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Research Article

Effect of Sidr Honey and Moringa Oleifera on Chemotherapy-induced Oral Complications: A Histological and Histomorphometrical Study in a Rat Model

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Abstract

Chemotherapy-induced oral complications significantly affect patient quality of life. 5-Fluorouracil (5-FU), a commonly used chemotherapeutic agent, being particularly associated with mucosal toxicity. This study aimed to evaluate the histological and Histomorphometrical effects of Sidr honey and Moringa oleifera on chemotherapy-induced oral mucosal damage in a rat model. Eighteen male albino rats were divided into three groups: control, 5-FU only, and 5-FU combined with Moringa oleifera and Sidr honey. Tongue tissues were harvested at 14 and 28 days for histological examination and histomorphometric analysis using H&E staining and ImageJ software, with statistical analysis performed via one-way ANOVA and paired t-tests ($p<0.05$). Results indicated that the 5-FU-only group exhibited progressive epithelial thinning, loss of rete pegs, and increased inflammatory infiltration, while the group receiving Moringa oleifera and Sidr honey showed significant epithelial regeneration, including increased thickness, intact keratinized surfaces, and partial restoration of rete pegs. Statistically significant differences in epithelial thickness were observed across all groups at both time points ($p<0.001$). Within-group analysis indicated improvements in both the control and treatment groups, whereas a decline was noted in the 5-FU-only group over time. These findings suggest that Moringa oleifera and Sidr honey possess protective and restorative properties against 5-FU-induced lingual mucosal damage, enhancing epithelial regeneration and reducing inflammation. Future research should focus on clinical trials to validate their therapeutic potential in human patients, explore the underlying molecular mechanisms of their protective action.

Keywords

Moringa Oleifera, Sidr Honey, 5-Fluorouracil, Oral Mucositis, Chemotherapy, Tongue Epithelium, Natural Therapy

1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, ranking second only to cardiovascular diseases. According to global statistics, approximately 19.3 million new cancer cases and 10 million cancer-related deaths

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were recorded in 2020, with projections indicating a continued rise in incidence over the coming decades [1, 2]. A variety of therapeutic modalities are employed in the management of cancer, including surgery, radiotherapy, targeted therapy, immunotherapy, and chemotherapy. Among these, chemotherapy remains a cornerstone of treatment for many solid and hematological malignancies due to its systemic action and efficacy against rapidly dividing cells.

Despite its clinical effectiveness, chemotherapy is associated with a range of adverse effects, which can severely compromise patients' quality of life. The cytotoxic nature of chemotherapeutic agents results in damage not only to malignant cells but also to healthy, fast-dividing cells, including those lining the gastrointestinal tract and oral mucosa [3]. One of the most common and distressing oral complications is oral mucositis, characterized by inflammation, ulceration, and atrophy of the oral epithelium, particularly affecting sensitive structures such as the tongue papillae. These lesions are often painful, interfere with eating and speaking, and may lead to malnutrition, weight loss, increased risk of infection, and treatment delays [4-6].

5-Fluorouracil (5-FU), a pyrimidine analog, is one of the most widely used chemotherapeutic agents. It interferes with DNA synthesis by inhibiting thymidylate synthase, resulting in cell cycle arrest and apoptosis in rapidly proliferating tissues. While 5-FU is recognized for its efficacy in treating various cancers, including colorectal, head and neck, breast, and gastrointestinal tumors, it is also notorious for inducing severe mucosal toxicity, particularly in the oral cavity [4, 5]. The World Health Organization lists 5-FU as an essential medicine due to its clinical utility and cost-effectiveness, making it especially prevalent in developing and resource-limited healthcare settings [6].

The oral side effects of 5-FU, including atrophy of the tongue papillae, significantly hinder patient tolerance to therapy and compromise the overall treatment experience. Managing these complications effectively is crucial to maintaining nutritional status, improving patient compliance, and enhancing clinical outcomes. While various pharmacological interventions have been proposed, their effectiveness remains limited, and many are costly or inaccessible in low-income regions. As a result, there is growing interest in identifying natural, affordable, and effective alternatives that can protect or repair chemotherapy-damaged tissues.

