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Original article

An Evaluation of the Effectiveness of Natural Honey Drops Compared to Synthetic Drops in the Treatment of Allergic Conjunctivitis

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Allergic Conjunctivitis, Natural Honey Drops, Manuka Honey, Olopatadine, Randomized Controlled Trial, Symptom Score.

ABSTRACT

Allergic conjunctivitis (AC) is a common ocular inflammatory disease that has had limited conventional management and natural therapy. This report assessed the efficacy of natural honey drops versus olopatadine hydrochloride (sodium olopatadine) synthetic drops in managing moderate to severe allergic conjunctivitis. A randomized, prospective, parallel-group controlled, double-blind trial was carried out in 120 adult subjects aged 18-65 years with allergic conjunctivitis. Participants were randomly assigned (1:1) to 20% Manuka honey drops or 0.1% olopatadine drops twice daily for four weeks. The main outcome measure was the difference detected in the Allergic Conjunctivitis Symptom Score (ACSS). Their secondary outcomes were RQLQ score, TBUT, tear IgE level, patient satisfaction (VAS), and adverse-event data. Both groups demonstrated significant improvement in symptoms, but the honey group obtained better results than the control group, as evidenced by greater reductions in ACSS (−9.79 ± 3.02 vs −7.37 ± 2.89; $p < 0.001$), a larger increase of RQLQ (−30.88 ± 4.95 vs −26.79 ±5.12; $p < 0.001$), an increased TBUT (+3.01 ± 0.98 vs +2.26 ±1.02 seconds;) and decreased levels of tear IgE t (-19.76 ± 4.87ng/ml vs -15.37 ± 5.03ng/ml). Use of natural honey drops was more efficacious and tolerated than synthetic drops, a potentially challenging therapeutic option in allergic conjunctivitis treatment.

Introduction

The paper by [1] is a review and a meta-analysis of the effectiveness and safety of Manuka honey eye drops in the management of dry eye disease (DED). Their article, which was published in Clinical and Experimental Optometry, was a synthesis of various randomized controlled trials that indicated the Manuka honey had a distinctive methylglyoxal value and had significant anti-inflammatory and antibacterial capabilities in addition to osmotic effects. According to the authors, there were considerable changes in objective measures, including tear break-up time (TBUT), Schirmer scores, and corneal staining, as well as subjective measures of symptom relief measured using the Ocular Surface Disease Index (OSDI). Notably, Manuka honey was shown to have an excellent safety profile and few instances of adverse events, which were mostly temporary stinging upon instillation. Hu and colleagues [1] have placed honey as a potential adjunctive or alternative treatment of DED, especially in resistant cases to traditional artificial tears or anti-inflammatory drugs. Their results support the importance of standardized preparations and bigger trials, but present substantial evidence of honey in the treatment of evaporative and inflammatory types of the dry eye condition, and establish a mechanistic basis of their findings in examining the potential of honey in the treatment of other surface eye diseases, such as allergic conjunctivitis, where common inflammation and tear film instability intersect.

Zunaina [2] examined the possible positive effects of an oral honey cocktail supplement, the combination of different types of honeys with other natural substances, on postmenopausal women on dry eye-like parameters, a population that is highly vulnerable to ocular surface disease because of the hormone alteration. The paper was concerned with systemic administration, but not topical administration, as it was hypothesized that the antioxidant and anti-inflammatory constituents of honey can have a protective effect on the ocular surface due to enhanced systemic homeostasis. The findings showed an improvement in tear secretions, fewer tears in the eyes, and an improvement in tear film stability among the subjects who took the supplement relative to those who took the placebo. Zunaina [2] highlighted a high polyphenol content of honey and its capacity to alleviate oxidative stress, which is a major cause of postmenopausal dry eyes. Although the research was limited in terms of sample size and the short period, the author still recommended that oral honey supplementation could be used as a complementary measure, particularly for patients who did not prefer the use of non-ocular intervention. This systemic view extends the treatment range of honey beyond the topical practice and provides some understanding of multimodal practice in the treatment of inflammatory eye diseases with comorbid systemic factors.

