

Herbs in Oral Mucositis

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ABSTRACT

Oral mucositis is an inflammatory mucosal destruction as a result of chemotherapy and/or radiation therapy, which in severe cases can impair patients' quality of life. Moreover, mucosal infection and/or systemic involvement due to compromised immunity leads to delay or discontinuation of the treatment. Many strategies and agents have been suggested for the management of this condition. Because of their lower side effects compared to chemical drugs, general interest in evaluating therapeutic effects of herbs has been increased intensively. Herbal plants apply their effect through different mechanisms of action: antioxidant, analgesic, anti-inflammatory, antifungal, antiseptic, and anticarcinogenic activity. Recently, various natural agents in plants have been noticed in mucositis, which may improve the symptoms through different interventions. The purpose of this review is to focus on the preventive or therapeutic use of herbal medicine to alleviate oral mucositis.

Keywords: Chemotherapy, Medicinal plant, Neoplasms, Radiotherapy, Stomatitis

INTRODUCTION

Cancer causes about 12% of deaths throughout the world [1]. Also, it is known as the leading reason of death in developing countries [1,2]. Cancer therapy usually consists of chemotherapy, radiotherapy or a combination of both, which might produce several complications in the patients [2-4]. Oral mucositis is an inflammatory mucosal destruction characterized by erythema and/or ulceration of oral mucosa as a result of chemotherapy (30-76%) and/or radiation therapy (over 50%) for the treatment of cancer all over the body [5]. The most common features of oral mucositis include oedema, erythema, ulcerations, bleeding, and pain, problems in swallowing, eating, drinking, talking and taste changes appearing in different levels of severity [6]. In severe cases (grade 3, 4) it can impair patients' quality of life [6-9]. Oral mucositis may be induced by several molecular pathways such as oxidation and apoptosis due to Nitric Oxide (NO), Cyclooxygenase (COX), protein kinases, cytokines, and nuclear factors as well as genetic-based risk factors like epigenetic changes of DNA methylation [7,10]. When a cancer diagnosis is established, it may lead to Post-traumatic Stress Disorder (PTSD), which in turn causes depression and anxiety as well as an increased level of biomarker expression, such as Interleukin-6 (IL-6), Tumor Necrosis Factor- α (TNF- α), cortisol, and high-reactive sensitive C-Reactive Protein (hs-CRP). It has been demonstrated that the incidence of oral ulceration is associated with the level of PTSD [7].

Many treatment modalities have been introduced to manage oral mucositis such as debridement, disinfection, topical or systemic analgesics, prevention and control of bleeding. Many agents have been used to prevent or lessen the symptoms and signs of oral mucositis such as alopurinol, chlorhexidine, diphenhydramine, aluminum hydroxide, and pallifermin [9]. Recently, general interest in assessing therapeutic effects of herbs has been increased dramatically (due to their lower side effects as compared to chemical drugs). However, only 1% of 250,000-500,000 plants found in the world have been studied for their pharmaceutical properties [11-14]. Many studies have evaluated the effects of plants on oral pathogens and other applications in dentistry. Herbal medicines apply their effect through different mechanisms of action including antioxidant, analgesic, anti-inflammatory, antifungal, antiseptic, and anticarcinogenic activity [11-15]. In recent years, various natural agents in plants have been studied in mucositis, which can improve oral mucositis symptoms via different interventions, e.g., their antioxidant and anti-inflammatory properties [4,12]. Although few studies pointed to the natural materials and herbs for the treatment

of oral mucositis, no comprehensive article regarding herbal agents was found to be used in oral mucositis [7,12]. The purpose of this narrative review was to introduce preventive or therapeutic use of herbal medicine to alleviate symptoms of oral mucositis.

Search strategy: Electronic searches through PubMed, MEDLINE, Cochrane Database, and Google Scholar were accomplished and a reference list of relevant articles was undertaken. Among them English-language papers with available full texts focusing on the medicinal herbs in the treatment of cancer therapy-induced oral mucositis were chosen. The keywords used were medicinal plant, chemotherapy, oral ulcer, mouth ulcer, oral mucositis, stomatitis, radiotherapy, and neoplasms.

Aloe vera: The Aloe vera plant includes several active agents which contain polysaccharides, anthraquinone, lectin, superoxide dismutase (an antioxidant enzyme), glycoprotein, amino acids, vitamins C and E and minerals.

