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Research article

Efficiency of honey–grape blend in reducing radiation-induced mucositis in locally advanced head and neck squamous cell carcinoma

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Abstract: Objectives: This study assessed the efficacy of a honey–grape blend in reducing the severity and onset of radiation oral mucositis (ROM) in patients with locally advanced squamous cell carcinoma of the head and neck. Oral mucositis is an acute side effect caused by chemotherapy or radiotherapy in the head and neck region. ROM affects patients' quality of life and treatment expenses. Various pharmaceutical and natural remedies, such as sucralfate, aloe vera, and amifostine are used to mitigate the effects of ROM. However, the available modalities' efficacy is low and is associated with many side effects. **Materials and methods:** This cohort study was conducted at the Ocean Road Cancer Institute and Besta Polyclinic in Tanzania. The study included 73 patients with locally advanced squamous cell carcinoma of the head and neck treated from March 2024 to August 2024. The World Health Organization mucositis grading system was used to assess patients' progress weekly. Data analysis was conducted using Statistical Package for Social Science (SPSS) version 27. **Results:** Delayed onset (15% Grade 3 for the honey–grape group and 45% Grade 3 for the control group at 28 days) and reduced the severity of ROM (only 20% Grade 3 with no Grade 4 for the honey–grape group while for the control group, it was 25% Grade 3 and 20% Grade 4 at 45 days) (p-value < 0.001). Body weight changes at starting and after completion of radiotherapy were observed (2.65 kg average weight loss for the control group and 1.8 kg, 0.45 kg weight gain for the honey group and honey–grape blend group). Prevalence between genders was 62% males and 38% females. **Conclusions:** Honey and honey

blended with grapes can minimize the severity and delay the onset of ROM in patients with locally advanced head and neck cancer. More studies are needed, since no study has been conducted addressing the efficacy of honey–grape blends in reducing ROM severity.

Keywords: mucositis; grapes; honey; head and neck; cancer; radiotherapy

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is among the high-incidence cancers, accounting for about 700,000 new cases worldwide in 2018, with a mortality rate of approximately 350,000 per year [1]. The incidence of SCCHN has been increasing and is associated with factors such as human papillomavirus (HPV) infections for oropharyngeal cancer, smoking, excessive alcohol consumption, Epstein–Barr virus infections (EBV), and environmental and genetic factors [2–4].

Radiotherapy (RT) with concomitant chemotherapy (CRT) is a standard treatment for locally advanced head and neck cancer (LAHNC) [1]. Despite its beneficial impacts, RT or CRT has some debilitating effects, and one of them is radiation-induced oral mucositis (ROM). This is an acute side effect that occurs during head and neck radiotherapy [5]. Nearly all head and neck radiotherapy cancer patients suffer from ROM [6]. This can interfere with patients' quality of life and local tumor control [7,8]. Several factors can accelerate ROM and can act as confounders during the design of clinical trials; hence, they should be addressed and taken into consideration. These confounders can be categorized into patient-related factors (example, gender, oral hygiene, smoking, and genetic factors), disease-related factors (primary disease anatomical site, and volume treated), and treatment-related factors (fractionation regime, RT technique, and concurrent use of chemotherapy) [9–11].

There are some methods used for the mitigation of ROM, such as chlorhexidine and amifostine [12–14]. However, the available modalities' efficacy is low and is associated with many negative side effects [5]. Honey and grapes were selected to be studied as alternative potential candidates for mitigating this side effect. They contain elements and compounds that meet some properties that are suitable for the desired purpose [15–19]. The efficacy of honey and grape seeds has been reported in some studies [13,20,21]. Therefore, this study aimed to investigate the potential improved efficacy of honey blended with grape juice in reducing the severity of ROM.

