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Review Article

## Urticaria (Shara): A Narrative Review of Contemporary and Unani Perspectives

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### Abstract

**Background:** Urticaria (Shara) is a common mast cell-mediated inflammatory skin disorder characterized by transient wheals, angioedema, or both, significantly affecting patients' quality of life. While contemporary management relies on second-generation antihistamines, biologics, and immunomodulatory agents, interest in complementary systems such as Unani medicine has increased because of their holistic therapeutic approach. **Objective:** To critically review the current evidence on the epidemiology, pathogenesis, clinical features, differential diagnosis, and management of urticaria, and to integrate contemporary scientific knowledge with Unani concepts and therapeutic principles. **Methods:** This narrative review integrates classical Unani literature with contemporary peer-reviewed evidence on urticaria, including international guidelines, systematic and narrative reviews, and clinical studies of Unani interventions. Priority was given to contemporary guideline recommendations and controlled clinical studies. No meta-analysis was performed, and the available evidence for Unani interventions was critically appraised with attention to study design, sample size, treatment duration, outcome measures, and limitations. **Results:** Current evidence identifies mast-cell activation, autoimmune mechanisms, and inflammatory mediators as central to chronic urticaria. The 2026 international guideline recommends a stepwise approach beginning with second-generation H1-antihistamines, followed by add-on targeted therapy for patients with inadequate control; omalizumab remains a key evidence-based option, while dupilumab and remibrutinib are incorporated into the evolving therapeutic landscape. Cyclosporine remains an off-label option for selected severe refractory disease. In Unani medicine, Shara is traditionally conceptualized in terms of Fasad-i-Dam and humoral imbalance, with management involving dietotherapy, pharmacotherapy, and regimental therapy. Preliminary controlled studies of selected Unani formulations report improvements in disease activity and quality of life; however, the evidence remains limited by small samples, short follow-up, and heterogeneous interventions. **Conclusion:** Contemporary guideline-directed therapy remains the evidence-based cornerstone of urticaria management. Selected Unani interventions show encouraging but preliminary efficacy signals that warrant rigorous, adequately powered evaluation before they can be recommended as adjuncts to standard care.

**Keywords:** Urticaria; chronic spontaneous urticaria; Shara; Unani medicine; mast cells; antihistamines; omalizumab; quality of life.

## 1. Introduction

Urticaria, known as Shara in Unani medicine, is a common inflammatory skin disorder characterized by the rapid appearance of transient pruritic wheals, angioedema, or both, resulting from mast-cell activation and increased vascular permeability. Individual lesions typically resolve within 24 hours without residual skin changes, although recurrent episodes can significantly impair patients' quality of life. Approximately 20% of the population experiences at least one episode of urticaria during their lifetime, while chronic urticaria, defined by symptoms persisting for more than six weeks, is frequently associated with autoimmune mechanisms.<sup>1,2</sup>

Contemporary management follows a stepwise approach using second-generation H1-antihistamines as first-line therapy, followed by dose escalation, biologic therapy with omalizumab, and immunosuppressive agents such as cyclosporine for refractory disease. Despite these therapeutic advances, a considerable proportion of patients remain inadequately controlled, highlighting the need for safe and effective complementary therapeutic strategies.<sup>2-4</sup>

Within the traditional Unani framework, Shara is conceptualized in terms of Fasad-i-Dam (vitiation of blood) and disturbance of the four humours (Dam, Safra, Balgham, and Sauda). Traditional management emphasizes correction of humoral imbalance (Ta'dil-i-Dam),

evacuation of morbid humours (Istifragh and Tanqiya), dietary regulation (Ilaj bil Ghiza), regimental therapy (Ilaj bil Tadbir), and herbal pharmacotherapy (Ilaj bil Dawa). These concepts represent the traditional Unani explanatory framework and should not be equated directly with established biomedical mechanisms.<sup>5,6,40</sup>

This review critically summarizes the current evidence regarding the epidemiology, immunopathogenesis, clinical manifestations, differential diagnosis, and management of urticaria, while integrating classical Unani concepts with contemporary scientific evidence to identify future directions for integrative management.