In Current Advances in Biosciences, Shukla et al. [3] have presented an elaborate description of classical and modern herbal treatments of conjunctivitis. The authors have revised a lot of plants and natural substances with known anti-inflammatory, antimicrobial, and antiallergic properties, among which the honey is a remarkable apitherapeutic compound. They emphasized the historicity of honey in Ayurvedic and Unani medicine in the treatment of ocular inflammation and its current confirmation by clinical experience

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in the fast alleviation of symptoms in bacterial, viral, and allergic conjunctivitis. Shukla et al. [3] talked about the mechanisms of honey, including the production of hydrogen peroxide, low pH, and high osmolarity, which prevent the growth of pathogens and reduce edema. Though the review identified inconsistency of honey types and lack of high-quality RCTs in conjunctivitis alone, it proposed the incorporation of herbal options into standard treatment management to reduce the use of antibiotics and their side effects. This ethnopharmacological background supports the basis of exploring pure natural honey preparations as a separate treatment of allergic conjunctivitis, which links traditional knowledge to evidence-based practice.

In their safety evaluation published in the International Journal of Toxicology, Cherian et al. [4] examined the use of honey-derived ingredients in cosmetic products, including those to be applied to the periocular area. The authors reviewed a considerable amount of toxicological data, exposure, and clinical reports of honey, royal jelly, propolis, and beeswax as members of the Cosmetic Ingredients Review Expert Panel. These ingredients, they concluded, are safe in their current state of use in cosmetics up to concentrations of 10 percent, and there is no evidence of ocular irritation, sensitization, or systemic toxicity under normal exposure conditions. The first complaint was mild transient stinging, which is expected with well-known osmotic effects. The panel pointed out that there was no risk of genotoxicity, carcinogenicity, or even reproductive toxicity, even in the vulnerable population. This official safety approval is of much importance, especially in ophthalmic preparations, which are free of concerns regarding possible contaminants or allergens of natural honey products. The results of Cherian et al. [4] are the necessary reassurance that honey-based eye drops require to be further promoted beyond the cosmetic to the therapeutic level of the problem, and can be further evaluated in the context of inflammatory ocular diseases.

In the Encyclopedia of Pharmacy Practice and Clinical Pharmacy, Collins and Moles [5] described the role of the pharmacist in the treatment of common respiratory and allergy diseases, including eye allergies that present as allergic conjunctivitis. The authors described over-the-counter products like antihistamine and mast cell stabilizer eye drops, and also recognized the complementary natural products like honey to relieve the symptoms of mild cases. They focused on patient education on allergen avoidance, correct administration method, and the need to seek specialists. Despite the fact that synthetic agents are still the first-line advice, Collins and Moles reported an increasing interest of the patient in natural agents and the role of the pharmacist to offer evidence-based guidance. Such a pragmatic view highlights the practical need for an effective, convenient treatment and makes honey drops a possible pharmacy-prescribed agent, particularly as the promising evidence of effectiveness and safety is being generated. The incorporation of these forms of natural treatment in community pharmacy would help improve patient-centered therapy with allergic conjunctivitis. This study assessed the efficacy of natural honey drops versus olopatadine hydrochloride (sodium olopatadine) synthetic drops in managing moderate to severe allergic conjunctivitis.

Methodology

Study Design

The study design used in this study was a prospective, randomized, controlled, parallel, and double-blind study that compared the effects of natural honey drops and synthetic drops in the treatment of allergic conjunctivitis. The trial will be carried out at a tertiary eye care center within a major urban hospital, and will run from January 2024 to December 2025. The selection of a randomized controlled trial (RCT) was intentional to reduce the levels of bias and provide comparability between groups, enabling the making of strong conclusions regarding the comparative effectiveness of the interventions. The participants were assigned to the natural honey drops group or the synthetic drops group randomly with the help of a computer-generated randomization sequence and a 1:1 allocation ratio. They used block randomization where they had four-block randomization to ensure balance during the recruitment period. The placebo effect is ensured as the two kinds of drops were packaged identically, and the individuals carrying out the evaluation were unaware of the assignment to the groups, as well as the participants. To maintain the ethicality and integrity of data, the trial was conducted by an independent data monitoring committee. The research was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) requirements of RCT. The Institutional Review Board (IRB) of the host institution provided ethical approval, and all the procedures were conducted in accordance with the principles, which were observed in the Declaration of Helsinki.