2. Material and methods

2.1. Sampling techniques

The allocation of patients to respective groups aimed to achieve homogeneity and normality within and across the groups to minimize confounders. Patients across the groups shared the same sociodemographic and clinical characteristics, although not by 100% (for example, out of nine oropharyngeal patients, each group got three patients, taking other factors into consideration, such as age and gender) (see Table 1). All patients received adjuvant RT. This study was conducted at two cancer hospitals, Ocean Road Cancer Institute (ORCI), and Besta Polyclinic, in Dar Es Salaam, Tanzania. The two hospitals were selected for this study because they accommodate more than 80% of cancer patients in the country. Seventy-three patients with locally advanced SCCHN were involved

in this study (50 patients from ORCI, and 23 patients from Besta Polyclinic). In total, 6 patients from Besta Polyclinic and 18 patients from ORCI were used as a control group, 6 patients from Besta Polyclinic and 18 patients from ORCI were recruited to the honey group, and 6 patients from Besta Polyclinic and 19 patients from ORCI were subjected to honey–grape juice. Thirteen patients (four from the control group, four from the honey group, and five from the honey–grape group) withdrew from the study. Four patients from the control group, and one each from the honey and honey–grape groups withdrew because of mucositis severity. One patient from the honey group suffered a treatment interruption after a motorbike accident while heading to the hospital. Two patients from the honey group and four from the honey–grape group quit because of their teeth's sensitivity to honey and the honey–grape blend, and hence they were excluded from the data analysis. This may have created an underestimation of the prevalence of mucositis, especially in the control group, as three out of four patients withdrew from the study in this group after developing Grade 3 mucositis, implying that they might have ended up with Grade 4. Furthermore, the inclusion criteria included patients who received 60–66 Grays of radiation, according to the treatment protocol in the country, and patients whose plan was three-dimensional external beam conformal radiotherapy (3D CRT), which is currently the standard practice for head and neck cancer patients in the country. Moreover, patients who were willing to participate in the study and signed an informed consent form were included. Exclusion criteria included children under 10 years old (this group was excluded because they could probably not comply with the instructions), patients who were allergic to honey and/or grapes, and those who did not meet the inclusion criteria.

Table 1. Patients' grouping across the study groups.

		Patient group			
		Control	Honey	Honey + grapes	Total
Modality	3D CRT	20	20	20	60
Gender	Male	13	12	12	37
	Female	7	8	8	23
Disease site	Hypopharynx	3	3	3	9
	Oral pharynx	3	4	4	11
	Oral cavity	2	2	3	7
	Larynx	3	4	4	11
	Nasopharynx	7	7	8	22
Chemotherapy	Concurrent chemo-radiation	17	17	17	51
	Radiotherapy only	3	3	3	9
	Smoking	2	1	2	5
	Alcohol consumption	10	10	10	30
	HIV positive	2	1	2	5
	HPV positive	4	4	5	13
Age	Below 45 years	3	3	3	9
	Above 45 years	17	17	17	51

Note: 13 patients withdrew from the study and were not included in the data analysis.

2.2. Fractionation regime and dose delivery

All patients received a minimum of 30 and a maximum of 33 fractions of external beam radiotherapy. Patients received 2 Grays (Gy) per fraction for five consecutive days a week for seven weeks in a row. Three-dimensional external beam conformal radiotherapy (3D CRT), which is a current standard practice for locally advanced SCCHN in the country, was used for dose delivery, using 6 MV of energy for all patients. Treatment verification was conducted for four consecutive days in the first week and then once per week throughout treatment.

2.3. Solution preparation and administration

A juice was prepared by blending honey from wild bees with grapes; no water was added. There were two intervention groups with 20 patients each. The first group received 50 mL of honey, and the second group received 50 mL of honey blended with grape juice, while the third group received a placebo.

Patients were instructed to rinse with 50 mL of the prepared solution at least 5 minutes before the delivery of radiotherapy and do the same immediately after the radiotherapy treatments under the supervision of a radiotherapist. The procedures were repeated every 8 hours (patients were provided with a 50 mL solution in a container every day after radiotherapy) to be used when the patients were at home under the guidance of a radiotherapist via phone call (or video call). All patients were outpatients. The reason for the patients repeating the procedures every 8 hours was to allow for anti-inflammatory and anti-microbial effects as well as to improve nutritional status. Clinical progress of the patients was conducted weekly by a radiation oncologist from the first week of treatment until the completion of the treatments.

