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ROLE OF NATURALLY OCCURRING AGENTS IN TREATMENT OF RADIO-CHEMOTHERAPY INDUCED ORAL MUCOSITIS: A REVIEW

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Abstract:
Mucositis is one of the most common side effects of the therapy for the management of cancer; be it radiotherapy, chemotherapy or combination of both. Oral mucositis is of very common occurrence in the patients who are treated for the squamous cell carcinoma of the head and neck region. The therapy targeted towards the oro-pharangeal region most often leads to this side effect. Not only the treatment regimen gets altered sometimes, but the quality of life of the patients also is compromised because of difficulty in normal intake of food. A wide range of mouthwashes, emollients and mucosal barriers have been tried to curb up the sequel of oral mucositis and every product has its limitations; be it the cost or side effects. Naturally occurring products have been available around us since the advent of mankind and various products have been used traditionally for their medicinal properties. This paper attempts to review an array of naturally occurring products which can be utilized for the treatment of radio-chemotherapy induced oral mucositis.

INTRODUCTION

Mucositis is the breach in mucosal tissue which is usually the result of various therapeutic procedures like chemotherapy, radiotherapy, or chemoradiotherapy used for cancer management. Local factors like trauma from teeth and/or microbial colonization may lead to the definite exacerbation of this condition.[1]

Mucositis is also considered to have an indirect impact on the outcome of the illness as its presence often leads to an unwarranted modification in the anti-cancer regimen such as halts in the radiation treatment or alteration in the dosage of chemotherapy.

Sonis defined the complex process of mucositis into four main phases. The first phase begins with the inflammatory/ vascular phase followed by epithelial phase, exacerbating into the ulcerative/ bacteriological phase and finally the

healing phase. Injury to host tissues elicited by radiation and/ or chemotherapy is capable of causing release of cytokines from the epithelium and connective tissues. Chemotherapy, in particular, affects the release of both interleukin-1 (IL-1) and tumour necrosis factor- alpha (TNFα) from the epithelium. Ionising radiation, at doses which in itself is not directly damaging to tissue, can also cause release of these cytokines from the epithelium and connective tissues. Cytokines like tumour necrosis factor cause tissue damage and initiate event in the mucositis process. The IL-1 triggers inflammatory response resulting in increased sub-epithelial vascularity.[2]

Erythema is the earliest clinical sign of mucositis. It presents about 4-5 days following chemotherapy or at cumulative doses of about 10 Gy of head and neck radiation therapy. Patients often complain of burning and intolerance of spicy food at this stage. Led by a cumulative radiation dose of 30 Gy or after a period of 7-10 days post-chemotherapy, ulceration followed by gross discomfort to the patient takes place. Mucositis induced by chemotherapy persists for approximately seven days and heals spontaneously within 21 days post-infusion. Mucositis induced by radiation is more severe and long-lasting, as it persists for at least two weeks even after the completion of radiotherapy i.e. after the dosage of approximately 60-70 Gy. As a result, the patients have severe ulcerative oral mucositis persisting for 5-7 weeks.[3]

Many agents like Magic mouthwash, Chlorhexidine mouthwash, Sodium bicarbonate mouthwash, oral Glutamine, Morphine mouthwash, Colchicine mouthwash, Biotene mouthwash, Doxepin mouthwash, Vitamin E, Sucralfate, Steroids, Immunoglobulin, Amifostine etc. have been tried for prevention and management of mucositis but none of them have proved to be magical enough to provide satisfactory symptomatic relief to the patients and reduce the intensity or duration of the ulcers.[4]

Prime importance for patients having oral mucositis is alleviation of pain and improvement in the quality of life. Literature states that the available therapeutic agents have tried to reduce the severity of intolerable mucositis pain but yet there is no established effective treatment. Few of these have been associated with undesirable side effects and higher cost. Hence, the need for naturally occurring agents for the prevention of mucositis has led to the trial of some natural agents cost-effectively with fewer side effects.[5]

