

REVIEW ARTICLE

A Narrative Review of Herbal Medications in the Management of Mucositis in Head and Neck Cancer Patients

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ABSTRACT

Head and Neck Cancers are generally treated with a combination of surgery, radiotherapy and chemotherapy. These patients inevitably suffer from oropharyngeal mucositis accompanied by xerostomia and salivary alterations like reduced buffering capacity, lowered pH, increased viscosity. These result in severe discomfort to the patients along with lowered quality of life on account of having pain, severe burning sensation, difficulty in day to day activities like speech, mastication, taste and swallowing. Till date various therapeutic agents have been tried for the management of radiotherapy and chemotherapy induced mucositis with partial success. As of now there is no standardized protocol which is being practiced throughout the world for managing this debilitating condition. There has also been a concern among the growing crowd of vegan population who would like to use only herbal products for themselves. This paper has tried to identify the herbal products which need to be investigated better. Future work using larger sample size and proper randomization is necessary for establishing a standardized protocol across the world and generalization of their applicability.

Keywords: Herbal, Oral Mucositis, Radiation Mucositis, Head & Neck cancers, Quality of Life

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INTRODUCTION

Radiation mucositis affecting the oropharyngeal region is one of the most common, debilitating, clinical side effects of radiotherapy or chemotherapy used in the management of head and neck cancers. This is usually the initial symptom seen in approximately ninety percent of patients who receive chemo radiation therapy. It presents as a severely incapacitating damage of oral mucosa which occurs as a result of the cancer treatment (1,2). It is characterized by features like inflammation, erythema, ulceration, and pseudo membrane formation and heals in around 2 months after the radiotherapy is completed with atrophic changes.

Patients receiving radiotherapy, more than 2000cGy or concomitant chemotherapy are most likely to develop radiation mucositis (3). One of the major factors influencing onset of Oral Mucositis (OM) is oxidative stress induced by release of inflammatory cytokines (3,4). Dysplastic cells involving those with a high rate of mitosis and a rapid turnover are particularly affected by the radiation energy (5).

WHO scale of OM toxicity is extensively used in regular

radiotherapy protocols as it is simple and straight forward tool for assessment and quantification of OM (Table I). This has been deployed rather in majority of researches concerned with this type of methodical appraisal. Patients with Grade 3 as well as Grade 4 OM present with severe oropharyngeal mucositis associated with ulceration and a severe burning sensation badly affecting the patient's quality of life. This may make it mandatory to necessitate interruption of subsequent doses, decreasing the subsequent doses or even stoppage of intended radiotherapy delivery.

Table I: Grading of Oral Mucositis (World Health Organization)

Explanation	Grade
No changes	0
Soreness ± Erythema	1
Erythema, ulcers, patients can swallow solid food	2
Ulcers with extensive erythema, patients cannot swallow solid food	3
Mucositis to the extent that oral alimentation is not possible	4

It is imperative to put an end to the discomfort associated with mucositis as well as to enhance the nutritional status, and to improve the quality of life so as to enhance the prognosis of the cancer. The range of therapeutic agents available for management of radiation induced damage for oral health care, as of now not very satisfactory. A universally acceptable and totally effective protocol is yet to be evolved.

A wide range of natural agents like aloe vera, honey, curcumin, olive oil has been tried with the aim of identifying a more effective agent to reduce the morbidity. This is done along with ensuring lesser amount of adverse reactions which are usually associated with the chemically derived medicines. Furthermore, they are easily available as most of them are natural herbal products. They are usually sold at supermarkets and grocery stores and obviously are sold without any prescriptions and in medical shops dealing with ayurvedic products often sold without a prescription based on symptoms. Thus these offer a wider scope of their usage by the patients without much of scientific process (4,7).

There has been a steadily increasing population of people across the world who are vegans who do not consume a substance if it is not purely of plant origin. This necessitates the need for identifying purely herbal products or products of purely plant origin which can be effective, beneficial and can be used or consumed by the vegans and non-vegans. This paper is in particular focused on herbal therapeutic agents used in management of radiation mucositis.