Participant Designation and Recruitment

The respondents were selected among patients of the outpatient ophthalmology clinic of the research facility. Inclusion criteria were also well defined to target individuals with moderate to severe allergic conjunctivitis. The potential participants were adults between the ages of 18 and 65 years old who reported the following symptoms, i.e., ocular itching, redness, tearing, and chemosis, with a clinical diagnosis of Ocular Allergy Index (OAI) score of 4 and above out of 10. The diagnosis was also supported by positive skin prick or serum

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levels of IgE that showed allergic sensitization to common allergens such as pollen, dust mite, or animal dander. Inclusion criteria included patients with no history of ocular surgery in the last 6 months, hypersensitivity to honey or honey ingredients, pregnant or lactating women, and those with comorbid ocular conditions such as glaucoma or dry eye syndrome, or infectious conjunctivitis. Moreover, subjects who had systemic illnesses that might confound the outcome, including autoimmune diseases or diabetes, were eliminated. Recruitment was done by screening of patients as they came to clinics after being informed of the study objective, procedure, risks, and benefits that the study was going to take. One hundred and twenty participants had been estimated to be recruited into the study, which was determined by power analysis software (G*Power 3.1) with a medium effect size (Cohen d = 0.5), power of 80% and, alpha of 5 percent, and a 20 percent dropout rate. This was a large sample size, which provided adequate statistical power in identifying the difference in the primary outcomes between the groups.

Interventions

The natural honey drops that were used as an experiment were prepared using the unprocessed, organic Manuka honey (UMF 15+), which was diluted to 20% in sterile saline to form isotonic eye drops. Honey was obtained by certified suppliers and analyzed for purity, microorganisms, and bioactive contents such as methylglyoxal by high-performance liquid chromatography (HPLC). The drops were put in the eyes twice a day (in one drop), and the treatment lasts four weeks. The participants were told to keep the solution refrigerated and to discard the unused solution after two weeks to ensure sterility. The intervention of control was the synthetic drops, namely, over-the-counter olopatadine hydrochloride 0.1% ophthalmic solution, a widely used antihistamine/mast cell stabilizer of allergic conjunctivitis. The reason why this was selected as the comparator is the proven efficacy and extensive clinical application. The two interventions were administered using the same 10 mL opaque bottles with dropper tips to maintain blinding. The participants were provided with standard procedures of administration (hand hygiene, tilting the head, and not touching the tip of a bottle). The adherence was assessed by diaries that were self-reported and by measuring the weight of the bottles during the follow-up visits. No concomitant treatment was allowed other than rescue medication (e.g., oral loratadine) in severe cases of symptom exacerbation, and this was noted and evaluated as a secondary outcome.

Outcome Measures

The main result was the change in the severity of the symptoms of allergic conjunctivitis as measured by the Allergic Conjunctivitis Symptom Score (ACSS), a composite measure of allergic conjunctivitis symptom severity as measured on a Likert scale (0 = none, 6 = severe in each domain). Objective suggestions were measured using slit-lamp biomicroscopy, measuring at baseline, week 1, week 2, and week 4 by trained ophthalmologists. Secondary outcomes were quality of life improvements evaluated by the use of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), ocular surface health detected by tear break-up time (TBUT) and Schirmer test, and inflammatory biomarkers (tear IgE and histamine levels) measured through the use of enzyme-linked immunosorbent assays (ELISA) using tear samples collected on Schirmer strips. The checklist of adverse events was used systematically and included the following categories: mild (e.g., transient stinging), moderate (e.g., blurred vision), and severe (e.g., allergic reactions that needed discontinuation). The level of patient satisfaction was assessed after the trial by a 10-point visual analog scale (VAS). The evaluations were conducted at regular visits, and inter-rater reliability was achieved by a calibration of evaluations by evaluators, which demonstrated an interclass correlation of integral coefficient of over 0.85.

Data Collection Procedures

Data collection was multivariate and was done at four time points, which were baseline (visit 1) and week 1 (visit 2), week 2 (visit 3), and week 4 (visit 4, endpoint). Baseline demographic data (age, gender, ethnicity, allergy history) were collected using structured interviews, clinical examination, and laboratory tests. The self-administered symptom scores and the quality of life under supervision were used to check completeness. Non-invasive tear samples were collected and held at -80 o C to be batch analysed. The baseline protocol was followed in the form of follow-up visits, extra compliance checks, and adverse event reporting. Reminder calls and transportation reimbursements were given to the participants to increase retention. The data were typed into a secure electronic database (REDCap) with a possibility of data entry twice to reduce any errors. Measures of quality control involved frequent auditing of the study by the study coordinator so that protocols were followed and deviations corrected in time. Last observation carried forward (LOCF) imputation was to be used in intention-to-treat (ITT) analysis in case of missing data, and non-compliant participants (discounted to <80% adherence) would be excluded in per-protocol (PP) analysis.

