

# The Effect of Honey and Propolis on Oral Mucositis in Patients Undergoing Radiotherapy and Chemotherapy

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### Abstract

**Background:** Oral mucositis (OM) is a common complication in cancer patients receiving radiotherapy or chemotherapy, impacting treatment outcome. Prevention and treatment of OM is an urgent problem in the field of anticancer therapy. This study aimed to evaluate the efficacy of honey with or without propolis in prevention and treatment of OM.

**Patients and methods:** This study was conducted at the Oncology Center, Mansoura University. Eighty patients were included and were classified into three groups: First group consisted of 30 patients, received pure natural commercial honey (40 ml divided into 4 times daily); Second group (30 patients), received same amount of honey in addition to propolis (0.5gram) and the third group (control group; 20 patients), only kept oral hygiene, or received anesthetic agents including benzocaine or lidocaine gel. Treatment started on the first day of chemotherapy or radiotherapy and continued for 3 weeks.

**Results:** Among the whole group of patients, forty-two patients developed OM. There was significant difference in the occurrence of mucositis among groups in favor of patients in both experimental groups (50%, 36.6 % and 80% in groups 1, 2 and 3; respectively). Severe mucositis was lower among patients in the study group (23.1%) compared to the control group (31.3%).

**Conclusion:** Oral intake of honey is valuable in reducing incidence and severity of oral mucositis compared to oral hygiene. Enrichment with propolis further decreases OM.

**Keywords:** oral hygiene; lidocaine gel; benzocaine; prevention of mucositis; anticancer therapy.

تأثير العسل و البروبوليس على التهاب الغشاء المخاطي للفم للمرضى الذين يخضعون للعلاج الإشعاعي و العلاج الكيميائي

الملخص العربي:

التهاب الغشاء المخاطي للفم هو أحد المضاعفات الشائعة في مرضى السرطان الذين يتلقون العلاج الإشعاعي أو العلاج الكيميائي، مما يؤثر على نتائج العلاج. تعد الوقاية من التهاب الغشاء المخاطي للفم وعلاجه مشكلة ملحة في مجال العلاج المضاد للسرطان. تهدف هذه الدراسة إلى تقييم مدى فعالية العسل مع أو بدون البروبوليس في الوقاية والعلاج من التهاب الغشاء المخاطي للفم. أجريت هذه الدراسة في مركز الأورام بجامعة المنصورة. تم تضمين ثمانين مريضاً وتم تقسيمهم إلى ثلاث مجموعات: المجموعة الأولى تتكون من ٣٠ مريضاً، تناولوا العسل التجاري الطبيعي النقي (٤٠ مل مقسمة على ٤ مرات يومياً)؛ المجموعة الثانية (٣٠ مريضاً)، تلقت نفس الكمية من العسل بالإضافة إلى البروبوليس (٠.٥ جرام) والمجموعة الثالثة (المجموعة الضابطة؛ ٢٠ مريضاً)، حافظت على نظافة الفم فقط، أو تلقت عوامل التخدير بما في ذلك البنزوكائين أو ليدوكائين جل. يبدأ العلاج في اليوم الأول من العلاج الكيميائي أو العلاج الإشعاعي ويستمر لمدة ٣ أسابيع. من بين المجموعة الكاملة من المرضى، اثنان وأربعون مريضاً طوروا التهاب الغشاء المخاطي للفم كان هناك اختلاف كبير في حدوث التهاب الغشاء المخاطي بين المجموعات لصالح المرضى في كلا المجموعتين التجريبيتين (٥٠%، ٣٦.٦% و ٨٠% في المجموعات ١، ٢ و ٣؛ على التوالي). كان التهاب الغشاء المخاطي الحاد أقل بين المرضى في مجموعة الدراسة (٢٣.١%) مقارنة بالمجموعة الضابطة (31.3%). تناول العسل عن طريق الفم له قيمة في تقليل حدوث وشدة التهاب الغشاء المخاطي للفم مقارنة بنظافة الفم وعند اضافته البروبوليس كان له التأثير الافضل على التهاب الغشاء المخاطي للفم.