This herbal agent provides antioxidant properties, COX-2 suppression and immune modulatory mechanisms. The result of a study that evaluated the oral aloe vera in the patient undergoing radiation therapy did not show any positive effects, but the quality of life scores were slightly improved [16]. Another study that was done in 2009, demonstrated that aloe vera juice is effective in reducing the incidence of mucositis in patients with radiation therapy, especially those with lower mucositis grading. Hence, aloe vera may not be able to completely prevent oral mucositis, but alleviates and reduce the progression of mucositis [17]. In a recent study by de Freitas Cuba L et al., the topical application of aloe vera has a positive effect in healing of lesions induced on the tongue of rats subjected to radiation [18]. In another study, Ahmadi A showed that aloe vera mouth wash alleviated oral mucositis due to head and neck radiation [19].

Borneol and borax powder: This agent is administered locally in oral inflammation and aphthous ulceration, which contains Borax, Borneolum, and *Indigo naturalis*. Borax extracts of natural borax mineral decrease genotoxic effects of heavy metal on human blood cell cultures and normalizes reduced antioxidant enzyme activities. *Indigo naturalis*, which is obtained from *Strobilanthus flaccidifolius*, *Indigo tinctoria*, *Isatis oblongata* or *Polygonatum tinctorium* suppresses superoxide anion generation, Mitogen-Activated Protein Kinase (MAPK) phosphorylation and calcium mobilization in Formyl-Methionyl-Leucylphenylalanine (FMLP)-activated human neutrophils. *Chrysanthemi flos* Plus *Gardeniae fructus* Plus *Hyperici perforati*

herba Plus *Scrophulariae radix* Plus *Sophorae tonkinensis radix* combination and, Borneol and Borax Powder were both evaluated by Zhou Z and Zhang Z on oral mucositis in chemotherapy and radiotherapy and compared to gentamycin/sodium/bicarbonate gargle solution. Nevertheless, the results showed improvement in oral mucositis symptoms and reduced healing period in herbal treatment group [7,20].

Camellia: Baxidil Onco® is a mouthwash containing *Camellia sinensis* leaf extract, which participates in the green tea production and palmitoyl hydrolyzed wheat protein. The most benefits of Baxidil Onco® are antioxidative properties related to *Camellia sinensis* extract. Also, it seems to neutralize the excessive production of Reactive Oxygen Species (ROS) and ulcerative destruction in oral mucositis. The results of a randomized, non-blinded clinical study in haematologic patients undergoing peripheral blood stem cell transplantation demonstrated that administration of Baxidil Onco® mouthwash (that rinsed at least one minute without swallowing four times daily along with the standard prophylaxis) successfully reduced incidence, severity and duration of oral mucositis. This herbal agent; however, showed a preventive effect resembled to palifermin and amifostine [10].

Catechu: The origin source of catechu is *Acacia catechu* extraction. This agent has both tissue regeneration and wound healing properties, which have been used as a mouthwash for oral ulcers. Additional benefits such as anti-inflammatory effects were observed, when it was used with *Scutellariae baicalensis radix*. Shi Y and Shan J showed more effects of catechu powder compared to local norfloxacin on oral mucositis (when used locally in patients who received chemotherapy). All treated patients (100%) with catechu were cured, but healing occurred just in 73.3% of patients treated with norfloxacin. The favorable findings of this *Acacia catechu* extraction; however, may lead us to promising treatment for oral mucositis [21].

Chamomile: This herb contains several substances such as chamazulene, alpha bisabolol, bisabolol oxides, spiroethers, and flavanoids with anti-inflammatory, antibacterial, and antifungal effects. Various studies evaluated the effect of this plant in oral mucositis. A pilot study showed that, chamomile could reduce oral mucositis in cancer patients; however, Fidler P et al., in 2004 demonstrated that chamomile mouthwash does not prevent oral mucositis induced by 5-FU [22]. On the other hand Mazokopakis E et al., reported a case of methotrexate-induced oral mucositis treated with wild Chamomile (*Matricaria recutita L.*) mouthwashes successfully [23]. Shabanloei R et al., also compared the preventive effect of allopurinol, chamomile and normal saline mouthwashes on mucositis in patients undergoing chemotherapy. The results showed the equal efficacy of allopurinol and chamomile in the prevention of chemotherapy-induced stomatitis [24]. Braga F et al., found that mouthwash containing 1% *chamomilla recutita* extract was effective against mucositis in adult patients receiving allogeneic haematopoietic stem cell transplantation [25].