## 2. Review Methodology

This narrative review integrates contemporary biomedical evidence with the traditional Unani conceptual framework of Shara. A targeted literature search was updated using PubMed/MEDLINE, Scopus, and relevant publisher and guideline websites. Search terms included combinations of “urticaria,” “chronic urticaria,” “chronic spontaneous urticaria,” “chronic inducible urticaria,” “Shara,” “Unani medicine,” “Nuq-e-Unnab,” “urticaria treatment,” “differential diagnosis of urticaria,” and “urticaria guideline.” Priority was given to international guidelines, systematic reviews, narrative reviews, randomized or controlled clinical studies, and relevant classical Unani texts. Studies were considered for inclusion when they addressed the epidemiology, pathogenesis, clinical features, diagnosis, management, or Unani conceptualization and treatment of urticaria.

Evidence was prioritized according to methodological quality and clinical relevance, with particular attention to randomized or controlled studies of Unani interventions. Because this was a narrative review rather than a systematic review, no formal risk-of-bias meta-analysis or quantitative synthesis was performed. Efficacy and safety claims for Unani interventions are therefore presented cautiously, and traditional Unani concepts are explicitly distinguished from established biomedical mechanisms.

## 3. Epidemiology and Disease Burden

Urticaria is a common mast cell-mediated skin disorder with an estimated lifetime prevalence of approximately

20% in the general population. Chronic urticaria (CU), defined as the recurrence of wheals, angioedema, or both for more than six weeks, affects approximately 0.5–1% of the population. Chronic spontaneous urticaria (CSU) is the most common chronic subtype and predominantly affects women, with peak incidence commonly reported in adulthood.<sup>1-3,7-10</sup>

### 3.1 Psychosocial and Economic Burden

Although urticaria is rarely life-threatening, it imposes a considerable burden on affected individuals and healthcare systems. Persistent pruritus, recurrent wheals, sleep disturbance, fatigue, anxiety, depression, impaired work productivity, and reduced social functioning contribute substantially to deterioration in health-related quality of life (HRQoL).<sup>1-3,7,9-12</sup> Population-based and cohort studies report a consistently higher frequency of anxiety and depression among patients with CSU compared with matched controls, with a bidirectional relationship proposed between psychological distress and disease activity.<sup>39</sup> Routine screening for psychological comorbidity is therefore increasingly advocated as part of comprehensive CSU care.<sup>39</sup>

A substantial proportion of patients with CSU experience clinically important impairment in quality of life, assessed using validated instruments such as the Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). CSU is also associated with increased healthcare utilization, absenteeism, presenteeism, and economic costs, underscoring the importance of early diagnosis, comprehensive disease assessment, and individualized long-term management.<sup>2,3,9-13</sup>

## 4. Classification of Urticaria

Urticaria is classified primarily according to duration and the presence or absence of an identifiable eliciting factor. The 2026 international guideline defines chronic urticaria as recurrent wheals, angioedema, or both for more than six weeks and distinguishes chronic spontaneous urticaria (CSU) from chronic inducible urticaria (CIndU). CIndU is characterized by reproducible symptoms in response to a specific trigger and may require provocation testing for confirmation<sup>2</sup> (Table1).

**Table 1.** Classification of Urticaria According to the 2026 International Guideline

| Classification             | Subtype                             | Characteristics                                                       | Common examples / notes                                                                                                                                                                     |
|----------------------------|-------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Based on duration          | Acute urticaria                     | Wheals, angioedema, or both lasting ≤ 6 weeks                         | Usually associated with infections, drugs, foods, or insect stings                                                                                                                          |
|                            | Chronic urticaria (CU)              | Wheals, angioedema, or both recurring for > 6 weeks                   | Includes chronic spontaneous and chronic inducible urticaria                                                                                                                                |
| Based on eliciting factors | Chronic spontaneous urticaria (CSU) | Symptoms occur spontaneously without an identifiable external trigger | Autoimmune or idiopathic disease; most common chronic subtype                                                                                                                               |
|                            | Chronic inducible urticaria (CIndU) | Symptoms induced by specific physical or environmental stimuli        | Symptomatic dermographism, cold urticaria, delayed pressure urticaria, heat urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, aquagenic urticaria |

Chronic urticaria may present with wheals, angioedema, or both. CSU occurs without a consistent external trigger, whereas CIndU occurs after exposure to a reproducible trigger. Some patients may have both CSU and CIndU, requiring careful clinical assessment and, when appropriate, provocation testing.

