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Original Article

The Added-on of *Ziziphus jujube* Syrup in the Treatment of Chronic Spontaneous Urticaria Resistant to Standard-Dose of Secondary-generation H_1 Antihistamine: A Double-Blind Randomized Clinical Trial

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What's Known

- Previous studies reported that there was no cure for chronic urticaria, and since this disease impairs people's quality of life of people, treatment is required.

What's New

- The present study indicated that treating patients with chronic urticaria, using *Ziziphus jujube* syrup, could help to reduce the complications of the disease.

Abstract

Background: Although antihistamines are the first-line treatment for chronic spontaneous urticaria (CSU), 50% of patients don't respond to standard doses. In this study, the effectiveness of *Ziziphus jujube* fruit syrup in combination with antihistamines was assessed in patients with CSU.

Methods: This double-blind randomized clinical trial was conducted in Shiraz between December 2019 and December 2020. 64 patients with CSU who had experienced hives for at least six weeks and did not respond to the usual treatments were enrolled in the study. They were randomly assigned to intervention and control groups using permuted block random allocation. For four weeks, the intervention group received 7.5 mL *Ziziphus jujube* syrup twice a day, while the control group received 7.5 mL simple jujube syrup twice a day. Both groups received cetirizine 10 mg every night. Urticaria activity score (UAS) and CU-Q_2oL questionnaires were used to assess urticaria state and sleep quality before and after each week for four consecutive weeks. Data were analyzed using SPSS software version 18, and $P<0.05$ was considered statistically significant.

Results: Before the intervention, there was no statistically significant difference between the two groups' mean of UAS ($P=0.490$) and sleep quality ($P=0.423$). During the follow-up, UAS in the intervention group was significantly lower ($P=0.001$). Moreover, this difference was significant on the day 28 ($P=0.046$). During the follow-up, the quality of sleep in both groups improved significantly, and this improvement was more significant in the intervention group.

Conclusion: *Ziziphus jujube* syrup could be an effective adjuvant treatment for CSU.

Trial Registration Number: IRCT20190304042916N1.

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Keywords ● Chronic urticaria ● Ziziphus, jujube ● Quality of life ● Sleep quality

Introduction

Chronic spontaneous urticaria (CSU) is known as the presence of hives, angioedema, or both for more than six weeks, with

symptoms occurring on most days of the week.[1] It is an intermittent disease (described in dermatology as the presence of urticaria, angioedema, or both for six weeks or more) with no treatment.[2] Although second-generation H1 antihistamines (sgAH) are the first line of treatment for individuals with CSU, the standard dose of sgAH has a poor response rate in nearly 50% of these patients.[3, 4] It affects one's quality of life more than cardiovascular diseases or respiratory allergies.[5] The actual mechanism behind the pathophysiology of this condition is complicated, and it is still unclear what triggers the onset of signs and symptoms in patients with CSU.[6] The use of herbal medicine has grown over the past few decades as a result of drug side effects and the failure to completely control the signs and symptoms of CSU patients.[5] Thus, the type of bioactive compounds, form, solubility, stability, and other factors, have a significant impact on the choice of foods and natural products.[6] One of the recommended-ancient Iranian remedies is *Ziziphus jujube* mill. (ZJM) fruit Oxymel.[7, 8] Oxymel is a traditional Iranian natural syrup with a sour taste,[9, 10] which is prepared from sugar or honey and diluted with acetic acid. From ancient times to the present, this syrup was used in different forms, alone or in medicinal forms, based on its physical properties such as taste, bioactivity, bioavailability, solubility, and stability.[10]

Over the past 20 years, numerous compounds were extracted from ZJM fruits, with properties such as influencing the immune system, protecting the body from oxidation, anti-ulcer, and anti-allergy.[7, 11, 12] Previous animal studies indicated that ZJM fruit compounds could inhibit cytokine production in the allergic reaction pathway, which aids in the prevention or reduction of allergy symptoms.[13] The primary plant components of the genus Zizyphus were identified as flavonoids, phenolic compounds, triterpene acids, and polysaccharide components.[14] There is no scientific proof that ZJM syrup has a therapeutic effect on CSU. A previous study found that the recommended traditional Iranian medicinal formula was effective in treating patients with CSU who had a poor response to sgAH.[14] Besides, it could be inferred that ancient physicians were aware of the disease and attempted to treat it. The main purpose of the present study was to assess the clinical efficacy of ZJM syrup on patients with CSU.