Chrysanthemi flos Plus Gardeniae Fructus Plus Hyperici perforati herba Plus Scrophulariae radix Plus Sophorae tonkinensis radix Combination: Geniposide derived from *Gardeniae Fructus* inhibits TNF- α , IL-6, and IL-1, to block the phosphorylation of I κ B α , transcription factor p65, p38, Extracellular-signal-Regulated Kinases (ERK) and c-Jun N-terminal Kinases (JNK), and diminishes the Toll-Like Receptor-4 (TLR4) expression in Lipopolysaccharide (LPS) simulated macrophages and LPS induced IL-8 production in Embryonic Kidney Cells of Human (HEK293-mTLR4/MD-2 cells). *Hyperici perforati* preclude LPS-induced Prostaglandins E-2 (PGE-2), COX-2, and NO via inhibition of cytokine signaling three activations in macrophages. *Sophorae tonkinensis radix* showed antiviral activity on Coxsackie, Echo, and Poliovirus; therefore, may have anti-inflammatory and wound-healing effects [7], but no research has been carried out to establish its effect on mucositis.

Clear the stomach powder: The components of this classic mixture include *Coptidis rhizoma*, *Cimicifugae rhizoma*, *Rehmanniae viridae radix*, *Moutan cortex*, *Angelicae sinensis radix*, and *Achyranthis bidentatae radix*. *Coptidis rhizoma* acts on IL-1 α , IL-6 inhibition and Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) secretion, inducible Nitric Oxide Synthase (iNOS) expression, and NO production in RAW 264.7 macrophages. *Cimicifugae rhizoma* decreases LPS-induced expression of IL-6, TNF- α , IFN- γ , and stimulation of IL-8 in LPS-induced human blood cells. *Moutan* inhibits activation of inflammation via genes in gingival fibroblasts. *Ligustilide* is a compound of *Angelica sinensis*, which inhibits NO production, PGE-2, and TNF- α in LPS stimulated RAW 264.7 macrophages, to reduce activator Evidence-Based Complementary and Alternative Medicine 9 protein-1 (AP-1), iNOS and NF- κ B activation, phosphorylation of the I κ B Kinase (IKK), MPAKs, ERK1/2, and c-Jun-N terminale Kinase (JNK) and to down regulate intracellular Reactive Oxygen Species (iROS). In a study of Zhu H and Zhang J on two herbal compounds Jade Woman Decoction and Clear the Stomach Powder, amelioration of mucositis symptoms occurred in 83.9% of patients, but further investigations are needed to clarify the underlying mechanisms [26].

Clear the ying level decoction: *Lonicerae Flos*, Plus *Platycodonis radix* and *Ophiopogonis radix* are components of the definite herbal mixture with the English name of Clear the Ying Level Decoction. Although the effect of *Ophiopogonis radix* is yet to be clear, this agent could stimulate the lymphocyte proliferation in-vitro. *Platycodonis radix* also has anti-inflammatory benefits, which inhibits COX-2, TNF- α , and PGE2 expression and reduces inflammatory markers such as the number of leukocytes and neutrophils and oedema. Chen J et al., investigated the employing of this Chinese herbal treatment and their results showed healing of ulcerations in 93%, compared to 73.8% in the control group [27].

Clear wind heat tea: A *Lonicerae Flos*, *Glycyrrhizae radix* and *Menthae haplocalycis herba* are integrants of Honeysuckle and Forsythiae powder. The action of *Chrysanthemi flos* is inhibition of NO, PGE-2, TNF- α , production of IL-1 β and expression of iNOS and COX-2 in LPS induced macrophages. In addition, *Ganoderma lucidum* reduces NO, PGE-2, and production of proinflammatory cytokines such as including IL-1 β , TNF- α and NF- κ B in microglia. *Menthae haplocalycis herba* has antimicrobial effect against *Streptococcus mutans* as well as ability to release histamine and Prostaglandins D-2 (PGD-2) synthesis in mast cells. This mixture examined in 2009, in the patients who received chemotherapy as a local ice cube application. Nevertheless, the results showed lower incidence of oral mucositis compared to control group [28].

Drain the yellow powder: This mixture contains *Codonopsis radix* Plus *Atractylodis macrocephalae rhizome* Plus *Glycyrrhizae radix* Plus *Angelicae sinensis radix* Plus *Rehmanniae viridae radix* Plus *Astragali membranacei radix* Plus *Dioscoreae oppositae rhizoma* Plus *Alismatis rhizoma* Plus *Agastachis herba* Plus *Lophatheri herba* in combination of *Ginseng radix* (or alternatively *Codonopsis radix*), *Atractylodis macrocephalae rhizoma*, *Glycyrrhizae radix*, *Angelicae sinensis radix*, *Rehmanniae radix*, *Poria alba*, *Paeoniae alba radix*, and *Ligustici chuangxiong rhizome*. This mixture of herbal medication was compared to oral administration of vitamin B2 and vitamin C in the control group, and positive effects on mucositis symptoms were seen in 98% of the treatment group compared to 72% of the control group [29].

