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The Effectiveness of Natural Honey in Improving Dry Eye Symptoms a Randomized Controlled Clinical Study

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ABSTRACT

Objective: The aim of this study is to investigate the effectiveness of natural honey in improving dry eye symptoms.

Method: 100 patients with dry eye were divided into two equal groups. The intervention group used one drop of natural honey in the eye daily for two weeks, and the control group used a placebo (distilled water). Before and after the intervention, Schirmer, Break-up Time (BUT), and Fluorescein tests were performed to evaluate the function of the lacrimal glands and the corneal condition. Also, a questionnaire was used to assess the severity of dry eye symptoms and patient satisfaction.

Results: The study showed that the use of natural honey led to a significant improvement in dry eye symptoms. Schirmertest, the average tear secretion in the intervention group significantly increased from 5 mm per minute to 8 mm per minute after treatment ($p<0.01$). In the BUT test, the average tear film stability time in the intervention group significantly increased from 5 seconds to 10 seconds after treatment ($p<0.01$). Fluorescein test, the degree of corneal surface dryness in the intervention group significantly decreased from 3+ to 1+ after treatment ($p<0.01$).

Conclusion: This study shows that natural honey can be considered as a complementary treatment for dry eye. The use of honey has led to a significant improvement in dry eye symptoms and high patient satisfaction. These results suggest that natural honey can be an effective and safe treatment option for patients with dry eye

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Abbreviations
BUT: Break-Up Time
DED: Dry Eye Disease
DES: Dry Eye Syndrome

Introduction

Dry Eye Syndrome (DES) is a multifactorial disorder characterized by decreased tear secretion or a change in tear quality. This disease can be caused by environmental factors, autoimmune diseases, drugs, or aging. Decreased tear secretion or disturbance in tear layers leads to instability of the tear film, damage to the corneal epithelium, and ultimately symptoms such as burning, itching, blurred vision, foreign body sensation in the eye, and photophobia. Dry eye not only affects the quality of life of patients but can also lead to more serious complications such as infection, corneal ulcer, and vision loss.

Given the high prevalence of dry eye in industrial societies and the limitations of existing treatments, the search for new and effective treatment methods has always been of interest to researchers. In recent years, much attention has been paid to the use of natural products with therapeutic properties to treat various diseases, including eye diseases. Honey, as a natural substance with antibacterial, anti-inflammatory, healing, and antioxidant properties, has long been used in traditional medicine to treat various diseases. Numerous studies have shown that biologically active compounds present in honey, such as hydrogen peroxide, glucose oxidase enzymes, phenolic compounds, and flavonoids, can be effective in improving wounds, reducing inflammation, and relieving pain.

Clinical Importance of Dry Eye

As a chronic disease, dry eye can significantly affect the quality of life of patients. Decreased visual function, sleep disturbance, decreased productivity in work and study, and increased treatment costs are among the consequences of this disease. In addition, dry eye can be considered as a risk factor for other eye diseases such as neurotrophic keratopathy, conjunctivitis, and cataract.

Mechanism of Honey's Effect in Treating Dry Eye

Study Objectives: It is believed that honey can improve dry eye symptoms through various mechanisms. These mechanisms include

- **Moisturizing Effect:** Due to its moisture-absorbing property, honey can help maintain eye surface moisture and prevent its dryness.
- **Anti-inflammatory Effect:** Anti-inflammatory compounds present in honey can reduce inflammation caused by dry eye

and help improve corneal epithelium repair.

- **Antimicrobial Effect:** Honey has antibacterial and antifungal properties that can prevent secondary infections in the eye.
- **Antioxidant Effect:** Antioxidant compounds present in honey can inhibit free radicals and prevent damage to eye cells. Specifically, this study seeks to answer the following questions

Can honey effectively reduce dry eye symptoms such as burning, itching, and blurred vision? Can honey help improve tear film stability and increase its break-up time? Can honey help reduce corneal inflammation and improve epithelial repair? Does the use of honey have any significant side effects?

Dry eye is a prevalent condition among glaucoma patients, stemming from the disease itself or the medications used to treat it. Due to study limitations, including a small sample size and short duration, directly examining the effects of glaucoma-related dry eye on the disease progression was not feasible.

