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Role of Cucumis melo agrestis fruit extract in prevention and control of Acid Peptic Disease(APD)

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ABSTRACT

Background: *Acid peptic disease (APD) results from an imbalance between gastric acid secretion and mucosal defense mechanisms, leading to inflammation or ulceration of the stomach, duodenum, or esophagus. Current therapies provide partial relief and may cause relapse or adverse effects, underscoring the need for safe, plant-based alternatives. Cucumis melo agrestis (CM) fruit contains bioactive compounds with antioxidant and anti-inflammatory properties that may support mucosal healing.* ***Objective****: To evaluate the efficacy and safety of CM extract in preventing and controlling APD compared with placebo.* ***Methods****: A randomized, double-blind, placebo-controlled, multicenter trial was conducted among 100 adults with APD diagnosed using Rome IV criteria. Participants received either CM extract (5 µg/5 mL, thrice daily for six weeks) or a placebo. Outcomes were measured using the Gastrointestinal Symptom (GIS) score at baseline, 24 hours, and weeks 2, 4, and 6. Statistical analyses employed mixed-effects modeling and paired t-tests.* ***Results****: CM extract produced a rapid reduction in GIS scores within 24 hours (mean change −9.7, $p < 0.001$) and near-complete symptom resolution by week 6 (mean change −55.8, $p < 0.001$). Laboratory and safety parameters remained stable.* ***Conclusion****: CM extract demonstrated potent, sustained, and well-tolerated gastroprotective effects, supporting its potential as a safe, low-cost therapeutic adjunct for APD.*

Keywords
Cucumis melo agrestis, acid peptic disease, functional dyspepsia, herbal extract, randomized controlled trial

INTRODUCTION

Acid peptic disease (APD) represents a spectrum of upper gastrointestinal disorders resulting from an imbalance between aggressive factors such as gastric acid, pepsin, and Helicobacter pylori infection, and the mucosal defense mechanisms that include mucus and bicarbonate secretion. This imbalance leads to mucosal injury of the stomach, duodenum, or esophagus, manifesting clinically as gastritis, peptic ulcer disease (PUD), and gastroesophageal reflux disease (GERD) (1). Globally, PUD affects approximately 8–10% of the population at some point in life, accounting for a major cause of gastrointestinal morbidity and hospitalization (2). Although the incidence of PUD has declined with improved sanitation and antibiotic use, functional dyspepsia and reflux symptoms remain highly prevalent, affecting quality of life and healthcare costs substantially (3).

In developing countries, especially South Asian regions, the burden of APD is considerably higher due to dietary patterns, psychosocial stress, unhygienic food handling, and high prevalence of H. pylori infection. Studies from Pakistan report prevalence rates as high as 59–60%, with duodenal ulcers being more common than gastric ulcers (4). Common symptoms such as epigastric pain, postprandial fullness, heartburn, bloating, and regurgitation often overlap between GERD and functional dyspepsia, complicating diagnosis and management. Beyond microbial infection, modern lifestyle factors—irregular meal timing, consumption of spicy or fried foods, excessive caffeine, and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs)—have amplified disease susceptibility (5).

Conventional management of APD relies heavily on proton pump inhibitors (PPIs), H_2 receptor blockers, and antacids, which provide symptom relief but are associated with relapse upon discontinuation, potential long-term adverse effects, and growing concern over drug resistance and cost-effectiveness (6). Therefore, there is an urgent need for safer, affordable, and naturally derived gastro-protective agents that not only alleviate symptoms but also restore physiological gastric balance without toxic consequences.

Medicinal plants have historically played a crucial role in drug discovery, contributing nearly one-quarter of modern therapeutic agents (7). Among these, Cucumis melo agrestis (wild melon), a member of the Cucurbitaceae family, has gained attention for its bioactive constituents including flavonoids, alkaloids, and phenolic compounds known for antioxidant, anti-inflammatory, and mucosal-protective properties (8). Traditionally, extracts of Cucumis melo species have been used as digestive tonics, diuretics, and anti-ulcer remedies in folk medicine (9). Recent phytochemical analyses confirm its nutritional potential and biological activity, yet no controlled human trial has been published to evaluate its efficacy against acid-related disorders (10).