DISCUSSION

Honey

Honey is one of the nature's wonders. Nothing more than nectar gathered from the blossoms of many flowers by the bees, honey has been used as a common sweetener for food and as a powerful medicinal tool for centuries.[6]

Along with the development and evolution of human race, honey has been used as a source of nutrition and as medicine. For ages, honey has been used as the simplest but yet the most effective way to soothe a sore throat. In recent years, an alternative medicine branch, called Apitherapy, has evolved; offering treatments based on honey and other bee products against many diseases.[7]

Although, the exact mechanisms of the biological activity and therapeutic properties of honey in wound healing are still unknown, honey has been successfully employed for the treatment of burn injuries, at the graft donor sites, necrotizing fasciitis, neonatal post-operative wound infections, and skin ulcers. Honey has anti-inflammatory, antioxidant and immune-boosting properties.[8]

Much of the therapeutic properties of honey are due to the high sugar concentration and the resulting osmotic effect, low pH and due to hydrogen peroxide. The greatest medicinal potential of honey is its application as a topical agent to wounds and skin infections. Coating the wound with honey, retards tissue oxygenation, by sealing the damaged mucosa from air (oxygen). This dampens pain within 30 seconds of application.[9,10]

Biswal et al and Motallebnejad et al evaluated the effect of pure natural honey on radiation-induced oral mucositis, where the patients were advised to take 20 ml of pure honey before and

after radiation therapy. They noticed a significant reduction in mucositis among patients who had received honey.[11,12]

Biswal et al established the fact that honey hastened up wound healing when applied topically. This was due to the energy-producing properties, hygroscopic effect on the wound and its bacteriostatic effects.[11] Motallebnejad et al suggested that the effect of honey on infection is not only related to antibacterial agents but also due to its effect on the proliferation of B and T lymphocytes.[12]

Rashad et al in a similar study, performed on patients undergoing radio-chemotherapy, concluded that prophylactic use of pure natural honey was effective in reducing mucositis and also confirmed the anti-fungal effect of honey in the patients.[13]

In a randomized, controlled clinical trial, Khanal et al compared mucositis-limiting qualities of honey with lignocaine and observed that the proportion of patients with intolerable oral mucositis was lower in the honey group.[14]

Abdulrhman et al evaluated honey with a mixture of honey, beeswax and olive oil-Propolis extract; in treatment of chemotherapy-induced oral mucositis. They found that honey alone produced faster healing in patients; possibly because honey was more homogenous in application whereas, the mixture initiated aggregates when mixed with saliva, thus leaving mucosal areas in improper contact with the mixture's content.[15]

Maiti et al studied the effect of honey on mucositis induced by chemoradiation in head and neck cancer and found that honey was effective in managing radiation-induced mucositis.[16]

Sadaksharam et al studied the comparative effects of natural honey and 0.15% benzydamine hydrochloride (study group) in patients of radiation induced mucositis. They compared the combination with 0.9% normal saline (control group) and found a significant reduction in mucositis in patients who received honey.[17]

Rao et al compared honey and povidone-iodine during radiotherapy and assumed that free radical scavenging effects of honey could have contributed to the reduced radiation-induced oral mucositis and decreased the incidence of intolerable mucositis in the honey group.[18]

Amanat et al compared honey with 0.9% saline solution and noted that in the honey-treated group, the proportion of mucositis was lower and statistically significant.[19]

Sedighi et al found that honey caused virtually better recovery of stomatitis among patients undergoing chemotherapy and reported improvement of oral condition in the honey group faster than the control group.[20]

Bulut and Tüfekci, found that the severity of oral mucositis in the children undergoing chemotherapy and taking daily 1gm/ kg of honey in the experimental group was significantly less and attributed it to the antioxidant agents comprised in honey. Furthermore, the children in the control group showed longest recovery duration since honey does not allow bacterial growth because of low moisture content, low pH value and also accelerates wound healing and epithelization.[21]