## 5. Pathogenesis of Urticaria

Urticaria is a mast cell-driven inflammatory disorder characterized by the rapid activation and degranulation of dermal mast cells. Following activation, mast cells release numerous preformed and newly synthesized inflammatory mediators, which induce vasodilation,

increased vascular permeability, sensory nerve stimulation, and dermal edema, resulting in the characteristic clinical manifestations of wheals, pruritus, and angioedema<sup>1-3,8,14-17</sup> (**Table2**).

**Table 2.** Principal Mast-Cell-Derived Mediators Implicated in Urticaria

| Mediator class              | Examples                                                                                                                    | Principal biological effect                                                             | Ref       |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------|
| Preformed granule mediators | Histamine, tryptase, heparin                                                                                                | Vasodilation, increased vascular permeability, pruritus via H1-receptor activation      | 1-3,15    |
| Lipid-derived mediators     | Leukotrienes (LTC <sub>4</sub> /D <sub>4</sub> /E <sub>4</sub> ), prostaglandin D <sub>2</sub> , platelet-activating factor | Sustained vasodilation and vascular permeability; amplify wheal-and-flare response      | 8,14,17   |
| Cytokines / chemokines      | IL-4, IL-5, IL-6, IL-13, TNF- $\alpha$ , CCL2                                                                               | Recruitment and activation of eosinophils, basophils, and T cells; chronic inflammation | 3,8,16,18 |
| Neuropeptides               | Substance P, CGRP                                                                                                           | Neurogenic inflammation and mast-cell activation via MRGPRX2                            | 15,17,20  |

Current evidence indicates that chronic spontaneous urticaria (CSU) is an immune-mediated disease. Two major autoimmune endotypes have been described. Type I autoimmunity (autoallergy) is mediated by IgE autoantibodies directed against self-antigens, whereas type IIb autoimmunity involves IgG autoantibodies targeting IgE or its high-affinity receptor (Fc $\epsilon$ RI) on mast cells and basophils. Both mechanisms can promote mast-cell activation and persistent inflammatory responses in a proportion of patients with CSU.<sup>1-3,8,15-19</sup>

Besides autoimmune mechanisms, numerous inflammatory and immune cells—including basophils, eosinophils, neutrophils, T lymphocytes, B lymphocytes, macrophages, endothelial cells, and sensory nerve fibers—participate in the pathogenesis of urticaria by releasing cytokines, chemokines, and neuropeptides that amplify and perpetuate cutaneous inflammation. In addition, coagulation pathways, complement activation, and neuroimmune interactions have been implicated in disease progression, reflecting the complex and multifactorial nature of CSU.<sup>3,8,14-19</sup>

Non-immunological factors such as viral and bacterial infections, medications (particularly NSAIDs), foods, physical stimuli, psychological stress, and environmental factors may also activate mast cells through IgE-independent mechanisms, especially via the Mas-related G-protein-coupled receptor X2 (MRGPRX2) pathway. Activation of this receptor results in rapid mast-cell degranulation and contributes to both acute and chronic forms of urticaria, representing a potential therapeutic target for future drug development.<sup>15,17,19-21</sup>

Within the traditional Unani framework, Shara is conceptualized in terms of Fasad-i-Dam (vitiation of blood) and disturbance of humoral equilibrium (Akhlāt Arba'a). Classical Unani descriptions interpret the disease through the framework of humoral imbalance and morbid humours. These concepts represent the

traditional explanatory model and should be distinguished from established biomedical mechanisms of mast-cell activation and mediator release.<sup>5,6,40</sup>

## 6. Clinical Features

Urticaria is characterized by the sudden appearance of pruritic wheals, angioedema, or both, resulting from transient plasma leakage into the superficial dermis. Wheals are well-circumscribed, erythematous or skin-colored, edematous plaques of variable size and shape that typically resolve spontaneously within 24 hours without residual pigmentation or scarring. In contrast, angioedema affects the deeper dermis and subcutaneous tissues, most commonly involving the eyelids, lips, face, tongue, genitalia, and extremities, and may persist for 24–72 hours before complete resolution.<sup>1-3,15,17,23</sup>

Patients with chronic spontaneous urticaria (CSU) usually experience recurrent episodes of intense itching, burning sensation, sleep disturbance, fatigue, irritability, anxiety, and impaired daily activities, all of which contribute significantly to reduced health-related quality of life. Disease activity often fluctuates over time and may be aggravated by infections, emotional stress, medications (particularly nonsteroidal anti-inflammatory drugs), alcohol, heat, pressure, and other physical stimuli.<sup>2,3,9,11,13,23,24</sup>

### 6.1 Differential Diagnosis

The diagnosis of chronic urticaria should be reconsidered when lesions persist for longer than 24 hours, are painful rather than pruritic, leave residual purpura or hyperpigmentation, or are accompanied by systemic manifestations such as fever, arthralgia, or malaise. These features raise suspicion for alternative disorders that mimic urticaria and require further clinical, serological, or histopathological evaluation<sup>2,3,23,25,38</sup> (**Table3**).

