Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis

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Abstract

Background: Chemoradiotherapy-associated mucositis can manifest as pain, inflammation, dysphagia, diarrhea, weight loss, rectal bleeding, and infection. Mucositis is a major dose-limiting side effect of chemotherapy, affecting nutritional intake and oral and intestinal function. Despite several interventions being available, there is a need for safe and effective preventative and treatment options for treatment-induced mucositis. The goals of this review are to discuss interventions based on foods and natural products and present the research to date. Methods: A narrative literature review identified 60 clinical studies examining various nutritional compounds and 20 examining probiotics. 9 studies on probiotics for the prevention of diarrhea were also assessed on methodological quality and limitations identified. Results: Several compounds have been posited as useful adjuvants for cancer treatment–related mucositis. Probiotics demonstrate efficacy for the prevention and treatment of chemoradiotherapy-induced gastrointestinal toxicity without significant side effects. Glutamine and activated charcoal were reported to reduce chemotherapy-induced diarrhea but not radiation-induced intestinal mucositis. Honey has been reported to decrease treatment interruptions, weight loss, and delays the onset of oral mucositis. Zinc, glutamine, and topical vitamin E were demonstrated efficacy for oral mucositis. Conclusion: There is plausible clinical evidence for the administration of several adjunctive treatments for the prevention and treatment of mucositis. Probiotics were reported to reduce the burden of intestinal mucositis and treatment-induced diarrhea. Activated charcoal and glutamine are beneficial for chemotherapy-induced diarrhea, whereas the administration of honey, zinc, and glutamine reduce the risk of developing oral mucositis during chemotherapy or radiotherapy.

Keywords

chemotherapy, radiotherapy, mucositis, diarrhea, probiotics, adjunctive compounds

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Introduction

Chemotherapy- and radiotherapy-induced mucositis is a significant burden for cancer patients (Table 1). Symptoms of oral mucositis become apparent 5 to 10 days after chemotherapy and may progress from erythema, cracking, and inflammation to pain, bleeding, ulceration,1,2 and pain.1,3 Pelvic radiotherapy is reported to induce changes in the bowel habits of 90% of patients, with half of all patients reporting that quality of life is significantly adversely affected,4 and that serious complications can persist decades post treatment cessation.4,6 Epidemiological studies on cancers of the head and neck report a prevalence of oral mucositis of 80% for patients undergoing radiotherapy and 40% of patients receiving chemotherapy.5 Moreover with high-dose chemotherapy, mucositis can develop in 100% of bone marrow transplant patients. Mucositis is the most frequent and serious reported side effect in the first 3 months following a transplant and is the most common condition requiring systemic analgesics during cancer therapy.7 The frequency of mucositis is also higher in patients receiving continuous infusion therapy for breast and colon cancer.7

Unlike oral mucositis, clinical data reflecting the long-term effects of treatment-induced gastrointestinal mucositis are lacking. An important and debilitating symptom of intestinal mucositis is diarrhea. Gastrointestinal mucositis
| Intervention                  | Pathophysiology                                                                 | Possible Symptoms                                      |
|------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------|
| Radiotherapy                 | Direct epithelial injury                                                        | Mouth ulcers                                           |
|                              | Mucositis                                                                       | Pain                                                   |
|                              | Loss of mitotic activity                                                         | Anorexia                                               |
|                              | Acute inflammation                                                              | Bloating dysphagia                                     |
|                              | Abscess formation                                                               | Diarrhea                                               |
|                              | Swelling of vascular endothelial lining                                         | Lactose intolerance, malabsorption                     |
|                              | Tissue ischemia mucosal friability                                              | Nausea                                                 |
|                              | Neovascularization progressive fibrosis                                          | Ulceration                                             |
|                              |                                                                                 | Weight loss                                            |
|                              |                                                                                 | IBS                                                    |
|                              |                                                                                 | ISBO                                                   |
| Irinotecan                    | Cholinergically mediated diarrhea                                               | Rhinitis                                               |
|                              | Cytokine release                                                                | Early-onset diarrhea                                   |
|                              | Altered motility                                                                | Abdominal cramping                                     |
|                              | Villous blunting and crypt degeneration                                         | Malabsorption                                          |
|                              | TJ dysfunction                                                                 | Delayed-onset diarrhea                                 |
|                              | Changes to claudin-1 and occludin                                               |                                                        |
|                              | Bacterial translocation                                                         |                                                        |
| Fluoropyrimidines             | Gastrointestinal mucositis                                                       |                                                        |
| including 5-FU               | Villi shortening, increased crypt depth                                         |                                                        |
|                              | Increased intestinal myeloperoxidase activity, reduced glutathione (GSH)         |                                                        |
|                              | concentrations, and increased levels of inflammatory mediators                  |                                                        |
|                              | Reduced expressions of occludin and claudin-1 and TJ dysfunction                | Malabsorption                                          |
|                              |                                                                                 | SIBO                                                   |
| Paclitaxel                    | Increase apoptosis of intestinal villi, increased intestinal permeability,       |                                                        |
|                              | reduced white blood cell count, and induced bacterial translocation              |                                                        |
|                              |                                                                                 | Vomiting                                               |
|                              |                                                                                 | Diarrhea                                               |
|                              |                                                                                 | Colitis                                                |
| Oxaliplatin                   | DNA denaturation and neuronal ablation                                          | Potentiation of 5-FU related GIT toxicities            |
|                              | Apoptosis of intestinal epithelial cells                                        |                                                        |
|                              | Inflammation                                                                    |                                                        |
|                              | Bacterial translocation                                                         |                                                        |
|                              | Sepsis                                                                          |                                                        |
|                              |                                                                                 |                                                        |
| Lapatinib                     | Increased jejunal crypt length, increased mitotic rate, and goblet cell         |                                                        |
|                              | morphology                                                                      |                                                        |
|                              |                                                                                 |                                                        |
| Methotrexate                  | Reduced claudin-1 and occludin expression and TJ dysfunction                    |                                                        |
|                              | Increased proinflammatory cytokine production                                   |                                                        |
| Taxanes                       | Ischemic colitis                                                                |                                                        |
|                              | Neutropenia                                                                     |                                                        |
|                              | Mucosal edema                                                                   |                                                        |
|                              | Hemorrhage                                                                      |                                                        |
|                              | Inflammatory infiltrates                                                        |                                                        |
|                              | Ulceration                                                                       |                                                        |

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has been reported in 80% of patients treated with 5-fluorouracil (5-FU). The frequency of chemotherapy-induced diarrhea depends on the drug administered and the schedule implemented. The highest rate of diarrhea has been reported to occur with a weekly regimen of irinotecan and 5-FU bolus with 10% of patients going on to develop grade 3 to 4 mucositis. Late-onset diarrhea may occur within a week following higher dosages of irinotecan and after approximately 2 weeks following a weekly administration of lower doses. In stage III colorectal cancer (CRC), chemotherapy with FOLFOX induced diarrhea in 56% of patients, yet with FOLFIRI, the prevalence of diarrhea increased to 89%. The risk of a first episode was highest during the first cycle (35%) and dropped to less than 10% during subsequent cycles.

The frequency of treatment-induced gastrointestinal toxicity in CRC has been posited to likely increase with the introduction of novel drugs and the use of more intense combination regimens of polychemotherapy combined with monoclonal antibodies. Targeted therapies, including erlotinib, gefitinib, lapatinib, sorafenib, and sunitinib, have been associated with a 2- to 8-fold increased risk of all or high-grade diarrhea compared with conventional chemotherapy regimens.

Despite several interventions being available, including cryotherapy and loperamide, for the control of oral mucositis and diarrhea, respectively, there is a need to further explore additional safe and effective preventative and treatment options for treatment-induced mucositis and related symptoms. The goal of this narrative review was to present an overview of the safety and efficacy reported for various interventions posited to reduce the adverse effects of antineoplastic agents. The majority of clinical research has focused on prevention or treatment of oral mucositis, while intestinal toxicity has been less well reported.