MATERIALS AND METHODS

In the process, systematic reviews of scientific texts concerning success of natural agents administered for relief from excruciating discomfort of OM was done. Model of PICO (population, intervention, control, and outcomes) was deployed to identify inclusion criterion as well as investigate expressions per involvement. Population was of sufferers with head and neck cancer, who had developed oral mucositis after chemo &/or radiotherapy. All types of association of natural agents or herbal medications were incorporated. Outcome was based on the lessening of severity of the disease.

As a secondary source, some medical databases like The Cochrane Library, Medline, Google scholar databases and some connected journals were reviewed, and the suitable evidence were selected with heightened accuracy. A total number of 213 records were reviewed preliminarily. Of these, 98 articles were removed due to very close resemblance suggestive of duplication and, then finally 142 records were remaining. After screening, 82 articles were additionally disqualified on basis of lack of sufficient relevance. Afterwards, sixty were identified and processed with full-text papers.

The MeSH terms were used to identify studies done to evaluate the competence of usual agents. They were “head and neck cancer”, “herbal medications”, “radiation mucositis”, “xerostomia” and “radiotherapy”. Systematically organized studies along with randomized clinical trials, and all related studies were included in this research. Research papers were selected which were published as full papers in English. The Prisma

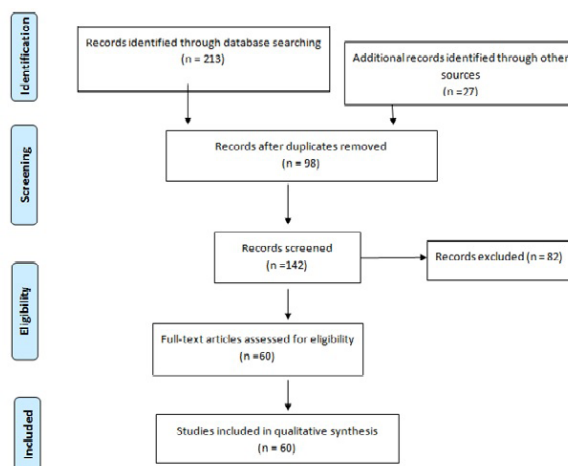


Figure 1: The selection mechanism schedule of records relevant to the present study in accordance with the PRISMA technique

flow chart is shown in Figure 1.

RESULTS

For this section, a total of 240 text were analyzed. There were 98 cases which were disqualified because of the similarity and copying and subsequently, 142 reports were sustained. About 82 superfluous disparate data were deleted after the viewing of the record (Table II).

Risk Factors for Oropharyngeal Mucositis

The oral and the pharyngeal mucosa are among the most responsive tissues for complications associated with chemotherapy and radiation therapy. Eighty percent of patients with cancer of head and neck are subjected to radiotherapy. Approximately fifteen percent of patients receiving radiotherapy in the head and neck region needed to be admitted to the hospital for management of radiotherapy associated complications (21,22).

Factors influencing the occurrence of radiation mucositis include oral hygiene status before and throughout the treatment period, mode of radiotherapy, radiotherapy dose, duration of radiotherapy, types of fields used, use of lead lined stents, use of radioprotectors or radiation mitigators, hemoglobin level and blood oxygenation, salivary gland functioning, staging of the malignancy, histopathologic nature of the malignancy, the nutritional status, dietary habits and dietary intake of the patient, renal function, hepatic function and the chemotherapy drugs concurrently prescribed (23,24). Almost forty to seventy percent of patients getting typical chemotherapy regimens are probable likely to contribute to the development of mucositis (25,26).