Natural substances with anti-inflammatory, antioxidant, and antimicrobial properties have been increasingly explored for their role in mitigating chemotherapy-induced tissue damage. Among these, Moringa oleifera and Sidr honey have gained considerable attention. Moringa oleifera, often referred to as the "miracle tree," is a plant native to South Asia and widely used in traditional medicine. Its leaves contain a rich array of bioactive compounds, including vitamins A, C, and E, polyphenols, flavonoids, and essential minerals, which contribute to its potent anti-inflammatory and antioxidant effects [7-9]. These properties make it a promising candidate for reducing oxidative stress and inflammation in damaged mucosal tissues.

Similarly, Sidr honey, produced by bees from the nectar of the *Ziziphus spina-Christi* tree, is known for its wound-healing, antibacterial, and anti-inflammatory properties. It has been used in traditional medicine for centuries and has demonstrated efficacy in promoting tissue regeneration, enhancing epithelial repair, and modulating immune responses in various clinical contexts [10-12].

Although the individual benefits of Moringa oleifera and Sidr honey have been documented, there is limited research on their combined effect, particularly in the context of oral mucosal damage induced by chemotherapy. Given their distinct but potentially synergistic mechanisms of action, the combination of these two natural products may offer enhanced protection and tissue regeneration in the oral cavity during chemotherapy. Exploring such combinations could lead to the development of low-cost, accessible therapeutic options, especially for use in countries where access to advanced oral care is limited.

This study aims to address this gap by investigating the histological and Histomorphometrical changes in the tongue papillae of rats subjected to 5-FU chemotherapy and treated with Moringa oleifera and Sidr honey. Through quantitative and qualitative tissue analysis, this research seeks to provide evidence for the potential protective and reparative effects of these natural agents on oral tissues compromised by chemotherapy.

2. Materials and Methods

2.1. Sample Size Calculation

Sample size calculation was performed using G*Power version 3.1.9.2, Faul et al, [2007 & 2013] University Kiel, Germany. Copyright (c) 1992-2014. [13].

$$f = \frac{\sigma_\mu}{\sigma}$$

$$\sigma_\mu^2 = \frac{\sum_{i=1}^{\kappa}\left(\mu_{i-\mu}\right)^2}{N}$$

Where: *F:* is the effect size; α= 0.05; β= 0.05; Power= 1- β = 0.80 (80%).

The effect size f was 0.82 using alpha (α) level of 0.05 and Beta (β) level of 0.05, i.e., power = 80%; the estimated sample size (n) should be at least 18 samples (Rats). The sample size in this study agrees with Eltokhey et al., 2013 who have published on this point [14].

2.2. Materials

1) Adrucil® (fluorouracil injection USP), purchased from a local pharmacy.

2) Moringa oleifera Leaf Powder: Fresh leaves of moringa (Moringa oleifera) were collected from the local market. The leaves were removed from the stems, washed several times with distilled water, and then air-dried at room temperature for one to two days. The leaves were then ground into a homogeneous powder when they were completely dried.
3) Sidr Honey: Sidr honey was sourced directly from local Libyan beekeepers.

2.3. Animals

Eighteen male albino rats, each weighing between 220 and 250 grammes, were used in this study. The experiment was conducted in the animal house, Faculty of Medicine, University of Benghazi. An approval for the experimental animal was given by the Scientific Research Ethical Committee (SREC) of the Faculty of Dentistry, University of Benghazi (Approval No: 0277).

The rats were maintained under standard laboratory conditions, housed in separate cages accommodating three rats each. The room temperature was kept between 20 and 25 ℃, and the rats were provided with a standard diet along with unrestricted access to water.

Rats were randomly divided into:

Group I: Control group which did not receive any treatment.

Group II: Chemotherapy group (which was administered with chemotherapy).

Group III: Chemotherapy group (which was administered with chemotherapy) and treated with Sidr honey and Moringa Oleifera.

Each group consisted of 6 rats and was further divided into two subgroups based on the treatment duration:

1: After 14 days; 2: After 28 days.

