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RESEARCH ARTICLE

Efficacy and Safety of a Food Containing Active Diamine Oxidase (DAO) in Patients with Chronic Urticaria: A Single-Center, Single-Arm, Open-Label Exploratory Study

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Abstract

Chronic Urticaria (CU) poses a significant therapeutic challenge, as conventional antihistamines are ineffective for about 40% of patients. This treatment gap is linked to key pathological drivers: impaired histamine metabolism due to low Diamine Oxidase (DAO) activity, immune dysregulation, and vitamin D deficiency. Addressing this need, our study evaluated NatureU Yan, a functional food designed to simultaneously target these pathways with active DAO, vitamin D, and Bifidobacterium longum BB536. In a 28-day trial involving 19 CU patients, this multi-targeted intervention led to striking clinical benefits. Patients exhibited a 170.71% improvement in disease control (UCT), an 80.82% reduction in symptom severity (UAS7), and an 88.24% enhancement in quality of life (DLQI), with an excellent safety profile. These findings position NatureU Yan as a promising, safe, and mechanistically grounded complementary option for CU management.

Introduction

Chronic Urticaria (CU) is a prevalent and debilitating inflammatory skin disorder, defined by the recurrent emergence of wheals, angioedema, and persistent pruritus for a duration

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exceeding six weeks [1]. With a global prevalence of 0.5-1% in the general population, CU inflicts a substantial burden that extends beyond the physical manifestations, significantly impairing patients' mental well-being, sleep quality, and overall social functioning [2]. The pathogenesis of CU is multifactorial and complex, primarily driven by immune dysregulation, aberrant release of histamine from mast cells and basophils, and impaired systemic metabolism of histamine [3]. This intricate pathophysiology underpins the persistent nature of the symptoms and presents a significant therapeutic challenge. While second-generation non-sedating antihistamines (sgAHs) represent the established first-line therapy, a considerable proportion of patients—approximately 40%—exhibit an inadequate response, remaining refractory or only partially responsive to standard or even increased doses [4]. This prominent treatment gap underscores the critical need for the development of alternative or adjunctive therapeutic strategies that address the underlying pathogenic mechanisms beyond mere receptor blockade.

Histamine, a key mediator of allergic and inflammatory responses, plays a central role in the pathophysiology of CU [5]. It is released from mast cells and basophils upon allergen exposure, binding to H1 and H2 receptors to induce vasodilation, increased vascular permeability, and pruritus [6]. Diamine Oxidase (DAO) is a critical enzyme responsible for the metabolism of extracellular histamine, primarily in the small intestine, and its deficiency or reduced activity can lead to histamine accumulation and exacerbation of CU symptoms [7]. Previous randomized controlled trials have shown that oral DAO supplementation can effectively reduce urticaria activity scores in patients with CU [8], supporting its potential as a targeted therapy for histamine-mediated symptoms.

In addition to histamine dysregulation, immune imbalance and vitamin D deficiency are closely associated with CU progression [9]. Vitamin D exerts immunomodulatory effects by binding to vitamin D receptors (VDR) expressed on immune cells such as T cells, B cells, and dendritic cells, regulating inflammatory pathways and suppressing excessive allergic responses [10]. Clinical studies have demonstrated that high-dose vitamin D3 supplementation can significantly improve symptom severity and quality of life in CU patients [11]. Probiotics, particularly Bifidobacterium longum strain BB536, have also been shown to modulate the gut-immune axis, restore immune homeostasis, and alleviate allergic symptoms including urticarial [12]. The synergistic effects of DAO, vitamin D, and probiotics may provide a comprehensive approach to addressing the multifactorial pathogenesis of CU.

Given the synergistic potential of targeting histamine metabolism, correcting vitamin D deficiency, and modulating gut immunity, a multi-targeted intervention may offer a more comprehensive and effective strategy for CU management. This exploratory study aimed to evaluate the efficacy and safety of precisely such an intervention—NatureU Yan, a functional food product combining active DAO, vitamin D, and Bifidobacterium longum BB536. The study was designed as a single-center, single-arm trial involving 19 adult CU patients (5 males, 14 females; mean age 39.47 ± 14.65 years) who received daily supplementation for 28 consecutive days. The primary objectives were to assess changes in disease control using the Urticaria Control Test (UCT), symptom severity via the 7-day Urticaria Activity Score (UAS7), and health-related quality of life through the Dermatology Life Quality Index (DLQI). Safety was rigorously monitored throughout the study period. This investigation seeks to provide preliminary clinical evidence for the application of this multi-targeted nutritional strategy as a safe and effective adjunctive therapy for patients with chronic urticaria

Subjects and Methods

This study aims to evaluate the effects of a new composite product containing active Diamine Oxidase (DAO), vitamin D, and Bifidobacterium longum BB536—NatureU Yan—on disease control, symptom severity, and quality of life in patients with chronic urticaria.