**الكلمات المفتاحية:** نظافة الفم، جل يدوكائين البنزوكائين، الوقاية من التهاب الغشاء المخاطي، العلاج المضاد للسرطان.

## Introduction

Radio/chemotherapy-induced OM is a common inflammatory complication in cancer patients, leading to negative clinical manifestations and impacting compliance with anticancer treatment.

Mucositis causes inflammation and ulceration of the oral cavity mucosa, so it becomes more liable to infection. [1] Common symptoms associated with OM are dysphagia, alterations in taste, weight loss, and secondary infections. These complications can significantly complicate treatment, extend hospitalization, and decrease the patient's quality of life. [2]

Although not endorsed by guidelines, a number of agents are available and are potentially effective in the prevention of OM associated with cancer treatment. Anti-inflammatory benzydamine was shown as an effective agent for the prevention of chemoradiotherapy induced OM. The results for antimicrobials and growth factors were varying and sometimes inconclusive. For many other vitamins, minerals and nutritional supplements, no positive recommendations were possible. Most herbal medicines and supplement interventions showed some level of efficacy. Mucoprotective agents, mucoadhesive hydrogel rinses; antimicrobial mouthwash, remain largely ineffective in prevention of chemo/radiotherapy induced OM. [3,4]

Honey is a product of flower nectar and the upper aero-digestive tract of the honeybee, which is concentrated through a dehydration process inside the bee hive. Honey has a long medical history and is recognized worldwide for its health-promoting properties. It has been proven to have anti-inflammatory, antioxidant, antimicrobial, and rapid tissue-healing properties. As a kind of herbal and traditional treatment agent, honey has been reported effective in promoting wound healing, facilitating reepithelization, and reducing microbial contamination [5].

Propolis or "bee glue" is a resinous waxy-like substance. Honey bees produce it by mixing their saliva and beeswax with the exudates obtained from plants like tree buds, sap flows, leaves, branches, and barks of plants found in the vicinity of the beehive. Propolis when used as an ingredient in mouthwashes showed protection against oral disease which is likely due to its antimicrobial efficacy [6].

Given that the nature of OM is fundamentally iatrogenic, it is reasonable that attempts have been made to prevent this serious complication of cancer treatment. Presently, a considerable body of scientific literature is available that describes possible interventions for preventing OM; however, due to the lack of solid evidence, the vast majority may not be effective or appropriate.

The aim of this single blinded prospective study is to evaluate the preventive and therapeutic effect of pure honey with or without propolis on radiotherapy/chemotherapy-induced oral mucositis in various cancer patients.

## **Patients and Methods**

This study is single blinded prospective study, which was conducted on 80 patients received chemotherapy or radiotherapy in a tertiary referral hospital affiliated to Medical University (Oncology Center, Mansoura University) in the period from May 2022 till November 2023.

Clinical assessment was done by attending physicians and nurses. Normal oral mucosa was defined by pink, moist appearance with no lesions, crusts, or debris. Normal gingiva was recognized by being pink and firm. Patients with healthy oral cavity were still counseled and encouraged to keep up their oral hygiene regimen.

### **1. Study Populations**

#### **I. Patients**

Patients aged  $\geq$  years18 from both genders, whom were treated from cancer with either chemotherapy and/ or radiotherapy were included in this study. However, patients who refused to participate in the study or suffering from diabetes mellitus, allergy to honey, or other systemic disease were excluded

#### **II. Methodology**

##### **A. investigational plan:**

Eighty patients were included and were classified into three groups: First group consisted of 30 patients, received pure natural commercial honey (40 ml divided into 4 times daily); Second group (30 patients), received same amount of honey in addition to propolis (0.5gram) and the third group (control group; 20 patients), only kept oral hygiene, or received anesthetic agents including benzocaine or lidocaine gel. Treatment started on the first day of chemotherapy or radiotherapy and continued for 3 weeks.

The oral cavity of all patients was examined before starting treatment. Follow-up evaluation of oral cavity was performed in all the participants weekly for three consecutive weeks and daily in case of development of oral mucositis. Patients, in the treatment groups, were asked to apply provided honey or honey with propolis to all areas of oral mucosa, gingiva, and tongue four times daily.

##### **B. Evaluation of Outcome.**

The severity of oral mucositis was described according to the World Health Organization's oral toxicity scale [7]. Grade 1: soreness with or without erythema, grade 2: erythema, ulcers, and patients' ability to swallow solid foods, grade 3: ulcers with extensive erythema and patients not being able to swallow solid foods, and grade 4: mucositis to the extent that alimentation is not possible.