Clinical Characteristics of Radiation Mucositis

Radiation Mucositis is basically the inflammatory reaction involving the oropharyngeal mucosa. It typically begins around the end of the second

Table II: Summary of Treatments with Herbal Products for Mucositis in Head and Neck Cancer Patients

S.No.	Herbal Product	Type of use	No.of Patients	Treatment	Results	Ref
1	Aloe vera	Oral juice	61	RT	Significant reduction in freq of mucositis	Puataweepong P et al. 2009 (8)
2	Calendula officinalis	Topical mouthwash	40	CT-RT	Significantly decreased intensity of mucositis	Neda Babae et al. 2013 (9)
3	Olive leaf extract	Topical mouthwash	25	CT	Significantly decreased intensity of mucositis	Ahmed KM 2013 (10)
4	Curcuma longa	Topical mouthwash	80	CT-RT	Reduction in the WHO, OMAS, and VAS scores	Rao Suresh et al. 2014 (11)
5	Matricaria recutita	Topical mouthwash	52	CT	Significant reduction in freq. of mucositis	Renani HA et al. 2012 (12)
6	Matricaria recutita	Topical mouthwash	1	CT	(case report) Treated case	Mazokopakis E et al. 2005 (13)
7	Matricaria recutita	Topical mouthwash	40	RT	Reduced incidence, intensity & duration of mucositis	Fernanda T.M.M. Braga et al. 2015 (14)
8	Matricaria recutita	Topical mouthwash	164	CT	No difference in freq of mucositis	Fidler P et al. 1996 (15)
9	Glycyrrhia glabra	Topical mouthwash	45	RT	Result showed better outcome for mucositis	Ismail AA Ismail AA et al. 2004 (16)
10	Peppermint	Topical mouthwash	40	CT	Significant reduction in freq of mucositis	Ashktorab T et al. 2010 (17)
11	Chamomile	Topical mouthwash	60	CT	Significant reduction in freq of mucositis	Abd Elwadoud AM et al. 2019 (18)
12	Indigo wood root	Topical mouthwash	20	RT	Reduction in severity of mucositis, anorexia, dysphagia	You WC et al. 2009 (19)
13	Turmeric	Topical mouthwash	80	CT-RT	Reduced incidence of mucositis, less weight loss	Rao Suresh et al. 2014 (20)

Abbreviations: OMAS, Oral Mucositis Assessment Scale; VAS, Visual Analog Pain Scale; WHO, World Health Organization; RT, radiotherapy; CT, chemotherapy

week of radiation therapy and is initially seen as mild erythematous appearance with a mild burning sensation. This soon progresses and becomes highly inflamed, and severe erythematous lesions are seen along with a moderately severe burning sensation. This is followed by development of erosive lesions and later frank ulcerations followed by pseudomembrane formation along with an extremely severe burning sensation (3). The development of radiation mucositis is accompanied by gradually increasing severity of xerostomia, salivary alterations like increased viscosity, lowered pH, reduction of buffering capacity, lubricating capacity, lowered salivary IgA status, reduction in levels of salivary antifungal and antibacterial substances all of which play a major role towards contributing to the development of radiation mucositis.

Management of Radiation Mucositis

Extensive work has been done in this genre as there is no globally acceptable standard of treatment for mucositis or its associated discomforts. Approach for curing oral mucositis comprise of anticipatory actions and curative methods (27) (Figure 2).

Enhanced oral cleanliness can be done to diminish the severity of the oral mucositis by eliminating the presence of any local irritants. Conventional NSAIDs (Non-steroidal anti-inflammatory drugs) and Opioid Analgesics are prescribed to reduce the pain and discomfort associated with radiation mucositis (28).

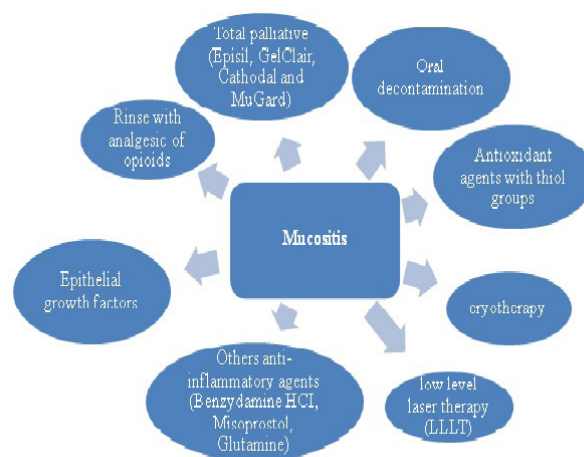


Figure 2: Strategies for Managing Oral Mucositis

Various topical agents like Caphosol, Episil, GelClair, and MuGard have been anecdotally used but data on their effectiveness in controlling mucositis-related discomfort are inadequate (28,29). Cryotherapy and sipping of ice chips for thirty minutes preceding to and throughout radiation therapy has been revealed to be of help to efficiently soothe the inflammation and pain associated with radiation therapy. Traditional Chinese Medicine (TCM) contains experimental herbal formulas for curing mouth ulcers which has regularly been used by the Chinese in the management of oral mucositis