**Table 3.** Selected Differential Diagnoses of Urticarial Lesions

| Condition                                           | Distinguishing clinical clue                                                                                    | Typical wheal duration | Key refs |
|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------|----------|
| Urticarial vasculitis                               | Painful/burning rather than pruritic lesions; residual purpura or hyperpigmentation; may have systemic features | > 24 h                 | 23,25,38 |
| Autoinflammatory syndromes (e.g., Schnitzler, CAPS) | Recurrent fever, arthralgia, elevated inflammatory markers; neutrophilic infiltrate on biopsy                   | Variable, often > 24 h | 25,38    |
| Mastocytosis / mast cell disorders                  | Fixed pigmented macules (urticaria pigmentosa), Darier sign, elevated baseline tryptase                         | Persistent lesions     | 3,38     |
| Bullous pemphigoid (urticarial phase)               | Pre-bullous urticarial plaques in older adults; later tense bullae                                              | Persistent, evolving   | 38       |
| Polymorphic eruption of pregnancy                   | Onset in third trimester, often periumbilical, striae-associated                                                | Variable               | 38       |

From the Unani perspective, Shara is clinically characterized by the sudden eruption of elevated erythematous lesions associated with severe itching, burning sensation, and irritation of the skin. The lesions are generally transient and are believed to arise from Fasad-i-Dam (vitiation of blood) and derangement of the humoral equilibrium (Akhlat Arba'a). Depending on the predominance of the affected humour, patients may exhibit variations in the severity of erythema, pruritus, warmth, and burning sensation.<sup>5,6,40</sup>

## 7. Diagnosis

The diagnosis of urticaria is primarily clinical, based on a comprehensive history and physical examination. Key aspects of the history include the onset, duration, frequency, and distribution of wheals; the presence or absence of angioedema; lesion duration (less than or greater than 24 hours); potential precipitating factors such as foods, medications, infections, insect stings, and physical stimuli; family history; associated autoimmune diseases; and the impact of symptoms on the patient's quality of life. Because wheals are transient, patient-taken photographs can provide valuable diagnostic

information when lesions are absent during clinical examination.<sup>1-3,23,26-28</sup>

Acute urticaria usually does not require laboratory investigations unless the clinical history suggests an underlying systemic disorder or specific trigger. In chronic urticaria, routine extensive laboratory testing is not recommended. A limited diagnostic evaluation, guided by the clinical history and examination, may include a complete blood count and inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein. Additional investigations, including thyroid testing, total IgE, antinuclear antibodies, complement studies, infection screening, allergy testing, or skin biopsy, should be reserved for patients in whom the history or examination suggests a specific indication.

Assessment of disease severity, disease control, and quality of life is essential for monitoring treatment response and guiding therapeutic decisions. Current international guidelines recommend the use of validated patient-reported outcome measures, summarized in **Table 4.**<sup>2,9,11,13,26-29</sup>

**Table 4.** Validated Patient-Reported Outcome Measures Used in Urticaria

| Instrument | Purpose                                                                                | Recall period | Key refs |
|------------|----------------------------------------------------------------------------------------|---------------|----------|
| UAS7       | Urticaria Activity Score – daily wheal count and pruritus severity, summed over 7 days | 7 days        | 2,29     |
| UCT        | Urticaria Control Test – patient-reported disease control                              | 4 weeks       | 2,29     |
| AAS        | Angioedema Activity Score – activity in patients with recurrent angioedema             | 28 days       | 2,29     |
| DLQI       | Dermatology Life Quality Index – generic dermatology-specific HRQoL                    | 1 week        | 9,11,13  |
| CU-Q2oL    | Chronic Urticaria Quality of Life Questionnaire – disease-specific HRQoL               | 2 weeks       | 9,11,13  |