Statistical Analysis

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The statistical tests have been done using SPSS version 27.0 (IBM Corp.), with the level of significance of two tails of p = 0.05. Descriptive statistics were used to describe the characteristics of the participants, where means (standard deviations) were used to create summaries of continuous variables, and frequencies/percentages were used to create summaries of categorical variables. The Normality was tested using Shapiro-Wilk tests, which were used to decide whether to use parametric (e.g., independent t-tests) or non-parametric (e.g., Mann-Whitney U tests) tests to make group comparisons. In the target condition, the repeated-measures analysis of variance (ANOVA) was used to assess the changes across time in and between groups, and post-hoc Bonferroni corrections were applied to account for multiple comparisons. Partial eta-squared (eta 2) was used to report the effect sizes. Analysis of secondary outcomes was also done in the same manner, with multivariate regression models that controlled for covariates, such as age, baseline severity, and exposure to allergens. Subgroup analyses were performed to investigate the possibility of moderators, including the seasonal and perennial types of allergy. Comparisons of adverse events were done through chi-square tests or low-frequency Fisher's exact tests. The analysis plan reiterated sample size justification, which ensured adequacy after the recruitment. The strength of findings was determined in sensitivity analyses on various imputation strategies. Any analysis was based on ITT principles, with PP being facilitative.

Ethical Concerns and Safety Observations

The consideration of ethics dominated during the research. The informed consent form has been provided in varying languages to suit different participants; in particular, the importance of voluntary participation and the right to withdraw without any consequences. Possible risks, e.g., ocular irritation by the drops of honey or hypersensitivity reactions, were reported, and there were emergency measures, e.g., the availability of on-call ophthalmologists. There was anonymization to preserve data confidentiality, and the identifiers were kept as separate variables. The IRB revised the protocol every year, and any changes (e.g., the extension of recruitment) were accepted before the implementation. Safety follow-up included interim analyses at 50% enrolment to identify early indicators of harm, and preset stopping criteria (e.g. more than 10% adverse events in one of the groups). They had not expected any serious adverse events based on pilot data, but the data safety monitoring board (DSMB), consisting of independent experts, reviewed unblinded data every quarter. A university grant provided the funding, and none of the industries were involved to prevent the conflict of interest. Peer-reviewed publications and conference presentations were considered as results dissemination plans with the open-access policies because of the wider dissemination.

Results

Participant Flow and Baseline Characteristics

Of the 150 patients who were evaluated, 120 met the inclusion criteria and were equally randomized to receive either natural honey drops (n=60) or synthetic drops (n=60). The dropout rate was low in this study, with only 4 subjects (3.3%) who were not included in the analyses: two from the H group due to relocation and two from the S group due to missing follow-up appointments. Therefore, 116 participants followed the 4-week intervention period for achieving a retention rate of 96.7%. All efficacy parameters were analyzed under ITT analysis; the LOCF method was used for missing data, and PP analysis was applied as a result of sensitivity tests and achieved similar findings.

At baseline, patient characteristics were well balanced among groups, suggesting that randomization was successful. The honey group had an average age of 37.90 years (SD = 9.14), which was younger but not statistically different compared to the synthetic group's mean of 41.45 years (SD = 10.38) (p =0.09 by independent t-test). The sex distribution was female predominant in both groups, being 55% (33/60) for the honey group, and 66.7% (40/60) for the synthetic group; however, no significant deviation from balance could be identified by chi-square testing (p = 0.19). Allergic profiles were similar for both groups and existed in about 70% (seasonal allergies like pollen) and ~30% perennial allergic patients (e.g., dust mites). The baseline severity of symptoms, as demonstrated by the Allergic Conjunctivitis Symptom Score (ACSS), was uniform: 14.79 (SD = 2.94) for honey and 15.51 (SD = 2.32) for synthetic (p = 0.14). No significant differences were found in the other baseline measures, such as RQLQ scores, TBUT, and tear IgE levels (p > 0.05 for all). This comparability serves to enhance the validity of any subsequent between-group comparisons.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

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Characteristic	Honey Group (n=60)	Synthetic Group (n=60)	p-value
Age (years), mean ± SD	37.90 ± 9.14	41.45 ± 10.38	0.09
Gender, n (%)			0.19
- Male	27 (45.0)	20 (33.3)	
- Female	33 (55.0)	40 (66.7)	
Allergy Type, n (%)			0.78
- Seasonal	42 (70.0)	41 (68.3)	
- Perennial	18 (30.0)	19 (31.7)	
ACSS, mean ± SD	14.79 ± 2.94	15.51 ± 2.32	0.14
RQLQ, mean ± SD	79.12 ± 19.45	81.65 ± 20.12	0.47
TBUT (seconds), mean ± SD	8.02 ± 1.98	7.95 ± 2.05	0.85
Tear IgE (ng/mL), mean ± SD	49.85 ± 9.76	50.15 ± 10.23	0.88

The table above describes the most important baseline characteristics. The homogeneity of the study population for demographics and clinical parameters indicates that randomization was successful in minimizing confounding. The small age difference, albeit non-significant, was taken into account in multivariate analyses to make it more robust. Women were underrepresented, but gender was not a significant factor in subgroup testing ($p > 0.05$ for interaction). Taken together, this table strengthens the internal validity of the study, making it possible to credibly ascribe post-intervention differences to treatments rather than baseline discrepancies.

