Original Article

Jujube Oxymel for the Treatment of Chronic Spontaneous Urticaria: Efficacy and Safety

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Abstract

Background: Chronic spontaneous urticaria (CSU) is a challenging disorder that severely impacts the quality of life. The current study objective was to evaluate the efficacy and safety of jujube oxymel (JO) for treating CSU.

Materials and Methods: In this randomized double-blind controlled trial, 92 patients (aged 12–65) with CSU were randomly allocated to JO or placebo groups. They received 30cc of each syrup three times daily with 10 mg cetirizine for 28 days, subsequently taking 10 mg cetirizine alone for the next 4 weeks. Outcomes were evaluated using the weekly urticaria activity score (UAS-7) and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL).

Results: After four weeks, the UAS-7 score mean and standard deviation in the JO group significantly decreased to 10.89 ± 4.87 compared to the placebo group at 15.06 ± 7.55 (*P*: 0.002). In the follow-up period, JO group participants achieved a score of 10.28 (4.67), while a significant increase occurred in the control group (18.33 ± 6.29) (*P* = 0.001). On day 28, there was a notable improvement in the quality of life within the JO group ($P < 0.05$). By the eighth week, both groups experienced an increase in CU-Q2oL score, but the changes in the control group were statistically significant (18.09 (5.96) vs 41.31 (10.34) (*P*: 0.001).

Conclusion: JO, as part of integrated therapy, exhibited potentially longer-lasting efficacy than cetirizine alone, contributing to enhanced quality of life and increased patient satisfaction due to minimal side effects.

Keywords: Chronic urticaria, jujube oxymel, Persian medicine

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Introduction

Urticaria is an inflammatory skin disease characterized by the development of pruritic, elevated, erythematous, and flare-type hives of varying sizes affecting nearly 20% of the general population. About 50% of patients have angioedema, the erythema or swelling of the lower dermis, and subcutis or mucous membranes with urticaria.[1-3] Although the disease is often self-limiting, in chronic urticaria, the lesions persist or recur for more than 6 weeks. The underlying causes of chronic urticaria which affected 1–2% of cases almost are not identified. Consequently, it is called chronic spontaneous urticaria (CSU) where there is no specific eliciting factor involved.[1,4] The release of inflammatory mediators from mastocytes, such as histamine, platelet activation factor, and cytokine, appears to be the cause of vasodilation, plasma extravasation, and cell recruitment in the formation of urticaria lesions. Also, autoantibodies to immunoglobulin E (IgE) on

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both mast cells and basophils and elevated levels of circulating proinflammatory cytokines like tumor necrosis factor-α and interleukins have been reported in patients with CSU.[1,4,5] Due to the complexity of the pathophysiology of chronic urticaria, the major option in therapies aimed at relieving symptoms is to reduce the effect of mast cell mediators.

The second-generation H1 antihistamines and their administration up to 4 times in unresponsive patients are recommended as first- and second-line treatments in chronic urticaria. Also, omalizumab, ciclosporin A, leukotriene antagonists, and systemic glucocorticosteroids are useful as supplementary therapies in refractory cases to high doses of H1-antihistamines.[1,5,6] While medical therapies have been almost as effective at controlling symptoms, high medication costs, adverse effects, and possible symptom recurrence pose a major limitation to patients.[3,7]

CSU often compromises the patient's quality of life and is associated with multiple physical and psychological comorbidities such as depression and anxiety.[8,9] It negatively impacts family structures, compromising performance at work, school, and even leisure activities. Therefore, unmet medical demands to control urticaria are always required.[7] Hence, complementary and alternative medicine (CAM) particularly Persian medicine (PM) could offer a possible option to provide efficient and sustainable treatments in integration with conventional medicine.

The humor-based PM concepts of two types of skin lesions, *Shara* and *Mashara*, have similarities with urticaria and angioedema, respectively.[2,10] In inflammatory skin diseases, the presence of excessively hot substances changes the normal texture of the humor in the body. When the abnormal hot humor and its vapors move quickly to the pores of the skin for excretion, pruritus-raised lesions occur.[2]

Jujube, the fruit of *Ziziphus jujube* (ZJ) Mill belongs to the Rhamnaceae family, also known as red date or Chinese date is a famous vital food that grows all over the world, especially in Asia.[11,12]

Anxiolytic, neuroprotective, antioxidant, anticancer, antiinflammatory, immunomodulatory activity, respiratory, liver, and gastrointestinal protective activities are some of its different pharmacological effects.[11,13] PM scholars believe that Jujube or *Annab* acts as a blood purifier, hematopoietic, antipruritus, expectorant, cough suppressant, antiasthmatic, laxative, and hepatoprotective. In skin inflammatory conditions like urticaria, jujube helps control inflammation and the heat of the blood.[14-16] Accordingly, the current study is designed to assess the effectiveness and safety of JO in chronic spontaneous urticarial through a randomized clinical trial.