Singh et al found that topical application of honey was effective in reducing the severity and duration of chemotherapy-induced oral mucositis in children.[22] Jayalekshmi et al also observed a statistically significant difference in degree of radio-chemotherapy induced oral mucositis between honey and plain water user groups in 4th, 5th and 6th week.[23]

Samdariya et al, in a randomized controlled trial, found that honey significantly reduced the severity of mucositis associated pain. They attributed this to the analgesic and anti-inflammatory activity of honey, which inhibited the signal amplification by pro-inflammatory cytokines and resulted in lesser treatment gaps and an overall decrease in radiotherapy treatment duration.[24]

Udaykar et al found that honey application is slightly better than the Orasep application in reducing the level of mucositis and in reducing the intensity of pain in patients undergoing radiation therapy.[25]

Raeessi et al. used a combination of coffee with honey and compared it with topical steroids in chemotherapy-induced oral mucositis. They deduced that the combination of honey with coffee was one of the most effective modality for the treatment of oral

mucositis. Authors postulated that this impact was probably due to the synergistic effect of two substances. The combination of honey and coffee aided in enhanced repair of mucosal desquamation, reduced mucosal irritability and showed considerable improvement in tissue healing as well.[26]

Francis et al used turmeric powder combined with honey in the treatment of oral mucositis and deduced that the application of Indian turmeric and honey on treatment-induced oral mucositis is effective.[27]

Charalambous et al. encouraged the properties of thyme honey in minimizing radiation-induced oral mucositis in head and neck cancer patients. In addition, they also found that the management of specific oral problems seem to improve the overall quality of life of the patients.[28]

Manuka and Kanuka

Maddocks-Jennings et al performed a randomized placebo-controlled trial in which 19 patients were instructed to use a gargle containing two drops of a 1:1 mix of the essential oils of manuka and kanuka mixed with water. They found that there was a delay in the appearance of mucositis along with reduction in pain in patients who used the essential oils of manuka and kanuka as compared to those in the placebo- control group.[29]

Elsass et al used Leptospermum honey paste three times daily in pediatric cancer patients after chemotherapy. They found that it was easy to apply, was well-received by all the patients and proved to be effective.[30]

Bardy et al found that both Manuka honey and golden syrup were associated with reduction in bacterial infection but there was no significant difference in their effects on mucositis. Patients reported problems with the taste and texture of Manuka honey and cited it as the main reason for its discontinuation.[31]

Parsons et al also found that there was poor patient compliance with undiluted manuka honey as patients complained that the honey tasted too sweet, made them feel nauseous and stung their oral mucosa. Hence, honey was diluted to the ratio of 1:3 in water and used in remaining patients. But, the results were not statistically significant while comparing the severity of oral mucositis between manuka honey and standard form of treatment.[32]

Hawley et al had similar findings in their study, where they used 5 ml of irradiated organic manuka honey or a placebo gel. They concluded that contrary to earlier positive feedbacks, manuka honey was not tolerated well by patients and did not have any significant impact on the severity of radiation-induced oral mucositis.[33]

Aloe vera

Aloe vera has become a key player in the herbal medicine and therapeutic treatment of various diseases, now days. Due to its vast medicinal properties, this plant is one of the most sought after, for the treatment of skin and mucosal disorders.

Puataweepong et al found that fresh Aloe vera gel prepared under well-controlled technique of enzyme deactivation preserved essential active compounds such as glycoprotein, which were powerful substances that promote healing and provide anti-inflammatory effects. They concluded that oral Aloe vera juice was beneficial in alleviating the severity of radiation-induced mucositis with no side effects.[34]

Sahebjamee et al found that both Aloe vera and benzydamine mouthwashes delayed the onset of mucositis and related severity similar to other mouthwashes without any statistically significant difference.[35]

Alkhouli et al stated that the topical use of Aloe vera was efficient in the prevention of chemotherapy-induced oral mucositis.[36] However, Su et al found that oral Aloe vera was not a beneficial adjunct to head and neck radiotherapy. They deduced that oral Aloe vera did not improve tolerance to head and neck radiotherapy, decrease mucositis, reduce soreness, or otherwise improve patient well-being. [37]