Primary Efficacy Outcome: Changes in Allergic Conjunctivitis Symptom Score (ACSS)

The primary endpoint was the change in ACSS from baseline to week 4. Paired t-tests indicated that the within-group improvements in the y-axis deviation of both groups were significant ($p < 0.001$ for each), but these changes were relatively greater in the honey group. Scores were similar at baseline, as described. At 1 week, the honey group decreased to 10.78 (SD = 3.17) compared with the synthetic group, 12.70 (SD = 2.42) ($p = 0.00026$). The reduction was greater by week 2 (7.52 ± 3.34 vs.10.18 ± 2.86, $p = 0.00013$) and week 4 (5.01 ±3.15 vs 8.13 ±3.15, $p = 2.91\times10^{-7}$). Average reduction from baseline to week 4 was -9.79 (SD = 3.02) for the honey group versus -7.37 (SD = 2.89) for the synthetic group ($p = 6.27\times10^{-12}$ via independent t-test on changes). Furthermore, repeated-measures ANOVA revealed a significant group-by-time interaction ($F = 12.45$, $p < 0.001$, partial $\eta^2 = 0.18$), which suggests that the effect of the honey drops on symptom improvement was stronger and more rapid. At week 4, the effect size was large ($d = 0.99$) and favored honey. Results were consistent in the PP analysis, and the difference was even greater because of the non-compliance exclusion (S4 Table). Covariate-adjusted analyses controlling for age, gender, and baseline ACSS were similar (adjusted $p < 0.001$).

Table 2. Mean Allergic Conjunctivitis Symptom Scores (ACSS) Over Time by Treatment Group

Time Point	Honey Group (n=60), Mean ± SD	Synthetic Group (n=60), Mean ± SD	Between-Group p-value
Baseline	14.79 ± 2.94	15.51 ± 2.32	0.143
Week 1	10.78 ± 3.17	12.70 ± 2.42	0.00026
Week 2	7.52 ± 3.34	10.18 ± 2.86	0.00013
Week 4	5.01 ± 3.15	8.13 ± 3.15	2.91×10^{-7}
Change (Baseline to Week 4)	-9.79 ± 3.02	-7.37 ± 2.89	6.27×10^{-12}

This table demonstrates the increasing disparity in symptom scores, where honey group subjects had clinically significant reductions (≥50% reduction) of symptoms in 75% of patients, whereas only for 55% in the synthetic drug group. P-values indicate statistical superiority of honey at each post baseline time point, favouring its higher anti-inflammatory, antimicrobial properties. Some reasons could be due to bioactive compounds, including methylglyoxal. The substantial change difference emphasizes honey as a possible natural alternative, while variability (SDs) implies individual responses may vary and be related to allergy severity. This finding is consistent with other research on the benefits of honey to the eyes, but this controlled study offers stronger evidence.

Secondary Efficacy Outcomes

The secondary results also supported the primary findings. Regarding quality of life (RQLQ) both groups improved, but the honey group showed more improvement, -30.88 (SD = 4.95) 26. /79 SD = 5.12 p =

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5.30×10^{-06}). Subdomain-specific evaluations revealed that the honey was more effective in ocular symptoms ($p < 0.001$) and daily activities ($p = 0.002$), but not in nasal symptoms ($p = 0.12$), as per topical use.
TBUT indicated more improvement in ocular surface integrity in the honey group: +3.01 seconds (SD = 0.98) compared to +2.26 (SD = 1.02) ($p = 0.00023$). This implies that the humectant properties of honey may enhance the stability of the tear film even better than artificial antihistamines.
Analysis of the tear IgE and IL-1β, TNFα, MMP9, and CCL2 levels showed anti-inflammatory properties with honey leading to a reduction of -19.76ng/mL (SD=4.87) for tear IgE compared to -15.37 (SD = 5.03) ($p = 1.66×10^{-06}$), indicating more potent immunomodulation. There was more user satisfaction with honey at week 4 (VAS 8.2 ± 1.4) than with synthetic (7.1 ± 1.6) (p <0,001). Rescue medication use was also diminished in honey (15% vs 28%, $p = 0.04$).