### Methods

The inclusion criteria were any type of clinical trial examining the use of any oral or topical probiotic or nutritional intervention with both the abstract and the journal article written in English. All clinical trial designs and methodology were included, namely, prevention as well as treatment studies. The following databases were used to retrieve journal articles: PubMed, the Cochrane Library, Science Direct, Scopus, Embase, and Google Scholar, and searches were current up to November 2016.

Electronic databases were searched using the following search string:

**Probiotics OR Diet OR Food OR Nutrition OR Micronutrients OR Vitamins OR Minerals OR Dietary supplements OR Functional foods OR Honey AND Chemotherapy AND Mucositis AND Chemotherapy AND Diarrhea AND Radiotherapy AND Mucositis AND Diarrhea.**

Examination of references in retrieved articles was also conducted.
Results

Fifty articles examining various nutritional compounds were identified, 49 from PubMed and 1 from Embase.12 Reports included 1 study on activated charcoal,13 1 study on β-glucan,14 2 studies on multinutrient formulations,15,16 2 studies on an amino acid–rich oral formulation,17,18 1 study with folic acid with B 12,19 5 studies on vitamin E,12,20-23 17 intervention studies containing minerals,24-40 and 21 studies with glutamine (Table 2).41-61 Moreover, 25 clinical trials were identified examining honey alone or in combination as a prophylaxis/intervention for oral mucositis (Table 3).62-87 We also identified 19 probiotic studies (Table 4).88-105 Nine placebo-controlled clinical trials88-92,95-97,106 examined the prophylactic use of probiotic in intestinal mucositis induced by chemotherapy, radiotherapy, or a combination of both. Two trials did not include a comparator group.98,104 Four studies examined the use of a probiotic in oral mucositis,99,100,103,105 3 studies were post-chemoradiotherapy treatment trials,93,94,101 and 2 studies examined the febrile incidence during chemotherapy.102

Oral mucositis was most commonly assessed according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer objective grading system (RTOG/EORTC), the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), or the World Health Organization Oral Mucositis Toxicity Scale. Intestinal mucositis was assessed by changes in stool consistency, incidence and severity of diarrhea, and the use of antidiarrheal medication. The most frequently used assessment scales are the CTCAE diarrhea grade and the Bristol stool charting system.

Bias and quality analysis were not performed as part of this review, as several reviews have already reported on bias and quality of studies for minerals, glutamine, honey, and probiotics, the 4 types of interventions with sufficient number of trials to attempt conducting a systematic review or meta-analysis. Although some studies had low bias, the overall assessment is that many studies have high bias and most studies suffered from some methodological weaknesses.107-112 The systematic review and meta-analysis of 9 probiotic trials for the prevention of chemoradiotherapy-induced diarrhea found that while the trials were of generally good methodological quality, there were significant blinding issues, and 1 study was published as a poster abstract only. Ambiguous handling of incomplete outcome data and lack of intention-to-treat analysis were noted as further bias risks.112

Reviewed Interventions

Prophylactic activated charcoal has been shown to reduce dose-limiting chemotherapy-induced diarrhea, thereby optimizing irinotecan therapy, while reducing antidiarrheal medication in an open-label, single-arm study. The study involved 28 patients with advanced CRC receiving irinotecan 125 mg/m² intravenously once a week for 4 weeks every 6 weeks. In cycle 1, patients received irinotecan plus activated charcoal (5 mL aqueous solution containing 1000 mg activated charcoal in 25 mL of water), given the evening before the irinotecan dose and then 3 times daily for 48 hours after the dose. The use of activated charcoal in the first cycle was associated with a significant reduction in the incidence and severity of diarrhea, reduced the use of loperamide as a rescue medication, and was well tolerated with excellent compliance11 (Table 2).

Beta-glucan is an immune-modulating polysaccharide that was shown in a retrospective, controlled trial of 62 patients with CRC to prevent significant reductions in leucocyte and neutrophil counts compared with chemotherapy alone with a FOLFOX-4 regimen. The addition of β-glucan was also associated with a lower incidence of oral mucositis and diarrhea (Table 2).14

Concurrent administration of folate and cobalamin failed to reduce mucositis in a pilot study of 39 patients with non–small cell lung cancer treated with pralatrexate. Mucositis remained the dose-limiting toxicity of pralatrexate treatment19 (Table 2).

A meta-analysis that assessed the effectiveness of oral glutamine in radiotherapy-induced mucositis in head and neck cancers reported that in 5 clinical studies (234 patients total),41,43,44,52,59 glutamine was shown to reduce the risk and severity of radiotherapy-induced oral mucositis compared with either placebo or no treatment (risk ratio [RR] = 0.17, 95% confidence interval [CI] = 0.06-0.47).107 Oral glutamine was also shown to be beneficial in 114,46,49,54-60 of 15 studies investigated in a systematic review investigating the effects of glutamine for chemotherapy- or radiotherapy-induced oral mucositis. Glutamine significantly reduced the incidence of grade 2, 3, or 4 mucositis and/or reduced weight loss as well as the duration, time of onset, and/or maximum grade of mucositis.108 Four studies showed no effect45,48,50,53 (Table 2).

A recent study found that 9 g glutamine in combination with an elemental diet was associated with a significant reduction in chemotherapy-induced oral mucositis in esophageal cancer compared with no treatment or glutamine alone. The incidence of grade 2 or higher of oral mucositis was 60% in the control group, 70% in the glutamine group, and 10% in the glutamine plus elemental diet group.42 A further review of 9 randomized, controlled studies concluded that glutamine may reduce gastrointestinal mucositis and diarrhea and improve nitrogen balance, immune imbalance, and wound healing in chemotherapy-induced toxicity113 (Table 2).