2.4. Nutrition and oral care hygiene

Patients were instructed to avoid extremely hot drinks, smoking, and alcohol, as these would accelerate mucositis and irritate the oral mucosa. A high-protein diet and adequate fluid intake were also encouraged. Patients were provided with soft toothbrushes and instructed on how to perform oral hygiene, such as avoiding excessive force while brushing teeth and gently brushing the tongue. Mucositis grading was done using the World Health Organization (WHO) mucositis grading system (as shown in Table 2). Grading was being performed by radiation oncologist.

Table 2. WHO mucositis grading criteria.

Grade	Clinical indications
0	None
1	Soreness with or without erythema
2	Erythema + ulcers and the patient can swallow solid foods
3	Ulcers with extensive erythema and the patient cannot swallow solid foods
4	Life-threatening mucositis such that alimentation is not possible
5	Death

2.5. Statistical analysis

Data were tested for normality using the Shapiro–Wilk test, and Levene's test was used for the homogeneity test. A t-test was used to measure significance differences between age groups of patients. Chi-square was used for gender prevalence and alcohol consumption among genders, whereby one-way analysis of variance (ANOVA) was used for testing significant differences in mucositis severity among the groups as well as mean weight differences among the three groups. A p-value of <0.005 was established as the threshold for rejecting the null hypothesis. Data analysis was conducted using SPSS version 27.

3. Results

Differences in age and gender distribution were observed among the patients (See Table 3). There were differences in lifestyle between genders, such as tobacco smoking, and alcohol consumption. There was also a difference in the sites treated.

Table 3. Sociodemographic and clinical characteristics among head and neck cancer patients at ORCI and Besta Polyclinic.

Sociodemographic characteristics		
Variable	Frequency No. (%)	p-value
Age group (years)		
0–35	12 (21.4)	<0.001
36–60	30 (48.3)	
Above 60	18 (30.03)	(t-test)
Gender		
Males	37 (62)	<0.001
Females	23 (38)	
Total	60 (100)	(Chi^2 test)
Alcohol consumption		
Alcohol consumption among males	20 (54.05)	0.550
Alcohol consumption among females	8 (34.8)	
Total	28 (46.67)	(Chi^2 test)
Smoking		
Smoking among males	5 (13.33)	
Smoking among females	0 (0)	
Total	5 (8.33)	
Clinical characteristics		
HIV-positive		5 (8.33)
Disease site		
Nasal pharynx		22 (36.67)
Tongue		9 (15)
Oral mucosa		7 (11.67)
Larynx		11 (18.33)
Oral and hypopharynx		11 (18.33)
Induction chemotherapy		38 (63.33)
Concurrent chemotherapy		50 (83.33)

3.1. Weight changes among patients

As shown in Table 4, before radiotherapy, the mean weights (W1) for the control, honey, and honey–grape juice groups were 65.55 kg, 63.85 kg, and 62.1 kg, respectively. After radiotherapy, the mean weights (W2) for these groups were 62.9 kg, 65.65 kg, and 62.55 kg, respectively. There was a variation in weight changes (weight difference between the weight measured on the first day of radiation therapy and the weight measured on the final day of radiotherapy) among the groups. There was a significant weight loss in the control group (average weight loss of 2.65 kg), the mean weight gain for the honey group was 1.8 kg, and the mean weight gain for the honey–grape group was 0.45 kg. Variation in weight was statistically significant ($p < 0.001$).

Table 4. A comparison of weight changes among the groups before and after radiotherapy at the ORCI and Besta Polyclinic hospitals.

Dependent variable		Weight difference		
Groups (I)	Groups (J)	Mean difference (I–J)	Std. Error	p-value
Control	Honey	−4.450*	0.789	<0.001
	Honey + grapes	−3.100*	0.789	<0.001
Honey	Control	4.450*	0.789	<0.001
	Honey + grapes	1.350*	0.789	0.210

Note: p-value < 0.005, ANOVA; Std. Error: Standard error; *: There were differences.

