

## REVIEW

# Potential Prevention: Aloe Vera Mouthwash May Reduce Radiation-Induced Oral Mucositis in Head and Neck Cancer Patients

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**ABSTRACT** In recent years, more head and neck cancer patients have been treated with radiotherapy. Radiation-induced mucositis is a common and dose limiting toxicity of radiotherapy among patients with head and neck cancers. Patients undergoing radiation therapy for head and neck cancer are also at increased risk of developing oral candidiasis. A number of new agents applied locally or systemically to prevent or treat radiation-induced mucositis have been investigated, but there is no widely accepted prophylactic or effective treatment for mucositis. Topical Aloe vera is widely used for mild sunburn, frostbites, and scalding burns. Studies have reported the beneficial effects of Aloe gel for wound healing, mucous membrane protection, and treatment of oral ulcers, in addition to antiinflammatory, immunomodulation, antifungal, scavenging free radicals, increasing collagen formation and inhibiting collagenase. Herein the author postulates that oral Aloe vera mouthwash may not only prevent radiation-induced mucositis by its wound healing and antiinflammatory mechanism, but also may reduce oral candidiasis of patients undergoing head and neck radiotherapy due to its antifungal and immunomodulatory properties. Hence, Aloe vera mouthwash may provide an alternative agent for treating radiation-induced oral mucositis and candidiasis in patients with head and neck cancers.

**KEYWORDS** Aloe vera, mouthwash, radiotherapy, mucositis, head and neck cancer, candidiasis

Patients with cancer in the head and neck area can be treated with surgery, radiotherapy, or a combination of both. A well-known side effect of radiation is mucositis.<sup>(1)</sup> Floyd<sup>(2)</sup> had defined oral mucositis as the inflammatory change of the oral mucosa resulting from the direct effect of radiotherapy. According to Beumer, et al<sup>(3)</sup>, inhibition of cell growth and maturation by radiation disrupts the primary mucosal barrier of the mouth and throat and thereby creates a pathway for the establishment of oropharyngeal infection by resident oral microflora. The consequences of this include oral mucositis and gingivitis, oral candidiasis, xerostomia, trismus, dental caries, osteoradionecrosis, cellulitis, and viral mucosal eruptions. These oral complications may cause significant patient discomfort and lead to poor nutrition; it may also be responsible for delays or dosage limitations in antineoplastic treatments. In addition, severe mucositis may require temporary or permanent cessation of radiation therapy before completion of the planned radiation therapy program. This is of marked concern, as there is strong clinical and radiobiologic evidence that protraction of overall treatment time has adverse influences on the radiocurability of certain human tumors, particularly squamous cell carcinoma of the head and neck region.<sup>(4)</sup> Various agents are used in order to

reduce the incidence and severity of oral mucositis. An ideal oral rinse for patients with head and neck malignancies should reduce the oral microflora, promote reepithelization of soft tissue lesions, normalize the pH of oral fluids, have an acceptable taste, and be nontoxic.<sup>(5)</sup>

### Hypothesis

Aloe vera (named *Aloe barbadensis* in Latin), a plant of dry and warm weather, contains polysaccharides, anthraquinone, lectin, superoxide dismutase (an antioxidant enzyme), glycoprotein, amino acids, vitamins C and E and minerals.<sup>(6,7)</sup> Several studies revealed the antiinflammatory, analgesic, liver protection, antiproliferative, anticarcinogenic and antiaging properties of Aloe vera.<sup>(8-11)</sup> It seems that these effects are a result of antioxidant properties, cyclooxygenase-2 suppression and immunomodulatory mechanisms.<sup>(11,12)</sup> The Aloe plant contains multiple pharmacologically active compounds which have healing and antiinflammatory effects. Up to

date, clinical studies have reported the beneficial effects of Aloe gel in wound healing,<sup>(13-15)</sup> and treatment of oral ulcers.<sup>(16-18)</sup> Several animal studies and clinical trials have assessed the effectiveness of Aloe gel in the treatment of skin burns,<sup>(19,20)</sup> skin exposure to ultraviolet (UV) and gamma radiation<sup>(21,22)</sup>, frostbite and psoriasis,<sup>(23-25)</sup> antiinflammatory effect,<sup>(26,27)</sup> immune-stimulating effect,<sup>(28-32)</sup> antiviral and antitumor activities.<sup>(33,34)</sup> Aloe vera has both antioxidant and antiinflammatory effects, which may significantly contribute to its clinical effects. According to the good therapeutic effects of Aloe vera on many different diseases and its antioxidant and anticancer effects, the most important hypothesis of this study is that oral mucositis induced by radiation in head and neck cancer patients undergoing radiotherapy might be prevented by Aloe mouthwash, the quality of life of patients could be improved remarkably.