All patients were informed about the objective of this study and the resulting possible benefits, the prescribed ways, and their own role. An informed consent was obtained before enrolling patients in the study. All personal data was kept confidential. Study protocol was approved by Institutional Research Board (IRB)

## 2. Statistical methods:

Data were analyzed using SPSS (statistical package for social sciences) version 28. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the Mean, Range and Standard Deviation were used to describe central tendency and dispersion.

Categorical variables were presented as frequencies (percentage). One-way ANOVA, Chi-square test, paired t test and post hoc tests were used to compare the groups. All outcomes were evaluated at a 0.05 level of significance.

## Results and Discussion

Among the whole group of patients, fifty-one (63.7%) were males, and 29 (36.3%) were females. Patient's age ranged from 19 to 72 years (median age 45.5). Forty-nine (61.2%) cases received chemotherapy and the remaining 31 patients received radiotherapy. Most of the patients included in the study (28.7%) had BMI between 18.5-24.9, while only 4 patients were under-weight with BMI less than 18. The baseline demographic and clinical characteristics of patients are presented in Table (1).

Table 1. Patient baseline characteristics

	<i>All cohort</i> <i>N = 80</i>	
	<i>N<sub>o</sub></i>	<i>%</i>
<b>No. of patients</b>		
Group 1	30	37.5. %
Group 2	30	37.5%
Group 3	20	25%
<b>Gender</b>		
Male	51	63.75%
Female	29	36.25%
Age Mean (range)	45 (19-72)	
<b>Treatment received</b>		
Chemotherapy	49	61.2
Radiotherapy	31	38.7
<b>BMI</b>		
>30	27	33.8
25-30	26	32.5
18.5-24.9	23	28.7
<18.5	4	5

N: number; BMI: body mass index



As shown in Table (2), Most of the patients included in this study were diagnosed with lymphoma (26.3%). Nineteen patients had breast cancer, and 17 patients had leukemia. On the other hand, six patients only had nasopharyngeal carcinoma.

**Table 2.Type of cancer in the studied groups**

Type of Cancer	Group 1	Group 2	Group 3
Leukemia	7	6	4
Lymphoma	8	7	6
Nasopharyngeal carcinoma	2	3	1
Bronchogenic carcinoma	2	5	2
CNS metastasis	3	2	3
Breast cancer	8	7	4

CNS: Central nervous system

In table (3), differences appeared to be comparable among groups at base line. One-way analysis of variances, showed that the differences between variables including age and body mass index (BMI) in all three groups were not significantly different ( $p > 0.05$ , Table 5). The Chi-square test showed that the distribution of variables including gender and treatment received were not significantly different between the three groups.

**Table 3. Characteristics of participants among the three groups**

Parameter		Group 1	Group 2	Group 3	P value
Age*	Mean $\pm$ SD	45.5 $\pm$ 14.13	45.8 $\pm$ 13.2	43 $\pm$ 17.26	0.82
Gender	Male	18	20	13	0.85
	Female	12	10	7	
Treatment*	Chemotherapy	17	16	12	0.89
	Radiotherapy	13	14	8	
BMI	>30	9	9	10	0.78
	25-30	9	12	6	
	18.5-24.9	10	8	3	
	<18.5	2	1	1	

SD: standard deviation; BMI: Body mass index

\*Variables compared by Chi-square test

Among the whole group of patients, forty-two patients developed oral mucositis during the course of intensive chemotherapy or radiotherapy. the number of patients who developed mucositis were 15 out of 30 patients (50%), and 11 out of 30 patients (30%) in groups 1 and 2, respectively. most patients in the control group developed mucositis (16 out of 20 patients, 80%). There was significant difference in the occurrence of mucositis among groups ( $p=0.01$ ) in favor of patients in both experimental groups compared to control group (table 4). According to the post hoc analysis and compared with the control group a significantly better result was reported for honey plus propolis at the end of the first week ( $P=0.001$ ).