(30). However, lack of suitable randomized controlled trials and non-availability of these Chinese herbs in other parts of the world has rendered any consideration for their use as non-feasible. In the western part of the world, several herbal medicinal plants exist like *Salvia officinalis*, *Matriciana camomilla*, *Hamamelis virginiana*, *Potentilla erecta*, *Commiphora mormol*, *Althaea spps*, *Malva spps*, *Cetraria islandica*, *Linum usitatissimum*, *Myrtillifructus*, *Hippophae rhamnoides*, *Aloe vera*, *Carica papaya*, *Centaurii herba*, *Gentianae radix*, *Menyanthes folium*, *Eriodictyon crassifolium*, *Oleum olivae* and *Citrus limon*. Of these, *Matriciana camomilla*, *Chimonanthus salicifolius* and *Aloe vera* have been used in some of the studies with a partial relief reported in some of them (2, 14, 21, 31, 32). Curcumin, a polyphenol isolated from the rhizome of *Curcuma longa*, has antioxidant, antimicrobial, and anti-inflammatory properties (33).

DISCUSSION

Energy of radiotherapy is partially absorbed by the oral mucosal cells which results in the development of a debilitating situation identified as oral mucositis (34). This condition begins as a mild erythematous appearance associated with burning sensation which progresses to ulceration and finally pseudomembrane formation. Patients find it difficult to masticate or ingest as a result of oral mucositis (35). It has an adverse effect on the treatment plan and prognosis of the illness, effecting the efficiency of radiotherapy (36). It has also been experimentally found that the aqueous extract of the betel nut is a potent carcinogen to mouse kidney cells *in vitro* (37). The fundamental treatment of oral mucositis is intended to alleviate discomfort and uneasiness related with it (38).

The search for ideal "herbal" and "natural" cure for a variety of signs has been steadily mounting throughout the last few decades largely due to the notion that they are completely safe. Most of such agents are inadequately studied and often accessible without a prescription. These cures can sometimes be associated with serious health perils (39). Curcumin, an herbal agent present in Indian spice 'Turmeric' has anti-inflammatory, immunomodulation and wound healing properties (40). Caffeic acid phenyl ethyl ester (CAPE) is a brawny antioxidant that can put off the proliferation of neoplastic cells (17,3 41). Basil is a significant medicinal with antioxidant, anti-inflammatory properties, Yashti-Madhu (*Glycyrrhiza glabra*) has of late acquired meaning (42). Peppermint spirit (PE) can lessen the side effects of cancer conduct (22).

Chamomile is made up of coumarins, flavonoids, terpenoids and alpha-bisabolol and chamazulene. Dos Reis et al. accounted that Chamomile has constructive resultson oral mucositis wounds (39). Researchers have shown inconsistent data on the healing effect of vitamins

on mucositis (43).

Aloe vera has been consumed traditionally to aid with healing of injuries and has been used to care for radiation induced dermatitis (44). Many researchers have also indicated that turmeric and its constituent curcumin have anti-inflammatory property, promote reepithelialization, and improve healing of wounds generated as a result of exposure to radiation (45, 46). These findings are suggestive of the valuable healing aspects of turmeric in management of radiation induced mucositis. Cruz (46) published report of a single blinded randomized control trial (RCT) using Virgin Coconut Oil in patients with nasopharyngeal neoplasms with a reduction of grade 2 and above radiation-induced mucositis. This has led to the reduction in incidence rate of mucositis, delay in onset of development of grade 2 and above radiation-induced mucositis and decreased toxicity suggestive that this maybe a useful adjunct in the management of radiation induced mucositis.