Materials and Methods

Study design

This study was a randomized, placebo-controlled, double-blind clinical trial conducted on patients with chronic idiopathic urticaria in the dermatology and allergy clinic of Rasool Akram Hospital complex and PM clinics under the supervision of the Iran University of Medical Sciences (IUMS) from May 2020 to April 2021. Dermatologists and PM physicians recruited the participants through clinical visits, considering their inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria included being diagnosed as chronic idiopathic urticaria by a dermatologist, ages from 12 to 65 years, not using any antiurticaria medications at least one week before enrollment, and signing informed consent. Patients with pregnancy and breast-feeding, severe angioedema, uncontrolled systemic diseases, such as cardiovascular, respiratory, hematologic, renal, liver, autoimmune, endocrine, and infectious diseases, sensitivity to antihistamine drugs as well as sensitivity to Jujube fruit were excluded.

Randomization

In the current study, permuted block randomization was used. First, all possible combinations of blocks were created with a block size of 4. Then, these blocks were numbered and randomly selected for the generation of random sequences before the start of the intervention. The trial administrator, uninvolved in clinical intervention or evaluation, conducted the randomization and allocation processes using surrogate names (A and B) stored securely in a box. Complete blinding of physicians, pharmacists, project managers, and participants was maintained throughout the trial. Jujube syrup and placebo were poured into containers of the same shape and color and the same label was placed on them.

Drug preparation

Jujube oxymel (JO) is manufactured by "Sobhomid Noor" (Zhanis) Company (Tehran, Iran). It obtained the license of the Iranian Food and Drug Organization with the Iranian registration code (IRC) "9878642325340134 " and was produced under the standards of this organization.

The JO's preparation formula was made according to the suggested formula from Qarabadin-e-Kabir, one of the most reliable and authoritative sources of PM, and consists of the Jujube fruits, honey, grape vinegar, and rose water.[17] The simple syrup as a placebo was made out of purified water and sucrose according to the British Pharmacopoeia method.[18,19]

Intervention

All eligible participants at the beginning of the study filled out the informed consent. Vital signs and baseline data including age, sex, occupation, weight, marital status, etc., were recorded.

Patients, randomly assigned to JO or placebo groups, received 30cc of each syrup three times daily and 10 mg cetirizine once daily for the initial 28 days, followed by 10 mg cetirizine alone daily until day 56.

Outcomes

Primary outcomes

The primary outcome, measuring urticaria symptom severity, utilized the well-validated self-administered questionnaire known as the urticaria activity score (UAS).

The basic level of this criterion on the first day of the study was recorded from 0 to 6 based on the severity of pruritus and the number of wheals of each patient. The total scores of UAS during each week were measured by a validated benchmark called UAS-7 to a score between 0 and 42 (daily score from 0 to 6 is summarized over one week) at the end of weeks 1, 4, and 8.[1,20]

Also, on days 0, 28, and 56, the validated Persian version of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) was used to evaluate the patient's quality of life and gave a score between 0 and 92. A higher value indicated a more negative impact of urticaria on the quality of life (QOL).[1,21]

The patient's satisfaction level with the treatment was measured by a range of 0–4 (completely satisfied, somewhat satisfied, dissatisfied, completely dissatisfied, and no opinion) at the end of the intervention.

It should be noted that due to budget constraints and the coronavirus pandemic in the country, the laboratory test evaluation was not accomplished.

Secondary outcomes

Assessment of safety and adverse events

The possible side effects of the medications, including fatigue, drowsiness, abdominal pain, nausea, vomiting, and flatulence, under version 5 of the Common Terminology Criteria for Adverse Events, were asked or reported by the patients at the end of each follow-up session or any time they happened.[22] In cases where complications interfered with the patient's health, only the classical treatment was continued under the supervision of a dermatologist.