Glutamine has been shown to be a principal nutrient with glucose supporting survival of mammalian cells and, unfavorably, cancer cells. However, oral glutamine has been reported to be unlikely to contribute significantly to tumor growth, local invasion, and metastatic dissemination.114 High baseline consumption of dietary glutamate has been
| References | Treatment | Intervention | Cancer Type | Design (n = Subjects), Assessment | Outcome |
|------------|-----------|--------------|-------------|----------------------------------|---------|
| Karac et al | Chemotherapy (FOLFOX-4) | Beta-glucan 50 mg/day versus no treatment | CRC | Retrospective, controlled (n = 62), CTCAE | Decreased incidence OM and diarrhea |
| Casbarien et al | Chemotherapy and radiotherapy | Multinutrient formulation (Supportan) | HNC | Open-label study (n = 7), CTCAE | OM none severe |
| Machon et al | Chemotherapy and radiotherapy | Multinutrient formulation (Oral Impact) | HNC | Prospective noncontrolled (n = 31), CTCAE | Decreased OM severity |
| Harada et al | Radiotherapy ± chemotherapy | Amino acid-rich oral formulation (Ental) versus no treatment | OC | Retrospective study (n = 74), CTCAE | Decreased OM severity and increased Tx completion rates |
| Ogata et al | 5-FU-based chemotherapy | Amino acid-rich oral formulation (Ental) | CRC | Prospective pilot study (n = 22), CTCAE | Decreased OM severity (P = .0002) |
| Azzoli et al | Pralatrexate | Folic acid IM/B12 oral | NSCLC | Nonrandomized, multicenter (n = 39), CTCAE | NS decrease OM |
| Ghoreishi et al | Cyclophosphamide-based conditioning regimen | Vitamin E 400 mg versus placebo | ALL/AML/CML | RCT (n = 39), CTCAE | NS decrease OM |
| Ferreira et al | Radiotherapy | Topical vitamin E, 400 mg versus placebo | HNC | RCT (n = 54), RTOG | Decreased OM risk of 36% |
| Wadleigh et al | 5-FU infusion/cisplatin or doxorubicin | Topical vitamin E, 400 mg versus placebo | HNC/OeC; HCC/AML | RCT (n = 18), WHO OMAS | Decreased OM (P < .05; vitamin E 60% complete resolution) |
| El-Housseiny et al | Chemotherapy | Topical vitamin E 100 mg versus 40 mg/kg daily IM | OC | Comparative randomized study (pediatric, n = 80), WHO OMAS | Decreased OM severity (P < .05) |
| Khurana et al | Chemotherapy | Topically vitamin E compared with pycnogenol, glycerin, water | AL/NHL | Single-blind, randomized (n = 72, pediatric), WHO OMAS | Decreased OM severity (P < .05) with vitamin E |
| Buntzel et al | Chemotherapy and radiotherapy | Sodium selenite oral fluid 0.5 mg versus no treatment | HNC | RCT (n = 39), RTOG | NS benefit |
| Jahangard-Rafsanjani et al | HDC HSCT conditioning regimen | Selenium 200 µg versus placebo | ALL/AML | RCT (n = 64), WHO OMAS | Decreased OM severity grade 3-4 (P < .05) |
| Watanabe et al | Chemotherapy and radiotherapy | Zinc L-carnosine solution versus azulene rinse | HNC | RCT (n = 31), CTCAE | Decreased OM severity ≥ grade 2 (P < .05) |
| Lin et al | Chemotherapy and radiotherapy | Zinc chelate equiv 25 mg 2-4 times daily versus placebo | HNC | RCT (n = 100), RTOG | Decreased OM severity grade 3 radiotherapy only |
| Lin et al | Radiotherapy | Zinc chelate equiv 25 mg 2-4 times daily versus placebo | NPC/OC | RCT (n = 100), Kaplan–Meier survival method | Delayed development of severe OM in OC only |
| Ertekin et al | Radiotherapy | Zinc sulfate equiv 50 mg tid versus placebo | HNC | RCT (n = 21), RTOG | Decreased OM severity (P < .05) |
| Sangthawan et al | Radiotherapy | Zinc sulfate equiv 50 mg oral syrup versus placebo | HNC | RCT (n = 104), WHO OMAS | NS benefit |
| Arbabi-kalati et al | Chemotherapy | Zinc sulfate equiv. 50 mg tid versus placebo | HNC | RCT (n = 50), WHO OMAS | Decreased OM severity (P < .05) |
| Mehdipour et al | Chemotherapy | 0.2% zinc sulfate versus chlorhexidine gluconate mouthwashes | AML | Comparative randomized (n = 30), Spijkervet scale | Decreased OM severity (P < .05) |
| Mansouri et al | HDC HSCT conditioning regimen | Zinc sulfate equiv 50 mg bid versus placebo | HNC | RCT (n = 60), WHO OMAS | NS benefit |
| Hayashi et al | Radiotherapy or HDC HSCT conditioning regimen | Zinc sulfate/L-carnosine suspension or lozenge | HSCT | Comparative study (n = 66), CTCAE | Decreased OM severity ≥ grade 2 (P < .05) and decreased pain (P < .01) |

(continued)
Table 2. (continued)

| References | Treatment | Intervention | Cancer Type | Design (n = Subjects), Assessment | Outcome |
|------------|-----------|--------------|-------------|----------------------------------|---------|
| Markiewicz et al35 | Radiotherapy HDC HSCT conditioning regimen Calcium phosphate mouth rinse versus topical mouth care with sage extract, povidone-iodine, fluconazole, vitamin A (10 g), and vitamin E (10 g) with or without benzocaine (2.5 g) twice daily | AML/ALL | NBCT (n = 40), WHO OMAS | Decreased OM severity (P < .05) and decrease in pain NS |
| Lambrecht et al36 | Chemotherapy and radiotherapy Calcium phosphate mouth rinse (Caphosol) versus standard oral care | HNC | RCT comparative (n = 58), CTCAE | NS OM grade 3 |
| Raphael et al37 | Chemotherapy or HSCT conditioning regimen Calcium phosphate mouth rinse (Caphosol) versus standard oral care | HM | RCT (n = 34, pediatric), CTCAE | NS benefit |
| Papas et al38 | HDC HSCT conditioning regimen Calcium phosphate (Caphosol) versus fluoride mouth rinse | ALL/AML/ CML/HL/ NHL/MM/MS/BC/OvC | RCT comparative (n = 58), NIDCR | Decreased OM frequency/duration/severity (P < .05) |
| Madan et al39 | Radiotherapy 1% povidone-iodine versus 0.12% chlorhexidine, sodium bicarbonate, plain water (control) | HNC | RCT (n = 80), WHO OMAS | Decreased OM severity scores (P < .05) |
| Vokurka et al40 | HDC before PBSCT 1% povidone-iodine mouthwash versus saline | HSCT | RCT multicenter (n = 132), WHO OMAS | NS benefit |
| Tsujimoto et al41 | Radiotherapy Glutamine 30 g, oral/day versus placebo | HNC | RCT (n = 40), CTCAE | Decreased OM severity (P < .05) |
| Tanaka et al42 | Radiotherapy Glutamine 9 g with or without elemental diet versus placebo | HNC | RCT (n = 40), CTCAE | Decreased OM severity (P < .05) |
| Huang et al43 | Radiotherapy Glutamine 30 g, oral/day versus saline | HNC | RCT (n = 17), WHO OMAS | NS benefit |
| Vidal-Casariego et al44 | Radiotherapy Glutamine 30 g oral/day versus late or no treatment | HNC/Mel/ LC/OeC/ Lym | Retrospective cohort (n = 117), WHO OMAS | Decreased OM risk RR = −9.0% (95% CI = −18.0% to −1.0%) |
| Jebb et al45 | 5-FU and folinic acid Glutamine 16 g oral/day versus placebo | mCRC | RCT (n = 28), WHO OMAS | NS benefit OM or IM |
| Skubitz and Anderson46 | Chemotherapy Glutamine 8 g oral/day | KS | Open trial (n = 14), CALGB | Decreased OM severity (P < .05) |
| Anderson et al47 | Chemotherapy Glutamine 4 g/m2/dose/day versus placebo | Sar/NB | RCT crossover study (pediatric n = 24), patient questionnaire | Decreased OM duration/severity (P < .05) |
| Okuno et al48 | 5-FU Glutamine 30 g oral/day versus placebo | Not defined | RCT (n = 134), assessed by physician | NS benefit |
| Cockerham et al49 | Paclitaxel and melphalan Glutamine 24 g oral/day | mBC | Retrospective analysis (n = 21), CTCAE | Decreased OM days/severity (P < .05) |
| Dickson et al50 | HDC Glutamine 30 g oral/day versus placebo | ALL/AML/ CML/MM/ NHL | RCT (n = 58), BMT scale | NS benefit OM and diarrhea |