CONCLUSION

Head and neck cancer patients undergoing radiotherapy inevitably suffer from radiation induced oral mucositis, which adversely affects their quality of life. Inflammatory mediators and ROS (Reactive oxygen species) are cellular level molecules closely correlated to mucositis. It is truly heartening to observe that agony of mucositis in head and neck cancer patients can be reduced to a great degree by usage of naturally occurring herbal preparations. In order to develop better standardized protocols which can effectively prevent and heal the oropharyngeal mucositis and lessen their associated discomfort and agony, well designed multicentric RCT sare required to identify and establish the ideal herbal drugs.

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REFERENCES

1. Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma: risk factors and clinical consequences. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2006 Jan 15;106(2):329-36.
2. Sonis ST. New thoughts on the initiation of mucositis. *Oral diseases*. 2010 Oct;16(7):597-600.
3. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dental Clinics of North America*. 2008 Jan 1;52(1):61-77.
4. D'Hondt Lionel LC, Marc A, Jean-Luc C. Oral mucositis induced by anticancer treatments:

- physiopathology and treatments. Therapeutics and clinical risk management. 2006 Jun;2(2):159.
5. Satheesh Kumar PS, Balan A, Sankar A, Bose T. Radiation induced oral mucositis. Indian journal of palliative care. 2009 Jul;15(2):95.
 6. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Frontiers in oncology. 2017 May 22;7:89.
 7. Matsuda C, Munemoto Y, Mishima H, Nagata N, Oshiro M, Kataoka M, Sakamoto J, Aoyama T, Morita S, Kono T. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. Cancer chemotherapy and pharmacology. 2015 Jul;76(1):97-103.
 8. Puataweepong P, Dhanachai M, Dangprasert S, Sithatani C, Sawangsilp T, Narkwong L, Puttikaran P, Intragumtornchai T. The efficacy of oral Aloe vera juice for radiation induced mucositis in head and neck cancer patients: a double-blind placebo-controlled study. Asian Biomedicine. 2009;3(4):375-82.
 9. Babae N, Moslemi D, Khalilpour M, Vejdani F, Moghadamnia Y, Bijani A, Baradaran M, Kazemi MT, Khalilpour A, Pouramir M, Moghadamnia AA. Antioxidant capacity of calendula officinalis flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized controlled clinical study. DARU Journal of Pharmaceutical Sciences. 2013 Dec;21(1):1-7.
 10. Ahmed KM, Talabani N, Altaei T. Olive leaf extract as a new topical management for oral mucositis following chemotherapy: a microbiological examination, experimental animal study and clinical trial. Pharmaceut Anal Acta. 2013;4:9.
 11. Rao S, Dinkar C, Vaishnav LK, Rao P, Rai MP, Fayad R, Baliga MS. The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer: an investigational study. Integrative cancer therapies. 2014 May;13(3):201-10.