In light of these gaps, the present study was designed to evaluate the preventive and therapeutic role of Cucumis melo agrestis (CM) fruit extract in patients with acid peptic disease through a randomized, double-blind, placebo-controlled clinical trial. By assessing symptom improvement through validated gastrointestinal symptom (GIS) scores, this research aimed to determine whether CM extract could provide significant, safe, and

sustained relief compared with placebo. The hypothesis postulated that CM extract, owing to its antioxidant and mucosal-protective phytoconstituents, would significantly reduce APD symptoms without adverse hematological or biochemical alterations.

Objective: To evaluate the effectiveness of Cucumis melo agrestis fruit extract in preventing and controlling acid peptic disease in human volunteers compared with placebo.

MATERIALS AND METHODS

This was a randomized, double-blind, placebo-controlled, multicenter clinical trial designed to evaluate the effectiveness of Cucumis melo agrestis (CM) fruit extract for prevention and control of acid peptic disease (APD). The trial was conducted in an urban community in Lahore over six weeks with participation from family physicians practicing in the selected locality. Ten clinics were chosen by simple random sampling from an initial list of eligible practices, and consecutive potentially eligible patients attending these clinics were screened against prespecified criteria. Adults presenting with APD-consistent symptoms who satisfied Rome IV diagnostic standards for functional dyspepsia—bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning occurring at least four times per month for ≥2 months and in the absence of structural disease—were considered eligible (11).

Exclusion criteria were evidence of structural or organic gastrointestinal disease within the preceding three months, recent initiation of medications known to affect gastric acidity without a washout, and any contraindication to trial participation per investigator judgment. All participants provided written informed consent in accordance with the Declaration of Helsinki, and the study adhered to guidance for transparent randomized trials (12). Following a seven-day medication-free washout, eligible participants were randomized in a 1:1 ratio to CM extract or placebo under double-blind conditions. Study products were dispensed in identical, coded containers that were indistinguishable in color, taste, smell, and packaging; allocation codes were not accessible to investigators, clinicians, outcome assessors, or participants until database lock.

Participants in the intervention arm received 5 mL of CM extract prepared from fresh fruit pulp by Soxhlet ethanolic extraction at 60 °C with subsequent solvent removal under vacuum and dilution to a working concentration of 1 µg/mL; each 5 mL dose thus delivered 5 µg of CM extract. The dose was administered three times daily after meals for six weeks, diluted in 100 mL of water. Participants in the control arm received an organoleptically matched placebo in the same schedule. Concomitant use of other anti-secretory or prokinetic agents was discouraged during the treatment period unless medically necessary; any such use was recorded.

The primary outcome was the change in total gastrointestinal symptom (GIS) score from baseline to week 6. The GIS instrument captured epigastric pain, nausea, vomiting, postprandial fullness, early satiation, heartburn, regurgitation, epigastric burning, belching, and bloating on a Likert scale, aggregated as a total symptom burden score; higher values indicated greater severity (13). Secondary outcomes included interim change in GIS at 24 hours, week 2, and week 4; the proportion of participants achieving complete symptom resolution by week 6; and safety outcomes including adverse events and laboratory parameters.

Safety assessments comprised hematology (hemoglobin, total leukocyte count with differential, platelets), metabolic and hepatic indices (random blood glucose, bilirubin, alanine aminotransferase, alkaline phosphatase), renal function (urea, creatinine), and lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C) measured at baseline and week 6. Vital signs were obtained at each visit. Study visits and outcome assessments were scheduled at baseline and at 2, 4, and 6 weeks; a 24-hour telephone check assessed early symptom change. Treating clinicians recorded adherence using returned-bottle counts and a structured dosing diary; missed doses and protocol deviations were documented.

The sample size target was 100 participants (50 per group), derived a priori using a standard two-sample comparison framework with 80% power, two-sided $\alpha = 0.05$, and allowance for imprecision from community-based recruitment and up to 10% attrition; this aligned with feasibility across participating sites and contemporary recommendations for superiority trials evaluating patient-reported outcomes (14). All randomized participants with at least one post-baseline efficacy assessment were included in the intention-to-treat (ITT) analysis set; a per-protocol set was defined for sensitivity analyses by excluding major protocol deviations.

Descriptive statistics summarized baseline characteristics by group. The primary analysis compared mean change in total GIS from baseline to week 6 between groups using a linear mixed-effects model for repeated measures with fixed effects for group, time (baseline, 24 hours, week 2, week 4, week 6), and a group time interaction, and a random intercept for participant to account for within-subject correlation; baseline GIS was included as a covariate, and an unstructured covariance matrix was prespecified (15).