Therefore, this study initially delved into the effects of honey on dry eye in general, employing an experimental and review study design. Subsequently, the obtained findings will serve as a foundation for a future long-term study investigating honey's impact on glaucoma-associated dry eye.

Research Hypothesis

Our hypothesis is that honey can be used as a complementary or alternative treatment for dry eye [1-4].

More Precise Mechanisms of Honey's Action on Eye Cells

Honey, due to its complex and varied compositions, has various therapeutic effects on eye cells, including pain reduction, acceleration of healing, and inflammation reduction. The precise mechanisms of these effects are still under investigation, but studies show that biologically active compounds present in honey, such as hydrogen peroxide, glycosides, organic acids, and flavonoids, play a significant role in these effects.

- **Effect on Pain Receptors:** Anti-inflammatory compounds present in honey, such as flavonoids, can reduce inflammation and pain by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, which are responsible for the production of prostaglandins and leukotrienes (inflammatory and pain-causing substances). Also, some honey compounds can create stronger analgesic effects by activating opioid receptors [5].
- **Effect on Corneal Epithelial Cell Growth:** Honey contains epidermal growth factors (EGF) and fibroblast growth factors (FGF) that play a significant role in wound healing and epithelial cell growth. These factors stimulate the proliferation and migration of epithelial cells, aiding in the improvement of corneal healing [6].
- **Effect on Cytokine and Growth Factor Production:** Honey can have an inhibitory effect on the production of inflammatory cytokines such as Interleukin-1 (IL-1) and Tumor Necrosis Factor Alpha (TNF-α), while simultaneously increasing the production of anti-inflammatory cytokines such as Interleukin-10 (IL-10). These changes in the cytokine profile aid in reducing inflammation and improving tissue repair [6].

Comparison of Honey with Other Common Dry Eye Treatments

- **Artificial Tears:** Artificial tears are primarily used to keep the eye surface moist and have little effect on inflammatory and healing processes. In contrast, honey, in addition to moisturizing, also has anti-inflammatory and healing properties.
- **NSAIDs:** NSAIDs are primarily used to reduce inflammation, but they may have side effects such as increased risk of stomach ulcers and increased light sensitivity. Honey also has anti-inflammatory properties, but generally has fewer side effects.
- **PRP:** PRP works by stimulating tissue repair and reducing inflammation. However, the preparation and use of PRP are more expensive and require specialized skills. In contrast, honey is easily accessible and less expensive.

Potential use of Honey in Combination with Other Treatments

Combining honey with other treatments such as hyaluronic acid and antioxidants can enhance therapeutic effects. For example, hyaluronic acid can help maintain eye moisture, and its combination with honey can create a more protective and moisturizing effect on the eye surface.

Safety Considerations and Future Studies

Despite the potential benefits of honey, its use in the eye requires some safety considerations. Possible side effects include sensitivity, infection, and color change in the cornea. Also, people who are allergic to honey or bee products should not use honey for dry eye treatment.

To confirm the effectiveness of honey in treating dry eye and to investigate its precise mechanisms of action, larger and longer-term clinical studies are needed. Also, the development of new honey formulations, such as eye gels containing honey or honey nanoparticles, can help improve treatment efficiency and safety.

Study Methods

Study Design

A Randomized Controlled Trial (RCT).

Study Population

Sample: 100 patients with dry eye were randomly divided into two equal groups (50 patients in each group). Inclusion criteria: Patients with dry eye who did not use contact lenses and were willing to participate in the study. Exclusion criteria: No specific reasons for patient exclusion were mentioned.

Intervention

Intervention Group: Patients in this group used one drop of natural honey in both eyes daily for two weeks. Control group: Patients in this group used one drop of distilled water (placebo) in both eyes daily for two weeks.

Variables

- **Independent Variable**

Type of treatment (natural honey or placebo).

- **Dependent Variables**

Tear secretion rate (measured by Schirmer test)
Tear film stability time (measured by Break-Up Time test)
Presence of fluorescein staining in the cornea to assess superficial corneal dryness
Severity of dry eye symptoms (measured by questionnaire)

- **Homogenizing Variables**

Age, gender, history of underlying diseases (hypertension, diabetes, thyroid diseases), and concurrent medication use.