Eight treasure tea: This mixture contains *Codonopsis radix* Plus *Atractylodis macrocephalae Rhizome* Plus *Glycyrrhizae radix* Plus *Angelicae sinensis radix* Plus *Rehmanniae viridae radix* Plus *Astragali membranacei radix* Plus *Dioscoreae oppositae rhizoma* Plus *Alismatis rhizoma* Plus *Agastachis herba* Plus *Lophatheri herba* in combination of *Ginseng radix* (or alternatively *Codonopsis radix*), *Atractylodis macrocephalae rhizoma*, *Glycyrrhizae radix*, *Angelicae sinensis radix*, *Rehmanniae radix*, *Poria alba*, *Paeoniae*

alba radix, and Ligustici chuangxiong rhizome. Agastachis herba, and Lophatheri herba have immune consolidating effects.

Extract of Codonopsis radix precludes NO, TNF- α , IL-3 IL-6, ERK signaling pathway, LPS-induced phagocytic uptake and CD29-mediated cell-adhesion in RAW 264.7 macrophages. Dioscoreae oppositae rhizoma reduces the NO and proinflammatory cytokine production such as contains IL-1 β , IL-6, TNF- α , and PGE-2, as well as iNOS, and the COX-2, and NF- κ B activation in RAW 264.7 macrophages. Alismatis rhizoma prevents the function of NF-B, COX-2, IL-1, iNOS, as well as induced Nuclear factor-like 2 (Nrf2)-regulated gene expression in RAW 264.7 cells. Agastachis herba extract has antioxidant property, due to which it increases activity of Heme Oxygenase-1 (HO-1) enzyme by Protein Kinase G (PKG) signaling pathway in RAW 264.7 macrophages. Lophatheri herba possess an anti-Respiratory Syncytial Virus (RSV) effect in vitro. Eight Treasure Tea evaluated by Chen C and Zheng Y on oral mucositis in patients undergoing chemotherapy. The results showed lower incidence of oral ulcers in herbal treated group compared to controls [30].

Evodiae fructus: Evodiae Fructus is a Chinese herbal medicine from Evodiamine, which causes nuclear factor kappa-lightchain-enhancer of activated B cells (NF- κ B) activation and the COX-2 presentation, inhibition of iNOS, Hypoxia-Inducible Factor 1- α (HIF-1- α) aggregation and Prostaglandin E-2 (PGE-2) synthesis, and Interferon-gamma (INF- γ) mediated processes in murine 264.7 macrophages. Xu T and Han J in 2006 investigated using the extraction of Evodiae Fructus on oral mucositis in patients undergoing chemotherapy. They reported significant effects of Evodiae Fructus on oral ulcers in mucositis, but further studies could be helpful to confirm the results [31].

Generate the pulse powder: Shengmai, a Chinese medicine including Ginseng radix, Ophiopogonis radix, and Schisandrae chinensis fructus, is called as Generate the Pulse Powder in English. The Origin source is Yu XueQi Yuan with anti-inflammatory activity. Schisandrin B causes suppression of IL- β -induced NO and iNOS expression and also transcription of IL-1 β and inflammatory cytokines.

In a clinical trial, intravenous Shengmai injection was evaluated in oral mucositis compared to dexamethasone, metoclopramide, and ondansetron injection. This study defined reduced incidence of oral mucositis in the treatment group [13].

Hangeshashinto (TJ-14): This herbal agent is a traditional Japanese medicine, which is a mixture of seven herbal extracts including Pinellia Tuber, Scutellarai Radix, Glycyrrhizae Radix, Ziziphi Fructus, Ginseng RADIX, Zingiberis Processum Rhizoma, and Coptidis Rhizoma. In Japan this drug is a conventional treatment of resistant oral mucositis. The mechanism of TJ-14 is the direct inhibition of PGE-2 production. Aoyama T et al., evaluated the preventive effect of Hangeshashinto in oral mucositis compared with placebo. The patients used it as a rinse solution three times daily during and after (chemo) radiation therapy. Their results showed that TJ-14 reduced the duration of mucositis without any reduction in the incidence of oral mucositis. This may be due to chemotherapy dose reduction before the experimental cycles [32]. Kono T et al. also supported the efficacy of Hangeshashinto for prevention and treatment of oral mucositis. Their method for using the drug was holding the rinse solution in the mouth. They suggested that, TJ-14 have also a direct therapeutic benefit even in patients with difficulty in swallowing [33]. Yamashita T et al., showed the efficacy of TJ-14 for improving oral mucositis as a result of chemo radiation in patients with head and neck cancers [34].

