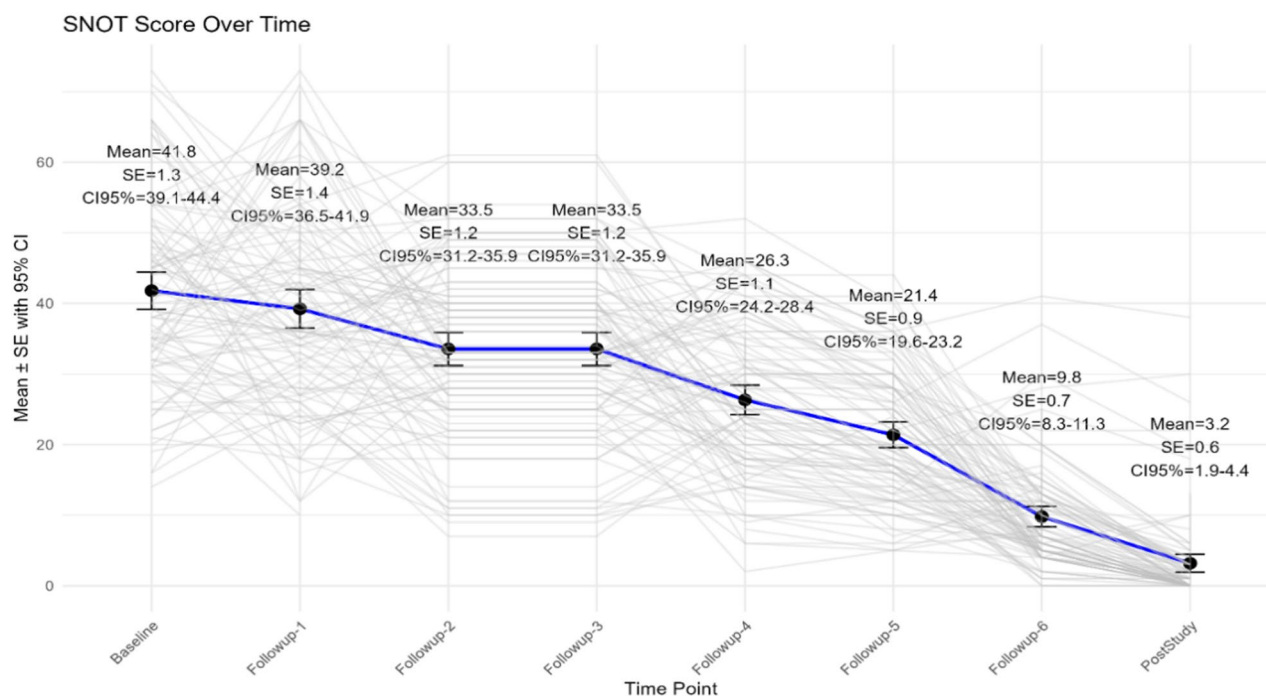


Fig. 4 Longitudinal changes in SNOT scores over time. The line plot illustrates the mean Sino-Nasal Outcome Test (SNOT) scores at each time point from baseline to post-study. Individual patient trajectories are shown in light grey, while the mean scores are represented by the bold blue line. Error bars indicate the standard error (SE) of the mean, and the 95% confidence intervals (CI) are displayed for each time point. The mean, SE, and 95% CI values are annotated above the corresponding time points

radiological status increased from 0 at baseline to 53% post-intervention. Most transitions originated from the One-Sided Sinusitis group ($n=30$), followed by B/L Sinusitis ($n=20$) and Frontal Sinusitis ($n=3$) Fig. 5.

Among patients with B/L Sinusitis ($n=31$), 64.5% ($n=20$) achieved complete normalization. Five improved to the One-Sided category, while five remained unchanged. One patient deteriorated to Frontal Sinusitis, representing the only observed worsening in this subgroup. In the One-Sided Sinusitis group ($n=64$), 30 patients achieved Normal status, whereas 27 (42%) remained stable and 7 experienced progression (5 to B/L Maxillary, 2 to Frontal Sinusitis). All patients with baseline Frontal Sinusitis ($n=5$) transitioned out of this category by study end; three exhibited complete resolution, while two improved to less severe categories.