### Supporting Evidence

#### Preventive Effect of Aloe Mouthwash in Oral Mucositis Induced by Radiation in Head and Neck Cancer Patients Undergoing Radiotherapy

Radiation-induced mucositis is a common side effect of head-and-neck radiotherapy. Mucositis can trigger a detrimental chain of events: pain, poor oral intake, weight loss, treatment interruptions, and, ultimately, diminished cure rates. Patients frequently use topical Aloe vera gel to prevent radiation-related dermatitis and oral Aloe vera to soothe esophagitis. Although the mechanism of action is not well established, one hypothesis is that Aloe vera may have antiinflammatory properties through the inhibition of cyclooxygenase.<sup>(35)</sup>

Oral and pharyngeal mucositis remains among the most disabling side effects of radiotherapy for head-and-neck cancer patients. It causes pain, difficulties with swallowing, weight loss, and treatment interruptions that can reduce the probability of tumor cure. Currently, narcotic pain medications, antifungal agents, meticulous oral hygiene, and alterations in diet, along with the knowledge that oral and pharyngeal mucositis is temporary, are the main strategies to help patients during radiotherapy.<sup>(36)</sup>

Topical Aloe vera is widely used for mild sunburn, frostbites, and scalding burns. Studies have reported the beneficial effects of Aloe gel for wound healing,<sup>(37)</sup> mucous membrane protection,<sup>(37,38)</sup> and treatment of oral ulcers.<sup>(37-40)</sup> Findings from *in vitro* and animal

studies have suggested that Aloe vera can enhance wound healing by reducing vasoconstriction and platelet aggregation at the wound site,<sup>(41,42)</sup> improving wound oxygenation,<sup>(41,42)</sup> scavenging free radicals,<sup>(37)</sup> increasing collagen formation,<sup>(41,43)</sup> inhibiting collagenase and metalloproteinase,<sup>(35)</sup> and activating macrophages.<sup>(41,44)</sup> In addition, an imbalance between the level of free radicals and reactive oxygen species probably has a significant influence on initiation and progression of oral inflammatory lesions.<sup>(45,46)</sup> Aloe vera exhibits some antiinflammatory effects by inhibiting cyclooxygenase and reducing leukocyte adhesion molecules and tumor necrosis factor alpha level.<sup>(47)</sup> Stimulatory effects of Aloe vera can increase antibody production and accelerate wound healing by increasing growth factors. Furthermore, it has antioxidant properties and eliminates production of free radicals.<sup>(7-9,48)</sup>

Radiation-induced mucositis is characterized by exposure of a large area of basal membrane and innervated mesenchymal tissue after erosion of the mucosal layer. Healing this type of injury may rely on regeneration and repopulation of basal membrane clonogens. In one study, the incision wounds in rats were rapidly healed by aloe gel and the effect was attributed to more rapid maturation of collagen.<sup>(49)</sup> Sarabia, et al<sup>(50)</sup> demonstrated the presence of antioxidant substances in Aloe vera that confer antiinflammatory and healing properties. Kuzuya, et al<sup>(51)</sup> also reported an antibacterial action of Aloe vera and attributed these properties to the presence of anthraquinones such as aloenin, barbaloin and iso-barbaloin in its chemical composition. Chitra, et al<sup>(52)</sup> also suggested that treatment with Aloe vera has a beneficial effect on the tissue proliferation phase, influencing fibroplasia and collagen synthesis and thus increasing the healing area. Mannose-6-phosphate is a major structural constituent of Aloe vera. Davis, et al<sup>(53)</sup> speculated that the binding of mannose-6-phosphate to fibroblast receptors activates fibroblast proliferation. Other researchers have suggested that aloe increases the oxygen access of tissues as a result of an increased blood supply<sup>(54)</sup> and others have suggested that aloe stimulates fibroblast activity and collagen proliferation.<sup>(55)</sup> Mannose-6-phosphate was identified as a cause of significant wound healing by aloe,<sup>(53)</sup> and the healing by aloe was found to be accompanied by higher levels of hyaluronic acid and dermatan sulfate, which were suggested to stimulate collagen synthesis and fibroblast activity.<sup>(56)</sup>