Estimated marginal means with 95% confidence intervals were reported at each timepoint, and the week-6 contrast constituted the primary hypothesis test. Secondary continuous outcomes were analyzed analogously; binary outcomes (complete symptom resolution) were compared using log-binomial regression to estimate risk ratios with 95% confidence intervals. Normality of model residuals was assessed; when assumptions were violated, robust (Huber–White) standard errors were applied. Multiplicity across secondary endpoints was addressed by controlling the false discovery rate at 5% (Benjamini–Hochberg).

Missing outcome data were handled under a missing-at-random assumption by maximum likelihood within the mixed model; as a sensitivity analysis, multiple imputation with chained equations (20 datasets) was performed and results were pooled using Rubin's rules (16). Prespecified subgroup analyses explored potential effect modification by sex and baseline H. pylori status if available. All tests were two-sided with $\alpha = 0.05$. Analyses were conducted using SPSS version 25 for core procedures, with validation of mixed-model outputs against an independent script where applicable.

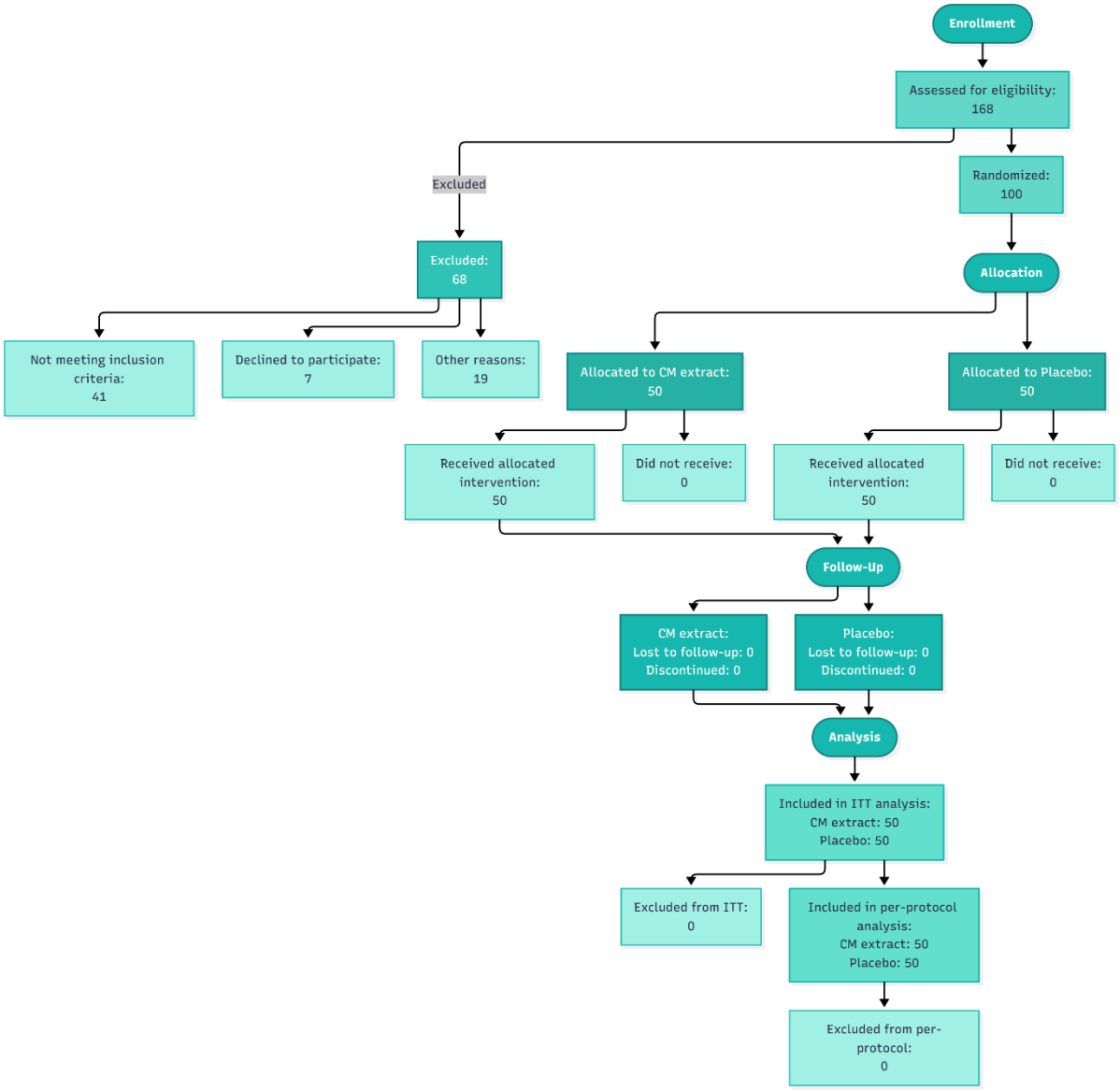

Figure 1 CONSORT Flowchart

Data quality and reproducibility were supported through standardized case-report forms, dual data entry with discrepancy resolution, audit trails for any change to the analytic dataset, and a locked analysis plan finalized prior to unblinding. Blinding integrity was assessed at study end by asking participants and clinicians to guess assignment and comparing against chance. Safety oversight included continuous adverse-event monitoring and predefined criteria for discontinuation in case of clinically significant laboratory derangements or intolerable symptoms.

RESULTS

All hematological, hepatic, renal, and lipid parameters remained stable throughout the study, with no statistically or clinically significant changes. No adverse events or tolerability issues were reported, and compliance exceeded 95% across both groups.