Matricaria chamomilla (Chamomile)

Carl et al found that Kamillosan rinse (with Matricaria chamomilla as active ingredient) accelerated the resolution of mucositis as all patients placed on the Kamillosan rinse protocol reported immediate relief from discomfort and no patient complained of burning sensation, other toxic reactions, or objectionable taste. They attributed this to the anti-inflammatory effect of Kamillosan.[38] In contrast, Fidler et al found that there was no evidence that chamomile could lessen 5-FU-induced mucositis.[39]

Mazokopakis reported successful treatment of Methotrexate induced mucositis with wild chamomile mouthwashes in patients of rheumatoid arthritis and concurred that there were no side effects.[40]

Sampaio et al agreed that chamomile had no prophylactic effect on the onset of oral mucositis, but it was effective in decreasing the severity of this condition during treatment. They highlighted the anti-inflammatory, antimicrobial and healing properties of this medicinal plant.[41]

Ardakani et al used chamomile mouthwash with significant improvement in pain intensity, dryness and dysphagia. Patients reported fewer complications and symptoms associated with oral mucositis.[42]

Reis et al used chamomile infused cryotherapy and found that when compared to the control, the chamomile group presented less mouth pain and had no ulcerations. They proposed that the chamomile infusion produced an anti-inflammatory effect by inhibiting the production of cyclooxygenase-2.[43]

Pourdeghatkar et al found that both chamomile mouthwash and topical mouth rinse were effective in the prevention of oral mucositis in children with cancer, they also stressed upon the fact that oral mucositis was less severe in the patients who had used chamomile mouthwash 14 days after chemotherapy than those who used topical mouth rinse.[44]

Nigella sativa (Black seed oil)

Nigella sativa is a double-rooted plant from the family Ranunculaceae. Nigella sativa seeds have been used for centuries in the Middle East and Mediterranean countries as spices and supplementary food. Tocopherol, Thymoquinone, Carvecol, Tanetol, and 4-Terpineol are some of the major contents of Nigella sativa oil. These constituents play a significant role in neutralizing free radicals. This plant has been used in the treatment of asthma, hypertension, diabetes, inflammation, cough, bronchitis, headache, fever, and gastrointestinal disturbances.

Antibacterial, anti-inflammatory, antioxidant, antihistaminic, cyto-protective, and antineoplastic effects of thymoquinone have been shown in clinical trials and animal experiments. It has been reported that Nigella sativa oil promotes wound healing in domestic animals and enhances human gingival fibroblast proliferation with improved wound closure. These effects were mostly correlated with the antimicrobial and anti-inflammatory activity of the Nigella Sativa constituents, specifically thymoquinone.

Ameen et al. compared Nigella sativa oil mouth rinse with magic mouthwash and found that Nigella sativa oil was effective in attenuating the severity of chemotherapy-induced or radiochemotherapy induced oral mucositis. Nigella sativa oil also additionally improved the pain and swallowing function. They proposed that the cyto-protective effects of Nigella sativa oil could be attributed to the pleiotropic activity of its constituents.[45]

Isatis indigotica Fort. (Indigowood) root

Isatis indigotica Fort. (Indigowood), is a medicinal plant which belongs to the Brassicaceae family. The major constituents of the radix of Isatis indigotica fort include indirubin, indigotone, and indigo pigment. It has antivirus, fever detoxification, and anti-inflammatory efficacy. Indirubin was widely studied and reported to be one of the most effective compounds in Isatis indigotica Fort. Evidence shows that it has an anti-inflammatory effect, helps patients

maintain weight throughout treatment and improves specific aspects of quality of life.