2.4. Induction of Chemotherapy

Treated animals received 5-FU (fluorouracil; 50 mg/mL - Adrucil®) intraperitoneally on the first 4 days at 15 mg/kg/day (equivalent in humans), and the next 4 alternate days at 6 mg/kg/day. The 15 mg/kg dose was given on the 14th day of treatment [15].

2.5. Treatment Protocol

The treatment groups received Sidr honey mixed with Moringa Oleifera powder orally, starting from the first day of chemotherapy and continuing for an additional 14 days post-chemotherapy.

2.6. Histological and Histomorphometrical Analysis

At the end of the experiment, all rats were euthanized by anesthetic overdose of thiopental. Rats' tongues were dissected and preserved. The specimens were processed to be stained by hematoxylin and eosin (H&E) to detect the histological changes [16].

Histomorphometrical analysis was conducted using the ImageJ 1.53 K application (source: NIH, USA; open-source application available at https://imagej.nih.gov/ij/download.html) for measurement of the thickness in the tissue on the slide.

2.7. Statistical Analysis

Data collected were analyzed using appropriate statistical methods, including one-way ANOVA for comparison between groups, followed by post-hoc analysis where applicable also, paired samples T test was used to compare Day 14 with Day 28 in each group. A p-value of <0.05 will be considered statistically significant. All analyses were performed using SPSS software.

3. Results

3.1. Histological Results

The samples were studied with a histological approach at two points, 14 days and 28 days post-treatment, to find out how the keratinized stratified squamous epithelium changed in each of the experimental groups.

3.1.1. Day 14 Observations

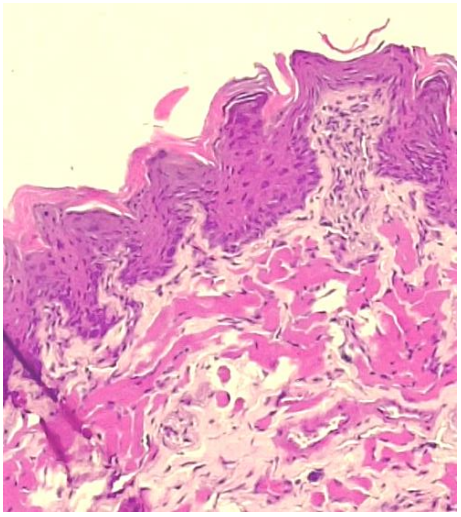

Figure 1. *A photomicrograph of a tongue from group I shows that it is covered by normal thickness of stratified squamous epithelium of filiform papillae with regular rete pegs (H&EX100).*

By the end of 14 days, the tissue in the control group was covered by keratinized stratified squamous epithelium of

filiform papillae of normal thickness with regular and uniform rete pegs [Figure 1]. In contrast, Group II had keratinized stratified squamous epithelium that was shorter, uneven, and devoid of rete pegs. The epithelial cells had shedded. The lamina propria showed obvious signs of inflammatory cell infiltration [Figure 2].

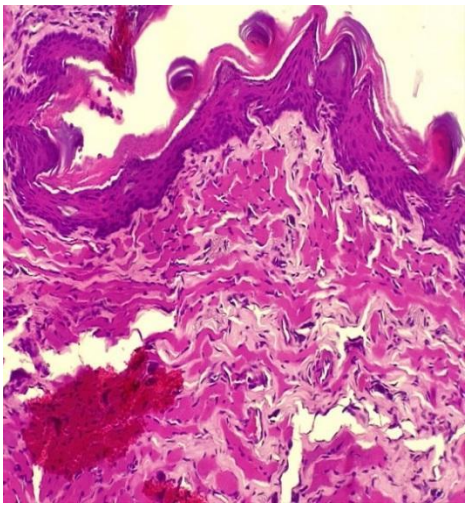

Figure 2. *A photomicrograph of a tongue from group II shows that the keratinized stratified squamous epithelium of filiform papillae appeared shorter, irregular with loss of rete pegs. Increase the numbers of inflammatory cells in lamina propria (H&EX100).*

Unlike Group II, the epithelium in Group III were more complex. Some sections of the keratinized stratified squamous epithelium showed a greater thickness which also had irregular rete pegs present. In particular, there was no change in the keratinized surface [Figure 3].