Patients and Methods

Study Design and Sampling Methods

This double-blind randomized clinical trial was conducted on 64 patients with CSU, who were referred to the outpatient Allergy Clinic of Namazi Teaching Hospital, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) from December 2019 to December 2020.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1398.131) and registered in the Iranian Registry of Clinical Trials (IRCT20190304042916N1). All the patients were informed about the purposes of the research and any possible side effects of the medicines and interventions. Written informed consent was obtained from the participants or their legal guardians. The study was carried out in agreement with the principles of the Helsinki Declaration.

The inclusion criteria were persistent chronic urticaria (having hives for at least six weeks that did not respond to standard treatments), age between 18 and 70 years, no history of autoimmune disease or known immunodeficiency, no history of drug use for diseases other than CSU, no pregnancy, no history of allergy to antihistamine drugs. The exclusion criteria included any sensitivity to the medications used in the study process, sensitivity to *Ziziphus jujube* (ZJ), and unwillingness to continue participating in the study.

Based on the study of Nabavizadeh and others,[15] and assuming a confidence interval of 95% and power of 90%, an allocation ratio of 1:1, and an effect size of 0.87, and with the possibility of samples dropping out during the study of about 10%, the minimum number of samples required in each group was estimated to be 32 patients. The patients were selected using a convenience sampling method.

Using the permuted block random allocation approach, 64 patients were randomized into intervention and control groups (32 patients in each group). The intervention group received 7.5 mL ZJ syrup (manufactured by School of Pharmacy, Shiraz, Iran), while the control group received 7.5 mL simple jujube syrup (manufactured by School of Pharmacy, Shiraz, Iran) twice a day for four weeks. During the trial period, patients in both groups were also given cetirizine 10 mg (Shafa Company, Iran) every night. The medicinal compounds were prepared in opaque bottles. The urticaria activity score (UAS) was used to assess the condition of urticaria in patients of both groups.[16] Utilizing a modified Persian version of the Chronic urticaria quality of life (CU-Q_2oL) questionnaire, the sleep quality of patients in both groups was also assessed.[16] Prior to the intervention as well as at the end of the first, second, and third weeks following the intervention, the urticaria condition and sleep quality of patients in two

groups were assessed. In addition, at each follow-up appointment, the patients' conditions were assessed in terms of the occurrence of allergic reactions to the medicinal compounds utilized in the study. The patients were also instructed to call the study researchers if they noticed any indications of an allergic reaction during the follow-up intervals. To minimize the observer bias on the study results, the data analyst and the person evaluating the outcomes of the intervention in the patient group were unaware of the distribution of the studied groups.

Ziziphus jujube Mill. Syrup Preparation

The preparation of this syrup was based on the methods in Traditional Iranian Medicine (TIM) resources. It was made using sugar, rosewater, vinegar, and jujube fruit. ZJM fruits were purchased from a local store. Then, it was microscopically examined by a botanist at Shiraz University of Medical Sciences, Shiraz, Iran (voucher number 1359). In brief, the plant powder was used for microscopic analysis. The sample powder was placed in a tube, mixed with a 0.5% chloral hydrate solution, and then gently heated. Afterwards, a slide containing some of the obtained solution was inspected under an optical microscope, and an image of its anatomical structure was taken with a camera. The *Salmonella* species*, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, and Candida albicans* contamination tests were conducted on the samples, and the results were negative. Therefore, the five mentioned pathogens indicated no growth. These tests were performed in compliance with the British Pharmacopoeia.[17]

For syrup preparation, 100 g of sliced ZJM fruit was mixed with 2000 mL of boiling distilled water and continued the boiling process until the volume of the solution reached 1000 mL. Then, 2000 g of sugar (Mazandaran Sugar Company, Iran) and 1000 g of vinegar (PH:5; Varda Company, Iran) were added to the product and heated. Then, the mixture was allowed to evaporate, and the solution volume was reduced to 1000 mL. As a preservative, 0.2% and 0.02% (w/w) methyl and propylparaben (Arshida Chemical Company, Iran) were added to the final syrup and then filled into 500 mL bottles.