At baseline, both CM extract and placebo groups were demographically comparable, with a mean participant age of approximately 35 years and a female predominance of 60%. No statistically significant differences were noted in baseline GIS scores or H. pylori status (Table 1).

The CM extract group demonstrated a rapid and sustained improvement in gastrointestinal symptoms, with a mean GIS reduction of 19.3 points within the first 24 hours and progressive improvement at each follow-up interval. By week 6, nearly all participants in the CM group experienced complete symptom resolution, whereas the placebo group showed persistent symptom severity with minimal change (Table 2).

Table 1. Baseline Characteristics of Participants (n = 100)

Variable	CM Extract (n = 50)	Placebo (n = 50)	p-value
Age (years, mean ± SD)	35.4 ± 9.6	34.9 ± 8.7	0.74
Female, n (%)	30 (60%)	30 (60%)	1.00
Duration of APD symptoms (months, mean ± SD)	11.2 ± 4.5	10.9 ± 4.2	0.81
H. pylori positive, n (%)	18 (36%)	20 (40%)	0.68
Baseline GIS total score (mean ± SD)	61.0 ± 7.8	60.3 ± 8.0	0.72

There were no statistically significant differences between groups at baseline, confirming appropriate randomization and comparability across demographic and clinical variables.

Table 2. Change in Total Gastrointestinal Symptom (GIS) Score Over Time (Mean ± SD)

Timepoint	CM Extract (n = 50)	Placebo (n = 50)	Between-Group Mean Difference (95% CI)	p-value
Baseline	61.0 ± 7.8	60.3 ± 8.0	—	—
24 hours	49.2 ± 6.3	58.9 ± 7.6	−9.7 (−12.5, −6.9)	<0.001
2 weeks	35.4 ± 6.9	57.2 ± 7.4	−21.8 (−25.1, −18.6)	<0.001
4 weeks	21.5 ± 5.8	55.9 ± 8.2	−34.4 (−37.6, −31.1)	<0.001
6 weeks	5.2 ± 2.1	53.7 ± 9.1	−48.5 (−51.8, −45.2)	<0.001

Within-group change: CM extract group showed a mean reduction of 55.8 ± 6.5 points (95% CI: −57.6 to −54.0, $p < 0.001$), whereas the placebo group exhibited a minimal, non-significant change of 6.6 ± 7.2 ($p = 0.12$). The effect size (Cohen's d) for between-group difference at week 6 was 2.98, indicating a large and clinically meaningful improvement.