Ethical consideration

The informed consent form was obtained from all participants. The trial was conducted under the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the IUMS (N# IR.IUMS.REC.1399.152) and was registered at the Iranian Registry of Clinical Trials (N# IRCT20200201046328N1). This research followed the CONSORT 2010 statement.[23,24]

Statistical analysis

Sample size estimation

After a clinical trial assessing the impact of Chinese herbal medicine on chronic urticaria,[25] a sample size of 48 participants per arm was determined to detect approximately a 30% improvement in the active treatment group. With a planned 10% dropout rate, 106 enrollments were targeted in a 1:1 ratio between the control and intervention groups. These parameters ensure an 80% power at a significance level of 0.05.

Statistical methods

Qualitative data were presented as percentage and frequency, while quantitative data were expressed as mean ± SD. Qualitative variable associations were assessed using the Chi-square or Fisher's exact test. Comparison of means involved the use of the Student *t*-test or Mann–Whitney test for two groups and the ANOVA test for more than two groups. A significance level of α: 0.05 was considered statistically significant. Data analysis was performed using SPSS (Statistical Package for the Social Sciences) software version 26.

Results

Between May 2020 and April 2021, 120 volunteer candidates were assessed and 106 individuals were randomized and allocated to either the JO or control group. Fifty-one participants in each group received cetirizine with either JO or placebo from days 0 to 28. In the JO group, four participants were excluded due to pregnancy, travel, and coronavirus infection. Also, six patients in the control group were lost because of traveling and coronavirus infection and not answering the phone.

The coronavirus pandemic and its various waves in the country caused many problems with the recruitment and follow-up of patients. Therefore, some of the participants missed the follow-up phase. Finally, 25 patients in the intervention group and 20 in the control group finished the trial and analyzed. Figure 1 shows the flow diagram of the study in detail.

Baseline characteristics

Considering the simultaneous conduct of the study and the COVID-19 pandemic and many limitations in visiting patients, more women than men were willing to participate. Thus, the number of females in the intervention and control groups was higher: 42 (89.3%) vs. 5 (10.6%) and 39 (86.6%) vs. 6 (13.3%), respectively, and no remarkable distinction was observed among the examined groups (*P*: 0.52, *P*: 0.47).

In terms of other baseline characteristics, no statistically significant distinctions were observed between the JO and control groups, involving factors such as patient age, body mass index (BMI), duration of urticaria, and comorbidities like angioedema, pain, and constipation. More information about these values are shown in Table 1.

Primary outcome

At the baseline, there was no statistical difference in the mean UAS between the two groups (*P*: 0.118). After the fourth week of therapy, the mean UAS reached 1.44 (0.95) and 3.40 (0.68) in the intervention and control groups, respectively; this disparity reached statistical significance (*P*: 0.001). Regarding the change score from the baseline to the end of the fourth week, a significant decreasing trend in both groups was observed (*P*: 0.001).

At the end of the first week, the mean and standard deviation of the UAS-7 score in the JO group reached 19.61 (6.90) and decreased significantly to 10.89 (4.87) at 28 days. Also, the UAS-7 in the participants, who could finish the follow-up period, reached 10.28 (4.67) at 56 days (*P*: 0.001).

In the other group, the mean score slightly decreased from 17.66 (6.54) at baseline to 15.06 (7.55) at 28 days, which was