Analysis of Ziziphus jujube Mill. Syrup

A high-performance chromatography technique was used for the chemical analysis of syrup. The presence of phenols and flavonoids was determined using an Agilent Technologies 1200 sequence instrument (Germany). The preliminary column temperature was set at 30 ºC, the run time was 40 min, and the flow rate was 1 mL/min. The phenol wavelength was 280 nm, and the flavonoid wavelength was 320 nm. The injection volume was 20 µL, and the detector was DAD and Chemstation Software (version: B.04.02, American for LC 3D system).

For extraction, the total phenol test soaking in the methanol method was utilized.[18] Using a rotary evaporator (KA-Werke GmbH & Co. Germany), all of the solvents were quickly separated, and the extract was entirely dried. Then, 1.2 mg of the extract was dissolved in 3 mL of distilled water (concentration of 400 mg/L). The sample was then preserved in the dark for an hour with the sampler. Afterwards, we poured 3 mL of the prepared solution into the quartz cell (Apel Company, Japan), and then measured them at 765 nm. For extracting the entire flavonoid, 1.5 mg of ZJ dry extract +5 mL methanol (concentration of 300 mg/L); 1:1 ratio of the sample and 0.1 mL aluminum chloride 2% (Samchun Chemical Company, Korea) were poured into a tube, and the combination were kept in the dark for an hour. Then, the absorbance rate was measured at 415 nm with a UV spectrophotometer (Jenway, England). In the preliminary vial, 0.0012 g of gallic acid (GA) was mixed with 200 µL of methanol and 3800 µL of distilled water, and a solution with a concentration of 300 mg/L was prepared. For different concentrations of standard GA (0.15, 0.075, 0.0375, 0.0187, 0.0093 mg/mL), total phenol was prepared in methanol, and then, 1 mL of distilled water was added to 1 mL of the previous concentration. The absorbance was measured at 760 nm (T80 plus, PG Instrument, UK) and converted to phenolic contents. The calibration curve was developed entirely based on different concentrations of GA. Using quercetin as a reference, the total flavonoid content was determined using the aluminum chloride method.[19] After 60 min, 1.5 mL of the test sample and 1.5 mL of aluminum chloride were added to a volumetric flask (Glassco Laboratory Equipments Pvt. Ltd, India). A spectrophotometer (Jenway, England) was used to measure the absorbance of the sample in comparison to the reference at 490 nm.

Measurements

In the present study, we used the UAS and the Persian model of CU-Q_2oL as Chronic urticaria (CU) and patient quality of sleep evaluation questionnaires. The global urticaria guiding principle[16] advocates for the use of UAS7 as a marker of disease activity and response to treatment. This index evaluates itching on a daily basis as well as the number of hives, which are

accounted for weekly. A higher UAS7 score (in the range of 0-42) indicates the severity of the disease.

UAS7 was designed for a five-band (0, 1-6, 7-15, 16-27, 28-42), which confirmed a demonstration of urticaria-free to severe disease conditions. Wheals and itching are graded on a scale of zero (no symptoms), one (mild), two (moderate), and three (severe). Total itching and wheals values range from zero to six, indicating disease severity. The patient's sleep quality was assessed using a Persian version of the CU-Q_2oL questionnaire. It had twenty-three items in six dimensions of quality of life including two items related to pruritus, six items related to the influence on lifestyle activities, five items related to sleep problems, three items related to restrictions, five items related to appearance, and two items related to edema.

This questionnaire was scored entirely based on the Likert scale, and the higher scores indicated a poorer quality of life and vice versa.[16] The patient-level data from baseline, days 7, 14, and 28 after the beginning of intervention for UAS7 and CU-Q_2oL were used to evaluate the effects on symptoms of refractory CSU. The UAS7 scores were reported at the baseline and every week until the fourth week. CU-Q_2oL data were collected at baseline, days 7, 14, and 28.

Statistical Analysis

The data were analyzed using SPSS software version 18 (PASW, Chicago INC, USA). The continuous data were expressed as Mean±SD, and categorical data were presented as frequency and percentage. Due to the non-compliance of quantitative data with a normal distribution, the Kolmogorov-Smirnov test was used to analyze quantitative data. In each follow-up period, the Chi square test was used to compare the frequency of sleep quality patterns of the two groups of patients. Fisher's exact test was used to compare the sex, the history of underlying diseases, and the angioedema status of two groups of patients.