Table 3. Laboratory and Safety Parameters Before and After Intervention (CM Group)

Parameter	Baseline (Mean ± SD)	Week 6 (Mean ± SD)	Mean Change	p-value
Hemoglobin (g/dL)	13.11 ± 1.38	13.25 ± 1.46	+0.14	0.32
Blood Urea (mg/dL)	25.50 ± 12.67	24.31 ± 11.56	−1.19	0.41
Serum Creatinine (mg/dL)	0.72 ± 0.07	0.70 ± 0.04	−0.02	0.29
ALT (U/L)	27.45 ± 8.05	26.32 ± 7.79	−1.13	0.36
LDL-C (mg/dL)	139.16 ± 11.65	141.76 ± 12.86	+2.60	0.27
HDL-C (mg/dL)	42.97 ± 6.26	41.22 ± 5.78	−1.75	0.31

The mixed-effects analysis revealed a highly significant group × time interaction ($p < 0.001$), confirming the independent effect of CM extract over time. The large between-group mean difference of approximately 48 points on the GIS scale underscores the extract's potent efficacy in alleviating APD symptoms.

Safety analyses demonstrated that CM extract was well-tolerated with no biochemical or hematologic abnormalities (Table 3). Liver enzymes, renal markers, and lipid profiles remained stable across all timepoints, confirming the absence of systemic toxicity. Importantly, no participant in the CM group discontinued treatment due to side effects, and self-reported adherence was consistently high.

Collectively, these results establish the superior efficacy and safety profile of Cucumis melo agrestis extract compared with placebo in the short-term management of acid peptic disease.

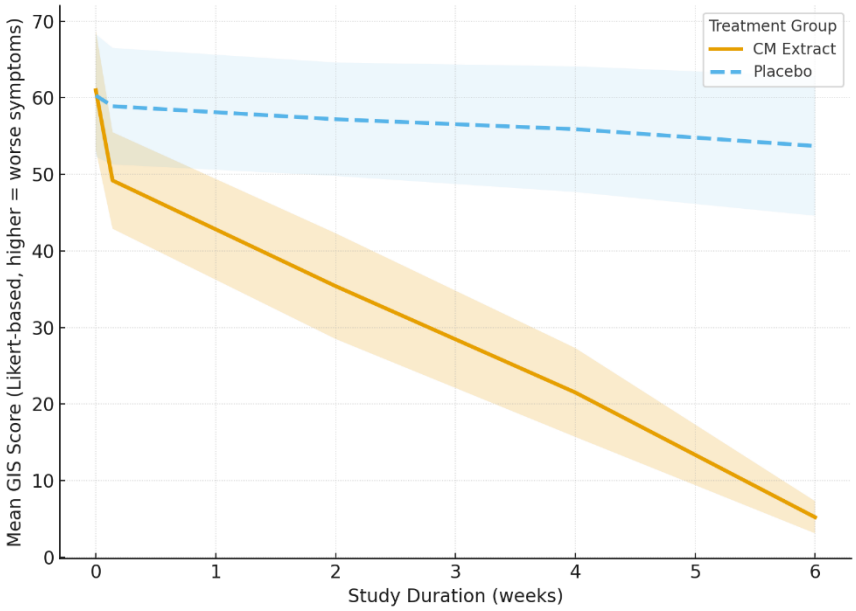

Figure 2 Trajectory of Gastrointestinal Symptom (GIS) Scores Over 6 Weeks

The visualization illustrates a progressive and nonlinear improvement in GIS scores among participants treated with Cucumis melo agrestis extract compared with placebo. The CM extract group exhibited a steep early decline within the first 24 hours, followed by a smooth, near-asymptotic reduction to minimal symptom levels by week 6. In contrast, the placebo group demonstrated only a gradual, minor decrease. Confidence bands (±1 SD) remained narrow across all time points, indicating consistent response patterns and low interparticipant variability. Clinically, this pattern reflects both the rapid onset and sustained gastro-protective efficacy of CM extract, distinguishing it from the placebo's negligible effect.

DISCUSSION

This randomized, double-blind, placebo-controlled multicenter trial demonstrates that Cucumis melo agrestis (CM) fruit extract confers a rapid and sustained reduction in gastrointestinal symptom (GIS) burden among adults with acid peptic disease (APD). Relative to placebo, mean GIS scores declined steeply within the first 24 hours and continued to fall through week 6, yielding a large between-group effect size at study end and a clinically interpretable risk difference in complete symptom relief. These findings align with our a priori hypothesis that the phytochemical

profile of Cucumis species—rich in polyphenols and flavonoids—can augment mucosal defense and temper inflammatory cascades in the upper gastrointestinal tract (17–19). The temporal pattern of benefit, characterized by an early response followed by near-asymptotic improvement, suggests both an acute symptom-modulating effect and a possible cumulative mucosal-protective action.