3.2. Mucositis severity among patients in different groups

As shown in Table 5, and Figure 1, except in the first week of radiotherapy, there was a significant difference in the severity of ROM between the control group versus the intervention groups (honey group and the honey–grape group). There was also a difference in the severity of ROM within groups when compared from one week to another week.

Table 5. Mean difference in the severity of mucositis for different study groups from the first week to the last week of radiotherapy at the ORCI and Besta Polyclinic hospitals in Dar Es Salaam, Tanzania.

Dependent variable	Groups	Std. Error	p-value
Mucositis severity, Week 1	Control vs. honey	0.041	0.444
	Control vs. honey + grape	0.041	0.444
	Honey + grapes vs. honey	0.041	1.000
Mucositis severity, Week 2	Control vs. honey	0.129	<0.001
	Control vs. honey + grape	0.129	<0.001
	Honey + grapes vs. honey	0.129	0.921
Mucositis severity, Week 3	Control vs. honey	0.159	0.039
	Control vs. honey + grape	0.159	0.039
	Honey + grapes vs. honey	0.159	1.000

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Dependent variable	Groups	Std. Error	p-value
Mucositis severity, Week 4	Control vs. honey	0.172	0.031
	Control vs. honey + grape	0.172	0.003
	Honey + grapes vs. honey	0.172	0.661
Mucositis severity, Week 5	Control vs. honey	0.157	0.001
	Control vs. honey + grape	0.157	<0.001
	Honey + grape vs. honey	0.157	0.417
Mucositis severity, Week 6	Control vs. honey	0.155	0.013
	Control vs. honey + grape	0.155	<0.001
	Honey + grapes vs. honey	0.155	0.388
Mucositis severity, Week 7	Control vs. honey	0.161	0.033
	Control vs. honey + grape	0.161	0.003
	Honey + grapes vs. honey	0.161	0.599

Note: p-value < 0.005, ANOVA-test; Std. Error: Standard error.