This trial is a single-center clinical study. It aims to recruit 19 participants, with at least 14 participants expected to complete the experiment.

Inclusion criteria

1. Adults aged 18-65 years, male or female;
2. Diagnosed with chronic urticaria by dermatologists based on clinical symptoms and medical history;
3. Presence of typical wheals accompanied by pruritus and/or angioedema;
4. Urticaria Control Test (UCT) score <12 or 7-day Urticaria Activity Score (UAS7) ≥7 at baseline;
5. Ability to comply with the study protocol, maintain normal healthy living habits during the study period, refrain from alcohol consumption, and avoid allergenic foods;
6. Signed written informed consent after fully understanding the study content, procedures, and potential adverse reactions.

Exclusion criteria

1. Severe visceral diseases (e.g., heart disease, kidney disease) that may affect drug metabolism;
2. Known allergies to any ingredients of the test product;
3. Comorbidities of other skin diseases or systemic diseases that may affect urticaria manifestations;
4. Participation in other clinical trials or use of prohibited medications for urticaria treatment;
5. Severe smoking, alcoholism, or other bad living habits that may affect study results;
6. Severe psychological disorders or cognitive impairments that may affect study compliance;
7. Dietary restrictions due to religious or personal reasons that prevent adherence to study requirements;
8. Abnormal laboratory test results (blood routine, liver and kidney function, etc.) beyond the normal range;
9. Special populations: minors, pregnant or lactating women, individuals with a history of liver or kidney diseases, and long-term medication users;
10. Other factors deemed inappropriate for study participation by investigators.

Criteria for withdrawal

1. All participants have the right to withdraw from the study at any time, regardless of the reason.
2. Severe adverse events during the study that require discontinuation of intervention;
3. Failure to comply with the study protocol (e.g., missed doses exceeding 3 days, consumption of prohibited foods/ medications);
4. Termination of the study by the sponsor or investigators for scientific or ethical reasons.

The workflow of the trial

The study implementation process consists of three phases: the screening period, the intervention period, and the end-of-study assessment.

- **Test Food:**

NatureUYan. Note: NatureUYan is provided by OmniSolutions Laboratory Holdings Limited. The product was manufactured by Unipharm Healthy Manufacturing Co. Ltd (New Zealand), with a manufacturing date of 20240509 and a shelf life of 24 months.

- **Outcome Measures:**

Urticaria Control Test (UCT): The Urticaria Control Test is a validated instrument used to assess the level of disease control over a recent period. The total score ranges from 0 to 16, with a higher score indicating better disease control. A score of ≥12 points is generally interpreted as indicative of well-controlled urticaria, whereas a score of <12 points suggests inadequately controlled disease.

- **Urticaria Activity Score over 7 Days (UAS7):** The Urticaria Activity Score is calculated daily based on the number of wheals and the intensity of pruritus. The daily score ranges from 0 to 6. The UAS7 is the sum of the daily scores over seven consecutive days, yielding a maximum possible score of 42. A UAS7 score of <7 signifies low disease activity, while a score of >28 indicates high disease activity and severe symptom burden.

- **Dermatology Life Quality Index (DLQI):** The Dermatology Life Quality Index is a 10-item questionnaire used to evaluate the impact of skin disease on a patient's quality of life over the previous week. The total score ranges from 0 to 30. The scores are interpreted using the following banding: 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect. A higher DLQI score corresponds to a greater impairment in health-related quality of life.

During the screening period (Day -7 to Day 0), the research staff are responsible for selecting suitable participants based on the inclusion and exclusion criteria. They will collect baseline data, including demographic information, medical history, physical examination findings, and laboratory test results (blood routine, blood biochemistry, and urine routine). Participants will also complete baseline UCT, UAS7, and DLQI assessments. Once participants meet all criteria, fully understand the study process, and voluntarily sign the informed consent form, they are formally enrolled in the trial.