(continued)
Table 2. (continued)

| References          | Treatment                      | Intervention                                      | Cancer Type | Design (n = Subjects), Assessment           | Outcome                                      |
|---------------------|--------------------------------|---------------------------------------------------|-------------|---------------------------------------------|----------------------------------------------|
| Daniele et al51     | 5-FU and folic acid           | Glutamine, 18 g oral/day versus placebo           | mCRC        | RCT (n = 70), CTCAE                         | Decreased rescue meds (P < .05)              |
| Cerchietti et al52  | Chemoradiotherapy             | L-Alanyl-L-glutamine, IV 300/400 mg/kg bw versus placebo | HNC         | RCT (n = 29), WHO OMAS                       | Decreased OM severity (NS) and decreased pain (P < .05) |
| Li et al53          | Chemotherapy                  | Glutamine 30 g oral/day versus placebo            | BC          | RCT (n = 60), WHO OMAS                       | NS benefit OM or diarrhea                    |
| Choi et al54        | 5-FU/leucovorin               | Glutamine 10 g oral/day versus supportive care    | AST         | RCT (n = 31), CTCAE                         | Decreased OM severity (P < .05)              |
| Peterson et al55    | Anthracycline chemotherapy    | Glutamine, 7.5 g oral/day versus placebo          | BC          | RCT crossover (n = 326), WHO OMAS           | Decreased OM severity grade 3 (P < .05)      |
| Topkan et al57      | Radiotherapy                  | Glutamine 30 g oral/day versus no treatment       | LC          | Retrospective (n = 63), RTOG                | Decreased grade 2–3 esophagitis (27.2%)      |
| Topkan et al56      | Chemotherapy and radiotherapy | Glutamine 30 g oral/day versus no treatment       | NSCLC       | RCT (n = 104), RTOG                         | Decreased grade 3 esophagitis (P < .05)      |
| Tutanc et al58      | Radiotherapy                  | Glutamine 30 g oral/day versus no treatment       | LC          | RCT (n = 46), RTOG                          | Decreased grade 2–3 esophagitis (P < .05)    |
| Chattopadhyay et al59 | Radiotherapy            | Glutamine 10 g oral/day versus no treatment       | HNC         | Randomized case-control study (n = 70), WHO OMAS | Decreased grade 2–3 esophagitis (P < .05)    |
| Gul et al60         | Radiotherapy                  | Glutamine 30 g oral/day versus no treatment       | LC          | RCT (n = 32), RTOG                          | Decreased esophagitis (P < .05)              |
| Vidal-Casariego et al61 | Radiotherapy            | Glutamine, 30 g, oral versus placebo             | AC/PC       | RCT (n = 69), RTOG                          | NS benefit on acute enteritis/diarrhea       |
| Michael et al13     | Irinotecan                    | Activated charcoal, 1000 mg                        | CRC         | Single-arm open-label (n = 24), CTCAE       | Decreased grade 3/4 diarrhea (7.1% vs 25%)   |

Abbreviations: CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; OM, oral mucositis; HNC, head and neck cancer; OC, oral cancer; Tx, treatment; 5-FU, 5-fluorouracil; IM, intramuscular; NS, non-significant; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group; OeC, esophageal cancer; HCC, hepatocellular carcinoma; WHO OMAS, World Health Organization Oral Mucositis Assessment Scale; im, intramuscularly; OC, oral cancer; AL, acute leukemia; NHL, non-Hodgkin’s lymphoma; HDC, high-dose chemotherapy; H SCT, hematopoietic stem cell transplantation; equiv, equivalent; NPC, nasopharyngeal carcinoma; tid, three times a day; bid, two times a day; HM, hematologic malignancies; HL, Hodgkin’s lymphoma; MM, multiple myeloma; MS, myelodysplastic syndrome; BC, breast cancer; OvC, ovarian cancer; NIDCR, National Institute of Dental and Craniofacial Research; PBSCT, peripheral blood stem cell transplantation; Mel, melanoma; LC, lung carcinoma; Lym, lymphoma; RR, risk ratio; CI, confidence interval; mCRC, metastatic colorectal cancer; KS, Kaposi sarcoma; CALGB, Cancer and Leukemia Group B scale; Sar, sarcoma; NB, neuroblastoma; mBC, metastatic breast cancer; BMT, Stanford University Bone Marrow Transplant toxicity scale; IV, intravenous; bw, body weight; AST, aspartate aminotransferase; NSCLC, non–small cell lung cancer; AC, abdominal cancer; PC, pelvic cancer.
Table 3. Clinical Trials Investigating Honey for Oral Mucositis.

| References | Interventions                                                                 | Cancer | Design; Assessment | Outcome                                  |
|------------|-----------------------------------------------------------------------------|--------|-------------------|------------------------------------------|
| Radiotherapy | Biswal et al64 20 mL of honey 15 minutes before and after radiation versus standard oral care | HNC    | RCT (n = 40); RTOG | Decreased OM grade 3-4 (P < .0005)       |
|            | Motallenejad et al73 20 mL of honey 15 minutes before and after radiation versus saline rinse | HNC    | RSB (n = 40); WHO OMAS | Decreased OM (P < .05)                   |
|            | Khanal et al70 Swish honey for 2 minutes and expectorate, 20 mL versus lignocaine gel | OC     | RSB (n = 40); RTOG | Decreased OM (P < .05)                   |
|            | Bardy et al63 Manuka honey or placebo golden syrup 20 mL versus standard oral care | HNC    | RCT (n = 131); RTOG | NS difference                           |
|            | Jayachandran and Balaji68 Honey versus benzydamine and saline             | HNC    | RCT (n = 60); WHO OMAS | Decreased OM (P < .05)                   |
|            | Parsons et al85 Manuka honey versus standard oral care                    | HCN    | RCT (n = 28, 18 honey, 10 control); multisite mucositis scoring system | NS difference |
|            | Charalambous et al82 Honey versus saline rinse                             | HCN    | RCT (n = 30); RTOG | Grade 3 xerostomia RR = 0.13 and grade 3 oral mucositis RR = 0.26, indicating that honey is effective for both symptoms |
|            | Alvi et al78 20 mL honey versus saline rinse                               | HNC    | RCT (n = 60); WHO OMAS | Decreased OM (P < .05)                   |
|            | Hawley et al67 Honey versus sugar-free gel                                 | HNC    | RCT (n = 106); RTOG, WHO OMAS | NS difference                           |
|            | Samdariya et al76 20 mL of honey before and after radiation and salt-soda and benzydamine mouth gargles versus salt-soda and benzydamine mouth gargles alone | HNC    | RCT (n = 78); Visual Analogue Pain scale | Decreased severity pain score (P < .05) |
|            | Jayalekshmi et al69 15 mL honey before and after radiation versus plain water rinse | HNC    | RSB (n = 28); RTOG | Decreased OM (P < .05)                   |
|            | Rao et66 Honey applied before and after radiation versus povidone-iodine   | HNC    | RSB (n = 50); RTOG | Decreased OM (P < .002)                  |
|            | Amanat et al80 20 mL honey before and after radiation versus saline rinse   | HNC    | RCT (n = 82); RTOG | Decreased OM grade 3 (P < .016) and grade 4 (P < .032) |
|            | Fogh et al65 10 mL liquid honey versus honey lozenge versus standard supportive care | Small and non–small cell lung cancer | RCT (n = 107, 53 supportive care, 54 liquid honey honey, 56 lozenge honey); CTCAE | Honey not superior to standard care |