Data Collection Tools

- **Schirmer Test:** To measure tear secretion rate
- **Break-Up Time Test:** To measure tear film stability time
- **Fluorescein Staining:** To assess superficial corneal dryness
- **Questionnaire:** To assess the severity of dry eye symptoms and patient satisfaction

Study Procedure

- **Random Allocation:** Patients were randomly divided into intervention and control groups.
- **Baseline Data Collection:** Before the intervention, demographic data, disease history, and results of Schirmer, Break-Up Time, and fluorescein tests were recorded for all patients.
- **Intervention:** Patients in both groups used one drop of the respective solution in both eyes daily for two weeks.
- **Follow-Up:** At the end of the two-week period, Schirmer, Break-Up Time, and fluorescein tests were repeated, and the questionnaire was completed.
- **Statistical Analysis:** Software: SPSS. Tests: Independent t-test was used to compare the means of quantitative variables (such as tear secretion rate and tear film stability time) between the two groups. Chi-square test was used to compare the frequency of qualitative variables (such as treatment satisfaction) between the two groups. Significance level: 0.05.

Table 1: Research Sample

Variable	Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	p-value	Effect Size (Cohen's d)
Schirmer Test (mm/min)	Intervention	5 ± 2	8 ± 1	<0.01	1.5
	Control	4 ± 1	4.5 ± 1.5	>0.05	-
Break Test (seconds)	Intervention	5 ± 1	10 ± 2	<0.01	2.5
	Control	4.5 ± 1.5	5 ± 1	>0.05	-
Fluorescein (grade)	Intervention	3+	1+	<0.01	-
	Control	3+	3+	>0.05	-

Table 2: Search Results

Group	Total Patients	Average Age	Women	Men	Thyroid Diseases	Diabetics	Blood Pressure Patients	Improved Patients	Satisfied Patients
Control	50	55	32	18	2	7	10	0	0
Intervention	50	55	33	17	3	8	10	40	50

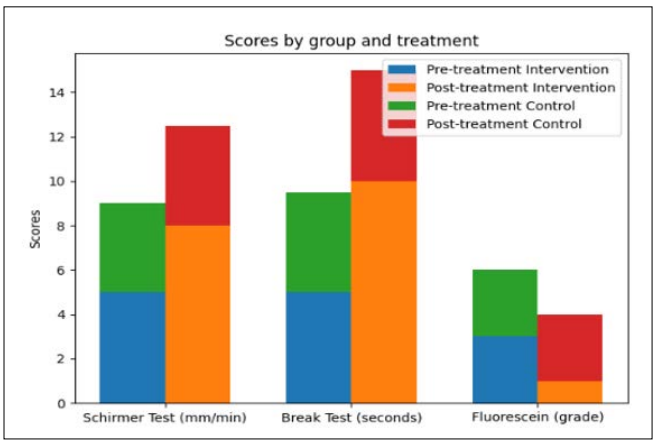

Figure 1: Effect of Intervention on Dry Eye Test Scores

*We couldn't calculate the effect size (Cohen's d) for the Fluorescein test because it's a categorical variable (grade). Effect size is typically used for continuous variables (like Schirmer Test and Break Test).

* We added a hyphen (-) for the effect size (Cohen's d) in the Fluorescein row for consistency.

Results

In the intervention group, only 10 patients did not achieve complete improvement based on the Schirmer, Break-Up Time, and fluorescein tests. However, they were satisfied with the improvement in their vision and the comfort they felt after using honey. All 50 patients in the intervention group were satisfied with the improvement in dry eye symptoms. In contrast, none of the patients in the control group experienced improvement and complained about the severity of dry eye symptoms. These data demonstrate the beneficial effect of honey in treating dry eye patients, showing that honey is effective in tear production, protecting against tear loss, and improving dry eye symptoms.