Honeysuckle and forsythiae powder: Honeysuckle and Forsythiae Powder is the English name of a traditional herbal combination, which composed of two major component including Lonicerae flos and Glycyrrhizae radix.

Lonicerae flos provides antioxidant properties and suppresses interleukin 1- β (IL-1 β), IL-6, as well as COX-2 gene expression.

Glycyrrhizae radix has anti-inflammatory effects including Glycerol inhibition LPS-induced NF- κ B, IL-1, and IL-6 mRNA activation. In addition, two studies evaluated this mixture compared to the control group and both of them revealed significant diminished mucositis symptoms [35,36].

Indigowood root: Indigowood (*Isatis indigotica* Fort) root is a common herb used in China. This plant belongs to Brassicaceae family. This agent provides antiviral, fever detoxification, and anti-inflammatory properties. A clinical trial evaluated the effect of indigowood on oral mucositis in patient undergoing radiation therapy, and the results showed its ability to decrease mucosal damage by anti-inflammatory effects [37].

Jade woman decoction: This herbal medicine consists of *Rehmanniae viridae radix*, *Gypsum fibrosum*, *Anemarrhenae rhizoma*, *Achyranthis bidentatae radix* and *Ophiopogonis radix*. *Gypsum fibrosum* is shown to have antipyretic effects against LPS-induced pyrexia in rats. *Rehmanniae viridae radix* can inhibit production of NO and iNOS, IL-6, PGE-2, a well as COX-2 expression in RAW 264.7 macrophages. Meanwhile, *Nyasol* found in *Anemarrhenae rhizoma*, diminishes NO, PGE-2 production and mRNA levels of TNF- α and IL-1 in LPS stimulated microglia cells.

Achyranthis bidentatae radix up regulates dendritic cell maturation of cell surface molecules such as CD40 and CD86 and Major Histocompatibility Complex II (MHC II) development and enhances IL-12 creation in mice, thus, progresses immune functions [7].

Kangfuxin: Kangfuxin as a herbal agent obtained from *Periplaneta Americana* extraction. The mechanism of its action on oral mucositis is expression of cytokine IL-4, Interleukin 5 (IL-5), IFN- γ , and TNF- α by decreased gene expression. It has also anti-inflammatory and wound healing benefits in oral ulcers. Zeng Y, investigated on this agent and showed that, Kangfuxin reduced the rate of oral mucositis on chemotherapy patients compared to saline rinsing. However, more studies are needed to confirm these results [38].

Lonicerae flos plus glycyrrhizae radix plus astragali membranacei radix: This mixture as a traditional herbal Chinese agent includes *Lonicerae flos*, *Glycyrrhizae radix*, *Astragali membranacei radix* with anti-inflammatory effects. It modulates the immune system by discharging IL-2 and suppressing IFN- γ and IL-4. Bao N et al., demonstrated lower grade of ulcers and reduced symptoms in topical usage of this herbal solution compared to control group. However, no marked decrease in healing period was seen [39].

MF 5232 (Mucotrol): MF 5232 (Mucotrol) is a mixture of herbal agent used as an oral gel wafer including sorbitol, Cyamopsis tetragonolobus, stearic acid, magnesium stearate, aloe, natural and artificial flavors, acesulfamek, extracts of glycyrrhizin, *Centella asiatica*, *Polygonum cuspidatum*, *Angelica sp* and *Camellia sinesis*. This is found to have local analgesic, antioxidant, immunomodulatory activity and wound-healing effects. A pilot study showed the positive effect of MF 5232 in oral mucositis, however, further studies should confirm these results [40].

Peppermint essence : The essence of Peppermint plant offers strong anti-bacterial and anti-fungal effects and it can provide cooling sensation in mucosa and skin. Ashktorab T et al., in 2010 evaluated the preventive effects of a Peppermint oral rinse on oral mucositis in patients undergoing chemotherapy. They also demonstrated the efficacy, safety and well-tolerance of Peppermint essence oral rinse in this condition [41].

