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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.[3] 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.[3] 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

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Table 1. Chemoradiotherapy-Induced Gastrointestinal Toxicities.

Intervention	Pathophysiology	Possible Symptoms
Radiotherapy[138-141]	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[6,142-144]	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 including 5-FU[8,145-149]	Gastrointestinal mucositis	Altered bowel movement
	Villi shortening, increased crypt depth	Diarrhea
	Increased intestinal myeloperoxidase activity, reduced glutathione (GSH) concentrations, and increased levels of inflammatory mediators	Lactose intolerance
	Reduced expressions of occludin and claudin-1 and TJ dysfunction	Malabsorption
		SIBO
Paclitaxel[150,151]	Increase apoptosis of intestinal villi, increased intestinal permeability, reduced white blood cell count, and induced bacterial translocation	Stomatitis
		Vomiting
		Diarrhea
		Colitis
Oxaliplatin[151,152]	DNA denaturation and neuronal ablation	Potentiation of 5-FU related GIT toxicities
	Apoptosis of intestinal epithelial cells	Anorexia
	Inflammation	Stomatitis
	Bacterial translocation	Nausea
	Sepsis	Emesis
		Diarrhea/constipation
Lapatinib[153]	Increased jejunal crypt length, increased mitotic rate, and goblet cell morphology	Malabsorption
		Altered bowel function
		Diarrhea
Methotrexate[154]	Reduced claudin-1 and occludin expression and TJ dysfunction	Inflammation
	Increased proinflammatory cytokine production	Sepsis
		Neutropenia
Taxanes[151]	Ischemic colitis	Nausea
	Neutropenia	Diarrhea
	Mucosal edema	Emesis
	Hemorrhage	Stomatitis
	Inflammatory infiltrates	Colitis
	Ulceration	Hepatitis

(continued)

Table 1. (continued)

Intervention	Pathophysiology	Possible Symptoms
Cisplatin, carboplatin[151,155]	Decreased total surface area of villi Reduced villus height and villus/crypt ratio Decreased intestinal motility Altered digestive and metabolic functions Inflammatory infiltrates	Anorexia Stomatitis Nausea Emesis Diarrhea Malabsorption
Anthracyclines[151]	Inflammation Steatosis	Stomatitis Ulceration Anorexia Diarrhea Nausea Emesis
Cytarabine, gemcitabine[151]	Necrotizing colitis Veno-occlusive disease	Anorexia Nausea Emesis Ulceration Diarrhea

Abbreviations: IBS, irritable bowel syndrome; ISBO, intermittent small bowel obstruction; TJ, tight junctions; 5-FU, 5-fluorouracil; SIBO, small intestinal overgrowth syndrome.

has been reported in 80% of patients treated with 5-fluorouracil (5-FU).[8] 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.[9] 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.[10]

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.[6,10] 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.[11]

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 Radiotherapy 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 trials[88-92,95-97,106] 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/m^2 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 compliance[13] (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 treatment[19] (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 11[41,44,46,49,54-60] 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 effect[45,48,50,53] (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 toxicity[113] (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

Table 2. Clinical Trials Investigating Nutrients for Oral and Intestinal Mucositis.

