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## Comparison of Therapeutic Effects of Magic Mouthwash with Natural Products on Chemotherapy/Radiotherapy-Induced Oral Mucositis

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### ABSTRACT

Oral Mucositis (OM) refers to the agonizing swelling and formation of sores to the lining of mucous membrane within the mouth cavity. It is a common complication experienced by patients having chemotherapy with or without radiation therapy for Head and Neck Cancer (HNC). Effective management of OM is crucial, as it can cause severe pain that, in some cases, leads to delays in cancer treatments like chemotherapy or radiotherapy. While there are commercially available treatments, with the most common being "magic mouthwash," recent studies suggest that natural remedies may be more beneficial in decrease the occurrence and severity of OM. Among these natural therapeutic agents, honey and aloe vera have shown promising results. Research indicates that both can be used individually to manage OM due to their positive therapeutic effects.

The current study, conducted as an randomized controlled clinical trial at the Oncology Radiation Department of Jinnah Postgraduate Medical Centre (JPMC) Karachi in collaboration with the Basic Medical Sciences Institute (BMSI), aimed to evaluate whether a combination of honey and aloe vera is more effective than magic mouthwash in reducing OM severity among HNC patients undergoing chemotherapy and/or radiotherapy. The study involved 80 patients who were randomly assigned to two groups: the HA Group (honey and aloe vera treatment) and the Control Group (magic mouthwash treatment). Patients were assessed at baseline (week 0, the start of chemotherapy/radiotherapy) and at subsequent intervals every two weeks (weeks 2, 4, and 6) using the WHO OM grading scale.

Statistical analysis was conducted, with a p-value of less than 0.05 regarded as statistically significant. By week 6, OM of Grade 3 or higher was observed in 16 patients (40%) from the Control Group compared to only 5 patients (12.5%) in the HA Group, a statistically significant difference (p-value = 0.031). The study concluded that the combination of honey and aloe vera is both effective and affordable, significantly reducing the severity and occurrence of OM in HNC patients undergoing chemotherapy or radiotherapy. These findings provide reassurance that severe OM in such patients can be mitigated to a substantial extent through this natural and cost-effective solution.

**Key words:** Aloe vera, Head and Neck Cancer, Honey, Magic Mouthwash, Oral Mucositis, Radiotherapy.

## INTRODUCTION

Cancer remains one of the leading causes of death globally, accounting for roughly 1 in 6 deaths and affecting nearly every household. In 2022, there were an estimated 20 million new cancer cases and 9.7 million cancer-related deaths worldwide. By 2050, the global cancer burden is projected to rise by 77%, further straining healthcare systems, individuals, and communities (World Health Organization).<sup>i</sup>.

Early detection and proper clinical management significantly improve the chances of successfully treating cancer. However, cancers in the head and neck region pose additional challenges due to structural deformities and disruptions to normal physiological functions, which can severely impact quality of life. Globally, Head and Neck Cancers (HNCs) rank sixth among all cancers, excluding those of the brain and eyes<sup>ii</sup>. HNCs include cancers of the sinuses, nasal cavity, oral cavity (tongue, gums, and palate), pharynx (nasopharynx, oropharynx, and larynx), lips (sometimes considered skin cancer), and the salivary glands (though rare)<sup>iii</sup>.

The selection of cancer treatment is influenced by various clinical factors, such as the type, location, and stage of the disease. The main goal is to eliminate cancerous cells while minimizing harm to nearby healthy tissues. Treatment options include surgery, chemotherapy (using chemical agents to kill cancer cells), and radiotherapy (utilizing radiation, such as X-rays), or a combination of these approaches<sup>iv</sup>.

Chemotherapy is one of the most widely used treatments for various cancers, including HNCs. While no treatment can guarantee a complete cure, these therapies significantly alleviate the pain caused by cancer and get better patients' endurance and quality of life<sup>v</sup>. Radiotherapy is another common treatment option and is especially effective in relieving symptoms of cancer. It is, however, expensive and requires skilled personnel for its administration. Globally, nearly half of all cancer patients undergo radiotherapy at some stage of their treatment, and around 40% of cancer cases rely on this treatment regimens include this method. Radiotherapy works by halting the multiplication of cancerous cells<sup>vi</sup>. However, it can also damage healthy cells, particularly those in the oral mucosa, leading to a condition known as Oral Mucositis (OM)<sup>vii</sup>.