Qingre liyan decoction (QYD): QYD, a traditional Chinese medicine, is extracted from twelve different herbs including *Flos Lonicerae* (*Lonicera japonica*), *Belamcandae Rhizoma* (*Belamcanda chinensis*), *Lasiosphaera seu calvatia* (*Lasiosphaera fenlzii Reich*, *Calvatia gigantean*), *Astragali Radix* (*Astragalus membranaceus*), *Glehniae Radix* (*Glehnia littoralis*), *Ophiopogonis Radix* (*Ophiopogon japonicas*), *Trichosanthes Radix* (*Trichosanthes kirilowii*), *Scrophu-*

lariae Radix (*Scrophularia ningpoensis*), Ligusticum wallichii Rhizoma (*Ligusticum chuanxiong*), Agrimoniae Herba (*Agrimonia pilosa*), Imperatae Rhizoma (*Imperata cylindrical*), and Glycyrrhizae Radix (*Glycyrrhiza uralensis*). Wu M-H et al., considered the preventive and therapeutic effects of QLD in acute oral mucositis in patients undergoing radiotherapy in the head and neck area. They showed that, the incidence of oral mucositis decreased when compared to the control group. Therefore, they suggested that, the mechanism of action might be due to improving immunity and increasing salivary Epidermal Growth Factor (EGF) [42]. Another research was done by Lambros MP et al., in 2015 that explained the preventive and therapeutic effects of this agent with utilization a 3-Dimensional cell culture model of oral mucositis. Their observation showed that treatment with QYD maintained the integrity of tissue-cultures and no apoptosis was detected. Moreover, up regulation of genes encoding metallothioneins, Heme Oxygenase 1 (HMOX1) and other ingredients of Nrf2 pathway makes a protection against oxidative stress. The genes interfering in repairing DNA, protective genes, and genes of the NF- κ B pathway were up regulated as well. Prophylactic effects of QYD showed prominent decrease of apoptosis, cytokines and chemokine's genes, and constrained damage-associated molecular patterns [43].

Rhodiola algida: Rhodiola algida is a herbal extract commonly administrated in traditional Chinese medicine. This drug regulates IL-2 in T helper cells type 1 (Th-1) cells and IL 4, 6, and 10 in T helper cells type 2 (Th-2), indicating an immunomodulatory effects. Loo WJ et al., evaluated the effects of Rhodiola algida on the healing time of oral ulcers in patients with cancer. Rhodiola algida was used after each cycle of chemotherapy. Their study, however, showed that Rhodiola algida enhances immune system and reduces oral ulcers in patients undergoing chemotherapy. Therefore, this herbal agent had significant profits in decreasing oral mucositis symptoms [44].

Traumeel S: Traumeel S is a complex homeopathic treatment with anti-inflammatory effects. It is a mixture of medicinal plants including *Arnica Montana*, *Calendula officinalis*, *Atropa belladonna*, *Aconitum napellus*, *Bellis perennis*, *Hypericum perforatum*, *Echinacea angustifolia*, *Echinacea purpurea*, *Symphytum officinale*, *Matricaria Chamomilla*, *Achillea millefolium*, *Mercurius solubilis hahnemanni*. Oberbaum M et al., demonstrated that, Traumeel is more effective than placebo for preventing or treatment of oral mucositis in children undergoing bone marrow transplantation when used five times daily [45]. Steinmann D et al., in 2012 studied the effect of Traumeel S in the treatment of radiation-induced oral mucositis in patients with head and neck tumors. They demonstrated some effects such as resolving lack of taste and swallowing problems with the use of Traumeel S, and mentioned that, Traumeel S may be potentially effective in the treatment of oral mucositis [46]. Sencer S et al., in 2012, evaluated Traumeel S in preventing and treating mucositis in young patients undergoing Haematopoietic Stem Cell Transplantation (HSCT). The patients rinsed and hold it for thirty seconds and then swallowed five times daily. This research did not report any positive effects after using of Traumeel S in mucositis [47].

Water grass decoction: Water Grass Decoction contains two drugs, Bubali Cornu and Callicarpae macrophyllae folium. Bubali cornu has antioxidant properties on proteins and suppresses TNF- α -induced PGE2 production. It also provides protection effects against Hydrogen Peroxide (H₂O₂) in endothelial cells. On the other hand, Callicarpae macrophyllae folium delivers anti-inflammatory, antimicrobial, and analgesic effects that is not fully recognized. A research on this herbal medicine was done in chemotherapy patients by topical and internal methods. There were superior results with this treatment compared to gentamycin/tetrahydropholate/saline control group, which was promising [48].