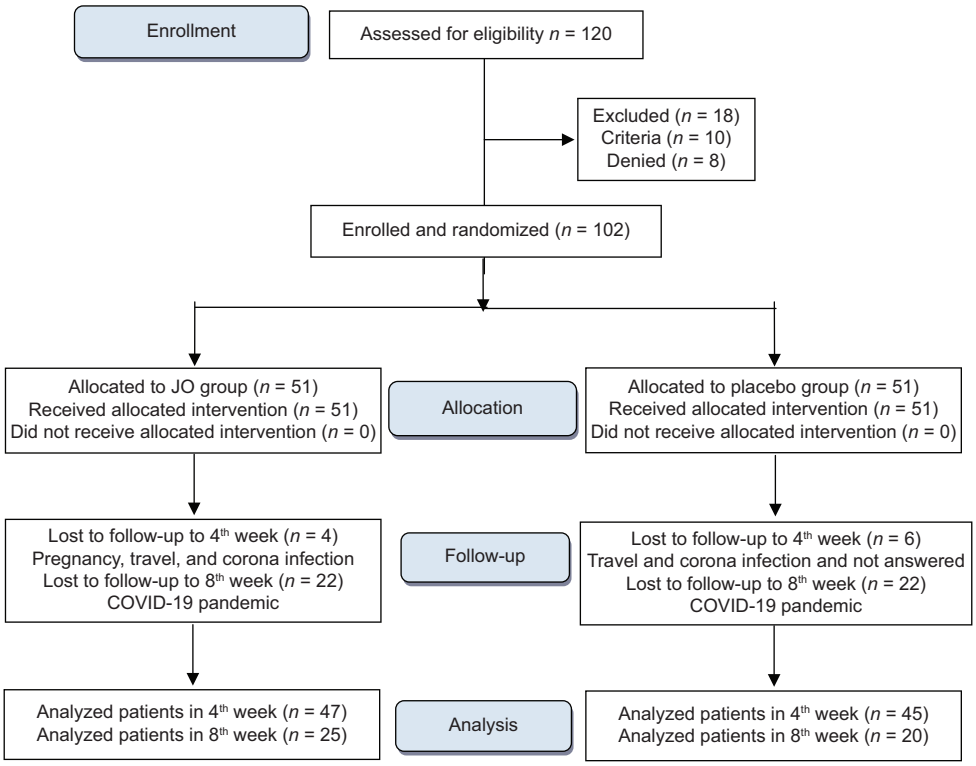

Figure 1: CONSORT diagram showing patient flow

Table 1: Baseline characteristics of understudied cases

Variable	Jujube oxymel *n*=51	Control *n*=51	*P*
Age (years)	36.79 (8.72)	39.13 (11.82)	0.32†
BMI (kg/m^2)	25.76 (4.06)	25.05 (2.58)	0.58†
Gender *n* (%)			
Female	42 (89.3%)	39 (86.6%)	0.52*
Male	5 (10.6%)	6 (13.3%)	0.47*
Duration of urticaria (years)	4.16 (5.47)	4.46 (5.20)	0.76†
Comorbidities *n* (%)			
Angioedema	17 (36.17%)	17 (37.77%)	0.87*
Pain	18 (47%)	15 (33.33%)	0.62*
Aggravation of the disease at night	33 (70.21%)	32 (71.11%)	0.925*
Genitourinary problems	23 (48.93%)	23 (51.11%)	0.83*
Constipation	26 (55.31%)	27 (60%)	0.65*
Gastrointestinal problems except constipation	30 (63.82%)	26 (57.77%)	0.55*
Malaise and fatigue	23 (48.93%)	26 (57.77%)	0.39*
Respiratory problems (nasal discharge)	27 (57.44%)	21 (46.66%)	0.30*

SD: Standard deviation, BMI: Body mass index. Statistics were evaluated using Chi-square for qualitative variables and the Mann–Whitney test to compare two means. *Chi-square test. †Mann–Whitney test

not significant (*P*: 0.800). However, in the eighth week, a significant increase value of 18.33 (6.29) was observed in the patients who finished the study (*P*: 0.001).

In general, on day 28, participants in the JO group experienced prominent symptom relief compared to the placebo group (10.89 ± 4.87 vs. 15.06 ± 7.55) (*P*: 0.002). By day 56, the UAS-7 score in the placebo group was notably elevated compared to the intervention group (10.28 ± 4.67 vs 18.33 ± 6.29) (*P* = 0.001) [Table 2 and Figure 2].

Quality of life and patient satisfaction

At the baseline, the mean of the CU-Q2oL was not statistically different between the two groups (*P*: 0.31). In the fourth week, these scores reached 17.57 (7.01) and 28.62 (9.75) in the JO and control groups, respectively (*P*: 0.001). Regarding the score changes, the life quality improvement in the JO and control groups was observed as statistically significant (*P*: 0.001). On day 56, the CU-Q2oL score of patients who completed the study slightly increased in the intervention

group at 18.09 (5.96), but this change in the control group at 41.31 (10.34) was statistically significant (*P*: 0.001).

After four weeks, participants in the JO group were more satisfied than the other group (3.02 (0.765) vs. 2.17 (1.00), (*P*: 0.001) [Table 3 and Figure 3].

Secondary outcome

The incidence of drowsiness and fatigue was significantly lower in the intervention group compared to the control group 0 (0%) vs. 16 (35.55%) and 2 (4.2%) vs. 7 (15.55%), respectively (*P*: 0.001 and *P*: 0.01). In the JO group, just five patients had complications such as bloating, nausea, and fatigue, which were not significantly different from the control group. No notable variations in the occurrence of other adverse events were observed between the two groups [Table 4].