**Table 4. Oral mucositis among groups of patients after one week**

			Number of cases (percentage)	P value
Oral mucositis N=42	Group 1	Yes	15 (50%)	0.01*
		No	15 (50%)	
	Group 2	Yes	11 (36.6%)	
		No	19 (63.3%)	
	Group3	Yes	16 (80%)	
		No	4 (20%)	

N: number

However, mucositis was present in severe forms, (Grade 3&4), in the control group, 5 out of 16 (31.3%), as compared to the study groups, 6 out of 26 (23.1%). Hence, it appears that Honey with or without propolis reduced the occurrence of severe mucositis (Table 5).

**Table 5. Comparison of grades of mucositis in the studied groups**

Mucositis grade	Group (1) N=15 (%)	Group (2) N=11 (%)	Group (3) N=16	p
Grade 1	5(33.3)	5 (45.5)	3 (18.7)	0.12
Grade 2	7(46.6)	3 (27.3)	8 (50.0)	
Grade 3	2(13.3)	2 (18.2)	3(18.7)	
Grade 4	1(6.6)	1 (9.1)	2 (12.5)	

N: number



Grade 1 mucositis



Grade 2 mucositis



Grade 3 mucositis



Grade 4 mucositis



**Figure 1. Representative images of our patients with oral mucositis induced by radio/chemotherapy**



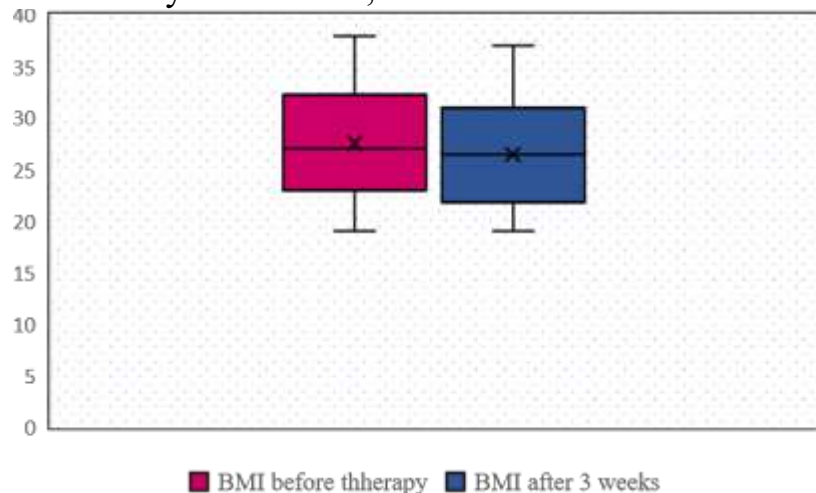
At study termination (week 3), most patients in group 2 were free of symptoms (5 out of 11 patients, 45.5%). Then after, Honey group (group 1) took the second place with 40 % of patients free of symptoms ( $P = 0.001$ ). Patients in the control group had the highest grade 3 and 4 experience of OM (25%).

Third week analysis of BMI showed significant reduction of BMI of 42 patients whom developed stomatitis with mean value of ( $27.23 \pm 5.42$ ), compared to the mean BMI value of the same group of patients assessed before therapy, denoting significant reduction of the body weight in the group of patients who developed oral mucositis (table 6). Furthermore, Significant reduction of BMI was also reported among each treatment group when compared to the values before treatment (Table 7 & figure 5).

**Table 6. Comparison of BMI before treatment and at the third week of treatment**

Parameter		Result	P
BMI Before treatment	Mean $\pm$ SD	$27.23 \pm 5.42$	0.001
	Range	17-39	
BMI After 3 weeks	Mean $\pm$ SD	$25 \pm 5.09$	
	Range	19-37	

BMI: Body Mass Index; SD: Standard Deviation.



**Figure 2. BMI before treatment and after 3 weeks**

**Table 7. Difference of Mean BMI between different groups at the third week of treatment**

	BMI (Mean $\pm$ SD) Before treatment	BMI (Mean $\pm$ SD) After 3 weeks	P value
Group 1	$27.8 \pm 5.68$	$26.12 \pm 5.04$	0.006
Group 2	$26.2 \pm 4.42$	$25.6 \pm 4.54$	0.001
Group 3	$27.5 \pm 5.32$	$26.4 \pm 5.09$	0.0001

BMI: Body Mass Index; SD: Standard Deviation

Oral mucositis is a common and feared adverse effect in patients with cancer who undergo anticancer treatment. The management of

mucositis can be quite vexing for both the patient and the oncologist. Various methods have been suggested in order to prevent and treat oral mucositis. A range of agents and management approaches are available to the practicing oncologist, with variable efficacy and data to support their use [8].