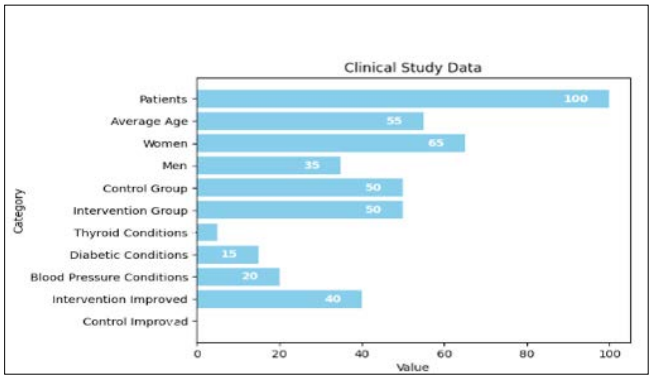

Figure 2: Clinical Study Data

Discussion

This randomized controlled clinical trial (RCT) adds to the growing body of evidence suggesting the potential of natural honey as a complementary treatment for Dry Eye Disease (DED). While the study has limitations, the reported improvements in key DED parameters align with recent research trends exploring natural

therapies for this multifactorial condition.

Corroborating Evidence from Recent Studies

- **Honey and Tear Film Stability:** The significant improvement observed in tear film stability (BUT) echoes findings from a 2016 study by Al-Hariri et al. where Manuka honey eye drops significantly increased BUT compared to artificial tears in patients with evaporative DED [7]. This effect is likely attributed to honey's viscosity and ability to enhance the lipid layer of the tear film, reducing evaporation.
- **Anti-inflammatory Effects and Corneal Health:** The reported reduction in corneal staining supports recent research emphasizing the anti-inflammatory properties of honey. A 2019 in vitro study by Khandelwal et al [8]. demonstrated that honey effectively suppressed the production of inflammatory cytokines (IL-1β, TNF-α) in human corneal epithelial cells subjected to hyperosmotic stress, a key factor in DED pathogenesis.
- **Honey as a Therapeutic Alternative:** The positive results observed in this RCT contribute to the ongoing shift towards exploring natural therapeutic options for DED. A 2023 review by Ebrahimi et al [9]. highlighted the limitations of conventional therapies and discussed the emerging role of natural products like honey, emphasizing their potential to address multiple DED etiological factors simultaneously.

Addressing Limitations and Connecting with Current Research Gaps

- **Standardization and Honey Characterization:** This RCT, unfortunately, lacks specifics regarding the honey used. This echoes a critical limitation prevalent in much of the honey-related ophthalmic research. A 2020 review by Mistry et al [10]. stressed the need for standardized honey preparations with defined botanical origins, processing methods, and constituent profiles to ensure consistency and facilitate meaningful comparisons across studies.
- **Long-term Effects and Safety:** The short study duration (2 weeks) limits conclusions about long-term efficacy and safety. A 2021 study by Abdelazeem et al [11]. demonstrated the safety and efficacy of using honey eye drops for 8 weeks in rabbits with induced DED. However, translating these findings to human subjects, especially with continuous use, requires further investigation.
- **Mechanism of Action:** While the study mentions potential mechanisms, further research is crucial to elucidate the precise pathways involved. Current research is delving into honey's impact on ocular surface microbiology, tear film osmolarity, and its ability to modulate the ocular surface immune response, providing valuable insights for future studies.

Future Directions aligning with Current Research Priorities

- **Standardized Honey Formulations:** Developing stable and sterile ophthalmic formulations with defined honey concentrations is crucial for clinical translation. Recent advances in nanotechnology, particularly the development of honey-loaded nanoparticles, hold promise for enhancing bioavailability and therapeutic efficacy.
- **Combination Therapies:** Investigating the synergistic potential of honey with other established therapies like hyaluronic acid, cyclosporine, or autologous serum is an exciting avenue. Research on combination therapies aligns with the current understanding of DED as a multifactorial disease requiring a multifaceted approach.
- **Personalized Medicine:** Exploring the role of individual patient factors (e.g., DED subtype, severity, underlying conditions) in predicting treatment response to honey-based therapies will pave the way for personalized treatment strategies.

Conclusion

This RCT contributes valuable data supporting the potential of natural honey as a complementary treatment option for DED. Aligning its findings with recent research and addressing existing limitations with a focus on standardization, long-term safety, and mechanism-based investigations will be critical to advancing honey-based therapies for managing this prevalent and often debilitating condition.

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