Discussion

CSU severely impairs the quality of life and affects up to 1% of the population. The unknown pathogenesis of urticaria, especially in chronic cases, has caused the existing treatment methods to reduce or stop the symptoms in most cases temporarily. In this way, patients are inevitably given multiple medications with higher doses, longer duration, and more side effects.[1,3,4,6] Considering these facts, there are numerous trends, in searching for and evaluating safe therapeutic options such as CAMs with more effective or additive response rates.[3,6]

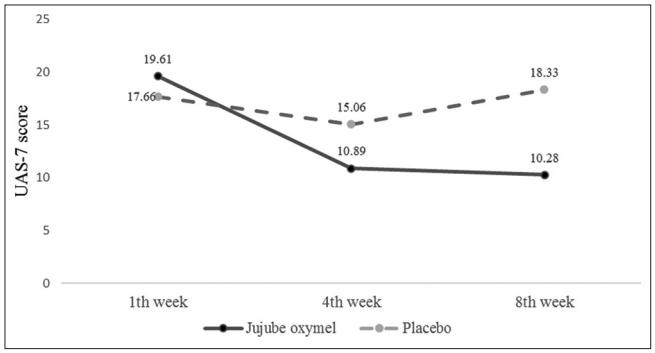

Figure 2: The trend of UAS-7 score during the study

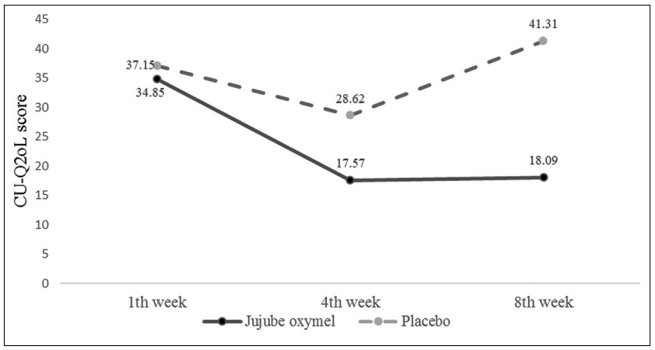

Figure 3: The trend of CU-Q2OL score during the study

Table 2: Compare Urticaria Activity Scores among understudied cases

Variable	Time	JO Mean (SD)	Control Mean (SD)	*P* between groups
UAS	Baseline	4.34 (0.96)	4.64 (0.88)	0.118†
	End of 4th week	1.44 (0.95)	3.40 (0.68)	0.001†
	P within groups‡	0.001	0.001	
UAS-7	1st week	19.61 (6.90)	17.66 (6.54)	0.16†
	4th week	10.89 (4.87)	15.06 (7.55)	0.002†
	8th week	10.28 (4.67)	18.33 (6.29)	0.001†
	P (4th week–1st week)†	0.001	0.800	
	P (8th week–4th week)†	0.642	0.001	
	P within groups‡	0.001	0.001	

Data presented as mean (standard deviation). UAS: Urticaria Activity Score, SD: Standard deviation, JO: Jujube oxymel. Statistics were evaluated using the Mann–Whitney test to compare two means and ANOVA for more than two means. †Mann–Whitney test. ‡ANOVA test

Table 3: Comparison of CU-Q2oL scores at different times between two groups

CU-Q2oL	Time	JO Mean (SD)	Control Mean (SD)	*P* between groups
P within groups‡	Baseline	34.85 (10.14)	37.15 (9.87)	0.31†
	End of 4th week	17.57 (7.01)	28.62 (9.75)	0.001†
	8th week	18.09 (5.96)	41.31 (10.34)	0.001†
	Overall	0.001	0.001	-
	Baseline and the end of 4th week	0.001	0.001	-
	4th week and 8th week	0.76	0.001	-
	1st week and 8th week	0.001	0.337	-
Satisfaction				
P within groups†	End of 4th week	3.02 (0.765)	2.17 (1.00)	0.001

Data presented as mean (standard deviation). CU-Q2oL: the Chronic Urticaria Quality of Life Questionnaire, SD: Standard deviation, JO: Jujube oxymel. Statistics were evaluated using the Mann–Whitney test to compare two means and ANOVA for more than two means. †Mann–Whitney test. ‡ANOVA test

Table 4: Compare different Secondary outcomes among understudied cases

Variable	Jujube oxymel *n* (%) (*n*: 47)	Control *n* (%) (*n*: 45)	*P**
Drowsiness	0 (0%)	16 (35.55%)	0.001
Fatigue	2 (4.2%)	7 (15.55%)	0.01
Nausea	2 (4.2%)	1 (2.2%)	0.18
Flatulence	2 (4.2%)	0 (0%)	0.09
Abdominal pain	1 (2.12%)	1 (2.22%)	1.00
Headache	0 (0%)	1 (2.22%)	0.20