OM was first described in the late 1980s and is defined as inflammation and irritation of the oral mucosa, a common non-hematological complication of cancer treatments such as chemotherapy and radiotherapy. While these methods are effective in targeting malignant cells, they also harm surrounding healthy tissues, including the oral mucosa. This triggers a complex biological response, resulting in ulcerative lesions that cause pain and discomfort. OM is a non-infectious and non-contagious condition, making antibiotics and antiviral medications largely ineffective. Studies show that 40–80% of HNC patients undergoing chemotherapy, and nearly all patients undergoing radiotherapy, develop OM. Approximately 19% of radiotherapy patients with OM

are hospitalized, leading to treatment delays. OM not only reduces quality of life but also increases financial burdens<sup>viii</sup>. Its severity and frequency largely depend on the treatment regimen and patient-specific factors, such as poor oral hygiene, smoking, or the use of substances like betel nut and gutka.<sup>ix</sup>

OM typically begins with discomfort and pain even before visible changes in the oral tissues appear. Early signs include patches of redness (erythema), followed by the formation of painful ulcers, which may appear as round or linear yellow/white plaques. The condition most commonly affects the inner cheeks, tongue, lips, and underside of the tongue. Mild ulcerations may cause discomfort, but severe cases result in significant pain, difficulty eating and drinking, and weight loss. In extreme cases, nasogastric tubes may be required to provide adequate nutrition and hydration. Radiation-induced damage to the salivary glands can lead to xerostomia (dry mouth), which further complicates eating and swallowing and can contribute to dental decay. Additionally, the destruction of taste buds—a common adverse effect of radiotherapy—can result in partial or complete loss of taste. Open lesions caused by OM are also vulnerable to infections, such as oral candidiasis.<sup>viii</sup>

Although there are various drugs and mouthwashes (commonly referred to as "magic mouthwash") available for treating OM, these products are often expensive and may cause side effects. Magic mouthwash typically contains at least three of the following ingredients: anesthetics to relieve pain, antifungal agents to prevent fungal growth, corticosteroids to reduce inflammation, antibiotics to fight bacterial infections, and antacids to coat and protect the oral mucosa.

For individuals from low-income groups, natural remedies are a more affordable alternative for managing OM and ensuring uninterrupted cancer treatment. Two such natural products are honey and aloe vera, both of which have been used individually to manage OM effectively. Honey, one of the oldest known natural remedies, has been recognized for its medicinal properties for centuries, even being referenced in the Quran for its therapeutic benefits. Research has shown that honey can help heal wounds, reduce ulceration, and alleviate inflammation associated with OM<sup>x</sup>. Similarly, aloe vera, widely available and inexpensive, is known for its analgesic, anti-inflammatory, antiseptic, and antimicrobial properties. It is often used as a home remedy for sunburns, radiation-induced dermatitis, and mucositis.<sup>xi</sup>

Numerous studies have demonstrated the individual efficacy of honey and aloe vera in managing OM caused by radiation and chemotherapy in HNC patients. This study aims to evaluate their combined effectiveness in treating OM and to provide an economical solution for financially disadvantaged patients. Using low-cost natural products not only alleviates the side effects of HNC treatments but also reduces the overall economic burden on patients and their families.

## MATERIAL & METHODS

This study was designed as a futuristic research study through Randomized Controlled Trial conducted at the Oncology Radiation Department of Jinnah Postgraduate Medical Centre (JPMC), the the largest public-sector tertiary care hospital in Karachi. The research was conducted in collabration with the Pharmacology Department at the BMSI (Basic Medical Sciences Institute). The target population included patients initiating treatment for Head and Neck Cancer (HNC) at JPMC's Oncology Department during the period from July 1, 2021, to December 31, 2021. A total of 80 patients were selected, with 40 patients randomly assigned to the HA Group (honey and aloe vera) and 40 to the Control Group, based on the criteria outlined in a prior study<sup>xii</sup>.