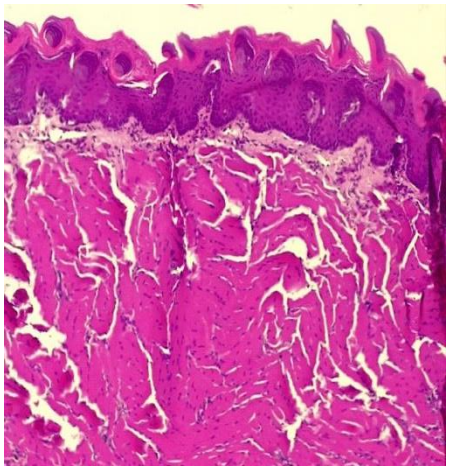

Figure 3. *A photomicrograph of a tongue from group III shows that the thickness of keratinized stratified squamous epithelium was increased with irregular rete pegs in some areas. The keratinized surface appeared undamaged. (H&EX100).*

3.1.2. Day 28 Observation

On evaluating the tissues at 28 days, the control group demonstrated that the filiform papillae were covered by keratinized stratified squamous epithelium of normal thickness, featuring regular and uniform rete pegs [Figure 4].

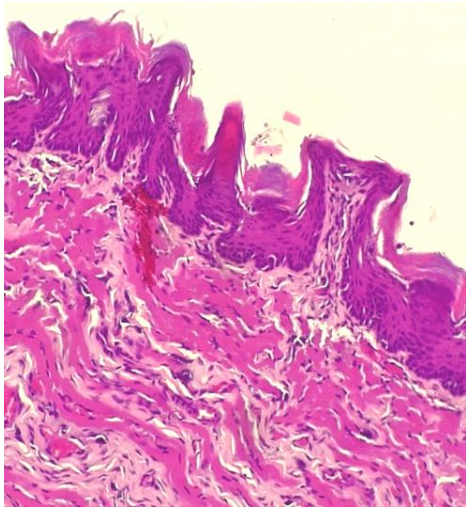

Figure 4. *A photomicrograph of a tongue from group I shows that it is covered by normal thickness of stratified squamous epithelium of filiform papillae with regular rete pegs (H&EX100).*

On the other hand, Group II had keratinized stratified squamous epithelium that appeared more irregular, shorter, and uneven, with more destruction of rete pegs as compared with day 14. The epithelial cells had a shed and keratin layer destructed in some areas. The lamina propria showed more inflammatory cell infiltration [Figure 5].

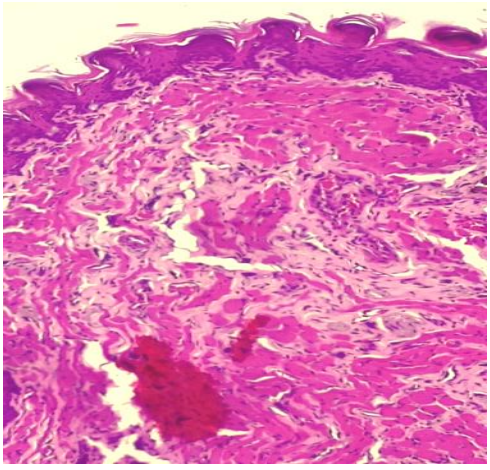

Figure 5. *A photomicrograph of a tongue from group II shows that the keratinized stratified squamous epithelium appeared more irregular, shorter, uneven, and more destruction of rete pegs as compared with day 14. More inflammatory cells in lamina propria (H&EX100).*

Conversely, Group III displayed remarkable improvement in epithelial features after 28 days. Notably, the epithelial layer was increased and revealed unevenly located rete pegs in a few areas. Moreover, the keratin layer was thicker compared to the previous assessment [Figure 6].