The average age of the patients, duration of the disease, and UAS of the patients of the two groups at each stage were analyzed with the Mann-Whitney test. The Wilcoxon rank test was used to compare the length of the follow-up period at each stage. Besides, Fridman test was used to compare the obtained results of the follow-up. Moreover, the efficiency of the new treatment cluster on sleep quality was assessed by generalized estimating equation (GEE) test.[20] In all stages of data analysis, P≤0.05 was considered statistically significant.

Results

Participant

Out of the 66 eligible individuals, 64 patients were ultimately included in the study. They were divided into two groups (32 in each group). One patient was excluded from the study due to not meeting the inclusion criteria, and one patient was excluded due to unwillingness to participate in the study. The CONSORT flow diagram of the study is shown in figure 1.

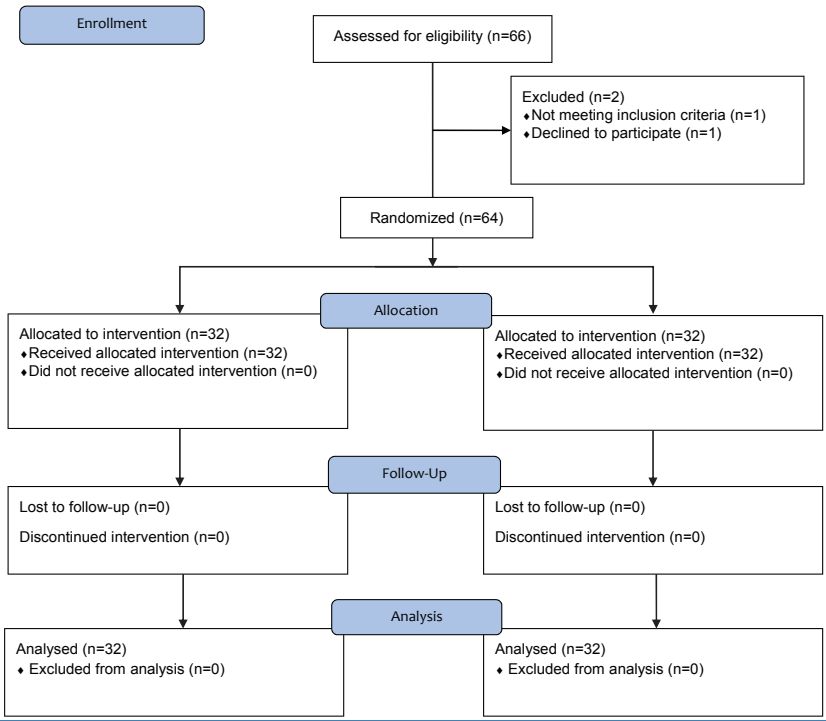

Figure 1: The figure represents the CONSORT flow diagram of the present study.

Baseline Characteristics

The treatment group included five men and 27 women with a mean age of 37.88±9.36 years, and the control group included 10 men and 22 women with a mean age of 36.66±13.53 years (table 1). The distribution of sex (P=0.223), marital status (P=0.572), occupation (P=0.405), and education level (P=0.495) was not statistically significant in both groups. Further baseline characteristics of the participants are summarized in table 1.

Primary Outcomes

The alterations in UAS7 as the primary outcome are summarized in figure 2. The trend analysis demonstrated that UAS7 was changed in the intervention group as compared to the control group. Besides, this difference was statistically significant on the seventh day (P=0.002). Both the intervention and control groups indicated a significant symptom improvement (figure 2).

In the intervention group, the mean CU-Q_2oL was 16.56±2.31 at baseline and reduced to 10.12±3.20 at 28 days. The mean score in the control group, on the other hand, decreased from 16.91±2.74 at baseline to 11.73±3.46 at day 28. Although the differences in quality of life scores between the intervention and control groups only achieved borderline significance on 7 and 28 days (P=0.002 and P=0.046, respectively), both groups demonstrated a gradual improvement in quality of life (P<0.001 for both groups in trend analysis; table 2).