References	Treatment	Intervention	Cancer Type	Design (n = Subjects), Assessment	Outcome
Oral mucositis					
Karac et al[14]	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[15]	Chemotherapy and radiotherapy	Multinutrient formulation (Supportan)	HNC	Open-label study (n = 7), CTCAE	OM none severe
Machon et al[16]	Chemotherapy and radiotherapy	Multinutrient formulation (Oral Impact)	HNC	Prospective noncontrolled (n = 31), CTCAE	Decreased OM severity
Harada et al[17]	Radiotherapy ± chemotherapy	Amino acid–rich oral formulation (Elental) versus no treatment	OC	Retrospective study (n = 74), CTCAE	Decreased OM severity and increased Tx completion rates
Ogata et al[18]	5-FU-based chemotherapy	Amino acid–rich oral formulation (Elental)	CRC	Prospective pilot study (n = 22), CTCAE	Decreased OM severity ($P = .0002$)
Azzoli et al[19]	Pralatrexate	Folic acid IM/B_{12} oral	NSCLC	Nonrandomized, multicenter (n = 39), CTCAE	NS decrease OM
Ghoreishi et al[12]	Cyclophosphamide-based conditioning regimen	Vitamin E 400 mg versus placebo	ALL/AML/CML	RCT (n = 39), CTCAE	NS decrease OM
Ferreira et al[20]	Radiotherapy	Topical vitamin E, 400 mg versus placebo	HNC	RCT (n = 54), RTOG	Decreased OM risk of 36%
Wadleigh et al[21]	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[22]	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[23]	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
Büntzel et al[24]	Chemotherapy and radiotherapy	Sodium selenite oral fluid 0.5 mg versus no treatment	HNC	RCT (n = 39), RTOG	NS benefit
Jahangard-Rafsanjani et al[25]	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[26]	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[27]	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[28]	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[29]	Radiotherapy	Zinc sulfate equiv 50 mg tid versus placebo	HNC	RCT (n = 21), RTOG	Decreased OM severity ($P < .05$)
Sangthawan et al[30]	Radiotherapy	Zinc sulfate equiv 50 mg oral syrup versus placebo	HNC	RCT (n = 104), WHO OMAS	NS benefit
Arbabi-kalati et al[31]	Chemotherapy	Zinc sulfate eqiv. 50 mg tid versus placebo	HNC	RCT (n = 50), WHO OMAS	Decreased OM severity ($P < .05$)
Mehdipour et al[32]	Chemotherapy	0.2% zinc sulfate versus chlorhexidine gluconate mouthwashes	AML	Comparative randomized (n = 30), Spijkervet scale	Decreased OM severity ($P < .05$)
Mansouri et al[33]	HDC HSCT conditioning regimen	Zinc sulfate equiv 50 mg bid versus placebo	HM	RCT (n = 60), WHO OMAS	NS benefit
Hayashi et al[34]	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 al[35]	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 al[36]	Chemotherapy and radiotherapy	Calcium phosphate mouth rinse (Caphosol) versus standard oral care	HNC	RCT comparative (n = 58), CTCAE	NS OM grade 3
Raphael et al[37]	Chemotherapy or HSCT conditioning regimen	Calcium phosphate mouth rinse (Caphosol) versus standard oral care	HM	RCT (n = 34, pediatric), CTCAE	NS benefit
Papas et al[38]	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 al[39]	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 al[40]	HDC before PBSCT	1% povidone-iodine mouthwash versus saline	HSCT	RCT multicenter (n = 132), WHO OMAS	NS benefit
Tsujimoto et al[41]	Radiotherapy	Glutamine 30 g, oral/day versus placebo	HNC	RCT (n = 40), CTCAE	Decreased OM severity ($P < .05$)
Tanaka et al[42]	Radiotherapy	Glutamine 9 g with or without elemental diet versus placebo	HNC	RCT (n = 40), CTCAE	Decreased OM severity ($P < .05$)
Huang et al[43]	Radiotherapy	Glutamine 30 g, oral/day versus saline	HNC	RCT (n = 17), WHO OMAS	NS benefit
Vidal-Casariego et al[44]	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 al[45]	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 Anderson[46]	Chemotherapy	Glutamine 8 g oral/day	KS	Open trial (n = 14), CALGB	Decreased OM severity ($P < .05$)
Anderson et al[47]	Chemotherapy	Glutamine 4 g/m^2/dose/day versus placebo	Sar/NB	RCT crossover study (pediatric n = 24), patient questionnaire	Decreased OM duration/severity ($P < .05$)
Okuno et al[48]	5-FU	Glutamine 30 g oral/day versus placebo	Not defined	RCT (n = 134), assessed by physician	NS benefit
Cockerham et al[49]	Paclitaxel and melphalan	Glutamine 24 g oral/day	mBC	Retrospective analysis (n = 21), CTCAE	Decreased OM days/severity ($P < .05$)
Dickson et al[50]	HDC	Glutamine 30 g oral/day versus placebo	ALL/AL/ 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 al[51]	5-FU and follinic acid	Glutamine, 18 g oral/day versus placebo	mCRC	RCT (n = 70), CTCAE	Decreased rescue meds ($P < .05$)
Cerchietti et al[52]	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 al[53]	Chemotherapy	Glutamine 30 g oral/day versus placebo	BC	RCT (n = 60), WHO OMAS	NS benefit OM or diarrhea
Choi et al[54]	5-FU/leucovorin	Glutamine 10 g oral/day versus supportive care	AST	RCT (n = 51), CTCAE	Decreased OM severity ($P < .05$)
Peterson et al[55]	Anthracycline chemotherapy	Glutamine, 7.5 g oral/day versus placebo	BC	RCT crossover (n = 326), WHO OMAS	Decreased OM severity grade 3 ($P < .05$)
Oesophagitis					