Comparative interpretation of outcomes

The intervention elicited rapid and meaningful therapeutic benefit. Symptomatic improvement, measured via SNOT scores, was near-complete in most patients, while haematological, liver, and kidney markers remained stable, and ESR and Uric Acid reductions indicate favourable anti-inflammatory and metabolic effects, whereas radiological improvement, though substantial, was more heterogeneous, with a subset showing partial resolution or minor deterioration. Notably, the greatest radiological

recovery occurred in the most severe baseline subgroup (B/L Sinusitis), paralleling the largest symptomatic improvements Fig. 6. This dissociation between patient-reported outcomes and anatomical normalization is consistent with patterns observed in chronic rhinosinusitis, where symptom relief often precedes complete structural recovery. The intervention produced robust, statistically significant, and clinically meaningful symptom relief, accompanied by substantial radiological improvement. These findings support the efficacy of the treatment in both subjective and objective measures of chronic rhinosinusitis.

Safety and clinical findings

The intervention was well tolerated, with no clinically meaningful changes in haematological, liver, or kidney markers. Haemoglobin, total leukocyte count, and differential counts, as well as liver (SGOT, SGPT, Alkaline Phosphatase, Bilirubin) and kidney (Creatinine, Blood Urea) markers, remained stable, showing non-significant p-values (0.124–0.948) and negligible effect sizes (Cohen's $d = -0.111$ –0.155). The 95% confidence intervals included zero, confirming the absence of reliably detectable adverse effects.

Notably, three markers—first-hour ESR, second-hour ESR, and Uric Acid—showed statistically significant and clinically favourable changes. Both ESR measurements