In terms of their quality of life toward urticaria recovery, individuals who scored higher on this questionnaire generally had worse conditions. As indicated in table 2, there was no statistically significant difference in the overall mean scores for the quality of life scores between the intervention and control groups at the time of referral (P>0.05). However, the difference between the mean total score obtained from the questionnaire in the two groups was significant in the second week of treatment (P=0.001), implying that the mean overall score obtained in the intervention group was significantly lower than the control group. A lower score indicated a better condition of CU. This difference indicated that the intervention group, who received ZJM syrup two weeks after taking the medicine, performed better in terms of the seven factors mentioned in the research questionnaire than the control group.

Furthermore, around 70% improvement was found in both groups, with the intervention group improving slightly more (figure 2). Besides, figure 3 demonstrates the comparison of the responder rates in the two groups.

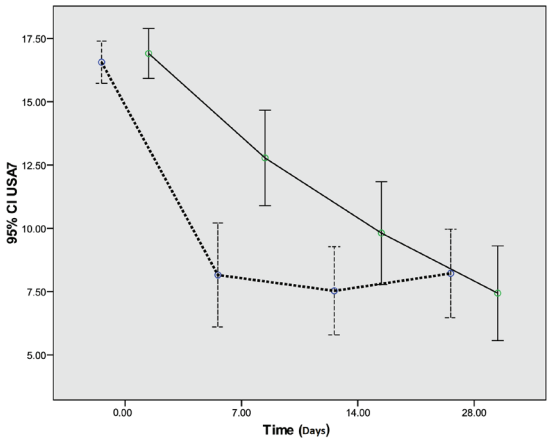

Figure 2: This figure shows the evolution of the activity of urticaria intensity (P<0.001 between the intervention and control groups), according to urticaria activity score (UAS).

Table 1: Comparison of the baseline characteristics between the *Ziziphus jujube* syrup intervention group and the control group

Variables		*Ziziphus jujube* syrup group (n=32)	Control group (n=32)	P value
Age (year)	Median (IQR)	37 (9.5)	37.5 (14.75)	0.978[a]
Sex	Male	5 (15.6%)	10 (31.2%)	0.223[b]
	Female	27 (84.4%)	22 (68.8%)	
Marital status	Single	7 (21.9%)	10 (31.2%)	0.572[b]
	Married	25 (78.1%)	22 (68.8%)	
Job	Employed	7 (21.9%)	11 (34.4%)	0.405[b]
	Unemployed	25 (78.1%)	21 (65.4%)	
Education level	Illiterate	2 (6.3%)	2 (6.3%)	0.495[c]
	Diploma and below	22 (68.7%)	21 (65.6%)	
	College Education	8 (25.0%)	9 (28.1%)	
Body Mass Index (Kg/m^2)	Median (IQR)	72.5(15)	70.5 (22.5)	0.909[a]
Angioedema	Yes	22 (68.8%)	14 (43.8%)	0.077[b]
	No	10 (31.2%)	18 (56.2%)	
History of Disease	Yes	25 (78.1%)	26 (81.3%)	0.568[b]
	No	7 (21.9%)	6 (18.7%)	
Disease duration (month)	Median (IQR)	33 (60.5)	21 (30)	0.882[a]

[a]Mann Whitney U test; [b]Fisher exact test; [c]Chi Square test; *P<0.05 was considered statistically significant.

Table 2: Total score of Chronic urticaria quality of life (CU-Q_2oL) and sleep quality score in patients of the *Ziziphus jujube* syrup group and control group

Variables		*Ziziphus jujube* syrup group (n=32)	Control group (n=32)	95% CI	P value*
Chronic urticaria quality of life score	Baseline	16.56±2.31	16.91±2.74	(-1.61-0.923)	0.49
	Fist week	8.16±5.69	12.78±5.23	(-7.356-1.893)	0.002
	Second week	7.53±4.83	9.81±5.63	(-4.901-0.339)	0.111
	Fourth week	8.22±4.85	7.44±5.18	(-1.726-3.289)	0.450
	Total	10.12±3.20	11.73±3.46	(-3.331-0.964)	0.046
Sleep quality score	Baseline	1.72±1.02	1.53±1.02	(-0.697-0.322)	0.423
	Fist week	0.75±0.92	0.59±0.98	(-0.630-0.318)	0.280
	Second week	0.38±0.79	0.41±0.76	(-0.356-0.418)	0.786
	Fourth week	0.19±0.59	0.34±0.75	(-0.180-0.493)	0.300
	Total	0.76±0.66	0.72±0.65	(-0.366-0.288)	0.668