*Chi-square test

PM's holistic perspective states that most diseases are caused by humor imbalances and malfunctions of the stomach and liver, which are the main production sites of humor.[26-28] Hence, a natural blood purifier product from ZJ fruit with gastrointestinal protective activity could be a suitable adjunct therapy to standard antihistamine medication in urticaria.[10,13,14,29]

This double-blind clinical trial revealed that JO, a PM remedy, combined with cetirizine has significantly more predominant efficiency in reducing urticaria severity and enhancing the quality of life of patients compared to cetirizine alone.

Based on the current study results, the itching intensity and number of hives decreased at the end of the fourth week of treatment in JO and placebo groups. However, the comparison of the UAS-7 score among the groups showed that it was significantly lower in the intervention group. Within a month of JO withdrawal, the severity of symptoms in participants who completed the study significantly increased in the control group during the follow-up period.

Regarding the quality of life, after 28 days, both groups demonstrated a significant improvement in the QOL. The participants who could terminate the study in the JO group have a constant betterment in their living conditions, unlike the control group.

The intensity of urticaria was reduced significantly by JO, especially in the long term, compared to cetirizine alone. Furthermore, it improved the patient's quality of life.

In previous studies, medicinal herbs have shown lasting effects, improved quality of life, and reduced adverse events in CSU.[3,25]

Furthermore, due to the low incidence of adverse events, JO can be introduced as a safe product that has greater compliance and meets the needs of urticaria sufferers.

For this reason, patients with chronic urticaria would be greatly affected by the additive effect of JO combined with cetirizine and it would not be necessary to have a higher dose or longer duration of cetirizine and advanced therapies. Yet, achieving more significant differences may demand a prolonged treatment period and an increased number of study participants.

It is now known that, although urticaria has always been considered a mast cell-driven disease, activation and degranulation of basophils, as well as other cells like eosinophils, B and T lymphocytes, endothelial, and epithelial cells, may be involved. The cascade of inflammatory mediators, vasodilation, and increased permeability of blood vessels can result in hives and angioedema in CSU.[1,8,9]

ZJ fruit, also known as *Annab*, is a well-studied herbal medicine that is a rich source of phytochemicals and has many pharmacological properties. Jujube's nutraceutical and cosmeceutical properties can help promote healthy skin.[12,13,29]

Research conducted by Naik *et al*.[30] confirmed the antiallergic and antianaphylactic properties of the ethanolic extract of ZJ fruit in rodents. The stabilization of mast cells by phytoconstituents like steroidal flavonoids and saponins in the membrane, inhibition of IgE formation, and free radicals scavenging activity were the possible causes of these properties.

ZJ's antiinflammatory impact on both acute and chronic inflammation, potentially achieved by suppressing nitric oxide expression, could be attributed to flavonoids, terpenes, and jujubosides.[31,32]

Regards to PM, blood quality and the development of hives are influenced extremely by liver function.[26] Animal and human studies revealed that ZJ fruit has hepatoprotective effects.[13,29] Pretreatment with water extract of ZJ fruit has significantly weakened ischemia/reperfusion-induced liver injury in rats.[33] In a pilot randomized clinical trial, Jujube syrup could prevent antituberculosis drug-induced hepatotoxicity in patients with tuberculosis.[34]

Accordingly, the role of jujube in hepatoprotection appears to be attributed to the significant antioxidant and free radical scavenging activity of phenols found in ZJ fruit.[29,34]

Oxymel, another important component of JO, is a medicinal syrup compounded in different mixtures of honey and vinegar. In PM, it is used alone or in combination with other medicinal ingredients.[35] Vinegar is a natural product that comes from fermentation and is becoming more popular worldwide. It possesses several therapeutic effects such as antioxidant, antiinflammatory, antitumor, etc.[36-38]

The present study's satisfactory results showed that the positive interaction effects of the medicinal compositions of JO may enhance the therapeutic effects of each other.

To the best of our knowledge, this is the first clinical trial that investigates JO as an additive therapy for patients with CSU.

The simultaneous coronavirus pandemic presents certain limitations to this study. Recruiting and following up with patients was a challenge due to the closure of many clinics and multiple COVID waves. Some patients opted out of the treatment in this situation.