- **Once all participants are enrolled, the research staff will arrange the intervention according to the following procedures:**

1. On Day 0, participants receive the test product at the study center and are instructed to take one tablet 20 minutes before dinner once daily for 28 consecutive days. It is preferable to take the product before the evening meal.
2. Participants are required to return to the study center for follow-up visits on Day 14 and Day 28. During these visits, they will complete the UCT, UAS7, and DLQI assessments and report any occurrence of adverse events.
3. Throughout the intervention period (Day 0 to Day 28), participants should maintain their usual diet and routine activities unless otherwise instructed. Any deviations from the study protocol or use of concomitant medication should be recorded and reported.

At the end of the study (Day 28), participants undergo a final physical examination and repeat laboratory tests (blood routine, blood biochemistry, and urine routine) to assess safety. All study-related data, including questionnaire responses, safety records, and compliance information, are collected and verified by the research staff.

The trial is considered complete when all participants have finished the 28-

day intervention, completed the required assessments, and all data have been reviewed and finalized.

Data statistics and analysis

All data were analyzed using SPSS 27.0 statistical software, and graphs were generated using Graphpad Prism 10. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Paired t-tests were used to compare differences in outcome measures (UCT, UAS7, DLQI) between baseline and post-intervention (Day 14 and Day 28). The change rate was calculated as [(post-intervention value - baseline value)/baseline value] × 100%. A two-tailed $p < 0.05$ was considered statistically significant, with $p < 0.01$ indicating highly significant difference and $p<0.001$ indicating extremely significant difference.

Participant information

A total of 24 participants were screened, and 19 were enrolled after eligibility verification (5 males, 14 females), with a completion rate of 100%. The demography and baseline characteristics of the participants are summarized in table 1 and table 2. The mean age was 39.47 ± 14.65 years, with a mean height of 162.49 ± 6.77 cm, mean weight of 59.82 ± 8.95 kg, and mean BMI of 22.90 ± 2.47 kg/m^2. The baseline laboratory parameters were within the normal range, including mean fasting blood glucose of 5.23 ± 0.51 mmol/L, mean systolic blood pressure of 113.21 ± 11.85 mmHg, and mean diastolic blood pressure of 78.16 ± 7.14 mmHg. The baseline UCT score was 5.21 ± 2.39, UAS7 score was 29.37 ± 6.87, and DLQI score was 15.21 ± 5.18, indicating poor urticaria control, high symptom activity, and severe impairment of quality of life.

Table 1: Participant demography.

Item	Information
Gender	Male and Female
Age	18 ~ 65
Recruit Number	24
Number of Participants Screened and Enrolled	19
Number of Withdrawal Participants	5
Validate participant	19

Table 2: Participant baseline characteristics ($\bar{x} \pm s$).

Parameters	Values
Age (years)	39.47 ± 14.65
Height (cm)	162.49 ± 6.77
Weight (kg)	59.82 ± 8.95
BMI (kg/m²)	22.90 ± 2.47
Fasting blood glucose (mmol/L)	5.23 ± 0.51
Systolic blood pressure (mmHg)	113.21 ± 11.85
Diastolic blood pressure (mmHg)	78.16 ± 7.14
Waist circumference (cm)	78.26 ± 8.85
UCT score	5.21 ± 2.39
UAS7 score	29.37 ± 6.87
DLQI score	15.21 ± 5.18

Results

Efficacy on Urticaria Control (UCT Score)

As shown in table 3 and figure 1, the UCT score showed a significant upward trend with prolonged intervention. After 14 days of intervention, the mean UCT score increased from 5.21 ± 2.39 to 9.68 ± 3.07, with a change rate of 85.86% ($p < 0.001$). After 28 days of intervention, the mean UCT score further increased to 14.11 ± 3.09, with a change rate of 170.71% ($p < 0.001$), and the score exceeded 12 points, indicating ideal urticaria control.

Efficacy on Urticaria Activity (UAS7 Score)

The UAS7 score significantly decreased after intervention (Table 4, figure 2). At baseline, the mean UAS7 score was 29.37±6.87, indicating high symptom activity. After 14 days of intervention, the score decreased to 17.79 ± 9.98, with a change rate of -39.43% ($p < 0.001$). After 28 days of intervention, the score further reduced to 5.63±6.30, with a change rate of -80.82% ($p < 0.001$), which was below 7 points, indicating low urticaria activity.