In the Unani system of medicine, the diagnosis of Shara is primarily based on clinical evaluation and determination of the patient's Mizaj (temperament), the nature of Fasad-i-Dam (vitiation of blood), dietary habits, environmental exposures, and associated

humoral imbalance (Akhlat Arba'a). Classical Unani physicians emphasize identifying the predominant humour involved and evaluating the patient's general constitution to formulate an individualized treatment plan.<sup>5,6,40</sup>

## 8. Management of Urticaria

The primary goal of urticaria management is to achieve complete symptom control, prevent disease recurrence, and restore the patient's quality of life while minimizing treatment-related adverse effects. Management begins with the identification and avoidance of potential triggers, including medications (particularly nonsteroidal anti-inflammatory drugs), infections, foods, alcohol, emotional stress, and physical stimuli whenever clinically relevant. Patient education, reassurance regarding the generally benign nature of the disease, and regular assessment of disease activity are essential components of long-term management<sup>2,3,13,26-30</sup> (Table 5).

Current international guidance recommends a stepwise approach to chronic urticaria. Standard-dose second-generation H1-antihistamines are first-line therapy because of their efficacy and favorable safety profile. When control is inadequate, the dose may be increased up to fourfold in appropriate patients. Patients who remain inadequately controlled despite high-dose antihistamines should be considered for add-on omalizumab. The 2026 guideline also supports consideration of dupilumab or remibrutinib as add-on treatments in appropriate patients, with the exact place in therapy influenced by regulatory status, availability, prior treatment response, and clinical context.

Cyclosporine remains an off-label option for selected severe disease refractory to licensed therapies and requires careful monitoring.<sup>2,31,32</sup>

The therapeutic landscape has expanded beyond omalizumab. Dupilumab, an IL-4 receptor  $\alpha$  antagonist, and remibrutinib, an oral Bruton tyrosine kinase inhibitor, have demonstrated efficacy in randomized clinical trials and are addressed in the 2026 international guideline. Remibrutinib received US FDA approval in September 2025 for adults with CSU who remain symptomatic despite H1-antihistamine treatment. Dupilumab received US FDA approval in April 2025 for patients aged 12 years and older with CSU who remain symptomatic despite H1-antihistamine treatment. Other investigational approaches, including anti-KIT therapies such as barzolvolimab, remain under evaluation.<sup>2,33,34,36</sup>

A short course of systemic corticosteroids may be considered for severe acute exacerbations when rapid symptom control is required. Prolonged or repeated corticosteroid therapy should be avoided because of its well-established systemic adverse effects. Regular assessment of disease activity and treatment response using validated instruments such as UAS7, UCT, and DLQI is recommended to facilitate individualized treatment decisions and optimize long-term outcomes.<sup>2,13,26,29,31,36</sup>

**Table 5.** Contemporary Stepwise Pharmacological Management of Chronic Urticaria

| Step                        | Recommended treatment                             | Clinical recommendation                                                                                               | Ref     |
|-----------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------|
| Step 1                      | Standard-dose second-generation H1-antihistamines | First-line treatment                                                                                                  | 2       |
| Step 2                      | Increase H1-antihistamine dose up to fourfold     | For inadequate control on standard dose                                                                               | 2       |
| Step 3                      | Omalizumab                                        | Add-on treatment for patients with chronic urticaria uncontrolled by high-dose second-generation H1-antihistamines    | 2,31,32 |
| Additional targeted options | Dupilumab; remibrutinib                           | Add-on options addressed in the 2026 international guideline; regulatory status and availability vary by jurisdiction | 2,33,34 |
| Refractory disease          | Cyclosporine                                      | Off-label option for selected severe disease refractory to licensed treatments; specialist supervision required       | 2,31    |
| Investigational therapies   | Barzolvolimab and other emerging agents           | Clinical evaluation ongoing; not yet established as standard therapy                                                  | 2,36    |

## 9. Unani Management and Clinical Evidence

The management of Shara in Unani medicine is traditionally based on restoring the equilibrium of the four humours (Akhlat Arba'a) and addressing Fasad-i-Dam. These principles belong to the traditional Unani explanatory and therapeutic framework and should not be equated directly with established biomedical mechanisms. The therapeutic aim is to relieve symptoms, address the patient's constitutional factors,

and reduce recurrence according to Unani principles.<sup>5,6,40</sup>

The therapeutic strategy of Unani medicine comprises three principal modalities: Ilaj bil Ghiza (dietotherapy), Ilaj bil Dawa (pharmacotherapy), and Ilaj bil Tadbir (regimental therapy).