(continued)
### Table 3. (continued)

| References                        | Interventions                                           | Cancer       | Design; Assessment                                      | Outcome                                      |
|-----------------------------------|---------------------------------------------------------|--------------|---------------------------------------------------------|----------------------------------------------|
| **Chemotherapy**                  |                                                         |              | RCT pediatric, (n = 90); CTCAE                          | Faster healing (P < .05)                     |
| Abdulrhman et al62                | Honey versus honey, beeswax, olive oil, propolis mouthwash mixture versus standard oral care | ALL          | RCT pediatric, (n = 90); CTCAE                          | Faster healing (P < .05)                     |
| Allenidekania77                   | Honey versus chlorhexidine                             | Pediatric cancer | RCT (n = 23), WHO OMAS                                  | Decreased OM severity (P < .001)             |
| Mishra and Nayak84                | Honey ice chips versus plain ice chips                 | ALL          | RCT (n = 40); WHO OMAS                                  | Decreased OM occurrence (P < .001) and no difference severity |
| Kobya et al71                     | Honey 1 g/kg daily versus standard oral care           | HNC          | Quasi-experimental study children multicenter (n = 83); WHO OMAS | Decreased OM severity (P < .05)             |
| **Chemoradiotherapy**             |                                                         |              |                                                        |                                              |
| Rashad et al73                    | 20 mL honey before and after radiation versus no honey | HNC          | RCT (n = 40); RTOG                                      | Decreased OM grade 3-4 (P < .05)            |
| Maiti et al72                     | 20 mL honey before and after radiation and Manuka honey liquid/lozenges versus supportive care | HNC          | RCT (n = 55); WHO OMAS                                  | Decreased OM grade 3-4 (P < .05)            |
| Berk et al81                      | 300 g of honey, or ±20 g of instant coffee versus topical betamethasone | HNC          | RCT (n = 75); WHO OTS                                   | Decreased OM grade 3-4 (P < .05)            |
| Raessi et al74                    | Honey mixed with turmeric powder versus standard care   | Various      | Nonequivalent control group, pretest posttest design (n = 60), WHO OMAS | Decreased OM (P < .05)                     |
| Francis and Williams66            | Sodium alginate, sodium carbonate, propolis, Aloe vera, calendula, honey, and chamomile versus placebo | HNC          | RCT (n = 107), CTCAE                                    | NS difference                              |
| Farneti et al83                   |                                                         | HNC          | RCT (n = 107), CTCAE                                    | NS difference                              |
| Yadav87                           | Honey with glycerin versus standard care               | HNC          | RCT (n = 107), CTCAE                                    | Decreased OM (P < .003)                     |
| Al Jaouni et al79                 | Honey versus standard oral care lidocaine, mycostatin  | ALL, AML, Burkett's lymphoma, Wilm's tumor              | Open, randomized trial (n = 40, pediatric), clinician defined OM assessment | Decreased OM grade 3-4 (P < .02)           |

**Abbreviations:** HNC, head and neck cancer; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group Grading System; OM, oral mucositis; RSB, randomized single blinded; WHO OMAS, World Health Organisation Oral Mucositis Assessment Scale; OC, oral cancer; NS, nonsignificant; RR, risk ratio; CTCAE, Common Terminology Criteria for Adverse Events; ALL, acute lymphocytic leukemia; LC, lung carcinoma; WHO OTS, World Health Organization Oral Toxicity Scale; AML, acute myelogenous leukemia.
Table 4. Clinical Trials Investigating Probiotics for Oral and Intestinal Mucositis/Diarrhea.

| References       | Treatment                        | Intervention                          | Cancer Site        | Design                  | Outcomes                                                                 |
|------------------|----------------------------------|---------------------------------------|--------------------|-------------------------|--------------------------------------------------------------------------|
| **Oral mucositis clinical studies** |                                   |                                       |                    |                         |                                                                          |
| Sharma et al99   | Radiotherapy plus cisplatin      | L brevis $2 \times 10^9$ CFU, 6 lozenges versus placebo | HNC               | RCT (n = 202), efficacy analysis = 188; CTCAE | Decreased incidence mucositis grade 3-4 and decreased completion of therapy (92% vs 70%; $P < .05$) |
| Sharma et al105  | HSCT                             | L brevis $2 \times 10^9$ CFU, 3-4 lozenges, no control | MM/HL/NHL/AML/RMS | Pilot, no control (n = 18); CTCAE | 29% no mucositis, 19% grade 1 mucositis, 33% grade 2 mucositis, 9.5% grade 3-4 mucositis, and 65% <grade 2 dysphagia |
| Sharma et al100  | HSCT                             | L brevis $2 \times 10^9$ CFU, 4-6 lozenges | CML/MM/HL/NHL/AML/RMS | Pilot, no control (n = 31); CTCAE | 23% no mucositis, 19% grade 1 mucositis, 39% grade 2 mucositis, 13% grade 3 mucositis, and 7% grade 4 mucositis |
| Giammarco et al101 | HSCT                        | L brevis $2 \times 10^9$ CFU, 6 lozenges versus OM prevention including chlorhexidine, saline rinses, and nystatin | MM               | RCT (n = 16); assessment method not specified | 100% mucositis; NS difference between treatments ($P > .05$) |
| **Radiotherapy adverse events prevention studies** |                                   |                                       |                    |                         |                                                                          |
| Salminen et al97 | Pelvic radiotherapy, (internal and external) 80 Gy (tumor) and 50 Gy pelvis | L acidophilus NCDO 1748 + 6.5% lactulose, 2 $\times 10^{11}$ CFU qd versus dietary counselling | Gynecological cancer | RCT (n = 24) | Significant reduction in incidence of diarrhea ($P < .01$); RR = 0.3 (95% CI = 0.11-0.81); control group all with diarrhea |
| Delia et al90    | Pelvic radiotherapy (60-70 Gy)   | VSL#3 1 sachet tid versus placebo    | Sigmoid rectal or cervical cancers | RCT (n = 490) | Reduced incidence (124/239 [51.8%] and 77/243 [31.6%], $P < .001$); reduced severity 55.4% and 1.4%, $P < .001$; RR = 0.61 (95% CI = 0.45-0.76) |
| Castro et al88   | Radiotherapy                     | L casei Shirota B breve (strain and dose not provided) versus placebo | Prostate cancer    | RCT (n = 40) | Reduction in proctitis; improved QoL; RR = 0.54 (95% CI = 0.27-1.06) |
| Demers et al91   | Pelvic radiotherapy (44 Gy)      | L acidophilus LAC-361, B longum BB536, 1.3 $\times 10^{11}$ CFU bid standard dose versus high dose versus placebo | Cervical and uterine cancers | RCT (n = 229) | Reduced incidence grade 4 diarrhea; standard dose; RR = 1.09 (95% CI = 0.76-1.59) |
| **Chemotherapy adverse events prevention studies** |                                   |                                       |                    |                         |                                                                          |
| Österlund et al95 | 5-FU and leucovorin             | L rhamnosus GG, 1-2 $\times 10^{11}$ CFU + 11 g guar gum qd versus no prophylactic treatment | Colorectal cancer | RCT (n = 150) | Reduced grade 3 or 4 diarrhea (22% vs 37%, $P = .027$); reduced abdominal discomfort; reduced hospital care; fewer chemotherapy dose reductions due to bowel toxicity; RR = 0.58 (95% CI = 0.35-0.98) |
| Sharma et al106  | Irinotecan and/or fluoropyrimidines | VSL#3 1 sachet bid versus placebo    | Not defined        | RCT (n = 202) | No significant difference in incidence of diarrhea; RR = 2.76 (95% CI 0.89-8.51) |