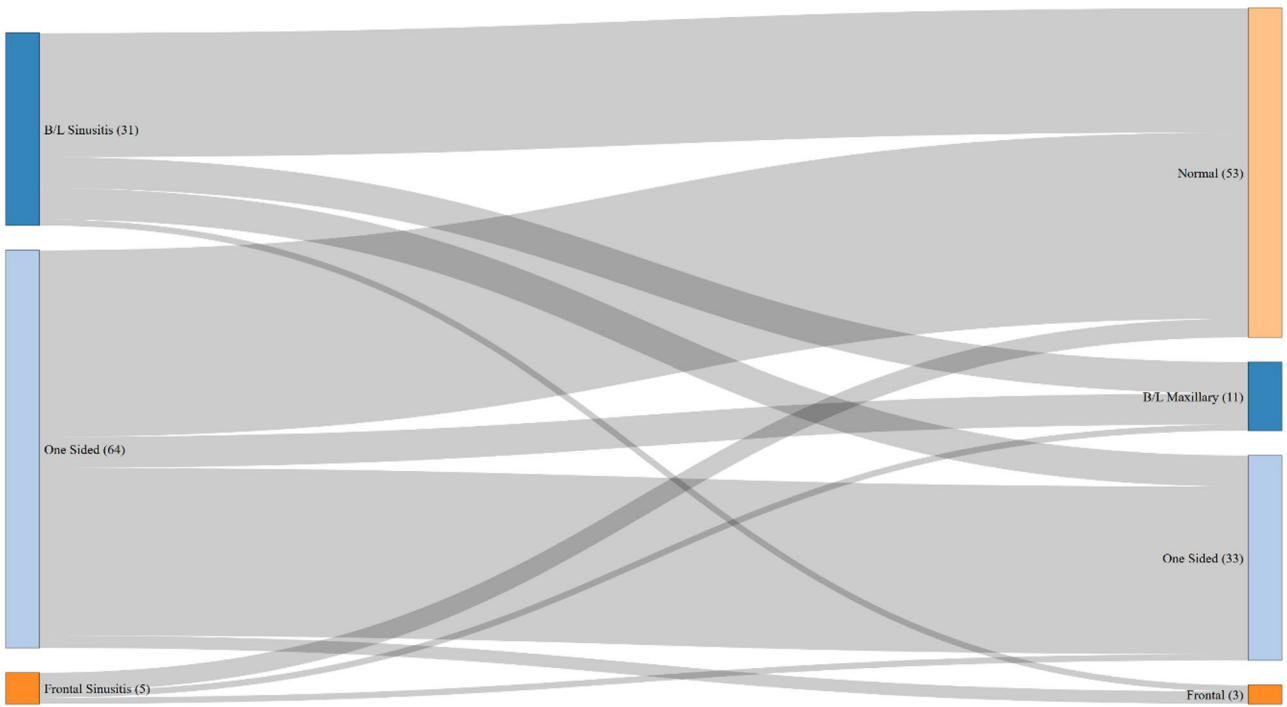


Fig. 5 Represents the pre and post treatment radiographic changes

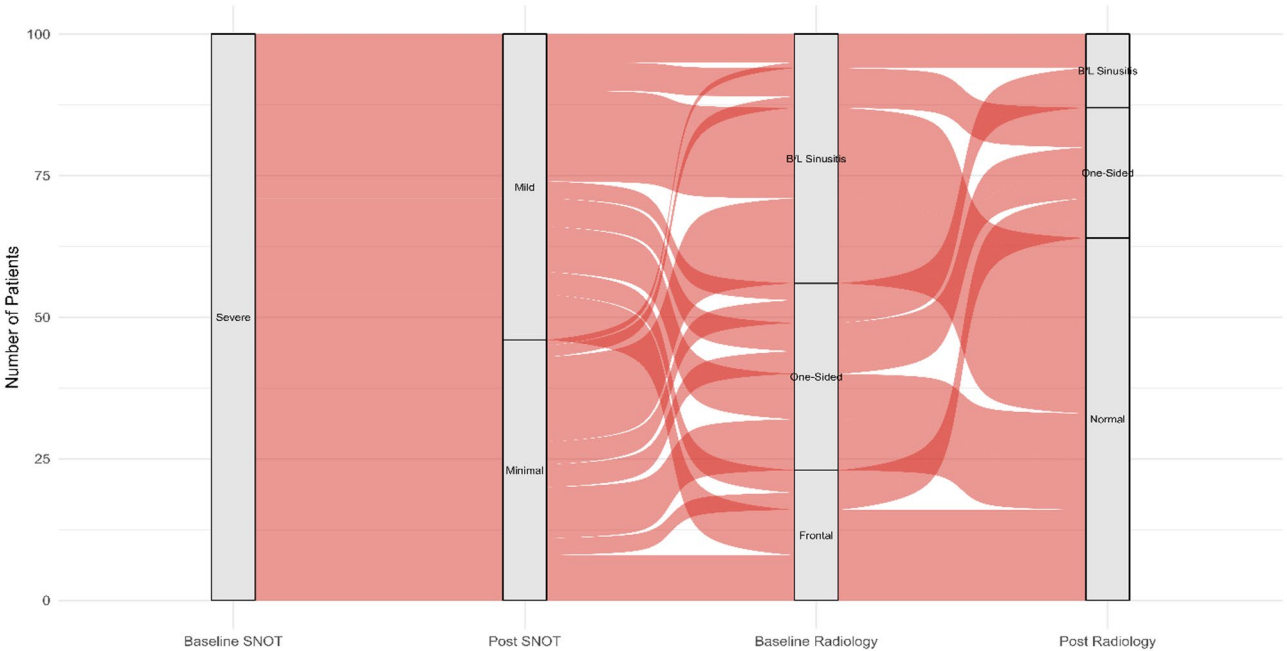


Fig. 6 Integrated Sankey diagram showing pre- and post-intervention sinus involvement. Flows represent the number of patients transitioning between Normal, Bilateral Maxillary, One-Sided Maxillary, and Frontal sinusitis categories. Flow width indicates patient count, and colour intensity reflects severity. The diagram highlights the shift toward less severe or normal sinus status following the intervention, providing a clear visual summary of treatment-related improvements

decreased ($p \leq 0.033$, $d = 0.215\text{--}0.339$), indicating reduced systemic inflammation, while Uric Acid levels declined ($p = 0.007$), reflecting an improvement in metabolic health. These changes highlight therapeutic benefits of the intervention without compromising safety Fig. 7.