A randomized trial failed to find any statistically significant improvement in mucositis-related outcomes from the use of oral Aloe vera gel. The addition of Aloe vera did not improve tolerance to head-and-neck radiotherapy, decrease objective measurements of mucositis, or improve quality of life ratings of health, soreness, or well-being. They did not systematically evaluate the duration and extent of post-treatment mucositis and may, therefore, have missed any beneficial effect that aloe may have had on reducing the overall duration of mucositis in enrolled patients.<sup>(36)</sup> This study evaluated oral intake of Aloe vera on the management of radiation-induced mucosities. Therefore, the author thinks the main reason that this study failed to find any beneficial effects of Aloe vera gel is due to its dosage form. In that study, Aloe vera gel was taken orally. Oral Aloe vera was absorbed in gastric and circulated into the blood. Therefore, oral Aloe vera acted as a systemic agent rather than as a local or topical. The author hypothesizes that if aloe applies as a local agent such as mouthwash, patients ask to rinse the mouth with Aloe vera mouthwash for a few minutes so that it can improve its effect because of more time of exposure and local absorption.

In a study conducted by Salazar-Sa'nchez, et al,<sup>(57)</sup> Aloe vera solution consisting of 70% aloe juice was used. Of 32 cases in the Aloe vera group, complete pain remission was achieved in 31.2% of the cases after 6 weeks and in 61% after 12 weeks. In the placebo group, these percentages were 17.2% and 41.6%, respectively. The results of their study revealed that the topical application of Aloe vera, three times a day, improves the pain, the oral lesions and the oral quality of life of the patients with oral lichen planus. This study completely supports the hypotheses that Aloe vera mouthwash may be useful in the prevention of oral mucosities. In other study, Aloe vera solution consisting of 94.5% of Aloe vera juice was used in the treatment of oral lichen planus. The better efficacy achieved in this study compared with that in the above-mentioned study may be due to the difference in concentration.<sup>(58)</sup>

Nowadays, orotransmucosal drug delivery methods are at the forefront of treatment of oral diseases. In addition, some regions in the oral cavity, including buccal, sublingual, palatal and gingival sites, could effectively absorb drugs. It seems reasonable to assume that gel form of a same medication should confer better efficacy in comparison with mouthwash

because of more time of exposure. However, it depends strongly on its bioadhesive properties, bioavailability, solubility and external factors such as mechanical stress and washing effect of saliva.<sup>(59)</sup> According to these studies, we postulate that Aloe vera mouthwash with 94.5% of Aloe vera juice can prevent radiation-induced mucosities during radiotherapy of head and neck cancer patients.

In a study conducted by Puataweepong, et al,<sup>(60)</sup> Aloe vera did not delay the onset of severe mucositis compared with the placebo. Patients who received Aloe vera developed less mucositis with statistically significant difference from the placebo group. It was also confirmed that there was a significant association between Aloe vera treatment and lower mucositis grading. Interestingly, Aloe vera could only reduce the incidence of severe mucositis but could not delay the onset of severe mucositis. The discordant outcome might mean that the Aloe vera effect is not strong enough for mucositis prevention but adequate for alleviating and slowing down the progression of mucositis.