Weleda ratanhia: Rathania (*Krameria triandra*) root extracts is approved in Germany and locally used in treatment of few

inflammations of the mucous membrane in oral cavity and larynx and seems to act its role by effects on tissue astringency. Weleda Ratanhia-Mundwasser (ratanhia mouthwash) includes horse chestnut extract and volatile oils as well as ratanhia roots extraction, myrrh and chamomile that provide anti-inflammatory, antibacterial and healing effects. It also has volatile oils (from peppermint, spearmint and fennel seeds) that may stimulate the mucosa. A clinical trial in 2007 evaluated regular use of this herbal mouthwash and dentifrice in combination with dental treatment on incidence and severity of oral mucositis in patients under chemotherapy. After professional dental cleaning three times daily the patients used these products over a four- week period. Positive effects of dental treatment along with regular use of Weleda Ratanhia-Mundwasser (herbal mouthwash) and Weleda Pflanzen-Zahngel (herbal tooth gel) on prevention and treatment of oral mucositis were demonstrated [49].

Yarrow distillate: The Yarrow plant (*Achillea millefolium*) is from Asteraceae family. This herb is a commonly used agent in ancient medicine and contains chamazulene, cineol, and borneol, which can provide antibacterial, anti-inflammatory and anti-spasmodic properties. Miranzadeh S et al., in 2014 showed that Yarrow distillate contained solution has a decreasing effect on the intensity of oral mucositis compared with the control group. The result may propose Yarrow distillate as a useful herb in oral mucositis treatment [50].

Yellow five decoction: Yellow Five Decoction is a herbal combination that contains Phellodendri Chinensis Cortex, forsythia Fructus, Verbenae officinalis Herba, Borneolum, Galla chinensis, and Catechu. Phellodendri chinensis cortex; however, was found to inhibit TNF- α , IL-1 β , and iNOS production and plays a role in the phosphorylation of Extracellular-signal Regulated Kinases (ERK) and NF- κ B activation in microglia cells. Forsythiae reduces proinflammatory cytokine production including TNF- α , IL-1 β , IL-6, and PGE-2 as well as NF- κ B and co-stimulating molecules such as peripheral membrane protein B7-1 and B7-2 in murine leukemic monocyte macrophage cells. Verbenae officinalis herba provides antioxidant, anti-inflammatory, and wound-healing properties. Borneolum delivers anti-inflammatory and antioxidant cell protective effects and reducing iNOS expression, NO and inflammatory factor release. It also could diminish NF- κ B translocation and caspase-related apoptosis. Galla chinensis also increases wound healing. In a clinical trial, this mixture was used in patients under chemotherapy as a gargling mouthwash, which ameliorated mucositis symptoms more than control group [51].

A summary of all the herbs has been presented in [Table/Fig-1].

DISCUSSION

The evolution of cancer therapy-induced oral mucositis has been classified in a five-phase model by Sonis ST: initiation, upregulation/activation, signal amplification, ulceration and healing [52].

In the initiation phase, radiation or chemotherapeutic agents cause direct DNA break, generation of ROS and consequently cell death in epithelia, endothelia and submucosal tissues. Thereafter, release of inflammatory substances such as IL-1 and IL-33 happens. This phase has no clinical manifestation. The upregulation/activation phase is characterized by activation of receptors of innate immune system and of the peripheral nociceptive nervous fibres, increase of proinflammatory cytokines (such as IL-6) and matrix metalloproteinase. Clinically, this phase presents with transient faint erythema and pruritus. In the phase of signal amplification, elevated serum levels of NF- κ B, TNF- α , IL-1 and IL-6 have been documented, which lead to mucosal edema and erythema. In the ulceration phase, mucosal barrier disrupts followed by bacterial colonisation. In addition, microorganisms penetrate the damaged mucosa and stimulate macrophage infiltration to produce additional proinflammatory cytokines. In this phase ulceration and local infection is evident clinically [53].