The referenced study reported that Grade III Oral Mucositis (OM) developed in 7.1% of patients treated with honey at a 95% confidence interval and with an absolute precision of 5%. Using the "OpenEpi Version 2" software for sample size calculation, the required number of participants was determined<sup>xiii</sup>.

Eligibility criteria included patients aged 20–65 years with histologically confirmed HNC who were undergoing radiation therapy with doses of 60–70 Gy (delivered five days a week over six weeks). Patients with systemic diseases or those deemed ineligible for other reasons were excluded from the study. Participants who met the inclusion criteria and consented to participate were randomized into the HA Group or the Control Group using a computer-generated randomization method. Careful precautions were taken to ensure proper randomization.

The honey and aloe vera solution utilized in the study was prepared under the supervision of Dr. Hakim Asif Iqbal, Professor and Dean of the Faculty of Eastern Medicine at Hamdard University, Karachi. The solution was produced by the Pakistan Research Institute of Eastern Medicine (PRIEM) Organic Products (Pvt.) Limited, adhering to standardized best practices (Figure-1a). A certificate from the manufacturer, outlining the ingredients and composition, was included in the study documentation (Figure-1b). Additionally, the solution underwent an Acute Oral Toxicity Test at the Pakistan Council of Scientific & Industrial Research (PCSIR) Laboratories Complex in Karachi, with the results showing no signs of toxicity or mortality during the observation period (Figure-1c).



### Figure-1a

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### Object:

To Prepare 100g of Aloe vera and Honey Complex.

### Composition:

|                   |      |
|-------------------|------|
| 1. Xanthan Gum    | 1g   |
| 2. Aloe vera gel  | 20g  |
| 3. Honey          | 20g  |
| 4. Methyl paraben | 1g   |
| 5. Glycerin       | 50ml |

### Procedure:

| Date | Details                                                                                                                                                                                                                                                                                          | Done by | Checked by |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|------------|
|      | <p>Step 1:</p> <p>Take a 1000ml stainless vessel and take the following material</p> <p>Boiled water ..... 30ml</p> <p>Xanthan Gum ..... 1g</p> <p>Mix the water upto 60C and add Xanthan gum and mix up to 30 minutes till the mixture homogenize.</p> <p>Start Time: ..... End Time: .....</p> |         |            |
|      | <p>Step 2:</p> <p>Take a 2000ml stainless vessel and take the following material</p> <p>Aloe vera gel ..... 30g</p> <p>Honey ..... 20g</p> <p>Water ..... 20ml</p> <p>Mix the materials until the mixture homogenize.</p> <p>Start Time: ..... End Time: .....</p>                               |         |            |
|      | <p>Step 3:</p> <p>Add step 2 into step 1 and mix well.</p> <p>Start Time: ..... End Time: .....</p>                                                                                                                                                                                              |         |            |
|      | <p>Step 4:</p> <p>Add the following material in step 3:</p> <p>Methyl Paraben ..... 1g</p> <p>Mix the materials until homogenize.</p> <p>Start Time: ..... End Time: .....</p>                                                                                                                   |         |            |

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**Figure-1b**

**300388**

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**Government of Pakistan (Ministry of Science & Technology)**  
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**KARACHI-75200**

**TEST REPORT**

**Test Report No. 15/ST-2021-1173**

**Date: 15-11-2021**

**Name and Address of Client:** M/s. Power Ocean Products (PVT) LTD.  
10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780,

**Figure-1c**

Magic mouthwash was formulated by Medical store (Kausar Medicos), Karachi, a leading pharmacy in the city. The preparation adhered to the standard recipe used in the Oncology Ward at JPMC, which includes Nystatin, Xylocaine, Decadron, Gravinate, and Mucaïne (Figure-2).