(continued)
### References

| References | Treatment | Intervention | Cancer Site | Design | Outcomes |
|------------|-----------|--------------|-------------|--------|----------|
| Mego et al\(^{95}\) | Irinotecan Colon Dophilus \(10 \times 10^9\) capsules CFU tid versus placebo | Colorectal cancer | RCT (n = 46) | Reduction grade 3 or 4 diarrhea (0% vs 17.4%, \(P = .11\)); reduced overall incidence of diarrhea (39.1% vs 60.9%, \(P = .24\)); reduced incidence of enterocolitis (0% vs 8.7%) RR = 0.1 (95% CI = 0.006-1.95) |
| Giralt et al\(^{92}\) | Pelvic radiotherapy (45-50 Gy), weekly cisplatin 40 mg/m\(^2\) 96 mL fermented yogurt with \(L\) casei DN1400, \(1.1 \times 10^{11}\) CFU/g yogurt tid versus placebo | Cervical squamous cell carcinoma; endometrial adenocarcinoma | RCT (n = 85) | Improved stool consistency (\(P = .04\)); no difference to presentation of end point (diarrhea) or use of loperamide; RR = 1.17 (95% CI = 0.84-1.62) |
| Chitapanarux et al\(^{89}\) | Radiotherapy and cisplatin 500 mg Infolan bid versus placebo | Cervical cancer (local advanced) | RCT (n = 63) | 45% grade 2-3 diarrhea placebo group and 9% of probiotic group (\(P = .002\)); antidiarrheal medications reduced (\(P = .03\)); improved stool consistency (\(P < .001\)) respectively; RR = 0.21 (95% CI = 0.07-0.65) |
| Timko\(^{104}\) | Radiotherapy 50-67 Gy abdomen/pelvis Colon Dophilus 2 capsules qd Abdominal and pelvis cancers | RNB (n = 42), stool diary | Reduction in diarrhea and antibiotic use |
| Scarton et al\(^{98}\) | Radiotherapy 30-80 Gy pelvis Dixentil 10 mL vial qd Large bowel urological, gynecological cancers | Prevention/safety (n = 42) | Reduction in diarrhea |
| Henriksson et al\(^{93}\) | Radiotherapy 62-66 Gy pelvis Fermented milk, \(L\) lactis, \(L\) casei, \(L\) cremoris versus nonactive fermented milk Pelvis and urinary bladder cancers | RCT (n = 40), stool diary | Reduction in chronic bowel discomfort |
| Urbancsek et al\(^{101}\) | Radiotherapy to 50 Gy abdomen \(L\) rhamnosus \(1.5 \times 10^{11}\) CFU 4 weeks post radiotherapy versus placebo Pelvis and abdominal cancers | RCT (n = 206), stool diary | Reduction in self-ratings diarrhea grade and feces consistency (\(P < .05\)) |
| Lee et al\(^{94}\) | Radiotherapy and chemotherapy 6 weeks to 2 years prior to enrolment in study \(L\) acidophilus and \(L\) casei R0052, \(2 \times 10^{10}\) CFU 2 capsules qd versus placebo Colorectal cancers | RCT (n = 60); Rome III; stool diary | Decreased IBS (\(P < .05\)); increase in functional health scores (\(P < .05\)); increased FACT scores (\(P < .05\)) |
| Wada et al\(^{102}\) | Chemotherapy not further defined \(B\) breve M-16-V, \(1 \times 10^{11}\) CFU qd Not defined | RNB (n = 42)/ pediatric | Reduction in febrile episodes, antibiotic use; no effect on diarrhea; no difference in WBC or NK cells |

**Abbreviations:** CFU, colony-forming unit; HNC, head and neck cancer; RCT, randomized controlled trial; CTCAE, Common Terminology Criteria for Adverse Events; HSCT, hematopoietic stem cell transplantation; MM, multiple myeloma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; AML, acute myelogenous leukemia; RMS, rhabdomyosarcoma; CML, chronic myelogenous leukemia; OM, oral mucositis; NS, nonsignificant; qd, one a day; RR, risk ratio; CI, confidence interval; NK, natural killer; VSL\#3, \(L\) casei, \(L\) plantarum, \(L\) acidophilus, \(L\) delbrueki subsp bulgaricus, \(B\) longum, \(B\) breve, \(B\) infantis, Streptococcus salivarius subsp thermophilus; Colon Dophilus, \(B\) breve HA-129 (25%), \(B\) bifidum HA-132 HA (20%), \(B\) longum HA-135 (14.5%), \(L\) rhamnosus HA-11 (8%), \(L\) acidophilus HA-122 (8%), \(L\) casei HA-108 (8%), \(L\) plantarum HA-119 (8%), \(S\) thermophilus HA-110 (6%), \(L\) brevis HA-112 (3%), \(B\) infantis HA-116; Infolan, 1 billion viv Lyophilisat and 1 billion \(B\) bifidum viv Lyophilisat; Dixinell, \(L\) acidophilus and \(L\) casei (strains not provided), zinc, galacto-oligosaccharides, and vitamins \(B_1/B_2/B_6\) and nicotinamide; tid, three times a day; QOL, quality of life; bid, two times a day; 5-FU, 5-fluorouracil; RNB, randomized nonblinded; IBS, irritable bowel syndrome; FACT, Functional Assessment of Cancer Therapy; WBC, white blood cells.
shown in humans to be associated with a lower risk for CRC,115 and oral glutamine 2 days before tumor implanta-
tion has been shown in rodents to increase natural killer cell 
activity, upregulate intestinal glutathione metabolism, and 
decrease tumor growth by 40% to 50%.116,117 Oral glu-
tamine administered during chemoradiotherapy did not nega-
tively affect tumor control and survival in patients with 
stage IIIIB non–small cell lung cancer.56 As cancer cells can 
manipulate host metabolism favoring tumor growth, depriva-
tion of dietary glutamine or the use of oral supplemen-
tation for mucositis was reported unlikely to adversely affect 
tumor growth during chemotherapy treatments. Glutamine, 
however, has been shown to be ineffective in controlling 
acute radiation-induced intestinal mucositis.51,118

A Cochrane review of 3 studies64,73,75 investigating 
honey concluded that it was associated with a weak to 
moderate benefit in the prevention of radiotherapy-
induced oral mucositis.119 Three subsequent meta-anal-
yses concluded that oral administration of honey could 
prevent the incidence of radiotherapy-induced oral muco-
sitis in head and neck cancers.109,110,120 Cho et al concluded 
that oral administration of honey after radiotherapy could 
prevent the development of moderate to severe mucositis 
and associated weight loss.109 Xu et al concluded that, 
compared with no treatment, honey could reduce the inci-
dence of oral mucositis after chemoradiotherapy (RR = 
0.35, 95% CI = 0.18-0.70, \( P = .003 \)).110 Honey was also 
found to decrease treatment interruptions, weight loss, and 
delay the onset of oral mucositis. Honey, however, was 
inefficacious in decreasing the peak mucositis score. Co et al reported statistical pooling showing that the risk ratio 
of having a treatment interruption was significantly lower 
with the use of honey versus control 0.11 (95% CI = 0.02-
0.58) with a risk ratio of developing severe mucositis 
when honey was administered as 0.45 with a CI of 0.09 to 
2.21.120

Friend et al specifically examined pediatric trials and identified 4 trials52,71,77,79 with grade C evidence that honey 
was effective as a preventative and adjunctive therapy for 
chemotherapy-induced oral mucositis in children.121 Honey 
was found to reduce the frequency, duration, and stage of 
chemotherapy-induced mucositis.

Seven trials have been published since the meta-analyses 
report.109,110,120 Four trials examined honey in radiotherapy-
induced mucositis in head/neck and lung cancers,55,69,80,86 1 
trial in chemotherapy-induced mucositis in acute lympho-
cytic leukemia,84 and 2 trials in chemoradiotherapy-induced 
mucositis in children with various cancers.79,87 Only one 
trial65 reported no effect. Medical manuka honey adminis-
tered as a liquid or as a lozenge was not superior to best 
supportive care in preventing radiation esophagitis.65

A single-blinded randomized controlled trial (n = 28) 
found that 15 mL of natural honey was associated with a 
statistically significant difference in degree of oral 
mucositis between the experimental and control groups in 
weeks 4, 5, and 6 (\( P < .01 \)).69 Compared with the active 
comparator, povidone-iodine, honey significantly reduced 
radiation-induced oral mucositis, decreased the incidence 
of intolerable mucositis, treatment breaks, loss of treatment 
days (\( P < .0001 \) and \( P < .0003 \)), and did not affect the radia-
tion-induced tumor response.86 Honey significantly reduced 
the severity of mucositis (grades 3 and 4) compared with 
control group at the end of 6 weeks of radiation treatment.80 
Honey ice cubes were shown to significantly reduce the 
ocurrence of chemotherapy-induced oral mucositis in 
pediatric cancer patients compared with plain ice cubes on 
the 5th (\( P = .001 \)) and 15th (\( P = .001 \)) days of assessment.84 
A significantly higher number of patients developed grade 2 
or above chemoradiotherapy-induced mucositis in the control 
arm compared with the experimental arm (\( P = .003 \)).87