The results of this trial showed that the use of honey has significantly reduced the incidence of OM at the first week after consumption compared with the traditional mouth wash. According to the post hoc analysis and compared with the control group, the addition of propolis with honey has further reduced the incidence of occurrence of OM at the end of the first week. These results illustrate the powerful effect of honey, which is further augmented by addition of propolis, in prevention of OM in the group of patients receiving chemotherapy or radiotherapy.

As regard severity of oral mucositis, our study reported lower percentage of grades (3 & 4) oral mucositis in both experimental groups of patients compared to the control group. This difference did not reach statistical significance, which may be attributed to the small number of cases with events in this cohort of patients. Furthermore, the patients who developed severe mucositis responded well to local application of honey alone as well as honey plus propolis throughout the study.

These results are in agreement with a randomized single blind clinical trial that included 40 patients received radiation to the oropharyngeal mucosa. They were randomly divided into 2 groups. Patients received pure natural honey or control. A significant reduction in mucositis in patients treated with honey was observed as compared with controls [9].

In a recently published article, authors collected data of children and adolescents with cancer from randomized controlled trial articles. They concluded that honey may significantly affect the treatment and prophylaxis of OM, and that honey enhanced recovery time and improved OM significantly when compared with those without honey treatment receiving pediatric patients. They suggested that honey must be included as one of the treatments or prevention of choice for chemotherapy-induced OM [10]. Furthermore, honey not only has been shown to have the capability for healing injured tissues but also it is more economical treatment, and it has fewer side effects compared to synthetic drugs. [11]

Similarly, another study was carried out on 60 patients to evaluate the effect of natural honey on radiotherapy induced oral mucositis. A significant reduction in mucositis in honey-received patients compared with benzydamine hydrochloride, normal saline applied patients was recorded. The differences between the groups were statistically

significant. Authors concluded that pure natural honey can be an effective agent in managing radiation induced oral mucositis. [12]

In contrast to our results, other studies on the topical application of Manuka honey, did not show positive effects on OM. Authors argue that "it is unclear if a combined topical and systemic application of Manuka honey will be effective in preventing OM. This difference in outcome may be explained by a number of probable causes; different study designs, patient characteristics, anticancer treatment protocols, degree of oral mucositis, and most important by the type and source of the used honey as well as its amount and form. [13, 14]

In agreement with our data, another randomized double-blind placebo-controlled trial was conducted to evaluate the potential effect of propolis mouthwash on head and neck tumor patients undergoing chemotherapy. In the treatment group, propolis mouth rinse was administered three times a day for 7 consecutive days. In the control group, the process was repeated with mouth rinse. OM, erythema, and eating and drinking ability were evaluated. In line with our results, when compared to the control group, the treatment group presented significant improvement in OM, wound healing, and erythema at the first week. Moreover, most of the patients in the propolis group were completely healed by day 7 of the trial [15].

In the current study, there was significant reduction of the mean BMI value at the end of the third week of treatment compared to the same value calculated at the beginning of the study. However, the same difference was not detected between different groups; calculation of BMI before and after treatment did not reveal significant difference between the three tested groups of patients. The reduction of BMI indicated weight loss in all included patients regardless of whether those patients were among the experimental or the control groups. This reduction of body weight is most probably referred to anorexia associated with malignancy, limitation of the oral intake due to oral mucositis, as well as nausea and vomiting associated with administration of either chemotherapy or radiotherapy.

In contrast to our results, researchers administered oral honey in cancer patients suffering from oral mucositis. They found that the honey intervention group had a higher body weight compared with the control group, which was contributed to preventing opportunistic infection by aerobic bacteria and Candida, improving the ecological balance of the oral microenvironment. [16]

## **Conclusion**

Based on the evidence reported in our study, honey with or without propolis was found to have beneficial effect on prevention and reduction of severity of OM. They may serve as effective agents in managing radiation and chemotherapy induced OM. Being simple, potent, inexpensive, available agents, they can be better therapeutic options in managing OM in developing countries

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