Table 3 Changes in Secondary Outcomes from Baseline to Week 4

Outcome	Honey Group, Mean Change ± SD	Synthetic Group, Mean Change ± SD	p-value
RQLQ Score	-30.88 ± 4.95	-26.79 ± 5.12	5.30×10^{-06}
TBUT (seconds)	+3.01 ± 0.98	+2.26 ± 1.02	0.00023
Tear IgE (ng/mL)	-19.76 ± 4.87	-15.37 ± 5.03	1.66×10^{-06}
VAS Satisfaction (0-10)	8.2 ± 1.4	7.1 ± 1.6	<0.001
Rescue Medication Use, n (%)	9 (15.0)	17 (28.3)	0.04

The uniform benefits across approaches to measurement further strengthen honey's multifaceted impacts, spanning symptom control and biomarker influence. These improvements in RQLQ result in real-world benefits, including less interference with work/sleep. Improvements in TBUT would correspond to long-term ocular health benefits, while reductions of IgE would indicate mechanistic superiority. Better tolerability (as suggested by higher satisfaction scores) may support adherence. Limitations include self-reported components , but objective biomarkers reduce bias.

Safety and Tolerability

A few mild adverse events (AEs) were reported. In the honey group, 15 participants (25%) experienced AEs: mild stinging (10/60, 16.7%) and blurred vision (5/60, 8.3%). Adverse events (AEs) 18/60 (30%) occurred in the synthetic group: there was mild stinging in 8/60–13.3% and, blurred vision in 7/60–11.7%, and allergic reactions in 3-5%. No serious AEs were reported, and no severe AE led to discontinuation. There was no difference between groups by Chi-square tests ($p = 0.52$).

Table 4: Frequency of Adverse Events by Treatment Group

Adverse Event	Honey Group (n=60), n (%)	Synthetic Group (n=60), n (%)
Mild Stinging	10 (16.7)	8 (13.3)
Blurred Vision	5 (8.3)	7 (11.7)
Allergic Reaction	0 (0)	3 (5.0)
None	45 (75.0)	42 (70.0)

The evidence on the comparable AEs profiles to confirm that both treatments are safe comes with this cautionary note: honey may have a slight advantage in terms of allergic responses avoided, possibly due to being natural. The high proportion of fleeting signs, such as burning, is consistent with the use of topical ocular treatments. Collectively, this aspect of honey's tolerability suggests it may be used as an alternative antimicrobial dressing especially in patients with some concerns over synthetics.

Subgroup and Sensitivity Analyses

The evidence on the comparable AEs profiles to confirm that both treatments are safe comes with this cautionary note: honey may have a slight advantage in terms of allergic responses avoided, possibly due to being natural. The high proportion of fleeting signs, such as burning, is consistent with the use of topical ocular treatments. Collectively, this aspect of honey's tolerability suggests it may be used as an alternative antimicrobial dressing especially in patients with some concerns over synthetics.

Discussion

The current randomized controlled trial has proven that natural honey drops which were specifically made using Manuka honey with a concentration of 20 per cent are significantly more effective than synthetic drops of olopatadine hydrochloride drops in relieving allergic conjunctivitis symptoms, based on greater improvements in the Allergic Conjunctivitis Symptom Score (ACSS) as well as the improvement of the quality

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of life using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), tear break-up time (TBUT), reduced tear IgE, and increased patient These data are consistent with an increasing literature on the therapeutic possibilities of honey and other natural products in inflammatory disorders of the eye as well as outlining the possibilities and obstacles involved in making such substitutes clinically viable. This discussion presents the mechanistic implications, comparative effectiveness, limitations, and future directions of our results by contextualizing them with recent research on herbal and honey-based interventions.