### Figure-2

At the start of radiotherapy, patients in the HA Group were instructed to use 20 ml (equivalent to two tablespoons) of a specially formulated honey and aloe vera solution three times a day. This included applying it 15 minutes before and 15 minutes after radiation therapy on treatment days, as well as before bedtime. This regimen was to be followed for the entire six-week treatment period. Patients were advised to hold the solution in their mouths for three to five minutes before spitting it out. Meanwhile, patients in the Control Group was instructed to use the 5 ml (one teaspoon) of mouthwash 3 times a day, following the same schedule as the HA Group. They were similarly instructed to hold the mouthwash for three to five minutes before spitting it out.<sup>xiv</sup>

## EVALUATION & ASSESSMENT

Clinical examination of the patients for the development of oral mucositis, was done before the treatment which is termed as 0 week and then after a regular interval of two weeks after the start of treatment termed as 2, 4 and 6 week. The assessment of severity of OM was done using grading system defined by WHO Oral Mucositis Assessment Scale (Figure-3a).

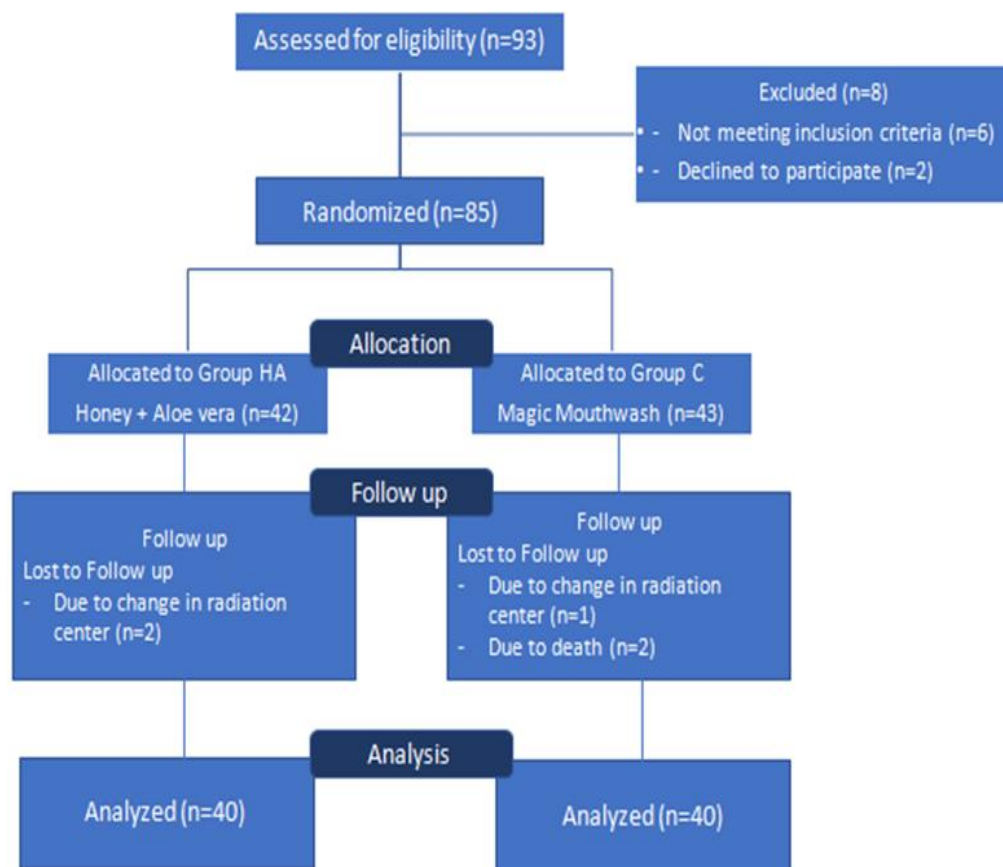
| <b>Table 1. World Health Organization Oral Mucositis Assessment Scale</b> |                                                                   |
|---------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Grade 0</b>                                                            | Normal oral mucosa                                                |
| <b>Grade 1</b>                                                            | Soreness and erythema                                             |
| <b>Grade 2</b>                                                            | Erythema ulcers; patient can swallow solid food                   |
| <b>Grade 3</b>                                                            | Ulcers with extensive erythema; patient cannot swallow solid food |
| <b>Grade 4</b>                                                            | Extensive mucositis; alimentation is not possible                 |
| <i>Note. Adapted from Athar &amp; Gentile (2009).</i>                     |                                                                   |

**Figure-3a**

The data was recorded and analyzed using SPSS version 22.0. A 95% confidence interval was applied for all calculations, and a p-value of less than 0.05 was considered statistically significant.