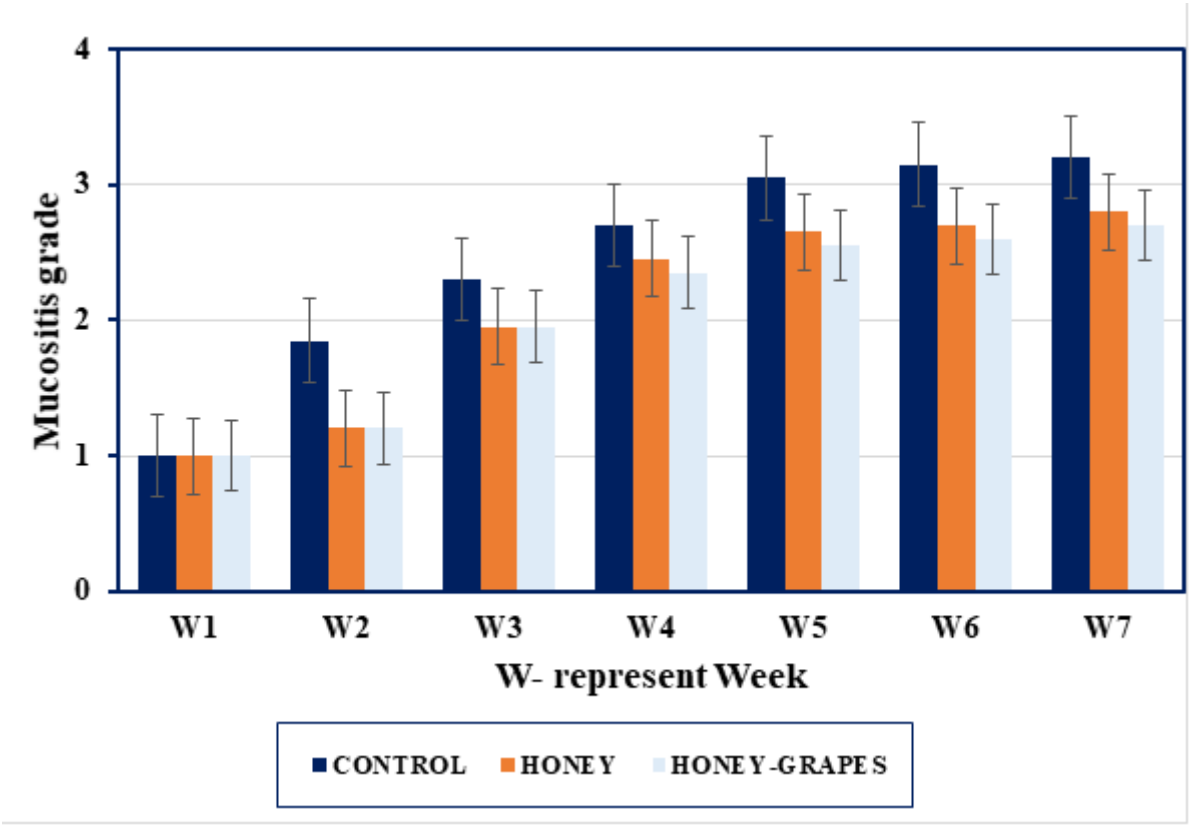

Figure 1. Mean average mucositis severity among patients' groups from the ORCI and Besta Polyclinic hospitals from March to August 2024.

3.3. Mucositis onset

As shown in Table 6, the time taken for the development of ROM was different between the intervention groups and the control group, and between the intervention groups.

Table 6. Time elapsed for the development of different mucositis grades among patient groups.

		Days elapsed from the first day of radiotherapy						
		7 days	14 days	21 days	28 days	35 days	42 days	45 days
Control group	No. of patients with Grade 1 mucositis	19	3	0	0	0	0	0
	No. of patients with Grade 2 mucositis	1	17	14	12	11	11	11
	No. of patients with Grade 3 mucositis	0	0	6	8	6	6	5
	No. of patients with Grade 4 mucositis	0	0	0	0	3	3	4
Honey Group	No. of patients with Grade 1 mucositis	20	10	5	0	0	0	0
	No. of patients with Grade 2 mucositis	0	10	13	16	12	14	14
	No. of patients with Grade 3 mucositis	0	0	2	4	8	6	5
	No. of patients with Grade 4 mucositis	0	0	0	0	0	0	1
Honey + grape	No. of patients with Grade 1 mucositis	20	16	6	0	0	0	0
	No. of patients with Grade 2 mucositis	0	4	12	17	17	16	16
	No. of patients with Grade 3 mucositis	0	0	2	3	3	4	4
	No. of patients with Grade 4 mucositis	0	0	0	0	0	0	0

4. Discussion

4.1. Weight changes

Table 4 shows remarkable weight differences among groups, whereby patients in the control group suffered weight loss in contrast to the intervention groups. Mucositis had a significant impact on the patients' ability to receive proper nutrition due to the pain associated with chewing and swallowing in the control group. Conversely, patients in the intervention groups experienced moderate side effects related to radiation-induced oral mucositis (ROM), resulting in fewer complications with feeding compared with the control group. Patients who received honey–grape juice experienced moderate ROM-related complications compared with those in the honey-only group, whereby the level of intolerable (Grade 3 and 4) ROM was 45%, 30%, and 20% for the control, honey, and honey–grape groups, respectively. However, patients in the honey group experienced more weight gain than the honey–grape group, possibly because of the higher calories in honey than in grapes, as honey has four times the calories in grapes [22,23]. The results on weight loss are supported by other studies, whereby significant weight loss due to mucositis (weight loss of 5%) was reported to range from 3 to 7 kg [5,7,8,24].

4.2. Mucositis severity

As seen in Table 5 and Figure 1, except for in the first week, there was a statistical difference in mucositis severity between the control group and the intervention groups. The severity of mucositis was highest in the control group, followed by the honey group, and was the lowest in the honey–grape juice group. There was a significant difference in scores between the control and intervention groups; however, there was only a slight difference in mucositis severity between the intervention groups. At the end of the first week, there was no difference observed among or within the groups. The reason is that most patients do not experience significant mucositis during the first week of radiotherapy, as the cumulative radiation dose is insufficient [25,26]. Several patients exhibited no more than Grade 1 mucositis even without any intervention.