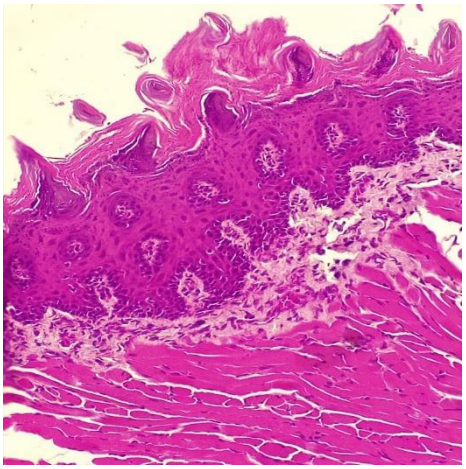

Figure 6. *A photomicrograph of a tongue from group III shows that the thickness of epithelium increased with uneven rete pegs. Undamaged keratinized surface was also seen with more keratin as compared with day 14 (H&EX100).*

3.2. Statistical Analysis

The table presents the comparison of thickness of epithelium among groups (GI, GII, GIII) at 14 and 28 days. At both 14 and 28 days, there were statistically significant differences in thickness of epithelium among the groups ($P < 0.001$ for both time points). Specifically, GIII consistently showed the highest mean thickness, followed by GI, while GII had the lowest mean thickness at both time points. When comparing within each group over time, GI and GIII showed a significant increase in thickness from 14 to 28 days ($P = 0.008$ and $P = 0.010$, respectively), while GII experienced a significant decrease in thickness from 14 to 28 days ($P = 0.045$). The pairwise comparison indicates significant differences between groups within each time point based on post-hoc analysis [Table 1], [Figure 7].

Table 1. *Comparison of epithelium thickness between groups at 14 and 28 days.*

	14 days		28 days		P value
	Mean	SD	Mean	SD	
GI	11.62 [b]	0.78	14.24 [b]	0.52	0.008**
GII	8.50 [c]	0.55	5.50 [c]	0.61	0.045*
GIII	16.89 [a]	0.34	21.17 [a]	0.42	0.010**
P value	<0.001**		<0.001**		

*and**; means significant at P<0.05 and <0.001 respectively.

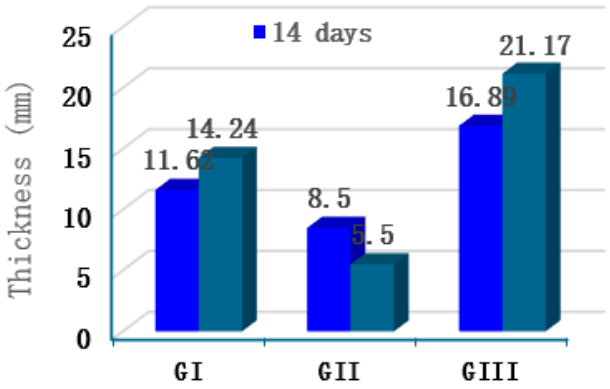

Figure 7. *A graph shows Comparison of epithelium thickness between groups at 14 and 28 days.*

4. Discussion

Cancer remains a major global public health burden, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. Chemotherapy remains an essential component of cancer treatment protocols due to its systemic efficacy against rapidly proliferating malignant cells. However, its non-selective cytotoxicity often results in adverse effects on normal tissues, particularly the mucosa, thereby compromising patient quality of life [17-19]. Managing these side effects is crucial not only for patient comfort but also for treatment adherence and overall clinical outcomes.

5-Fluorouracil (5-FU) is one of the most commonly used chemotherapeutic agents and has been included in the World Health Organization's list of essential medicines due to its broad-spectrum efficacy and affordability, especially in developing countries [20]. Despite its clinical benefits, 5-FU is associated with significant oral complications, including mucositis and atrophy of the tongue papillae, which result from epithelial damage and inflammation [21, 22].

The present study investigated the potential protective and regenerative effects of Moringa oleifera and Sidr honey on 5-FU-induced tongue epithelial damage in a rat model. After 14 days, the control group exhibited histologically normal, well-organized keratinized stratified squamous epithelium with intact rete pegs, consistent with previous studies that confirm the structural resilience of oral mucosa in the absence of cytotoxic stress [23-25]. In contrast, Group II (5-FU only) showed marked epithelial thinning, loss of rete pegs, and inflammatory cell infiltration, which align with documented

mucotoxic effects of fluorouracil in both animal models and human studies [26].