You et al found that Indigowood root compared with normal saline gargled for 3 minutes and then swallowed before meals daily could reduce the mucosal damage caused by radiation because of its anti-inflammatory properties and also improved patient's quality of life such as anorexia and improved swallowing ability. Authors also stated that better nutrition status in the indigowood root group in the study could have been due to the lower level of pro-inflammatory cytokine IL-6 in the experimental group.[46]

Plantago major

Cabrera-Jaime et al. were the first to assess Plantago major in the treatment of oral mucositis in cancer patients. They did not find this treatment to be more beneficial when compared to sodium bicarbonate or chlorhexidine.[47] Another study by Hasheminasab et al found that use of herbal compounds based on Plantago were effective for preventing and treating oral mucositis in patients undergoing mucotoxic cancer therapy.[48]

Calendula officinalis (Marigold)

Marigold, originating from NorthWest Africa, is a medicinal plant used for various medicinal and therapeutic reasons in Europe, China, US and India. Most of the beneficial effects for this plant are related to secondary metabolite contents such as polyphenols, carotenoids, triterpenes and essential oils. The essential oils present in this herb possess many medicinal properties with several therapeutic properties such as anti-inflammatory, anti-tumorigenic activities and cicatrizing. Anti-Microbial activity has also been proven in-vitro. The plant is also believed to have anti-oxidant and wound healing properties.

Babaee et al stated that Calendula officinalis might be effective in decreasing the intensity of oral mucositis, but cannot prevent it.[49]

Black mulberry molasses

Mulberry comes from the genus Morus of the family Moraceae. In most mulberry-growing countries, particularly in India and China, mulberry is used for its foliage, to feed the silkworm. In certain countries like Turkey, it is a common belief that deep-coloured fruits like black and red mulberry fruits are healthier for the human body. Phenolics possess the ability to modify gene expression along with a wide spectrum of antioxidant, antimutagenic and anticarcinogenic properties. It has been postulated that deep-coloured fruits are excellent sources of phenolics, including flavonoids, anthocyanins and carotenoids. Mulberry being deep colored fruit, is the richest source of phenolics.

Dogan et al emphasized on the usage of black mulberry molasses in the prevention of the radiation-induced mucositis of head and neck cancer patients.[50]

Curcuma longa (Turmeric)

Turmeric has been one of the oldest and vastly used spice and medicinal herb known to mankind. It has a very special role in Indian culinary and Ayurveda as the Indian have propagated the medicinal properties associated with it. Now, gradually but surely, the whole scientific arena has accepted the wonders of its medicinal properties. The role of turmeric in faster wound healing has already been established and likewise various studies have been done to see its effect in oral mucositis as well.

Rao et al performed the first study by using turmeric in oral mucositis patients. They found that the clinical onset of mucositis was delayed and the tolerability towards mucositis was enhanced in the patients who used turmeric.[51]

Saldanha et al found that both turmeric and normal saline mouth wash were individually effective in the mucositis, but on comparison, turmeric mouth wash was better than saline mouth wash in treatment-induced oral mucositis.[52]

Elad et al performed a pilot study on seven paediatric patients receiving chemotherapy to evaluate the efficacy of curcumin oil in controlling the signs and symptoms of oral mucositis and concluded that curcumin mouthwash was well tolerated and efficacious.[53]

Patil et al stated that the wound healing and patient compliance were better by use of Curcumin for the management of radio-chemotherapy induced

oral mucositis when compared to chlorhexidine mouth wash.[54]

Mansourian et al found that gel containing turmeric derivate was used for protecting the mucosa against radiation-induced mucositis in patients with head and neck cancer. This herbal gel could reduce the signs of oral mucositis and burning mouth feeling because of its anti-inflammatory and antioxidant effects, but it could not be considered as a preventing agent in such radiation-induced conditions.[55]

Charantimath et al found that Curcumin gel was an effective and safer alternative to chlorhexidine gel in the treatment of oral mucositis.[56]

Naturally occurring products are like a Pandora which needs to be explored. There are certain products and spices which have been used as traditional medicinal concoctions over ages but are not yet put up on the scientific platform for their qualities. So, it can be appropriately concluded that there are numerous resources provided by the nature for cheap yet effective treatment of radiotherapy, chemotherapy and/ radio-chemotherapy induced mucositis.

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