Topkan et al[57]	Radiotherapy	Glutamine 30 g oral/day versus no treatment	LC	Retrospective (n = 63), RTOG	Decreased grade 2-3 esophagitis (27.2%)
Topkan et al[56]	Chemotherapy and radiotherapy	Glutamine 30 g oral/day versus no treatment	NSCLC	RCT (n = 104), RTOG	Decreased grade 3 esophagitis ($P < .05$)
Tutanc et al[58]	Radiotherapy	Glutamine 30 g oral/day versus no treatment	LC	RCT (n = 46), RTOG	Decreased grade 2-3 esophagitis ($P < .05$)
Chattopadhyay et al[59]	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 al[60]	Radiotherapy	Glutamine 30 g oral/day versus no treatment	LC	RCT (n = 32), RTOG	Decreased esophagitis ($P < .05$)
Intestinal mucositis/diarrhea clinical studies					
Vidal-Casariego et al[61]	Radiotherapy	Glutamine, 30 g, oral versus placebo	AC/PC	RCT (n = 69), RTOG	NS benefit on acute enteritis/diarrhea
Michael et al[13]	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, nonsignificant; 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; HSCT, 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 al[64]	20 mL of honey 15 minutes before and after radiation versus standard oral care	HNC	RCT (n = 40); RTOG	Decreased OM grade 3-4 ($P < .0005$)
Motallebnejad et al[73]	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 al[70]	Swish honey for 2 minutes and expectorate, 20 mL versus lignocaine gel	OC	RSB (n = 40); RTOG	Decreased OM ($P < .05$)
Bardy et al[63]	Manuka honey or placebo golden syrup 20 mL versus standard oral care	HNC	RCT (n = 131); RTOG	NS difference
Jayachandran and Balaji[68]	Honey versus benzydamine and saline	HNC	RCT (n = 60); WHO OMAS	Decreased OM ($P < .05$)
Parsons et al[85]	Manuka honey versus standard oral care	HCN	RCT (n = 28, 18 honey, 10 control); multisite mucositis scoring system	NS difference
Charalambous et al[82]	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 al[78]	20 mL honey versus saline rinse	HNC	RCT (n = 60); WHO OMAS	Decreased OM ($P < .05$)
Hawley et al[67]	Honey versus sugar-free gel	HNC	RCT (n = 106); RTOG, WHO OMAS	NS difference
Samdariya et al[76]	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 al[69]	15 mL honey before and after radiation versus plain water rinse	HNC	RSB (n = 28); RTOG	Decreased OM ($P < .05$)
Rao et al[86]	Honey applied before and after radiation versus povidone-iodine	HNC	RSB (n = 50); RTOG	Decreased OM ($P < .002$)
Amanat et al[80]	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 al[65]	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				
Abdulrhman et al[62]	Honey versus honey, beeswax, olive oil, propolis mouthwash mixture versus standard oral care	ALL	RCT pediatric, (n = 90); CTCAE	Faster healing ($P < .05$)
Allenidekania[77]	Honey versus chlorhexidine	Pediatric cancer	RCT (n = 23), WHO OMAS	Decreased OM severity ($P < .001$)
Mishra and Nayak[84]	Honey ice chips versus plain ice chips	ALL	RCT (n = 40); WHO OMAS	Decreased OM occurrence ($P < .001$) and no difference severity
Kobya et al[71]	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 al[75]	20 mL honey before and after radiation versus no honey	HNC	RCT (n = 40); RTOG	Decreased OM grade 3-4 ($P < .05$)
Maiti et al[72]	20 mL honey before and after radiation	HNC	RCT (n = 55); WHO OMAS	Decreased OM grade 3-4 ($P < .05$)
Berk et al[81]	Manuka honey liquid/lozenges versus supportive care	LC	RCT (n = 163); CTCAE	NS difference
Raeessi et al[74]	300 g of honey, or ±20 g of instant coffee versus topical betamethasone	HNC	RCT (n = 75); WHO OTS	Decreased OM grade 3-4 ($P < .05$)
Francis and Williams[66]	Honey mixed with turmeric powder versus standard care	Various	Nonequivalent control group, pretest posttest design (n = 60), WHO OMAS	Decreased OM ($P < .05$)
Farneti et al[83]	Sodium alginate, sodium carbonate, propolis, *Aloe vera*, calendula, honey, and chamomile versus placebo	HNC	RCT (n = 107), CTCAE	NS difference
Yadav[87]	Honey with glycerin versus standard care	HNC	RCT (n = 107), CTCAE	Decreased OM ($P < .003$)
Al Jaouni et al[79]	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 Oraganization 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 al[99]	Radiotherapy plus cisplatin	*L brevis* 2 × 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 al[105]	HSCT	*L brevis* 2 × 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 al[100]	HSCT	*L brevis* 2 × 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 al[103]	HSCT	*L brevis* 2 × 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 al[97]	Pelvic radiotherapy, (internal and external) 80 Gy (tumor) and 50 Gy pelvis	*L acidophilus* NCDO 1748 + 6.5% lactulose, 2 × 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 al[90]	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 al[88]	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 al[91]	Pelvic radiotherapy (44 Gy)	*L acidophilus* LAC-361, *B longum* BB536, 1.3 × 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 al[96]	5-FU and leucovorin	*L rhamnosus* GG, 1-2 × 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 al[106]	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)