Interestingly, rats in Group III, treated with both Moringa oleifera and Sidr honey, exhibited significantly improved epithelial thickness by day 14. This suggests a protective and reparative role for these natural substances. The antioxidant and anti-inflammatory properties of Moringa oleifera, derived from its high content of polyphenols, flavonoids, and vitamins, have been shown to promote tissue regeneration and modulate immune responses [10]. Sidr honey, rich in phenolic compounds and enzymes, also demonstrates antimicrobial and wound-healing effects, which support mucosal recovery [27, 28]. Their synergistic activity likely enhances epithelial healing by reducing oxidative stress, stimulating collagen synthesis, and supporting reepithelialization [29, 31].

At 28 days post-treatment, histological differences became more pronounced. The control group retained normal mucosal structure, while the chemotherapy group showed progressive tissue deterioration, including further destruction of rete pegs and increased inflammatory infiltration. This finding is consistent with the known cumulative cytotoxicity of 5-FU, which induces DNA synthesis inhibition and epithelial cell apoptosis [30]. Conversely, Group III showed a marked recovery of epithelial features, including increased thickness, partial restoration of rete pegs, and a thicker keratin layer, indicating ongoing epithelial regeneration and long-term tissue remodeling.

The statistical findings further reinforce the histological observations. Group III consistently exhibited the highest epithelial thickness at both 14 and 28 days, while Group II had the lowest. Significant increases in epithelial thickness were noted from day 14 to day 28 in Groups I and III ($p = 0.008$ and $p = 0.010$, respectively), whereas Group II showed a significant decrease ($p = 0.045$). These results clearly support the protective role of Moringa oleifera and Sidr honey and highlight their potential as adjuncts in managing chemotherapy-induced oral complications.

4.1. Study Limitations

While the findings are promising, several limitations must be acknowledged. First, the study was conducted on a small animal sample, and extrapolation to human physiology should be made cautiously. Second, the study focused primarily on histological and morphometric analysis; inclusion of biochemical and molecular data (e.g., inflammatory cytokines, oxidative stress markers) would provide a more comprehensive understanding of the mechanisms involved. Lastly, the dosage and administration of Moringa oleifera and Sidr honey were tailored to experimental conditions and may require further standardization and safety evaluation for clinical application.

4.2. Clinical and Research Implications

This study provides preliminary evidence supporting the use of Moringa oleifera and Sidr honey as potential adjunctive therapies for the management of chemotherapy-induced oral mucositis. Given their natural origin, accessibility, and affordability, they are especially suitable for use in resource-constrained healthcare settings. Their integration into supportive care protocols could offer a safe, low-cost, and effective strategy to minimize oral complications, enhance mucosal healing, and improve overall quality of life for cancer patients. Future randomized controlled trials in humans, along with detailed pharmacological studies, are essential to validate these findings and establish standardized dosing guidelines.

4.3. Conclusion

In conclusion, this study demonstrated that Moringa oleifera and Sidr honey have significant protective and regenerative effects on 5-FU-induced epithelial damage in the tongue papillae of rats. Their use was associated with improved epithelial thickness, reduced inflammation, and partial restoration of mucosal integrity. These findings suggest that these natural agents may be valuable adjuncts in supportive cancer care, particularly in the management of oral complications caused by chemotherapy. Future research should focus on clarifying the molecular mechanisms by which Sidr honey and Moringa oleifera exert their protective effects against chemotherapy-induced oral mucositis. Given the promising results in this rat model, clinical trials are necessary to confirm the potential synergistic effects of these natural agents against mucositis, which significantly enhance patient care.

Abbreviations

5-FU	5-Fluorouracil
DNA	Deoxyribonucleic Acid

Author Contributions

Fatema Elturki: Writing - original draft, Supervision

Ghada Gehani: Formal Analysis, Writing - review & editing

Karima Ahmed: Writing - review & editing, Software

Somaya Salawat: Methodology, Writing - review & editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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