Also, the laboratory test for evaluating changes in serum markers was not completed as a result of insufficient funding.

Additional investigation is needed to pinpoint the active compounds in JO for their therapeutic effects, alongside an increased participant count.

Conclusion

In this trial, ZJ oxymel, as a potential adjunct to cetirizine, demonstrated prolonged and improved control of chronic urticaria. Additionally, JO proved to be a safe and well-tolerated herbal remedy. However, further research is required to investigate the potential benefits of alternative medicinal plants and identify their active components.

Acknowledgments

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Availability of data and materials

The identified datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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The cost of this trial was paid by the Vice-chancellor for research of IUMS.

Conflicts of interest

There are no conflicts of interest.

References

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff A, Baker D, Ballmer-Weber B, *et al*. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
2. Taghavi Shirazi M, Mohammadi Kenari H, Eghbalian F. The role of bloodletting and cupping in severe acute urticaria and angioedema as skin emergencies in Persian medicine. J Pharmacopuncture 2022;25:7-14.
3. Eghbalian F, Esmaili N, Karimi M, Mohajerani F, Rahimi R, Atyabi A, *et al*. Comparison of the efficacy and tolerability of an oral dosage form made from Fumaria vaillantii versus cetirizinein management of chronic urticaria: A single-blind, randomized, clinical trial. Biomedical research and therapy (BMRAT) 2018;5:2389-401.
4. Firooz A, Lajevardi V, Mansouri P, Nassiri-Kashani M, Norouzi Y, Handjani F. Management of urticaria: Update of Iranian Society of Dermatology clinical practice guideline. Iran J Dermatol 2018;21:35-123.
5. Mohamed AA, Hussein MS, Salah EM, Eldemery A, Darwish MM, Ghaith DM, *et al*. Efficacy and safety of active vitamin D supplementation in chronic spontaneous urticaria patients. J Dermatolog Treat 2022;33:427-32.
6. Atefi N, Fallahpour M, Sharifi S, Ghassemi M, Roohaninasab M, Goodarzi A. Probiotic as an adjuvant therapy in chronic urticaria: A blinded randomized controlled clinical trial. Eur Ann Allergy Clin Immunol 2022;54:123-30.
7. Mobeen A, Ahmad AK. The efficacy and safety of herbal combination of Unani Medicine in chronic urticaria: A randomized, controlled study. J Tradit Complement Med 2021;11:303-10.
8. Sánchez-Borges M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, *et al*. The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. World Allergy Organ J 2021;14:100546.
9. Sánchez-Borges M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, *et al*. The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management. World Allergy Organ J 2021;14:100533.
10. Iranzadasl M, Taghavi Shirazi M, Bioos S, Eghbalian F. A comparative study of urticaria and angioedema symptoms, etiology and diagnosis based on Persian and conventional medicine. J. Maz. Univ. Med. 2022;31:111-22.
11. Liu SJ, Lv YP, Tang ZS, Zhang Y, Xu HB, Zhang DB, Cui CL, Liu HB, Sun HH, Song ZX, Wei SM. Ziziphus jujuba Mill., a plant used as medicinal food: A review of its phytochemistry, pharmacology, quality control and future research. Phytochemistry Reviews. 2021 Jun;20:507-41.
12. Ghobadi A, Amini-Behbahani F, Yousefi A, Taghavi Shirazi M, Nasim B. Medicinal and nutritional properties of Ziziphus jujuba Mill. in traditional Persian medicine and modern phytotherapy. Crescent J Med Biol Sci 2019;6:146-50.
13. Aafi E, Reza M, Mirabzadeh M. Jujube (Ziziphus jujuba Mill. (Rhamnaceae)): A review on its pharmacological properties and phytochemistry. Tradit Med Res 2022;7:1-9.
14. Aghili Khorasani M. Makhzan al-Advieh. Tehran: Chogan; 2017.
15. Tonkaboni M. Tohfeh al-Momenin. 1. Tehran, Iran: Shahid Beheshti University of Medical Sciences; 2007.
16. Nafis I. Alshamel fi Sana'at Tebbi'at. Tehran: Iran University of Medical Sciences, Research Instiute for Islamic and Complementary Medicine; 2008.
17. Aghili Khorasani M. Qarabadin-e-Kabir. Tehran: Safirardehal; 1970.
18. Motaharifard MS, Effatpanah M, Akhondzadeh S, Rahimi H, Yasrebi SA, Nejatbakhsh F. Effect of sweet almond syrup versus methylphenidate in children with ADHD: A randomized triple-blind clinical trial. Complement Ther Clin Pract 2019;36:170-5.
19. Britsh Pharmacopoeia. 2024 ed: The Stationery Office.
20. Hollis K, Proctor C, McBride D, Balp M-M, McLeod L, Hunter S, *et al*. Comparison of urticaria activity score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: Results from the ASSURE-CSU study. Am J Clin Dermatol 2018;19:267-74.
21. Tavakol M, Mohammadinejad P, Baiardini I, Braido F, Gharagozlou M, Aghamohammadi A, *et al*. The persian version of the chronic urticaria quality of life questionnaire: Factor analysis, validation, and initial clinical findings. Iran J Allergy Asthma Immunol 2014;13:278-85.
22. Common terminology criteria for adverse events (CTCAE) version 5.0: US Department of Health and Human Services; 2017. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7accessed date: 15-9-2019.
23. Moher D, Schulz KF, Altman D. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.
24. Pandis N, Chung B, Scherer RW, Elbourne D, Altman DG. CONSORT 2010 statement: Extension checklist for reporting within person randomised trials. BMJ 2017;357:j2835.
25. Yang S-H, Lin Y-H, Lin J-R, Chen H-Y, Hu S, Yang Y-H, *et al*. The efficacy and safety of a fixed combination of Chinese herbal medicine in chronic urticaria: A randomized, double-blind, placebo-controlled pilot study. Front Pharmacol 2018;9:1474.
26. Sina I. Al-Qanun Fi al-Tibb (The Canon of Medicine). Beirut: Dar Ehya Alterase Al Arabi; 2005.
27. Aghili Khorasani M. Kholase al-Hekmah. Qom: Esmailian; 2006.
28. Mohammadian Rasanan F, Mohammadi Kenari H, Ghassemi M, Sabbagh AJ, Aliasl J, Ghobadi A. Non-pharmacological treatments of psoriasis in Persian medicine a narrative review. J Pharmacopuncture 2022;25:1.
29. Agrawal P, Singh T, Pathak D, Chopra H. An updated review of Ziziphus jujube: Major focus on its phytochemicals and pharmacological properties. Pharmacological Research-Modern Chinese Medicine 2023;8:100297.
30. Naik SR, Bhagat S, Shah PD, Tare AA, Ingawale D, Wadekar RR. Evaluation of anti-allergic and anti-anaphylactic activity of ethanolic extract of Zizyphus jujuba fruits in rodents. Rev Bras Farmacogn 2013;23:811-8.