Table 4. (continued)

References	Treatment	Intervention	Cancer Site	Design	Outcomes
Mego et al[95]	Irinotecan	Colon Dophilus 10×10^9 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)
Chemoradiotherapy adverse events prevention studies					
Giralt et al[92]	Pelvic radiotherapy (45-50 Gy), weekly cisplatin 40 mg/m^2	96 mL fermented yogurt with *L casei* DN11400, 1.1×10^{11} CFU/g yogurt tid versus placebo	Cervical squamous cell carcinoma; endometrial adenocarcionoma	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 Infloran 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)
Radiotherapy adverse effects prevention studies (no comparator groups)					
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
Scartoni 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
Radiotherapy treatment studies					
Henriksson et al[93]	Radiotherapy 62-66 Gy pelvis	Fermented milk, *L lactis, L diacetylactis, 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* 1.5×10^{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	Lacidofil with *L rhamnosus* R0011, *L acidophilus* R0052, 2×10^{11} 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 ($P < .05$)
Clinical trials investigating infectious complications					
Wada et al[102]	Chemotherapy not further defined	*B breve* M-16-V, 1×10^{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 delbruekii* subsp *bulgaricus, B longum, B breve, B infantis, Streptococcus salivarius* subsp *thermophiles*; Colon Dophilus, *B breve* HA-129 (25%), *B bifidum* HA-132 HA (20%), *B longum* HA-135 (14.5%), *L rhamnosus* HA-111 (8%), *L acidophilus* HA-122 (8%), *L casei* HA-108 (8%), *L plantarum* HA-119 (8%), *S thermopilus* HA-110 (6%), *L brevis* HA-112 (2%), *B infantis* HA-116; Infloran, 1 billion viv Lyophilisat and 1 billion *B bifidum* viv Lyophilisat; Dixentil, *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 implantation 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 glutamine administered during chemoradiotherapy did not negatively affect tumor control and survival in patients with stage IIIB non–small cell lung cancer.[56] As cancer cells can manipulate host metabolism favoring tumor growth, deprivation of dietary glutamine or the use of oral supplementation 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.[61,118]

A Cochrane review of 3 studies[64,73,75] 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-analyses concluded that oral administration of honey could prevent the incidence of radiotherapy-induced oral mucositis 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 incidence 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 trials[62,71,77,79] 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,[65,69,80,86] 1 trial in chemotherapy-induced mucositis in acute lymphocytic leukemia,[84] and 2 trials in chemoradiotherapy-induced mucositis in children with various cancers.[79,87] Only one trial[65] reported no effect. Medical manuka honey administered 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 < .0003), and did not affect the radiation-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 occurrence 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] Absolute risk reduction between honey and control for developing grades III and IV oral mucositis was found to be significant in a study of pediatric cancer patients receiving chemoradiotherapy (P < .05[79]; Table 3).

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 experienced less peak oral mucositis compared with controls.[111] The analysis examined 7 studies with zinc,[26-31,33] 3 with calcium,[36-38] 2 with selenium,[24,25] and 2 with iodine.[39,40] Significant study bias was observed though and study heterogeneity, making it difficult to make specific clinical recommendations. Mineral formulations did not overall significantly reduce mean duration of mucositis, pain duration, or use of analgesics.[111] Of the 14 studies included in the meta-analysis, the 3 excluded[26,32,122] and 2 recent studies[34,98] 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 mucositis[27-29,31] (Table 2).

Four studies examining the effects of *multinutrient formulations* that consisted of a mixture of open-label, retrospective, 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.[17] 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 ($P < .0001$[18]; 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.[123] 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 allogenic bone marrow transplantation.[12] 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 ($P = .025$).[21] 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.[22] 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.[20] Topical vitamin E reduced the risk of mucositis by 36%.[20] 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[23] (Table 2).