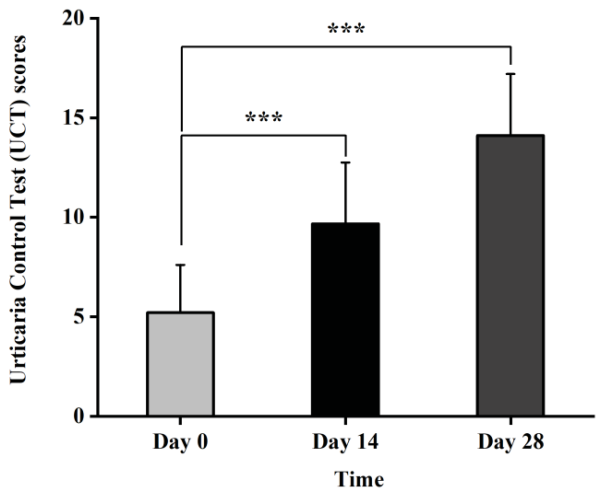

Figure 1 Changes in Urticaria Control Test (UCT) scores before and after 14 days and 28 days of intervention. Data are presented as mean ± standard deviation. ***$p < 0.001$ compared with baseline.

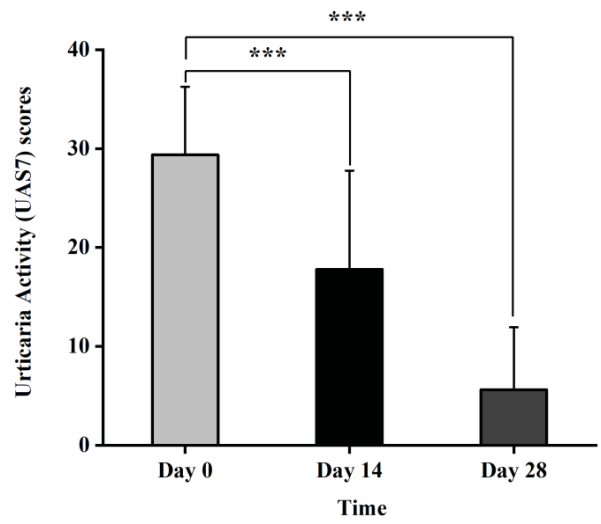

Figure 2 Changes in 7-day Urticaria Activity Score (UAS7) before and after 14 days and 28 days of intervention. Data are presented as mean ± standard deviation. ***$p < 0.001$ compared with baseline.

Efficacy on Quality of Life (DLQI Score)

The DLQI score showed a significant downward trend with intervention (Table 5, figure 3). The baseline mean DLQI score was 15.21 ± 5.18, indicating severe impairment of quality of life. After 14 days of intervention, the score decreased to 7.11 ± 5.80, with a change rate of -53.29% ($p < 0.001$), indicating moderate improvement. After 28 days of intervention, the score further decreased to 1.79 ± 3.68, with a change rate of -88.24% ($p < 0.001$), indicating minimal impact on quality of life.

Efficacy of Macromolecular technology: sustained-release DAO+ Macromolecular Vitamin D

DAO is a proteolytic enzyme highly susceptible to degradation by gastric acid, which limits its systemic bioavailability. NatureU employs an advanced macromolecular technology to protect DAO from enzymatic and acidic degradation in the stomach, enabling targeted release in the intestine and significantly improving its in vivo bioavailability.

Using our proprietary MASTER (Macromolecular Assembly for Stabilization and Targeted Enzyme Release) technology, we demonstrated markedly enhanced stability of DAO under both acidic conditions (simulating gastric fluid) and low-temperature storage. As shown in figure 4 (left panel), the enzymatic activity was evaluated across a range of pH values. The blue line represents unprotected DAO, while the red line shows macromolecular-protected DAO. Under acidic conditions, the protected DAO maintained 20–30% higher enzymatic activity compared to the unprotected form. Furthermore, as illustrated in figure 4 (right panel), after 30 days of storage at 4°C, the macromolecular-protected DAO retained 4.5 times higher activity than conventional DAO.

Table 3: Changes in UCT score before and after intervention ($\bar{x}$ ± s).

Time Points	UCT Score	Change Rate (%)	*p* - value
Baseline (Day 0)	5.21 ± 2.39	-	-
Day 14	9.68 ± 3.07	85.86	<0.001
Day 28	14.11 ± 3.09	170.71	<0.001

Table 4: Changes in UAS7 score before and after intervention ($\bar{x}$ ± s).