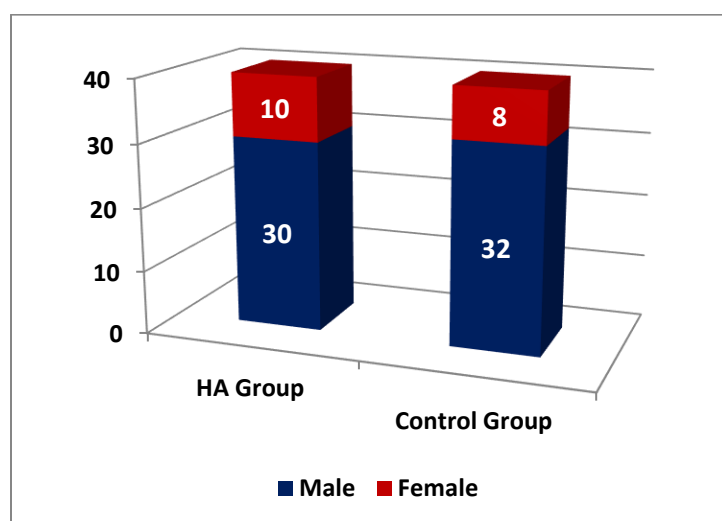
## RESULTS

For this study, a total of 93 patients were initially interviewed to assess their eligibility based on the inclusion criteria and to obtain their consent for participation. Among them, 6 patients were found ineligible, and 2 patients declined to provide consent. Of the 85 eligible patients, 3 discontinued their treatment and were excluded from the study, while 2 patients from the Control Group passed away due to cancer during the study period. As a result, the final study population consisted of 80 patients, evenly divided into two groups: the HA Group (n=40) and the Control Group (n=40). The flowchart below illustrates the selection and progression of the eligible patient population for this study.



**Figure-4 Flow Chart of Data Collection for the study**

The demographic distribution of the study population shows that the HA Group consisted of 30 males (75%) and 10 females (25%), while the Control Group included 32 males (80%) and 8 females (20%).



**Data distribution on basis of Gender**

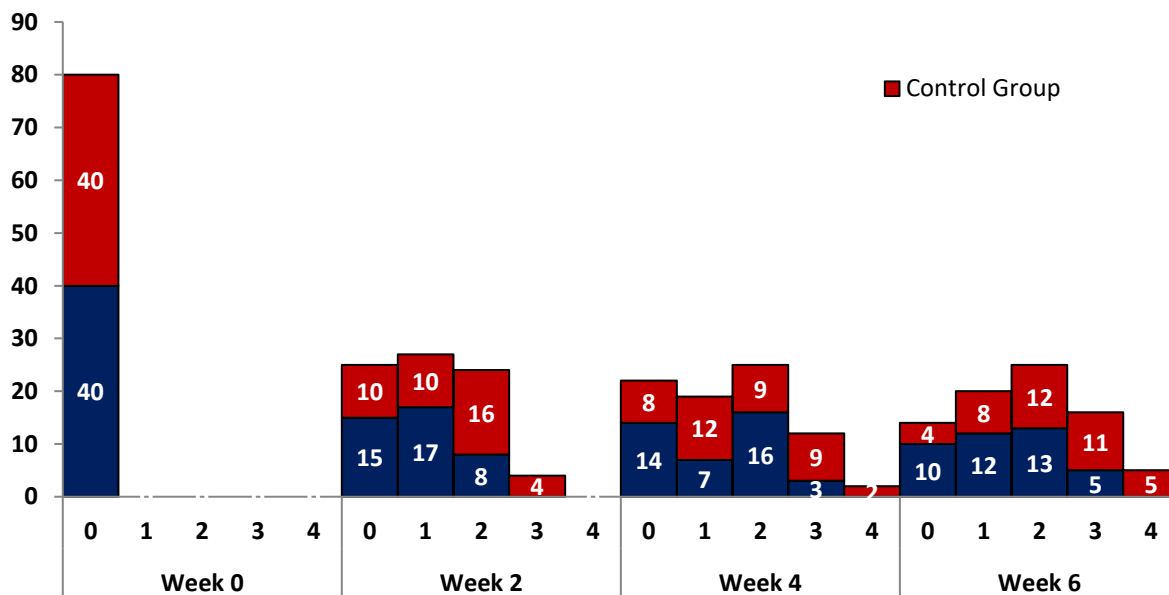
Baseline data was collected on nodal involvement, metastasis, tumor stage, and histopathology, revealing an equitable distribution across the study population. All patients in the study were diagnosed with Squamous Cell Carcinoma, except for one patient in the HA Group who was diagnosed with Adenocarcinoma.