*Mann Whitney U test

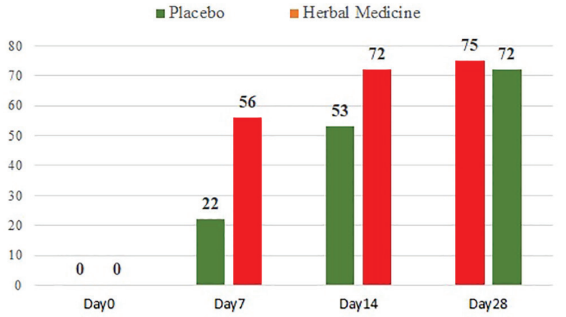

Figure 3: This figure shows the percentage of responder rate in the two groups.

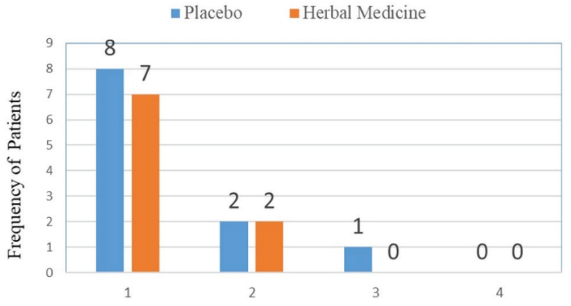

Figure 4: This figure shows the effect of herbal medicine on the frequency of patients with night awakenings during the study course.

Secondary Outcomes

As indicated in figure 4, GEE analysis showed that herbal medications significantly improved sleep quality between the control and intervention groups (P<0.001 and P=0.049, for time and treatment variables, respectively).

Composition of Ziziphus Jujube Mill. Syrup

The results of high performance liquid chromatography (HPLC) are shown in table 3 and figure 5. According to HPLC analysis, the amount of chemicals in ZJM syrup is shown, with GA and hesperetin being the two primary components. Microscopic analysis of ZJM is illustrated in figure 6.

Table 3: The number of compounds in jujube by High-Performance Liquid Chromatography analysis

Variables	Lab code	Sample code	Retention time (min)
	P990300	Syrup	
Sinapic acid (mg/L)		Nd*	16.5
Gallic acid (mg/L)		2882.729	3.3
Catechin (mg/L)		Nd	8.3
Caffeic acid (mg/L)		Nd	11.6
Chloregenic acid (mg/L)		Nd	10.5
Quercetin (mg/L)		Nd	21.6
p-Coumaric acid (mg/L)		Nd	15.6
Coumarin (mg/L)		Nd	17.4
Carvacrol (mg/L)		Nd	28.4
Vanilin (mg/L)		Nd	13.5
Trans-ferulic acid (mg/L)		Nd	16.3
Hesperedin (mg/L)		Nd	18.5
Ellagic acid (mg/L)		Nd	19.02
Eugenol (mg/L)		Nd	23.7
Hesperetin (mg/L)		53.95306	22.4
Rosmarinic acid (mg/L)		Nd	19.2
Thymol (mg/L)		Nd	28.9

*Non-detectable

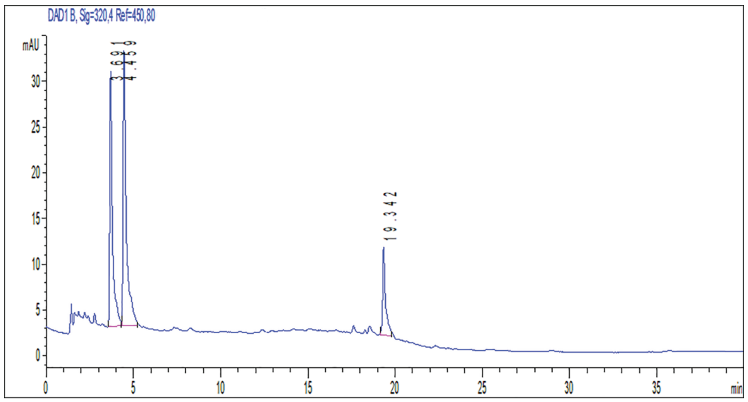

Figure 5: This figure shows the high performance liquid chromatography (HPLC) results of compounds in Jujube.