At the end of the second week, there was a slight difference within the group between the first week and second week for the honey group and the honey–grape group; however, there was no difference between them. This was different for the control, where there was a big difference between the first week and the second week, and there was a big difference between the control group and the other two groups. This can be explained by considering the steps of mucositis development.

In the second week, ulceration occurs and there is also infiltration by Gram-negative bacteria, yeast colonization, signal amplification, or upregulation of inflammation by the release of more inflammatory cytokines [26]. Honey and the honey–grape blend counteracted these events, unlike the placebo.

There was a big difference within the groups from Week 2 to Week 4. This might result from the upregulation of inflammatory cytokines from injured tissues, causing more damage to the tissues. At the end of Week 3, no difference in mucositis severity was seen between the intervention groups (the honey group and the honey–grape group) for the same reason as in Week 1 and Week 2. However, a slight difference started to show up from Week 4 to Week 7. This might be because of the strong antioxidant power of grapes, which have an antioxidant power 50 times higher than vitamin C and 20 times higher than vitamin E [19].

From Week 5 to Week 7, the differences within groups were fairly small, whereas mucositis severity kept on increasing, possibly because at this point, the intervention fails to counteract the effects of ongoing radiation damage. In all cases, the difference between the honey group and the honey–grape juice group had no statistical difference in terms of mucositis severity; however, there was a difference, but it was not statistically significant. A small sample size might be one of the reasons for this observation; a large sample size might bring an improved and statistically significant outcome. Moreover, honey and grapes may act in the same ways/principles regarding ROM mitigation. Replacing a certain volume of honey with grapes might have little added advantage. Another reason is that 25 mL of honey is not equivalent to 25 mL of grapes. Maybe the outcome could be improved if the volume of honey were replaced with an equivalent volume of grapes in terms of phytochemical concentrations and not the same volume, or if weight were used, the outcomes could have been significant. More differently designed studies may bring improved results.

4.3. Efficacy of honey–grape juice when compared with other studies

The results for the efficacy of various remedies vary across different studies, even with repeated studies. For example, Table 7 below shows a huge difference from other studies for honey ranging

from 4.55 to 50% for intolerable mucositis grades. These differences might be attributed to differences in radiotherapy delivery techniques and differences in the composition of natural remedies; for instance, honey's quality differs according to the geographical location, affecting the amount of some medicinal properties of honey and grapes. This implies that even this study might have different results (improved or decreased efficacy) when conducted in other places. However, the results are still valid, as there was a significant improvement when compared with a placebo group, and were significant, but to compare the results with findings from other studies, there is a need to conduct a study with the desired remedy to be compared.

Table 7. The efficacy of various remedies for mitigating ROM.

Intervention used	No of studies	% of patients developed Grade 3–4 mucositis	Article reference
This study	1	20	–
Grapes	1	39.13	[21]
Black mulberry	1	40.63	[21]
Lactobacillus brevis	1	40.6	[24]
Aloe vera	1	38.46	[14]
Benzydamine	1	95	[13]
Chlorhexidine	3	9.38, 25.00, 30.77	[14]
Honey	2	50	[13]
Povidone–iodine	4	4.00, 24.00, 32.00, 50.00	[14]
Curcumin	2	36.67, 30.56	[14]
Chamomile	1	2.7	[14]
Sodium bicarbonate	1	75	[24]
Sucralfate	1	92.86	[14]
Benzydamine	1	30.77	[14]
Honey	2	4.55, 9.10	[14]

It is interesting that even with placebo groups, the results have varied from one study to another, with some studies showing a very big difference (as shown in Table 8). The reasons for these discrepancies are not clear; however, this is an indication that there might be a very big gap in clinical practices in different hospitals or inadequate addressing of the confounders during the study design process. The efficacy of any remedy should be evaluated by its ability to mitigate mucositis when compared with a placebo or other remedies in the same working environments. For example, in a setting where Grade 3 to 4 mucositis is only 22.07% in patients receiving a placebo, it might seem that there is no need to introduce a remedy that reduces ROM to 20%. However, in reality, it might be possible that in a such setting, this remedy might reduce ROM severity from 20% intolerable mucositis to even lower than 10%.