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).[99] 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.[105] The second pilot study by the same research group found that 20% developed grade III or IV mucositis.[100] 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 for resolution of mucositis was 6 days and 8 days, respectively. No adverse events were reported with usage of study drug.[100] 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[103] (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.[112] A recent meta-analysis that grouped 7 studies for the prophylactic use of probiotics for cancer therapy–induced diarrhea[124] 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 $\geqslant 2$ diarrhea (Figure 1). The coadministration 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.[85] In an additional study, Bardy et al found no difference between golden syrup and manuka honey,[63] suggesting that perhaps the high sucrose content was responsible for the antibacterial effect observed.

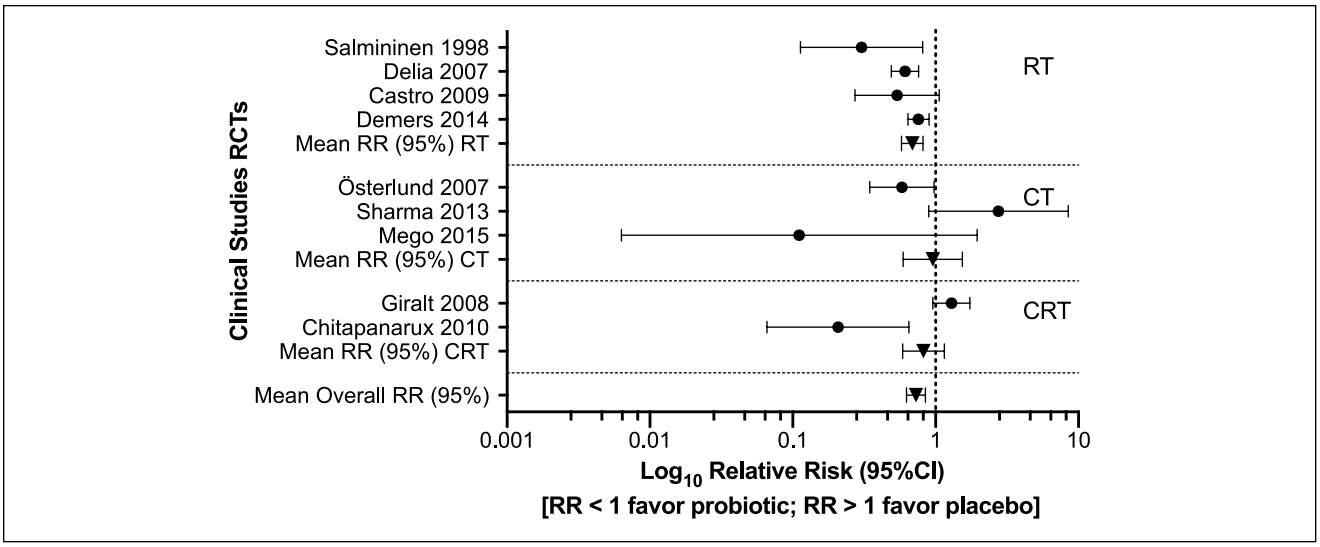

Figure 1. Forest plot of RCTs of chemotherapy-/radiotherapy-induced diarrhea.
RCT, randomized controlled trials; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy; RR, relative risk, risk ratio.

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.[72] Patients undergoing radiotherapy for head and neck cancers have been reported to be prone to a range of dental complications,[125] and a concern was the added risk of developing dental caries, in spite of research suggesting otherwise.[126] 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.[127] However, honey has also been shown to prevent radiation-induced decrease enamel microhardness in xerostomic patients compared with patients with normal salvia.[128] 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.[129] 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.[112] Okawa et al reported 1 death but no evidence of an association with the probiotic intervention was reported.[130] A few probiotic trials have been performed in children.[102,131] 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.[102] A safety and feasibility study did not report *Lactobacillus plantarum*–associated bacteremia in children undergoing allogenic hematopoietic cell transplant;[131] 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.[132]

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.[13,112,121,133] 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 chemoradiotherapy 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 antineoplasitic therapies, the implementation of adjunctive treatments still remain a challenge.[134]

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.*[103] 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.[103] 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.[103] 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.[99,103,105] This local oral benefit did not, however, extend to the intestines, with 14 out of 16 patients developing diarrhea.[103]

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.[135] Adverse shifts in the intestinal microbiota has 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.[111] 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[25] to sodium selenite oral fluid 200 to 500 μg an hour prior to radiotherapy sessions.[24] 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)[133] 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.[136] The safety of glutamine has also been reviewed in view of emerging evidence that malignant cells can utilize glutamine as a mitochondrial substrate.[137] 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.[124] 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,[136] 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.

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