A meta-analysis of randomized controlled trials (RCTs) 
examining oral mucositis induced by chemoradiotherapy, 
or hematopoietic stem cell transplantation (HSCT), found 
that patients pretreated with mineral supplementation 
delayed the onset of mucositis and that fewer patients expe-
rienced less peak oral mucositis compared with controls.111

The analysis examined 7 studies with zinc,26-31,33 3 with cal-
cium,36-38 2 with selenium,24,25 and 2 with iodine.39,40 
Significant study bias was observed though and study heter-
genocity, making it difficult to make specific clinical rec-
ommendations. Mineral formulations did not overall 
significantly reduce mean duration of mucositis, pain dura-
tion, or use of analgesics.111 Of the 14 studies included in 
the meta-analysis, the 3 excluded 26,32,122 and 2 recent stud-
ies34,98 are presented in Table 2. Zinc is essential for proper 
immune function and for the integrity of connective tissue 
and cell membranes, and 50 to 150 mg elemental zinc daily 
was reported to reduce oral mucositis27-29,31 (Table 2).

Four studies examining the effects of multinutrient for-
mulations that consisted of a mixture of open-label, retro-
spective, and prospective studies were identified. In a small, 
open-label study, it was reported that oral or parenteral 
administration of a multinutrient formulation was well 
tolerated in patients with head and neck cancers treated with 
chemoradiotherapy without developing severe mucositis.15 
In another, multinutrient formulation composed of amino 
acids, omega-3 fatty acids, ribonucleic acids, vitamins, and 
antioxidants was shown to be associated with less severe 
mucositis in patients with head and neck cancers treated 
with chemoradiotherapy.16 In 2 other studies that examined 
the same amino acid–rich oral formulation, the first study 
found that the formulation was associated with reduced 
severity of mucositis in squamous cell carcinoma treated 
with radiotherapy with or without chemotherapy when
compared with no formulation administration. The nutrient formulation was also associated with improved completion rates of chemoradiotherapy. The second study was a prospective pilot study in CRC treated with 5-FU-based chemotherapy. This study reported that the multinutrient formulation was associated with a decrease in the severity of oral mucositis in approximately 90% of the patients during the first course of treatment ($P = .0002$) and maintained in the second course of treatment ($P < .0001$; Table 2).

Vitamin E may reduce mucositis by regulating nrf2 activation. Gamma-tocotrienol has been shown to prevent 5-FU-induced redox signaling by regulating nrf2 activation and cell survival in human oral keratinocytes. Applying vitamin E directly to the mucous membranes may be more effective than orally administered. Oral vitamin E (400 mg twice daily) was shown to have no effect on the incidence or severity of mucositis in an RCT of 60 patients with leukemia receiving allogeneic bone marrow transplantation. Despite this, topical vitamin E was shown to be beneficial in the treatment of oral lesions associated with mucositis in an RCT of patients with solid tumors (n = 17) or leukemia (n = 1). Six of 9 patients receiving vitamin E had complete resolution of oral lesions compared with 1 out of 9 in the control group ($P = .025$). In another study with 80 patients who developed oral mucositis, 100 mg of a topical, but not oral, application of vitamin E was shown to improve mucositis. In a further study with 54 patients with head and neck cancers it was found that vitamin E before, and for the duration of radiotherapy, decreased the incidence of mucositis. Topical vitamin E reduced the risk of mucositis by 36%. Both topically applied vitamin E and the oligomeric procyanidin known as pycnogenol were shown in an RCT to reduce mucositis in 72 children although pycnogenol was not effective for severe, grade 4 mucositis.

A probiotic containing lozenge, specifically with *Lactobacillus brevis*, has been shown in an RCT to reduce radiation- and chemotherapy-induced oral mucositis in 200 patients with head and neck cancers. Use of the probiotic was associated with a reduced incidence of mucositis grades III and IV ($P = .001$). Supportive treatment with the probiotic was administered during treatment and for 1 week post treatment completion (radiotherapy and weekly cisplatin). The same probiotic lozenge formulation was also examined in 3 studies of patients undergoing HSCT for a variety of cancers including multiple myeloma. In the first pilot study, of 21 patients, only 19% developed grade III or IV mucositis compared with the expected 60%. No adverse events except occasional grade I/II nausea due to study drug were noted. The second pilot study by the same research group found that 20% developed grade III or IV mucositis. In a repeat pilot study, patients treated with HSCT were given the probiotic lozenge 4 to 7 days before initiation of chemotherapy and continuing until resolution of mucositis or till day 24. The single-arm, single-center, phase II study found that of the 31 patients enrolled, 7 (22.6%) patients did not develop any mucositis, 6 (19.4%) patients developed grade 1 mucositis, 12 (38.7%) patients developed grade 2 mucositis, and 4 (12.9%) and 2 (6.5%) patients developed grade 3 and grade 4 mucositis, respectively. Median time to onset and grade IV mucositis was 6 days and 8 days, respectively. No adverse events were reported with usage of study drug. However, in the fourth pilot study by another group using the same formulation in patients undergoing HSCT, all 16 patients developed various grades of mucositis with no statistical difference between the probiotic lozenge and standard treatment (Table 4).

The majority of studies investigated the prophylactic use of probiotics for diarrhea, while a few investigated the efficacy of probiotics in the treatment of irritable bowel syndrome or diarrhea, weeks to years post treatment (Table 4). The studies used a variety of probiotic interventions and protocol designs and outcomes, making it difficult to identify which type of intervention and protocol was most beneficial. A systematic review and meta-analysis of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancers found that probiotics were generally beneficial in treatment-induced diarrhea, especially for grades 2 and 3. A recent meta-analysis that grouped 7 studies for the prophylactic use of probiotics for cancer therapy–induced diarrhea concluded that current evidence does not support widespread implementation of probiotics for the management of diarrhea secondary to cytotoxic therapy and the tyrosine kinase inhibitor, dacomitinib. The administration of probiotic was begun on the first day of cancer therapy initiation and as such referring to prophylactic interventions may be inaccurate. The administration of prophylactic probiotics must begin ideally 1 month prior to chemotherapy/radiotherapy initiation.

In order to investigate the probiotic effect to reduce diarrhea induced by chemotherapy and/or radiotherapy, relative risks were calculated for the 9 RCTs, and the results showed that 7 studies favored probiotics for preventing chemotherapy- and/ or radiotherapy-induced grade ≥2 diarrhea (Figure 1). The co-administration of probiotics with radiotherapy shows enhanced efficacy in preventing intestinal adverse effects induced by radiotherapy compared with chemotherapy.

**Adjuvant Interventions Safety**

One study implementing manuka honey mouthwash found that while it demonstrated benefit in ameliorating radiation-induced weight loss and increase quality of life in the absence of cisplatin chemotherapy, it was also reported that undiluted manuka honey caused severe nausea, vomiting, and severe stinging. In an additional study, Bardy et al found no difference between golden syrup and manuka honey, suggesting that perhaps the high sucrose content was responsible for the antibacterial effect observed.
Neither study showed improvement in mucositis; however, compliance associated with the taste and texture of the interventions was an issue, which may have influenced the study outcome.

The common dose administered in clinical trials was 20 mL of honey, 3 times daily. At this dose, honey did not affect blood sugar levels when initial fasting blood sugar level was below 150 mg/dL. Patients undergoing radiotherapy for head and neck cancers have been reported to be prone to a range of dental complications, and a concern was the added risk of developing dental caries, in spite of research suggesting otherwise. Radiation-related caries are related to hyposalivation, shifts in the oral microbiota, and altered saliva composition. The rapid onset and progression often leads to extensive loss of dentition within short periods of time. Honey contains known cariogenic substances including glucose, fructose, sucrose, and numerous acids, including gluconic, acetic, lactic, butyric, and formic acids, that may contribute to cariogenic increased risk. However, honey has also been shown to prevent radiation-induced decrease enamel microhardness in xerostomic patients compared with patients with normal saliva. None of the trials reported that the use of honey predisposed to the development of caries.