Dietary management involves avoiding foods believed to aggravate humoral imbalance, such as spicy, fried, fermented, and excessively hot foods, while encouraging cooling and easily digestible foods including barley

water, pomegranate, cucumber, bottle gourd, and buttermilk. Adequate hydration and regulation of lifestyle habits are also considered important components of management.<sup>5,35,37</sup>

Ilaj bil Dawa (pharmacotherapy) includes herbal and mineral preparations traditionally described as possessing Musaffiyat-i-Dam (blood purifying),

Mubarrid (cooling), Muhallil-i-Waram (anti-inflammatory), Daf'-i-Hassasiyat (antiallergic), or Musakkin-i-Hikka (antipruritic) properties. **Table 6** summarizes selected formulations described in classical and contemporary Unani literature, together with their traditionally attributed actions and any available clinical or pharmacological evidence.<sup>5,6,22,35,37,40,41</sup>

**Table 6.** Selected Unani Formulations and Single Herbs Traditionally Used in Shara (Urticaria)

| Formulation / herb                                                      | Traditionally attributed property                                               | Composition / notes                                                                                                         | Ref      |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------|
| Nuqu-e-Unnab (± Sikanjabeen-e-Sada)                                     | Musaffi-i-Dam, Mubarrid, antipruritic                                           | Ziziphus jujuba-based decoction; evaluated in a randomized single-blind trial against levocetirizine                        | 6,22     |
| Herbal Combination of Unani Medicine (HCUM)                             | Anti-allergic, anti-inflammatory, antioxidant (attributed to phytoconstituents) | Rosa damascena, Bambusa arundinacea, Cinnamomum camphora, Mentha arvensis                                                   | 6        |
| Sharbat Unnab / Sharbat Unnab wa Banafsha                               | Mubarrid, Musaffi-i-Dam                                                         | Ziziphus jujuba and Viola odorata based syrup                                                                               | 5,35     |
| Sharbat Sandal                                                          | Mubarrid (cooling), Musakkin-i-Hikka                                            | Santalum album (sandalwood) based preparation                                                                               | 5,35     |
| Pitkiryā (poly-herbal)                                                  | Daf'-i-Hassasiyat, anti-inflammatory                                            | Lavandula stoechas, Acorus calamus, Rauwolfia serpentina, Nardostachys jatamansi, Fumaria officinalis, Achillea millefolium | 41       |
| Luab-e-Behidana / Sheera-e-Unnab / Sheera-e-Sandal with Sharbat Nelufar | Ta'dil-i-Dam (correction of blood humour)                                       | Combined mucilaginous and cooling preparation, applied per classical Unani texts                                            | 35,37,40 |

Ilaj bil Tadbir (regimental therapy) includes procedures such as Fasd (venesection) and Hijama (cupping therapy), which are described in classical Unani literature. Contemporary clinical evidence supporting these procedures specifically for urticaria is limited; therefore, they should be presented as traditional practices rather than evidence-established treatments for chronic urticaria.

The available controlled clinical evidence for Unani interventions is promising but preliminary. Two randomized controlled studies identified in the literature evaluated specific Unani formulations and reported improvements in disease activity and quality-of-life measures. However, both studies were relatively small and short in duration, and the interventions and comparators differed, limiting direct comparison and generalizability.<sup>6,22</sup> A broader systematic review of herbal remedies for urticaria similarly concludes that, despite encouraging preclinical and early clinical signals, standardized formulations and larger controlled trials are needed before herbal and Unani interventions can be integrated confidently into mainstream care.<sup>41</sup>

## 10. Critical Appraisal of Unani Clinical Evidence

Conventional pharmacotherapy remains the evidence-based cornerstone of urticaria management. In contrast, the Unani evidence base consists mainly of small, single-

center controlled trials. The 2021 randomized study of a herbal combination of Unani medicine enrolled 42 patients, of whom 40 completed four weeks of treatment; the study reported greater reductions in UAS7 and CU-Q2oL scores with the Unani formulation than with levocetirizine. A 2025 randomized single-blind trial of Nuqu-e-Unnab with Sikanjabeen-e-Sada enrolled 60 patients and reported reductions in UAS7 and DLQI over six weeks, with efficacy reported as comparable to levocetirizine. These findings are encouraging but should not be interpreted as establishing equivalence, superiority, or long-term safety compared with guideline-directed therapy.<sup>6,22</sup>

The main limitations of the available Unani trials include small sample sizes, single-center designs, short treatment periods, heterogeneous formulations and dosing regimens, limited long-term follow-up, and limited independent replication. In addition, some studies were open-label or analyzed per protocol, which may introduce bias. Future studies should use adequately powered multicenter randomized designs, prospectively registered protocols, standardized formulations with quality-control data, predefined outcomes, appropriate blinding where feasible, intention-to-treat analyses, and systematic reporting of adverse events.