### RESULTS OF WHO ORAL MUCOSITIS SCALE GRADING:

At the start of the study, none of the patients had developed Oral Mucositis (OM), and all were reported as Grade 0 (100%) in both the HA Group and the Control Group. After two weeks of chemotherapy/radiotherapy treatment, 4 patients (10%) in the Control Group progressed to clinically significant Grade 3 mucositis, while no patients (0%) in the HA Group developed Grade 3 mucositis. This difference in OM grades between the two groups was statistically significant ( $p$ -value = 0.023).

By the end of the 4th week, 11 patients (27.5%) in the Control Group had developed Grade 3 or higher mucositis, compared to only 3 patients (7.5%) in the HA Group. The results remained statistically significant, with a  $p$ -value of 0.042.

Finally, at week 6, the data revealed that 16 patients (40%) in the Control Group had developed Grade 3 or higher mucositis, whereas only 5 patients (12.5%) in the HA Group reached this severity. Once again, the difference in OM grades between the two groups was found to be statistically significant ( $p$ -value = 0.031).



### DISCUSSION

This study focused on evaluating the efficacy of magic mouthwash in treating induced by chemotherapy and radiotherapy Oral Mucositis (OM) in Head and Neck Cancer (HNC) patients and comparing its effectiveness with that of a honey and aloe vera solution. The findings demonstrate that the honey and aloe vera solution positively impacts both the rate and harshness of OM. Numerous studies have previously shown that honey and aloe vera, when used individually, are effective in treating and preventing severe OM caused by chemotherapy and radiotherapy in HNC patients. The results of this study align with existing reviews and meta-analyses. Specifically, 12.5% of patients using honey and aloe vera developed Grade 3 or 4 OM (based on the WHO scale) by week 6 of treatment, compared to 40% of patients in the control group. This significant difference supports the conclusion that honey and aloe vera are highly effective in reducing both the occurrence and severity of OM, particularly severe cases (Grades 3 and 4).<sup>xv</sup>

Additionally, the results of this study are consistent with prior research where honey combined with lemon spray, another natural product, was found effective in reducing OM occurrence rates.<sup>xvi</sup> The positive effects observed in this study are further supported by previous findings where honey was shown to serve as an effective prophylactic agent against chemotherapy- and radiation-induced OM.<sup>xvii</sup>

Similarly, other studies examining the impact of aloe vera on OM have produced comparable results. For instance, in one study, the severity at the 7th-week follow-up, chemotherapy-induced OM was significantly less severe in the aloe vera group compared to the sodium bicarbonate group ( $p = 0.001$ ). further corroborating the findings of the present study.<sup>xviii</sup>

It is also noteworthy that during this study, no complications were reported in the administration of the honey and aloe vera solution, and none of the patients experienced intolerance to the treatment.

## CONCLUSION & RECOMMENDATIONS

This study serves as a pioneering effort to explore the combined use of two individually effective natural products—honey and aloe vera—for the management of Oral Mucositis (OM) in Head and Neck Cancer (HNC) patients. While the findings demonstrate that the honey and aloe vera solution is beneficial in reducing the occurrence and severity of OM in patients undergoing chemotherapy and/or radiation therapy, the study also has its limitations.

To further validate these results, it is recommended that future research should involve larger sample sizes and include participants from diverse socio-economic backgrounds. Such comprehensive studies would help to further authenticate the efficacy of the honey and aloe vera solution as a treatment option for OM in HNC patients.

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