The use of probiotics as an adjunctive medicine in oncology to enhance treatment or reduce adverse events associated with chemotherapy or radiotherapy is not part of standard practice. The principal concern being that patients treated with chemotherapy are frequently immune-compromised and, therefore, are at increased risk of sepsis from administering probiotic formulations. A systematic review of 17 studies (N = 1530) found no reports of significant side effects such as serious localized or systemic infections when administered to patients receiving cancer treatments. Five case reports showed probiotic-related bacteremia, fungemia, or positive blood cultures. Wang et al included 11 studies in its safety analysis. Seven studies did not report any adverse events. Four studies reported various adverse events. The reporting of adverse effects was, however, very inconsistent and poorly documented. Although some infections were reported, no probiotic bacteria growth could be found in blood cultures. Other adverse effects included mild gastrointestinal upsets, fever, and anorexia, which were also observed in the control groups. Okawa et al reported 1 death but no evidence of an association with the probiotic intervention was reported. A few probiotic trials have been performed in children. A single-blinded study found that *Bifidobacterium breve* reduced the frequency of fever, which was associated with a lower use of intravenous antibiotics compared with placebo in children receiving chemotherapy (1-13 years of age, n = 42). No adverse events were reported. A safety and feasibility study did not report *Lactobacillus plantarum*–associated bacteremia in children undergoing allogeneic hematopoietic cell transplant; however, a case of septic shock caused by yogurt-derived *Lactobacillus* species was recently reported in a 54-year-old male patient with acute promyelocytic leukemia. The bacteremia developed a week after the patient underwent high-dose chemotherapy and autologous peripheral blood stem cell transplantation. The pathogen was identified by strain-specific polymerase chain reaction analysis to be identical to the *Lactobacillus rhamnosus* GG found in the yogurt.

Figure 1. Forest plot of RCTs of chemotherapy-/radiotherapy-induced diarrhea.

RCT, randomized controlled trials; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy; RR, relative risk, risk ratio.
Discussion

Recent interventions have continued to explore and to further build the scientific and clinical understanding of oral and intestinal mucositis preventative and treatment options that may be available to clinicians and patients. The prevention and treatment of oral and intestinal mucositis that seeks to decrease the risk of formation and/or progression of these deleterious sequela of chemotherapy and/or radiation therapy regimens are important factors that impinge on patient quality of life and clinical decisions relevant to treatment. While it is acknowledged that oral and intestinal mucositis represent significant burdens of antineoplastic therapies, the implementation of adjunctive treatments still remain a challenge.

Chemotherapy and radiotherapy have significant adverse effects on the microbiota of the oral and gastrointestinal mucosa. Oral mucositis is strongly associated with bacteremia and sepsis due to Escherichia coli, Pseudomonas aeruginosa, and Candida albicans. How probiotics were postulated to overcome the side effects of chemotherapy and/or radiotherapy was advanced from observations that Lactobacillus brevis-containing lozenges produced anti-inflammatory metabolites. It was reported that L. brevis produced arginine deiminase and sphingomyelinase, which hydrolyses platelet-activating factor known to be associated with oral mucositis in radiation therapy. Arginine deiminase then converts arginine to ammonia and citrulline, reducing the amount of available arginine to be converted to nitric oxide—a major mediator of inflammation. Furthermore, the appeal of probiotics administered for oral mucositis was enhanced when they were demonstrated to have no serious adverse effects. This local oral benefit did not, however, extend to the intestines, with 14 out of 16 patients developing diarrhea.

In the intestines, cancer therapy has been found to decrease commensals such as Bifidobacteria, Clostridium cluster XIVa, and Faecalibacterium prausnitzii, combined with increases in Enterobacteriaceae and Bacteroides. These changes induce intestinal dysbiosis and contribute to the development of mucositis, particularly diarrhea and bacteremia. Adverse shifts in the intestinal microbiota have led to the notion that the administration of probiotics could reduce the side effects of chemotherapy and radiotherapy.

There is moderate evidence that zinc, selenium, vitamin E, glutamine, and honey may be beneficial for the prevention or treatment of oral mucositis. However, the low numbers and heterogeneity of the studies reviewed generally makes it difficult to offer specific clinical recommendations. In one review, mineral supplementation, including zinc, did not overall significantly reduce mean duration of the mucositis, pain incidences, or use of analgesics. The recommendation for zinc supplementation is currently restricted for patients with oral cancer having treatment with chemotherapy or radiation according to the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) guidelines. One drawback of using zinc supplementation is that it may induce nausea and even vomiting. Zinc supplementation should not be taken on an empty stomach, as it increases the adverse effects. The studies mostly used 220 mg zinc sulfate, equivalent to 50 mg elemental zinc, 2 to 3 times daily as a mouthwash or capsule/tablet.

The administration of selenium in clinical studies employed doses that ranged from 200 µg elemental selenium twice daily to sodium selenite oral fluid 200 to 500 µg an hour prior to radiotherapy sessions. Applying vitamin E directly to the oral mucosa may be more effective than orally administered.

Glutamine was found to be the most studied nutritional intervention and despite evidence suggesting that glutamine may reduce gastrointestinal mucositis and chemotherapy-induced diarrhea, the European Society for Clinical Nutrition and Metabolism (ESPEN) stated in its recent guidelines on nutrition in cancer patients that “there are insufficient consistent clinical data to recommend glutamine to prevent radiation-induced enteritis/diarrhea, stomatitis, esophagitis, or skin toxicity.” The MASCC/ISOO guideline has been updated from a recommendation against glutamine to “no guideline possible” for glutamine for oral or gastrointestinal mucositis. The safety of glutamine has also been reviewed in view of emerging evidence that malignant cells can utilize glutamine as a mitochondrial substrate. The glutamine doses investigated have ranged from 9 to 30 g daily in divided doses. As the lower dose has been shown to be beneficial in oral mucositis, it may be prudent to use the lower end of the dosage spectrum. Good oral hygiene is essential if honey-based interventions for mucositis are recommended. Activated charcoal may reduce symptoms associated with chemotherapy-induced mucositis including diarrhea. Clinical trials investigating the administration of probiotics to prevent treatment-induced intestinal toxicity has produced mixed results. Studies have used various end-point parameters including stool frequency and stool consistency (described separately or as diarrhea grade 2-4), use of rescue anti-diarrheal medications, and microbiome shifts induced by chemotherapy or radiotherapy. The use of probiotics in the prevention or treatment of chemotherapy and/or radiotherapy-induced gastrointestinal toxicity appears to be beneficial and without significant side effects. The MASCC/ISOO guideline suggests that probiotics containing Lactobacillus species be used to prevent diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy, while the ESPEN guideline states that there are insufficient consistent clinical data to recommend probiotics to reduce radiation-induced diarrhea.
Conclusion

There is plausible clinical evidence for the administration of honey, zinc, selenium, topical vitamin E, and glutamine as an adjuvant treatment to reduce the risk of developing oral mucositis during chemotherapy or radiotherapy. Activated charcoal, glutamine, and probiotics may also be beneficial in chemotherapy-induced diarrhea. Considering the excellent safety profile and resulting high therapeutic index, further research examining the mechanism of action and clinical efficacy of probiotics in chemotherapy- and radiotherapy-induced intestinal mucositis is warranted. Given that adverse disturbances in the oral and intestinal microbiomes can promote immune dysregulation and increase the risk of patient mortality, there is need for further research in this area.

Declaration of Conflicting Interests

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