31. Goyal R, Sharma PL, Singh M. Possible attenuation of nitric oxide expression in anti-inflammatory effect of Ziziphus jujuba in rat. J Nat Med 2011;65:514-8.
32. Yu L, Jiang B, Luo D, Shen X, Guo S, Duan J, *et al*. Bioactive components in the fruits of Ziziphus jujuba Mill. against the inflammatory irritant action of Euphorbia plants. Phytomedicine 2012;19:239-44.
33. Chen CF, Lee JF, Wang D, Shen CY, Shen KL, Lin MH. Water extract of zizyphus jujube attenuates ischemia/reperfusion–induced liver injury in rats (PP106). Transplant Proc 2010;42:741-3.
34. Maddahi SZ, Jokar A, Kamalinejad M, Behnampur N. The efficacy of Jujube syrup on the prevention of drug-induced hepatotoxicity in pulmonary tuberculosis patients: A pilot randomized double-blind placebo-controlled clinical trial. Pharmacol Res Perspect 2022;10:e00902.
35. Zargaran A, Zarshenas MM, Mehdizadeh A, Mohagheghzadeh A. Oxymel in medieval Persia. Pharm Hist (Lond) 2012;42:11-3.
36. Naghibi Z, Rakhshandeh H, Jarahi L, Hosseini SM, Yousefi M. Evaluation of the effects of additional therapy with Berberis vulgaris oxymel in patients with refractory primary sclerosing cholangitis and primary biliary cholangitis: A quasi-experimental study. Avicenna J Phytomed 2021;11:154-67.
37. Budak NH, Aykin E, Seydim AC, Greene AK, Guzel-Seydim ZB. Functional properties of vinegar. J Food Sci Technol 2014;79:R757-64.
38. Samad A, Azlan A, Ismail A. Therapeutic effects of vinegar: A review. Curr Opin Food Sci 2016;8:56-61.