 12. Alijani Renani H, Keikhai B, Ghadimi Mahani H, Latifi M. Effect of chamomile mouthwash for preventing chemotherapy-induced stomatitis in children. Journal of Mazandaran University of Medical Sciences. 2012 Feb 10;21(86):19-25.
 13. Mazokopakis EE, Vrentzos GE, Papadakis JA, Babalis DE, Ganotakis ES. Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis. Phytomedicine. 2005 Jan 10;12(1-2):25-7.
 14. Braga FT, Santos AC, Bueno PC, Silveira RC, Santos CB, Bastos JK, Carvalho EC. Use of Chamomilla recutita in the prevention and treatment of oral mucositis in patients undergoing hematopoietic stem cell transplantation: a randomized, controlled, phase II clinical trial. Cancer nursing. 2015 Jul 1;38(4):322-9.
 15. Fidler P, Loprinzi CL, O'Fallon JR, Leitch JM, Lee JK, Hayes DL, Novotny P, Clemens-Schutjer D, Bartel J, Michalak JC. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1996 Feb 1;77(3):522-5.
 16. Ismail AA, Behkrite AA, Badria FM, Guemei AA. Licorice in prevention of radiation induced mucositis. Journal of Clinical Oncology. 2004 Jul 15;22(14_suppl):8268-.
 17. Ashktorab T, Yazdani Z, Mojab F, AlaviMajd H, Madani H. Preventive effects of an oral rinse Peppermint essence on chemotherapy-induced oral mucositis. Koomesh. 2010 Sep 10;12(1):8-13.
 18. AbdElwadoud A, Hassanein S, El-Deen D, Abdou I. Using chamomile for alleviating oral mucositis among patients with head and neck cancer receiving radiotherapy. Egyptian Nursing Journal. 2019 Sep 1;16(3):186-.
 19. You WC, Hsieh CC, Huang JT. Effect of extracts from indigowood root (*Isatisindigotica* Fort.) on immune responses in radiation-induced mucositis. The Journal of Alternative and Complementary Medicine. 2009 Jul 1;15(7):771-8.
 20. Rao S, Dinkar C, Vaishnav LK, Rao P, Rai MP, Fayad R, Baliga MS. The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer: an investigational study. Integrative cancer therapies. 2014 May;13(3):201-10.
 21. Rodríguez-Caballero A, Torres-Lagares D, Robles-García M, Pachyn-Ibáñez J, González-Padilla D, Gutiérrez-Pérez JL. Cancer treatment-induced oral mucositis: a critical review. International journal of oral and maxillofacial surgery. 2012 Feb 1;41(2):225-38.
 22. Su CK, Mehta V, Ravikumar L, Shah R, Pinto H, Halpern J, Koong A, Goffinet D, Le QT. Phase II double-blind randomized study comparing oral aloe vera versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms. International Journal of Radiation Oncology* Biology* Physics. 2004 Sep 1;60(1):171-7.
 23. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, Komaroff E, Nalysnyk L, Zilberberg MD. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy and oncology. 2003 Mar 1;66(3):253-62.
 24. Chaveli Lypez B, GavaldóEsteve C, Sarriñy Pérez MG. Dental treatment considerations in the chemotherapy patient.
 25. Chaveli-Lypez B. Oral toxicity produced by chemotherapy: A systematic review. Journal of clinical and experimental dentistry. 2014 Feb;6(1):e81.