Su, et al<sup>(36)</sup> reported the use of oral Aloe vera for reduction of radiation-induced mucositis in 2004. It was shown that oral Aloe vera was not a beneficial adjunct to head and neck radiotherapy compared with placebo. The findings from Puataweepong, et al<sup>(60)</sup> might be explained by a difference in the preparation of their solution. In this study, they used a fresh Aloe vera gel prepared under well-controlled technique of enzyme deactivation. For this reason, their solution could preserve more essential active compounds, such as glycoprotein, which are powerful substances to promote healing and antiinflammatory effects. As these studies used oral intake of Aloe vera juice, we thought again the main reason that Aloe vera did not delay the onset of severe mucositis is due to its dosage form. We think that Aloe mouthwash will delay the onset of severe mucositis because of its more time of exposure to the cavity, as beneficial effect obtained by using aloe mouthwash to prevent oral inflammation and mucosities in the patients with oral lichen planus.<sup>(57,58)</sup>

Perventive Effect of Aloe Mouthwash in Oral/ Pharyngeal Candidiasis Induced by Radiation in Head and Neck Cancer Patients Undergoing Radiotherapy

On the other hand, radiotherapy-induced hyposalivation encourages oral candidal colonization that often leads to oral/pharyngeal candidiasis.<sup>(61)</sup>

Patients undergoing radiation therapy for head and neck cancer are at increased risk of developing oral candidiasis. Compromised salivary function secondary to destruction of glandular tissue by radiation is thought to be a major factor leading to *Candida* infection.<sup>(62,63)</sup> Rossie, et al<sup>(64)</sup> found an increase in colonization and an increase in the risk of clinical infection during radiation therapy. After radiation therapy, the *Candida* species colonized approximately half of patients.<sup>(64-66)</sup> Patients who received higher total doses of radiation and doses treated with bilateral fields that included the salivary glands were at greater risk of candidiasis.<sup>(64)</sup> This infection is marked by oral pain and/or burning and can lead to significant patient morbidity that requires management during and after radiation therapy and it is important in immunocompromised patients with cancer when local extension of infection and systemic infection may result in morbidity and mortality.<sup>(62,67,68)</sup> Many such patients may develop mycotic infections which may lead to discontinuation of irradiation with possible consequences for the local control of these cancers.<sup>(69)</sup>

According to the literature on the therapeutic effect of aloe, immunostimulation frequently appears as a contributory factor. In addition, Aloe gel extracts, when applied after UV exposure, were found to prevent suppression of local and systemic immunity to haptens and delayed type hypersensitivity responses to *Candida albicans*.<sup>(70,71)</sup> This was attributed to the presence of polysaccharides in the Aloe vera gel. They have no significant antioxidant activity; the immune-protective action of aloe polysaccharides takes place at a step downstream from DNA damage and repair, possibly by modulating the DNA damage-activated signal transduction pathways.<sup>(71)</sup> These compounds may act by novel mechanisms to block the signal transduction pathways and the production of immunosuppressive cytokines. An acetylated glucomannan in aloe was found to be the biologically active, dominant polysaccharide, so much so that it was named acemannan.<sup>(49)</sup> Acemannan from aloe was shown to increase collagen biosynthesis, and perhaps this occurred through macrophage stimulation.<sup>(72)</sup> In addition, active glycoproteins have been demonstrated in Aloe gel and they may well play some part in aloe's therapeutic activity, either immunologically as lectins or as proteases such as anti-bradykinins. Superoxide dismutase activities have also been reported from Aloe vera gel.<sup>(73)</sup>

## Conclusion

Accordingly, we consider Aloe vera mouthwash not only as a potent agent for prevention mucositis, but also as a prevention of candidiasis in patients undergoing radiotherapy of head and neck with its antifungal and immunomodulation properties.

We have sufficient reasons to confirm that a well-designed prospective trial will most likely result in success in the prevention of radiation-induced oral mucositis in head and neck cancer patients by Aloe vera mouthwash. As a potential choice, Aloe vera mouthwash for cancer patients undergoing head and neck radiotherapy may not only prevent oral mucositis and candidiasis, but also may improve their comfort and nutrition supply. As a result, the oral complications of radiotherapy will disappear; patients continuous their treatment procedure until the planned radiation therapy program will be finished. With the aid of a well-designed prospective study and further study on the efficacy of Aloe vera mouthwash containing 94.5% aloe juice, a safe mouthwash, for prevention radiation induced oral mucosities, this hypotheses could be partially or fully confirmed.

## Conflicts of Interest Statement

None declared.

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