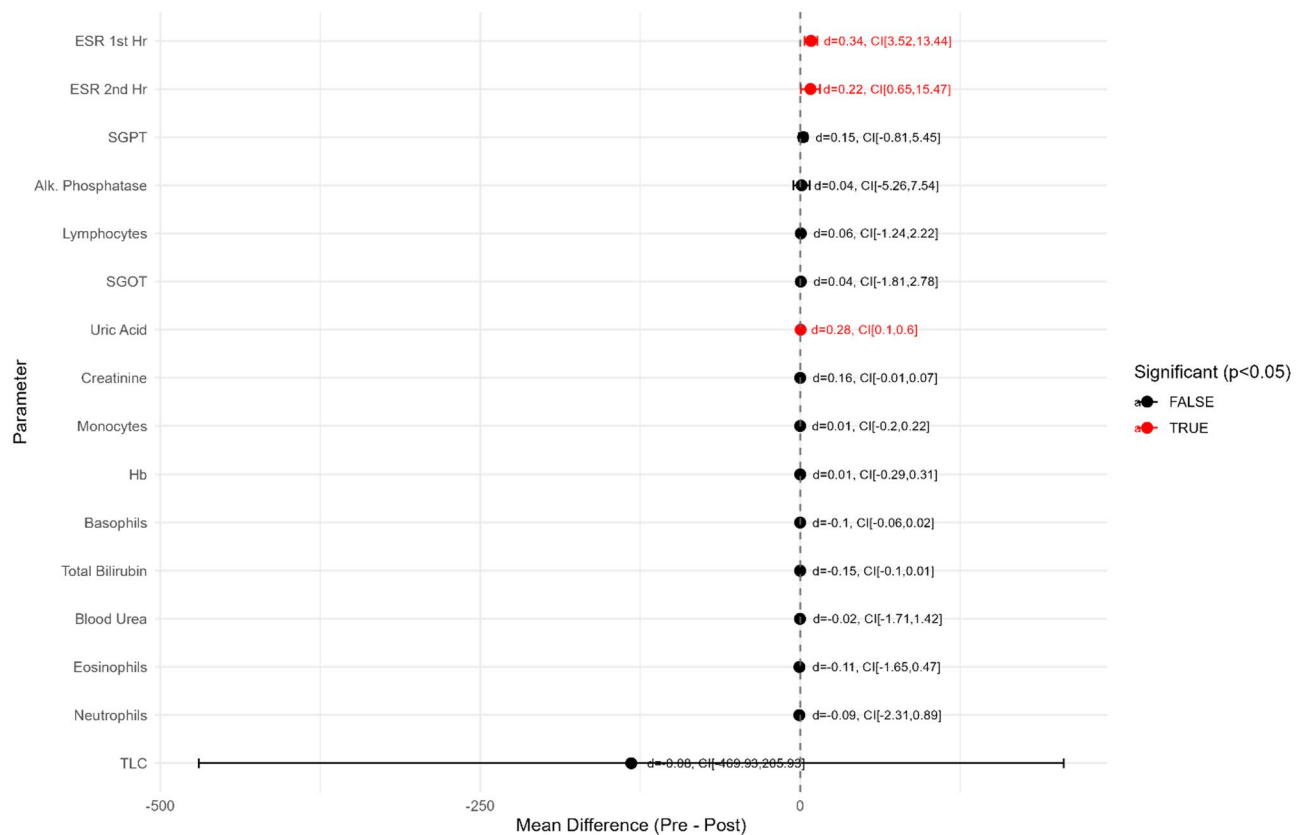


Fig. 7 The plot showing pre- and post-intervention changes in safety and favourable parameters. Mean differences (Pre – Post) are plotted with **95% confidence intervals (CI)** for haematological, inflammatory, liver, kidney, and metabolic parameters. **Red points indicate statistically significant changes ($p < 0.05$)**. Labels display **Cohen's d effect sizes and 95% CI**. Significant reductions in **ESR and Uric Acid** reflect therapeutic benefits, while non-significant changes confirm the **safety profile** of the intervention. Abbreviations: Hb, Haemoglobin; TLC, Total Leukocyte Count; ESR, Erythrocyte Sedimentation Rate; CI, Confidence Interval

Overall, the findings demonstrate a robust safety profile and suggest that the intervention may confer additional anti-inflammatory and metabolic advantages.

Discussion

The present study describes the demographic and clinical characteristics of patients with chronic rhinosinusitis (CRS) and situates these findings within the broader epidemiological literature. A higher proportion of female participants was observed, consistent with previous reports documenting female predominance in CRS across diverse populations [29, 30]. Although the mean age was marginally lower among females, this difference was not statistically significant, suggesting minimal age-related confounding within the study cohort. The predominance of female participants and their relatively younger age at presentation may reflect differences in symptom perception, healthcare-seeking behaviour, or sex-related biological susceptibility, as women have been reported to have a higher risk of CRS compared with men [31].