26. Cirillo N, Vicidomini A, McCullough M, Gambardella A, Hassona Y, Prime SS, Colella G. A hyaluronic acid-based compound inhibits fibroblast senescence induced by oxidative stress in vitro and prevents oral mucositis in vivo. *Journal of cellular physiology*. 2015 Jul;230(7):1421-9.
27. Villa A, Sonis ST. Mucositis: pathobiology and management. *Current opinion in oncology*. 2015 May 1;27(3):159-64.
28. Allison RR, Ambrad AA, Arshoun Y, Carmel RJ, Ciuba DF, Feldman E, Finkelstein SE, Gandhavadi R, Heron DE, Lane SC, Longo JM. Multi-institutional, randomized, double-blind, placebo-controlled trial to assess the efficacy of a mucoadhesive hydrogel (MuGard) in mitigating oral mucositis symptoms in patients being treated with chemoradiation therapy for cancers of the head and neck. *Cancer*. 2014 May 1;120(9):1433-40.
29. Migliorati CA, Oberle-Edwards L, Schubert M. The role of alternative and natural agents, cryotherapy, and/or laser for management of alimentary mucositis. *Supportive Care in Cancer*. 2006 Jun;14(6):533-40.
30. Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, Maes A, Goemaere S, Rottey S, Foubert I, Debruyne PR. Echinium oil is not protective against weight loss in head and neck cancer patients undergoing curative radio (chemo) therapy: a randomised-controlled trial. *BMC complementary and alternative medicine*. 2014 Dec;14(1):1-4.
31. Elkerm Y, Tawashi R. Date palm pollen as a preventative intervention in radiation-and chemotherapy-induced oral mucositis: a pilot study. *Integrative cancer therapies*. 2014 Nov;13(6):468-72.
32. Russi EG, Raber-Durlacher JE, Sonis ST. Local and systemic pathogenesis and consequences of regimen-induced inflammatory responses in patients with head and neck cancer receiving chemoradiation. *Mediators of inflammation*. 2014 Jan 1;2014.
33. Borges GA, Elias ST, Amorim B, de Lima CL, Coletta RD, Castilho RM, Squarize CH, Guerra EN. Curcumin downregulates the PI3K-AKT-mTOR pathway and inhibits growth and progression in head and neck cancer cells. *Phytotherapy Research*. 2020 Dec;34(12):3311-24.
34. Song JJ, Salcido R. Use of honey in wound care: an update. *Advances in skin & wound care*. 2011 Jan 1;24(1):40-4.
35. De Smet PA. Herbal remedies. *N Engl J Med*. 2002 347:2046-2056
36. Ahmed KM. The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial. *The Saudi dental journal*. 2013 Oct 1;25(4):141-7.
37. Chatterjee S, Chakrabarti S, Sengupta B, Poddar S, Biswas D, Sengupta S, Talukder G. Prevalence of CYP1A1 and GST polymorphisms in the population of northeastern India and susceptibility of oral cancer. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*. 2009 Sep 1;17(9):397-403.
38. Bolouri AJ, Pakfetrat A, Tonkaboni A, Aledavood SA, Najafi MF, Delavarian Z, Shakeri MT, Mohtashami A. Preventing and therapeutic effect of propolis in radiotherapy induced mucositis of head and neck cancers: a triple-blind, randomized, placebo-controlled trial. *Iranian journal of cancer prevention*. 2015 Oct;8(5).
39. RAS Noronha V, S Araujo G, T Gomes R, H Iwanaga S, C Barbosa M, N Abdo E, Ferreira e Ferreira E, CC Viana A, A Souza A, RL Abreu S, R Santos V. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. *Current clinical pharmacology*. 2014 Nov 1;9(4):359-64.
40. Shah S, Rath H, Sharma G, Senapati SN, Mishra E. Effectiveness of curcumin mouthwash on radiation-induced oral mucositis among head and neck cancer patients: A triple-blind, pilot randomised controlled trial. *Indian J Dent Res*. 2020 Sep-Oct;31(5):718-727. doi: 10.4103/ijdr.IJDR_822_18. PMID: 33433509.
41. Dos Reis PE, Ciol MA, de Melo NS, de Souza Figueiredo PT, Leite AF, de Melo Manzi N. Chamomile infusion cryotherapy to prevent oral mucositis induced by chemotherapy: a pilot study. *Supportive Care in Cancer*. 2016 Oct;24(10):4393-8.
42. Branda RF, Naud SJ, Brooks EM, Chen Z, Muss H. Effect of vitamin B12, folate, and dietary supplements on breast carcinoma chemotherapy-induced mucositis and neutropenia. *Cancer*. 2004 Sep 1;101(5):1058-64.
43. Lypez-Jornet P, Camacho-Alonso F, Jimenez-Torres MJ, Orduca-Domingo A, Gymez-Garcna F. Topical curcumin for the healing of carbon dioxide laser skin wounds in mice. *Photomedicine and laser surgery*. 2011 Dec 1;29(12):809-14.
44. Jagetia GC, Rajanikant GK. Role of curcumin, a naturally occurring phenolic compound of turmeric in accelerating the repair of excision wound, in mice whole-body exposed to various doses of γ -radiation. *Journal of Surgical Research*. 2004 Jul 1;120(1):127-38.
45. Jagetia GC, Rajanikant GK. Acceleration of wound repair by curcumin in the excision wound of mice exposed to different doses of fractionated γ radiation. *International wound journal*. 2012 Feb;9(1):76-92.
46. Cruz MC. Randomized Controlled Trial Comparing Virgin Coconut Oil and Salt and Soda Mouthwash Versus Salt and Soda Mouthwash Alone in Preventing Grade 2 and Above Radiation-Induced Mucositis in Patients With Nasopharyngeal Neoplasm (VCO-PRIM STUDY). *International Journal of Radiation Oncology Biology Physics*. 2014 Sep 1;90(1):S179-80.