Time Points	UAS7 Score	Change Rate (%)	*p* - value
Baseline (Day 0)	29.37 ± 6.87	-	-
Day 14	17.79 ± 9.98	-39.43	<0.001
Day 28	5.63 ± 6.30	-80.82	<0.001

Table 5: Changes in DLQI score before and after intervention ($\bar{x} \pm s$).

Time Points	DLQI Score	Change Rate (%)	*p* - value
Baseline (Day 0)	15.21 ± 5.18	-	-
Day 14	7.11 ± 5.80	-53.29	<0.001
Day 28	1.79 ± 3.68	-88.24	<0.001

PS. $p < 0.001$ means statistical significance.

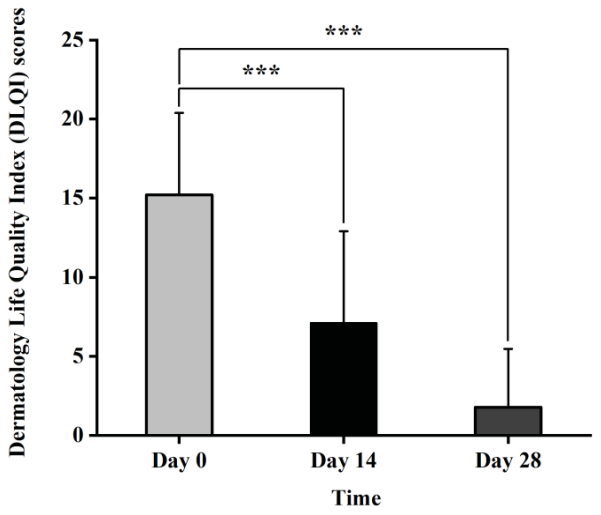

Figure 3 Changes in Dermatology Life Quality Index (DLQI) scores before and after 14 days and 28 days of intervention. Data are presented as mean ± standard deviation. ***p < 0.001 compared with baseline.

Safety evaluation

During the 28-day intervention period, the product demonstrated a favorable safety and tolerability profile. None of the 19 enrolled participants reported any adverse events, including but not limited to gastrointestinal discomfort, skin rashes, or systemic allergic reactions. Comprehensive laboratory investigations conducted after the intervention—encompassing blood routine, blood biochemistry (with emphasis on liver and renal function markers), and urinalysis—revealed no clinically significant deviations from baseline values. Based on the absence of subjective complaints and the stability of objective laboratory parameters, the principal investigator confirmed that NatureU Yan is well-tolerated and exhibits a reliable safety profile in the management of chronic urticaria patients presenting with typical symptoms of wheals, pruritus, and/or angioedema.

Data availability statement

All data generated or analyzed during this study are included in this published article, and further data (if any) is available from the corresponding author upon reasonable request

Discussion

This exploratory study evaluated the efficacy and safety of NatureU Yan, a food product containing DAO, vitamin D, and Bifidobacterium longum strain BB536, in 19 CU patients. The results showed that 14 and 28 days of intervention significantly improved urticaria control, reduced symptom activity, and enhanced quality of life, with a favorable safety profile. These findings support the potential of NatureU Yan as an adjunctive therapy for CU management.

The significant improvement in UCT, UAS7, and DLQI scores observed in this study is consistent with the synergistic mechanisms of the active ingredients. DAO, as a key histamine-metabolizing enzyme, plays a critical role in reducing extracellular histamine accumulation [13]. The polymer-based controlled-release technology used in NatureU Yan protects DAO from gastric acid degradation, ensuring targeted release in the small intestine and maintaining its enzymatic activity, which is supported by in vitro studies showing that protected DAO retains 20-30% higher activity under acidic conditions and 4.5-fold higher stability during storage compared with free DAO. A previous randomized controlled trial by Yacoub, et al. [14] demonstrated that oral DAO supplementation reduced UAS7 scores by 3.8 ± 1.2 points in antihistamine-refractory CU patients, which is consistent with the significant reduction in UAS7 observed in our study (23.74 points reduction after 28 days), highlighting the potent histamine-lowering effect of DAO.