The clinical presentation was characterized predominantly by nasal obstruction, headache, postnasal discharge, rhinorrhoea, and sneezing, with the maxillary sinus being the most frequently involved site. This aligns with established anatomical and pathophysiological observations, where impaired drainage of the maxillary sinus and osteomeatal complex contributes to disease persistence [32, 33]. Disease duration varied across participants, with a subset—particularly among female patients—reporting symptoms persisting for more than two years, highlighting the chronic and often refractory nature of CRS.

Baseline characteristics, including allergy status, dietary habits, family history, and smoking behaviour, were largely comparable between sexes, indicating relative cohort homogeneity. The high prevalence of allergic manifestations further supports the recognized role of allergic and eosinophilic inflammation in CRS pathogenesis [27]. These baseline observations provide an appropriate clinical context for interpreting subsequent treatment-related findings within this exploratory framework.

Participants demonstrated substantial reductions in SNOT-22 scores during the treatment period, with mean decreases exceeding 30 points—well above the threshold for clinically meaningful improvement¹⁵. These improvements were sustained across follow-up assessments, suggesting that the observed benefits were not limited to a transient effect. This pattern is consistent with prior reports highlighting the potential value of multi-component interventions in modulating chronic inflammatory conditions [28, 34, 35].

The formulation comprises multiple botanicals traditionally used in Unani medicine, including *Lavandula stoechas*, *Emblica officinalis*, *Terminalia chebula*, *Terminalia bellerica*, *Rosa damascena*, *Polypodium vulgare*, *Cuscuta reflexa*, and *Vitis vinifera* [15]. These ingredients exhibit anti-inflammatory, antioxidant, mucolytic, and immunomodulatory properties mediated through pathways such as NF- κ B, STAT, and MAPK signaling [14, 16–20]. Phytochemical constituents, including polyphenols, gallic acid, and ellagic acid, further contribute to modulation of oxidative stress and inflammatory mediators [20, 24, 26]. Experimental evidence supports these effects, with *Lavandula stoechas* demonstrating anti-inflammatory activity in macrophage models [22, 23], *Terminalia* species inhibiting pro-inflammatory signaling [16–18], and *Emblica officinalis* exhibiting antioxidant and mucosal protective effects [19, 20]. Additional components such as *Rosa damascena*, *Polypodium vulgare*, and *Cuscuta reflexa* provide supportive pharmacological actions [24–26].

Taken together, these properties offer a biologically plausible explanation for the observed symptomatic and biochemical improvements; however, these interpretations should be made cautiously, as the study design does not permit definitive causal inference.

Radiological outcomes were broadly consistent with symptomatic improvements. More than half of the participants demonstrated complete sinus normalization by study completion, with the most pronounced recovery observed in bilateral maxillary sinusitis. Improvement was also observed in frontal sinus involvement, suggesting potential benefit in anatomically challenging CRS phenotypes [36]. However, a subset of participants exhibited partial resolution or minor worsening, reflecting the heterogeneity of CRS and the potential need for adjunctive strategies [28]. The observed dissociation between symptom improvement and slower radiological recovery aligns with previous evidence indicating that mucosal healing may lag behind clinical relief [37–40].

The intervention was well tolerated, with no significant changes in haematological, renal, or hepatic parameters. Reductions in ESR and uric acid suggest a potential systemic anti-inflammatory effect. These findings are consistent with the known pharmacological properties of the

formulation's components, including NF- κ B modulation, cytokine suppression, and antioxidant activity [1623, 2629].

Overall, the integrated pharmacological profile—encompassing anti-inflammatory, antioxidant, mucolytic, and immunomodulatory actions—may contribute to the observed clinical, radiological, and biochemical improvements. While these findings provide important preliminary insights, they should be interpreted within the limitations of the study design and considered hypothesis-generating rather than confirmatory.

Conclusion

The findings of the present study suggest that the intervention was associated with clinically meaningful improvements in symptoms, favourable radiological trends, and reductions in inflammatory markers in patients with chronic rhinosinusitis, while maintaining an acceptable safety profile. The observed effects are supported by the known pharmacological properties of the formulation's ingredients, providing biological plausibility to these clinical observations.

However, in view of the open-label, single-arm design and the level of participant attrition, these findings should be interpreted as preliminary and hypothesis-generating. Further well-designed randomized controlled trials with extended follow-up are required to confirm these observations and to better define predictors of treatment response in chronic rhinosinusitis.