For Nuqu-e-Unnab, the 2025 trial compared the Unani regimen with levocetirizine and reported similar reductions in UAS7 and DLQI over six weeks. Adverse effects were reported in both groups. The findings

support further investigation but do not establish long-term safety, disease modification, or superiority over standard therapy.

**Table 7.** Clinical Evidence for Selected Unani Interventions in Urticaria

| Intervention                                    | Design                                    | Participants                | Duration | Comparator              | Main outcomes                                                                           | Key limitation                                                       |
|-------------------------------------------------|-------------------------------------------|-----------------------------|----------|-------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Herbal combination of Unani medicine (HCUM) [6] | Randomized, open-label controlled trial   | 42 randomized; 40 completed | 4 weeks  | Levocetirizine 5 mg     | Greater reductions in UAS7 and CU-Q2oL in the HCUM group                                | Small, single-center, open-label; per-protocol analysis              |
| Nuqu-e-Unnab + Sikanjabeen-e-Sada [22]          | Randomized, single-blind controlled trial | 60; 30/group analyzed       | 6 weeks  | Levocetirizine 5 mg/day | Significant reductions in UAS7 and DLQI in both groups; efficacy reported as comparable | Small, single-center; short follow-up; formulation-specific evidence |

Overall, the current evidence supports describing selected Unani interventions as potentially useful complementary approaches that warrant further study, rather than as replacements for guideline-directed therapy. Future research should prioritize standardized formulations, mechanistic studies, multicenter trials, longer follow-up, transparent adverse-event reporting, and evaluation of clinically meaningful patient-reported outcomes.<sup>6,22,41</sup>

## 11. Integrative Perspectives and Future Directions

●Standardization: chemical fingerprinting and quality-control data for Unani formulations to ensure batch-to-batch reproducibility.

●Mechanistic studies: preclinical evaluation of candidate anti-inflammatory, antihistaminic, and mast-cell-stabilizing activity of key Unani herbs (e.g., *Ziziphus jujuba*, *Santalum album*).

●Adequately powered multicenter randomized trials with intention-to-treat analysis, prospectively registered protocols, and validated outcome measures (UAS7, UCT, DLQI, CU-Q2oL).

●Transparent, systematic adverse-event reporting and long-term safety follow-up.

●Clear communication to patients that Unani interventions should complement, and never replace, guideline-directed therapy for moderate-to-severe or refractory disease.

Where future trials establish reproducible efficacy and an acceptable safety profile, selected Unani interventions may have a role as adjunctive options for mild disease or for patients seeking complementary approaches alongside standard antihistamine therapy, always under appropriate clinical supervision.<sup>6,22,41</sup>

## 12. Conclusion

Urticaria is a common mast-cell-driven disorder with substantial effects on symptoms, daily functioning, and quality of life. Contemporary management is guided by clinical diagnosis, differential exclusion of urticarial mimics, assessment of disease activity and control, and a stepwise therapeutic strategy centered on second-generation H1-antihistamines and targeted therapies for patients with inadequate control. The 2026 international guideline provides the current framework for classification, diagnosis, and treatment.<sup>2</sup>

From the Unani perspective, Shara is traditionally conceptualized through Fasad-i-Dam and humoral imbalance, with treatment approaches including *Ilaj bil Ghiza*, *Ilaj bil Dawa*, and *Ilaj bil Tadbir*. Available clinical studies of selected Unani formulations show encouraging improvements in disease activity and quality of life, but the evidence remains preliminary and is insufficient to replace guideline-directed therapy.<sup>5,6,22,40</sup>

The principal priority for future research is rigorous evaluation of Unani interventions using standardized formulations, multicenter randomized controlled trials, appropriate comparators, longer follow-up, and robust safety monitoring. Integrative use may be considered where appropriate, provided that established evidence-based treatment is not displaced by interventions whose efficacy and safety remain uncertain. Clear distinction between traditional theoretical concepts and experimentally established mechanisms will strengthen the scientific credibility of future integrative research.

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