Table 8. Intolerable (Grade 3–4) mucositis among placebo patient groups in different studies involving head and neck radiotherapy patients.

% of Grade 3–4 mucositis	Study conducted by
45	This study
41.6	[24]
28	[27]
95	[13]
75	[28]
26	[14]
37	[14]
23	[14]
35.3	[14]
93.33	[14]
78.57	[14]
49	[14]
73.74	[14]
22.07	[14]
44.9	[14]
30.6	[14]
58.82	[14]
22.39	[14]
31.34	[14]
45	[14]
72.25	[14]

4.4. Mucositis onset

There was a significant difference in time for the development of severe mucositis among patients starting from the second week (Table 5). There was a delay in ROM onset in the intervention groups when compared with a control group. This indicates that there was an improvement in patients' quality of life in the intervention groups. A delay in mucositis onset resulting from the application of honey was observed in another study [13]. Only 10% of patients in the honey and honey–grape juice groups developed Grade 3 mucositis at 21 days after the initiation of radiotherapy, whereas in the placebo group, 30 patients developed Grade 3 mucositis. These results can be supported by Jayachandran and Balaji, who found that the average time for the development of Grade 3 ROM was 21.1 days for benzydamine butfor the honey group, it was 25 days [13].

5. Conclusions

Honey and honey blended with grapes were statistically significant in minimizing the severity of radiation-induced mucositis and its onset compared with a control group (patients who were provided with no intervention). However, more studies with different ratios of honey to grape juice and various volumes of honey and grape juice are needed. There is also a need to conduct studies with large sample sizes to test for some factors such as the effects of smoking on radiation-induced mucositis, which seems to be contradictory in many studies.

6. Strengths and limitations of the study

This study effectively minimized confounders, included all eligible patients treated during the study period, and represented the total population of head and neck cancer in the country. However, this study faced some limitations such as the following.

1. The absence of Intensity modulated radiotherapy (IMRT) and Volumetric modulated arch therapy (VMAT) planning, also broad cases in the head and neck were studied which reduced the power of the study.

2. The sample size was limited and there is a need to conduct more studies with large sample sizes to have enough evidence of honey–grape juice's efficacy in ROM mitigation. Moreover, the small sample size resulted in failures to determine the influence of some factors such as age and sex on mucositis severity.

3. The study could be narrowed into a single case (e.g., dealing only with the oropharynx) and not multiple cases.

4. Honey and grape quality differ according to the geographical location; this might have resulted in different results from other studies. There is a need to emphasize the characterization of these natural remedies in terms of their composition, viscosity, and pH to ensure maximum reproducibility for repeated studies.

5. In this study, 25 mL of honey was replaced by 25 mL of grape juice. This might have resulted in a nonstatistical difference being observed. This is because the concentration of phytochemical compounds present in honey is not the same as that present in the same volume of grapes.

Author contributions

Magaisha Edward Kyomo: manuscript preparation, study concept, study design, data acquisition; Nelson Mpumi: supervisor, quality control of data and algorithms, data analysis and interpretation; Elingarami Sauli: manuscript review, supervisor, editing the manuscript; Salum Lidenge: supervisor, statistical data analysis.

Use of AI tools declaration

The authors declare they have not used artificial intelligence (AI) tools in the creation of this article.

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Ethical approval of the research and informed consent

Ethical clearance was obtained from the Ocean Road Cancer Institute Ethical Committee (on behalf of the National Institute for Medical Research, NIMR). All participants provided written informed consent and assent, as appropriate, prior to study enrollment.

Conflict of interest

The author declares that no competing financial or personal interests/relationships that could have appeared to influence the work reported in this paper.

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