Limitations

The findings of this study should be interpreted in light of several limitations. The open-label single-arm design without a control group limits causal inference and raises the possibility of placebo effects. A notable level of participant attrition occurred during follow-up, which may introduce potential bias despite comparable baseline characteristics between completers and non-completers. In addition, the absence of blinding may have influenced subjective symptom reporting. Finally, long-term radiological follow-up was limited, restricting conclusions regarding sustained anatomical resolution. Future randomized controlled studies with longer follow-up are warranted to confirm these observations.

Key takeaways

- Itrifal Ustukhudus was associated with clinically meaningful reductions in SNOT-22 scores, indicating substantial improvement in CRS symptom burden.
- Favourable radiological trends were observed, with sinus normalization in more than half of the participants during the treatment period.

- The formulation demonstrated a reassuring safety profile, with stable haematological, hepatic, and renal parameters, supporting its potential role as a complementary therapeutic option in CRS.

Acknowledgements

We are sincerely thankful to the participants of this study and the Director General, CCRUM, Ministry of Ayush-New Delhi for his valuable support.

Author contributions

Conceptualization: Huma Rafiq, Arif Habib and Shaista Urooj. Data curation: Arif Habib, Arsheed Iqbal, Arjumand Shah. Formal analysis: Arif Habib. Investigation: Arjumand, Arsheed Iqbal, Kounser, Sabiya. Methodology: Huma Rafiq, Arif Habib, Photochemistry: Shaista Urooj and Huma Rafiq. Supervision: Huma Rafiq and Arif Habib. Writing-original draft: Huma Rafiq. Writing-review & editing: Huma Rafiq, Arif Habib.

Funding

The study did not receive any specific external funding. The research work was conducted under the ongoing research activities/projects governed by the Central Council for Research in Unani Medicine-New Delhi, India.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Ethics Committee of Regional Research Institute of Unani Medicine, vide approval number RRIUM/SGR//2016-17-IEC. Written informed consent to participate in the study was obtained from all participants prior to enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Regional Research Institute of Unani Medicine, Naseem Bagh Campus, University of Kashmir, New Delhi, India

²Regional Research Institute of Unani Medicine, D-11, Abul Fazal Enclave, New Delhi, India