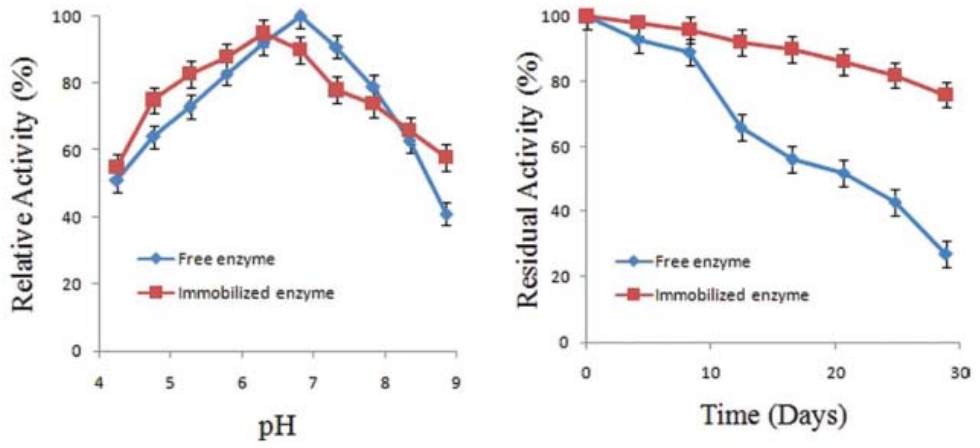

Figure 4 Enzymatic activity of unprotected and macromolecular-protected DAO under varying pH conditions (simulating gastric to intestinal environments) and after 30-day storage at 4°C. Data are presented as mean ± standard deviation.

Vitamin D and Bifidobacterium longum strain BB536 contribute to the therapeutic effect by regulating immune homeostasis. Vitamin D binds to VDR on immune cells to suppress excessive inflammatory responses and promote immune tolerance. Oguz, et al. [15] reported that vitamin D supplementation significantly improved UAS4 and CU-Q2oL scores in CU patients with vitamin D deficiency, and a systematic review showed that high-dose vitamin D3 supplementation alleviates CU symptoms [16]. Probiotics such as Bifidobacterium longum strain BB536 modulate the gut-immune axis, enhance intestinal barrier function, and reduce the production of pro-inflammatory cytokines. Xiao, et al. [12] demonstrated that BB536 supplementation improved pollen allergy symptoms, and similar immunomodulatory effects may contribute to the reduction of urticaria activity in our study.

This study has several limitations. First, it is a single-arm, open-label study without a control group, which may introduce bias due to placebo effect. Second, the sample size is small (n = 19), and the study duration is 28 days, limiting the generalizability of the results and the assessment of long-term efficacy. Third, the study did not measure serum DAO activity, histamine levels, or vitamin D concentrations, which could provide direct evidence for the mechanism of action. Future studies should address these limitations by conducting large-scale, randomized, double-blind, placebo-controlled trials with longer follow-up periods, and incorporating laboratory biomarkers to clarify the underlying mechanisms.

Despite these limitations, the significant improvements in key clinical outcomes and favorable safety profile observed in this study provide valuable preliminary evidence for the use of NatureU Yan in CU management. Given the unmet needs of antihistamine-refractory CU patients, this product offers a novel, well-tolerated adjunctive therapy option that targets multiple pathogenic pathways, including histamine metabolism and immune regulation.

Conclusion

In conclusion, this single-center, single-arm, open-label exploratory study demonstrates that 28-day intervention with NatureU Yan, a food containing active DAO, vitamin D, and Bifidobacterium longum strain BB536, significantly improves urticaria control, reduces symptom activity, and enhances quality of life in CU patients. The product exhibits a reliable safety profile with no adverse events reported. The synergistic effects of the active ingredients,

combined with advanced controlled-release technology, contribute to its therapeutic efficacy. Although the study has limitations such as small sample size and lack of a control group, the results support the potential clinical application of NatureU Yan in CU management. Future large-scale, randomized controlled trials are warranted to confirm these findings and evaluate long-term efficacy and safety.

Acknowledgment

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Author contribution statement

Lorry Luo and Luke Law conceived and designed the work that led to the submission, acquired data. Naining Zhang experimented and agreed 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. Miexin Yang drafted, revised the manuscript, and approved the final version.

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Role of funders

The funders proposed the conduct of the trial but played no role in the interpretation of the results.

Ethical approval

The study protocol was approved by the Ethics Committee of Daoxian People's Hospital (Approval No.: 2024080001) on August 20, 2024. All procedures were conducted in accordance with the Declaration of Helsinki and relevant national regulations.

Competing interests

All authors declare no conflicts of interest related to this study.

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