Honey has a complex array of anti-inflammatory and antimicrobial activities as evidenced by our main result - a significant decrease in ACSS with honey drops (-9.79 vs. -7.37 vs synthetic, $p < 0.001$) - and these findings might be beneficial compared to traditional antihistamine-based interventions. In their review article, Salaman et al. [15], in their article titled Exploring Herbal Alternatives to Conjunctivitis Management: Opportunities and Challenges highlight how vulnerable the ocular surface is to inflammation and the limitations of synthetic drugs, including side effects and antibiotic resistance. They point out bioactive compounds in herbs such as Euphrasia officinalis, Matricaria chamomilla, and Aloe vera that suppress mast cell degranulation and inflammatory processes that honey also does. It is important to note that they cite a clinical trial of honey drops in the management of vernal keratoconjunctivitis (VKC), a severe allergic eye disease, which reduces inflammation and does not produce serious side effects. This is similar to what we observe, in that the methylglyoxal and phenolic compounds in honey probably helped resolve the symptoms, especially itch and redness, faster as they prevented the release of proinflammatory cytokines and stabilized the tear film. Nevertheless, Salaman et al. warn against such issues as the need for standard formulations and additional clinical data, and our project addresses these problems by designing RCT rigorously and purifying formulations through HPLC.

Based on this, the article by Salehi et al. [6], titled A Double Blind Clinical Trial on the Efficacy of Honey Drop in Vernal Keratoconjunctivitis, presents direct comparison evidence. In their research, 60 patients with VKC were administered 60 percent honey drops as adjuncts with cromolyn and fluorometholone, with significant reductions in both redness and limbal papillae as compared to placebo ($p < 0.05$), with little intraocular pressure rise. This is similar to our subgroup analysis in which honey was more effective in seasonal allergic conjunctivitis, which may be attributed to its anti-eosinophilic properties since VKC and allergic conjunctivitis have similar pathways through which they are mediated by IgE. The reduction of eosinophils and neutralization of free radicals that were associated with Honey as described in their paper, could explain the better biomarker results in our trial, including lower tear IgE (-19.76 ng/mL vs. -15.37 ng/mL, $p < 0.001$). However, where Salehi et al. have pointed to the potential of honey to reduce the use of steroids, our head-to-head analysis with substitutes in synthetic drops would imply the possibility of honey as a first-line choice for mild to moderate cases and avoid the use of pharmaceuticals that can result in tachyphylaxis.

Dry eye disease (DED) is a disease that has been of interest to a number of studies, with many researchers emphasizing the condition due to its similarity to allergic conjunctivitis in terms of shared inflammatory pathophysiology. In The Effectiveness of Natural Honey in Improving Dry Eye Symptoms: A Randomized Controlled Clinical Study by Borsi et al. [7], 100 DED patients were studied with Honey drops (daily), and the results showed significant improvements in Schirmer test (5 mm to 8 mm, $p < 0.01$), TBUT (5 s to 10 s, $p < 0.01$) and fluorescein staining (3+ to 1+, $p < 0.01$) and patient satisfaction was These findings support our secondary findings in which honey increased TBUT (+3.01 s vs. +2.26 s, $p < 0.001$), presumably because honey is a humectant and osmotic liquid that maintains the tear film. Borsi et al. placed honey as a complementary medication, but our statistics indicate that it is better than synthetics in allergic situations, and DED worsens the symptoms. Likewise, 323 patients were included in the meta-analysis by Prinz et al. [8] in their article titled Honey-related treatment strategies in dry eye disease and involved in 5 RCTs; the study found that honey has a positive impact on TBUT (+1.1 s, $p = 0.01$), OSDI (-12.8 points, $p < 0.0001$), and Schirmer (+1.8 mm, $p = 0.0001$), and no harmful adverse effects were reported. Even though no notable differences were obtained compared to controls, the fact that they focused on the feasibility of honey is consistent with our low AE rate (25% mild events) and contributes to its safety profile. Prinz et al. promote specific studies on variety, and we confirm their results that Manuka honey with high UMF has great bioactivity.

In "Exploring novel pharmacological trends: Natural compounds in the management of dry eye disease", Rak and Csutak [9] build on this by reviewing apitherapeutic products such as Manuka honey and propolis for DED with antibacterial, antioxidant, and anti-inflammatory properties through compounds such as pinobanksin and chrysin. They mention the Manuka honey drops (e.g., Optimel) as an option in the treatment of evaporative DED and MGD, bacterial growth, and inflammation prevention, which is similar to our results, where the rescue medication was reduced (15% vs. 28%, $p = 0.04$). Nevertheless, they emphasize interdisciplinary cooperation and patient education, which is also reflected in our trial with compliance monitoring and standardized instructions. The mechanistic details of the effect of low dose honey on the

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apoptosis and inflammation gene expression of the corneal limbal stem cell and keratocyte and its effectiveness as an ophthalmic formulation in the treatment of dry eye are provided by Sanie-Jahromi et al. [10] in the article Effect of low dose honey on the apoptosis and inflammation gene expression of the corneal limbal stem cell and keratocyte and its efficacy as an ophthalmic formulation in the treatment of dry eye: in-v This anti-inflammatory role, through a cytokine-regulating effect, is probably the basis of our RQLQ changes (-30.88 vs. -26.79, $p < 0.001$), indicating that honey maintains the ocular surface integrity better than synthetics.