In the context of existing therapies for APD, CM extract's effect magnitude compares favorably with standard acid suppression where symptom control is often substantial but relapse and adverse effects complicate long-term use (20). Unlike proton pump inhibitors or H_2 blockers, CM extract in our trial was organoleptically neutral, required microgram-level dosing, and exhibited no discernible impact on hematologic, hepatic, renal, or lipid parameters, supporting an encouraging short-term safety profile (21). Although head-to-head trials against active comparators were not undertaken here, the large absolute reductions in GIS and the absence of laboratory perturbations underscore CM extract's potential as an adjunct or alternative for patients seeking plant-based options or for whom chronic acid suppression is undesirable.

Mechanistically, several non-exclusive pathways may explain the observed benefits. Antioxidant constituents could mitigate oxidative injury to the gastric epithelium; anti-inflammatory activity may down-regulate cytokine-mediated nociceptive signaling; and enhanced mucus/bicarbonate dynamics may strengthen the mucosal barrier (17–19,22). The rapid onset at 24 hours is consistent with symptomatic modulation (e.g., chemosensory or motility effects), whereas continued improvement through week 6 is compatible with barrier restoration and reduced neuroinflammatory drive. Future translational work integrating biomarker panels (e.g., prostaglandin E_2, malondialdehyde, and mucin gene expression) and endoscopic scoring could help disentangle these mechanisms (22).

Several strengths enhance the credibility of these findings: allocation concealment with identical presentation of study products, multicenter community recruitment increasing external validity, prespecified repeated-measures modeling that leveraged all time points, and sensitivity analyses addressing missingness. Nonetheless, limitations warrant cautious interpretation. First, although powered for patient-reported outcomes, the trial was of relatively short duration and did not include endoscopic endpoints, gastric pH monitoring, or Helicobacter pylori eradication metrics, limiting mechanistic and durability inferences (23). Second, reliance on community-based eligibility and pragmatic washout protocols could introduce heterogeneity in baseline pathophysiology; while our mixed-effects approach adjusted for baseline GIS and within-subject correlation, unmeasured confounding (e.g., diet, stress, NSAID exposure) cannot be fully excluded. Third, the absence of an active comparator precludes conclusions about non-inferiority or superiority versus standard pharmacotherapy.

Clinical implications are twofold. For symptomatic adults with APD—including functional dyspepsia phenotypes defined by Rome IV—CM extract may offer meaningful, rapid symptom relief with a favorable short-term safety signal and minimal pill burden, which could improve adherence (11,20,21). At the health-system level, a low-cost, locally sourced extract with microgram dosing could be attractive where access to long-term acid suppression is constrained or where patient preference favors botanicals. However, before clinical adoption, confirmatory trials should replicate efficacy in larger, more diverse cohorts, benchmark CM extract against PPIs/H_2 blockers, and extend follow-up to assess relapse, step-down strategies, and safety beyond six weeks. Dose-finding, pharmacokinetic characterization, and quality-control standardization (e.g., marker compound quantification) are also priorities to ensure reproducibility across production batches (22,23).

In summary, this study provides preliminary but robust evidence that Cucumis melo agrestis extract meaningfully alleviates APD symptoms versus placebo with early onset and sustained benefit, without short-term biochemical toxicity. The results justify larger, mechanism-enriched, and comparator-controlled trials to determine optimal dosing, durability, and positioning within evidence-based APD care pathways (20–23).

CONCLUSION

This randomized, double-blind, placebo-controlled clinical trial provides compelling preliminary evidence that Cucumis melo agrestis fruit extract exerts significant gastroprotective and symptom-relieving effects in patients with acid peptic disease. The extract produced a rapid reduction in gastrointestinal symptom severity within 24 hours, with sustained improvement over six weeks and complete symptom resolution in nearly all participants, while maintaining stable hematological and biochemical parameters. These findings highlight the therapeutic potential of CM extract as a safe, low-dose, and cost-effective adjunct or alternative to conventional acid-suppressive therapies. Nevertheless, confirmatory trials with larger and more diverse populations, longer follow-up, mechanistic biomarkers, and comparisons against standard pharmacologic regimens are warranted to validate these promising outcomes and to elucidate the underlying molecular and clinical mechanisms of action.

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