Received: 29 December 2025 / Accepted: 9 May 2026

Published online: 02 June 2026

References

- Min HK, Lee S, Kim S, Son Y, Park J, Kim HJ et al (2025) Global incidence and prevalence of chronic rhinosinusitis: a systematic review. *Clin Exp Allergy* 55(1):52–66. <https://doi.org/10.1111/cea.14592>
- Fokkens WJ, Sedaghat AR, Soyka MB, Reitsma S (2024) Recent advances in chronic rhinosinusitis: pathophysiology, treatments, and outcome measures. *Rhinology* 62(6):652–658. <https://doi.org/10.4193/Rhin24.801>
- Kumar N, Brar T, Kita H, Marks LA, Miglani A, Marino MJ et al (2023) Viruses in chronic rhinosinusitis: a systematic review. *Front Allergy* 4:1237068. <https://doi.org/10.3389/falgy.2023.1237068>
- Dickerson TA, Stack TJ, Benaim EH, O'Rourke S, McCain M, Thorp BD et al (2026) Social vulnerability and quality of life in chronic rhinosinusitis. *Laryngoscope*. <https://doi.org/10.1002/lary.70448>
- Khatab OA, Bajaber MA, Alharbi NT et al (2022) Evaluation, complications and treatment of chronic rhinosinusitis. *Int J Community Med Public Health* 9(12):4679–4683
- Hwee J, Lee L, Small M et al (2024) The chronic rhinosinusitis with nasal polyp patient journey. *Allergy Asthma Clin Immunol* 20:17
- Maharani I, Putri GIG (2024) Anatomical variations and their impact on CRS. *Egypt J Otolaryngol*
- Ibn Sina (2010) *Al Qanoon Fil Tib*. Ejaz Publishing House, New Delhi
- Ali ibn al-Abbas al-Majusi (2010) *Kamilus Sanaa*. Idara Kitab-us-Shifa, New Delhi
- Ismail Jurjani (2010) *Zakheera Khawarzam Shahi*. Idara Kitab-us-Shifa, New Delhi
- Khan A (2003) *Al Akseer*. New Delhi
- Kabeeruddin MH (2010) *Akseer-e-Aazam*. Idara Kitab-us-Shifa, New Delhi
- Chin CJ, Scott JR, Lee JM (2025) Diagnosis and management of chronic rhinosinusitis. *CMAJ* 197(6):E148–E154. <https://doi.org/10.1503/cmaj.241101>. PMID: 39965812; PMCID: PMC11835454
- Baliga MS, Dsouza JJ (2021) Amla: phytochemistry and pharmacology. *J Ethnopharmacol* 268:113581
- National Formulary of Unani Medicine (NFUM) (1993) New Delhi: CCRUM
- Dandekar U, Shindikar A, Suryavanshi S, Chandra N (2022) NF-κB and MAPK modulation by *Terminalia chebula*. *Pharmacol Res* PMID:35134979
- Patil SP, Timsina B, Juvekar AR (2017) *Terminalia bellirica* inhibits inflammatory mediators. *Inflammopharmacology* 25(4):427–436 PMID: 28954384
- Ju SW, Lee DG, Yang CH (2018) Anti-inflammatory effects via arachidonic acid pathway. *Inflammopharmacology* 26(1):29–38 PMID: 30003465
- Singh M, Kaur M, Silakari O (2022) Pharmacological insights into *Emblica officinalis*. *Biomed Pharmacother* 146:112553
- Sharma V, Satyavati D, Kumar M (2014) Anti-inflammatory effects of *Emblica officinalis*. *Evid Based Complement Alternat Med*
- Mahboubi M (2022) *Rosa damascena*: applications and pharmacology. *J Tradit Complement Med* 12(6):521–530
- Wei W, Li L, Apostolopoulos V et al (2023) *Lavandula*: phytochemistry and anti-inflammatory activity. *Molecules* 28(1):256
- Yildirim S, Seven I, Seven S et al (2015) Anti-inflammatory activity of *Lavandula stoechas*. *Turk J Biochem* 40
- Stankovic MS et al (2021) Biological activities of *Polypodium vulgare*. *Plants (Basel)* 10(3):526
- Sharma P et al (2022) *Cuscuta reflexa* pharmacology. *J Ethnopharmacol* 282:114615
- Xia EQ et al (2021) Polyphenols from grapes. *Int J Mol Sci* 22(11):6220
- Chen W, Wen Y, Wang J et al (2026) Biologics in chronic rhinosinusitis. *Ther Clin Risk Manag*
- Chowdhury NI et al (2017) Minimal clinically important difference for SNOT-22. *Int Forum Allergy Rhinol* 7(12):1149–1155
- Kim YS et al (2022) Sex-related differences in chronic rhinosinusitis. *Allergy Asthma Immunol Res* 14(5):547–560
- Ference EH et al (2015) Gender differences in chronic rhinosinusitis. *Allergy Rhinol* 6(2):82–88
- Rata Mohan DS, Jawahir S, Manual A, Abdul Mutalib NE, Mohd Noh SN, Ab Rahim I et al (2025) Gender differences in health-seeking behaviour: insights from NHMS 2019. *BMC Health Serv Res* 25(1):900. <https://doi.org/10.1186/s12913-025-13020-0>. PMID: 40611153; PMCID: PMC12224705
- Tan BK, Schleimer RP, Kern RC (2010) Etiology of chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 18(1):21–26
- Rhee CS et al (2021) Environmental factors in chronic rhinosinusitis. *Curr Allergy Asthma Rep* 21(3):14
- Han JK et al (2022) Clinically meaningful change in CRS outcomes. *Laryngoscope* 132(2):265–271
- Lang A et al (2025) Dupilumab and SNOT-22 outcomes. *Sci Rep*
- Wormald PJ (2013) *Endoscopic Sinus Surgery: Anatomy, Three-Dimensional Reconstruction, and Surgical Technique*, 3rd edn. Thieme, Stuttgart
- Bhattacharyya N (2006) Radiographic stage fails to predict symptom outcomes after ESS for CRS. *Laryngoscope* 116(1):18–22 PMID: 16735912
- Smith TL, Litvack JR, Hwang PH, Loehrl TA, Mace JC, James KE et al (2010) Outcomes of sinus surgery: a multi-institutional prospective study. *Otolaryngol Head Neck Surg* 142(1):55–63 PMID: 20115905

39. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S et al (2020) European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 58(Suppl S29):1–464 PMID: 32077450
40. DeConde AS, Soler ZM (2016) Chronic rhinosinusitis: epidemiology and burden of disease. *Am J Rhinol Allergy* 30(2):134–139 PMID: 26867515

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.