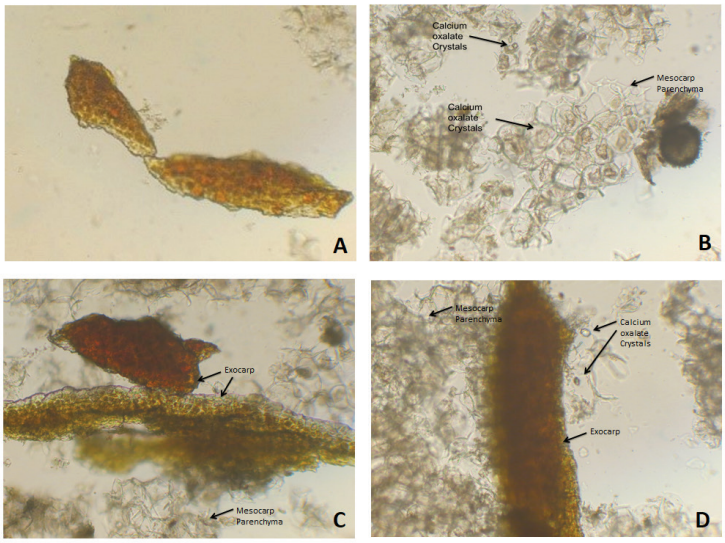

Figure 6: This figure shows the microscopic analysis of *Ziziphus jujube* mill. fruit: A) Exocarp tissue, B) Parenchyma in the mesocarp, C) Exocarp tissue, and D) Mesocarp tissue containing calcium oxalate.

Discussion

Over 50% of CSU patients are resistant to a standard dose of sgAH.[21] International Guidelines for this group recommend increasing the dose of sgAH up to four times the standard level, although long-term intake has many side effects.[22, 23] The response rate to a high dose of it is approximately 50%. Therefore, developing new treatment strategies in patients with antihistamine-resistant CSU has been one of the main goals of physicians at different times. The present study indicated that the add-on therapy of the recommended TIM formula to the standard dose of cetirizine could reduce the severity of symptoms in standard-dose of antihistamine-resistant CSU in the first two weeks of treatment. The analysis of the TIM-prescribed compound using the HPLC technique revealed that GA made up the majority of the mixture. The mainstay of CSU is mast cell-dependent and release of their mediators such as histamine.[24] As histamine performs a central function in allergic diseases, it is feasible that the TIM formula modulates allergy-related histamine signaling. Recent studies showed that GA had anti-inflammatory, anti-allergic, anti-depressant, anti-histaminic, and anti-oxidant properties via different mechanisms at the cellular and animal levels.[25, 26] The findings of a previous animal study animal studies indicated that GA inhibited the release of histamine from mast cells, and IL-4 and IL-2 from helper T cells.[26]

A new investigation reported that quercetin may also suppress histamine release within *in vitro* mast cells. A 500 mg dose of quercetin three times a day may also provide some alleviation from urticaria.[27] Another advantage of this syrup is its very quick reaction in alleviating the patient's symptoms. These findings concerning GA and quercetin confirmed the anti-CSU efficacy of ZJ syrup. The findings of previous studies shed light on the mechanisms behind the anti-allergic activity of TIM syrup. Furthermore, the research on the impacts of its bioactive components could help prevent or treat mast cell-mediated allergic disorders such as CSU.

A major limitation of this study was the small sample size, which limited its power and possible generalizability. The short duration of follow-up was another limitation of this study. The other was the lack of investigation of dose-related effects of the medicine on the most important skin symptoms and QOL of urticarial patients.

Multicenter studies are recommended to evaluate the long-term effects of this medicine. Although there were no side effect in patients taking this medicine, and it was well tolerated and safe, a long-term follow-up is required to evaluate the relapse and remission rates. It is also suggested to assess the curative or symptomatic effects of ZJM syrup.

Conclusion

Treatment with ZJ fruit syrup appeared to be a good adjuvant method as well as a new approach for the management of CSU that did not respond to standard-dose antihistamines. It is an effective adjuvant method with no significant side effects.

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Authors' Contribution

H.Z: Supervision, conception, design, literature search, data acquisition, data analysis, drafting; SH.N: Supervision, conception, design, data acquisition, drafting; AM.J: Supervision, conception, design, data acquisition, drafting; MM.Z: Literature search, data acquisition, data analysis, drafting; A.B: Statistical analysis, drafting; N.N: Data analysis, drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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