Scientific research on similar eye disorders shows again and again that the versatility of honey is not limited to DED. Abd Rashid et al. [11] in "Therapeutic potential of honey and propolis on ocular disease" discuss the use of honey for conjunctivitis, keratitis, blepharitis, and corneal damage with reported benefits from H2O2 production, osmotic effects, and flavonoid-associated antioxidant activity. They refer to the effectiveness of honey in a model of bacterial conjunctivitis, equivalent to gentamicin, and in blepharitis by anti-demodectic action, but closely related to N-coumaroyltyramine, for which we invoke an antimicrobial effect for Manuka honey. Viswambaran et al. [12] in the paper on "Blepharitis: A Review on Human Clinical Trials with Synthetic and Natural Remedies" concentrate on natural options, such as Manuka honey eye cream, which resulted in a safe reduction of symptoms (in 25 subjects), causing only transitory stinging. This corresponds to our AE profile, and assigns honey a role beyond what we know – bringing the anti-inflammatory into eyelid-adjacent inflammation, which is frequently seen in allergic conjunctivitis. Sahdev et al. [13] in “Conjunctivitis: Types, diagnosis and treatment with different therapies” comprehensively review treatments instead of promoting natural remedies like Ayurvedic herbs (eg Trifala lotion) for safe side effect free control, though without honey specific mention, their alert to patient preference for non-allopathic solutions parallels our high VAS satisfaction (8.2 vs 7.1 $p < 0.001$).

Even in otorhinolaryngology, Tharakan et al. [14] in “Honey in treatment of otorhinolaryngology: Review by subspecialty” report topical honey benefits for refractory rhinosinusitis, and a patient with blepharitis and conjunctivitis improvement, suggesting nasal- ocular communication relevant to allergic conjunctivitis. Their systematic review of evidence for oral honey in mucositis is indirectly relevant to the potential of honey for mucosal healing. Mechanistically, honey might have the edge because of its bioactive armoury - antioxidants scavenging ROSs, antimicrobials warding off secondary infections, and humectants enhancing tear stability - versus synthetics' lone antihistamine action. Reduced biomarkers in our study (including tear IgE) indicate immunomodulation as per work such as Sanie-Jahromi et al. However, limitations of our four-week study, the absence of data on long-term effects, and a single-center design preventing generalization, have been mentioned (Salaman et al). Sample size (n=120) gave sufficient power; however, larger multicentre trials could overcome any variability of honey types - a concern noted by Prinz et al. The implications are far-reaching: Honey drops may help ameliorate the reservoir of reliance on synthetic drugs, reducing resistance and expenses where resources are not abundant. Dose-response curves, the combinational use of herbs (per Rák and Csutak), and their use in pediatrics due to their common occurrence in children would be worth further research.

Conclusion

In summary, this double-blinded randomized controlled study clearly demonstrates that natural honey drops, sourced from high-UMF Manuka honey, are more effective than common synthetic olopatadine hydrochloride drops for the relief of some forms of moderate to severe allergic conjunctivitis. The much better symptom severity reduction (ACSS) and quality of life improvement (RQLQ), the degree of ocular surface stability enhancement, biomarker of inflammation modulation (tear IgE), as well as higher patient satisfaction in the honey group demonstrates its versatility from a therapeutic point of view, covering anti-inflammatory, antioxidant, humectant , and immunomodulatory actions. Given a good safety profile similar to the synthetic therapy, and only a few side effects, honey drops could be considered as a safe and effective natural alternative. This is supported by the correlation of our findings with new-emerging literature on apitherapy in ocular diseases, as honey appears to overcome the disadvantages of synthetic agents, including possible tachyphylaxis and patient preference for natural remedies. Given that natural honey drop is cost-effective, convenient, and potentially steroid-sparing therapy, the use of natural honey drop topically applied in the affected eyes could have a role in the therapeutic prescription among patients, especially in areas with high allergy prevalence or restricted pharmaceutical availability. However, larger multi-center studies with longer duration of follow-up, including broader populations, will be necessary to validate the long-term efficacy, optimize formulations, and establish guidelines for universal use. Finally, this work adds to the emerging paradigm of integrative ophthalmology, which connects historical knowledge with scientific rationale as a means to enhance patient outcomes in allergic conjunctivitis.

Conflict of interest. Nil

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