Herbal Agent	Mechanism of Action	Ingredients	Preventive	Therapeutic
Aloe vera Juice	Immunomodulator antioxidant	polysaccharides, anthraquinone, lectin, superoxide dismutase, glycoprotein, amino acids, vitamins C, E, minerals		+
Borneol and Borax Powder Gargle Solution	Immunoregulator, Antitoxic	Yi Zong Jin Jian	+	
Camellia1 Mouthwash	Antioxidant, Protective effect	Camellia Sinensis leaf extract	+	
Catechu Mouthwash	Anti-inflammation, Tissue regeneration, Wound healing	Acacia catechu extract		+
Chamomile Mouthwash	Anti-inflammation, Antifungal, Antibacterial, Antiseptic, Sedative	Chamazulene, alpha bisabolol, bisabolol oxides, spiroethers, and flavenoids	+	+
Chrysanthemi flos Plus Gardeniae Fructus Plus Hyperici perforati herba Plus Scrophulariae radix Plus Sophorae tonkinensis radix Combination Gargle Solution	Immunoregulator, Anti-inflammation, Wound healing, Antitoxic, Moistening tissues	Chrysanthemi flos, Gardeniae fructus, Hyperici perforati herba, Scrophulariae radix, Sophorae tonkinensis radix Combination	+	+
Clear the Stomach Powder Oral Administration	Immunoregulator, Anti-inflammation	Coptidis rhizoma, Cimicifugae rhizoma, Rehmanniae viridae radix, Moutan cortex, Angelicae sinensis radix, Achyranthis bidentatae radix		+
Clear the Ying Level Decoction Oral Administration	Anti-inflammation	Lonicerae flos, Ophiopogonis radix, Platycodonis radix		+
Clear Wind Heat Tea Topical Ice Cube Application	Immunoregulator, Antimicrobial	Lonicerae flos, Glycyrrhizae radix, Chrysanthemi flos, Ganoderma lucidum, Menthae haplocalycis herba	+	
Drain the Yellow Powder Oral Administration	Anti-inflammation	Gypsum fibrosum, Saposhnikoviae radix, Gardeniae fructus, Agastachis herba, Glycyrrhizae radix		+
Eight Treasure Tea Oral Administration + Gargle Solution	Anti-inflammation, Immune consolidating	Codonopsis radix, Atractylodis macrocephalae Rhizome, Glycyrrhizae radix, Angelicae sinensis radix, Rehmanniae viridae radix, Astragali membranacei radix, Dioscoreae oppositae rhizoma, Alismatis rhizome, Agastachis herba, Lophatheri herba	+	
Evodia rutaecarpa Acupoint Application	Immunomodulator	Evodiae fructus extract		+
Generate the Pulse Powder Intravenous Injection	Anti-inflammation	Ginseng radix, Ophiopogonis radix, and Schisandrae chinensis fructus and originates from Yu XueQi Yuan		+
Hangeshashinto Rinse Solution	Anti-inflammation	Pinellia Tuber, Scutellarai Radix, Glycyrrhizae Radix, Ziziphi Fructus, Ginseng RADIX, Zingiberis Processum Rhizoma, and Coptidis Rhizoma	+	+
Indigowood Root Gargling and Swallowing	Antiviral, Anti-inflammation	Indigowood	+	
Jade Woman Decoction Oral Administration	Immunoregulator, Anti-inflammation	Gypsum fibrosum, Rehmanniae viridae radix, Anemarrhenae rhizoma, Ophiopogonis radix, Achyranthis bidentatae radix		+
Kangfuxin Gargle Solution	Anti-inflammation, Wound healing	Periplaneta americana extract		+
Lonicerae fl. Ophiopogonis r. Astragali memb. r. Gargle Solution	Anti-inflammation, Immunoregulator	Lonicerae flos, Glycyrrhizae radix, Astragali membranacei	+	
MF 5232(Mucotrol) Oral Gel Wafer	Local analgesic, Antioxidant, Immunomodulator, Wound healing	Sorbitol, Cyamopsis tetragonolobus, Stearic acid, Magnesium stearate, Aloe, Natural and artificial flavors, acesulfamek, Extracts of glycyrrhizin, Centella asiatica, Polygonum cuspidatum, Angelica sp, Camellia sinensis		+
Peppermint Essence Oral Rinse	Anti-bacterial, Antifungal, Sedative	Peppermint	+	
Qingre liyan decoction	Protective effect, Improving immunity	Flos Lonicerae, Belamcandae Rhizoma, Lasiosphaera seu calvatia, Astragali Radix,	+	+
Gargling and Swallowing		Glehniae Radix, Ophiopogonis Radix, Trichosanthes Radix, Scrophulariae Radix, Ligusticum wallichii Rhizoma, Agrimoniae Herba, Imperatae Rhizoma, Glycyrrhizae Radix		+
Rhodiola Algida	Immunomodulator	A Tibetan plant	+	+
Traumeel S Mouth Rinse	Anti-inflammation	Pinellia Tuber, Scutellarai Radix, Glycyrrhizae Radix, Ziziphi Fructus, Ginseng RADIX, Zingiberis Processum Rhizoma, and Coptidis Rhizoma		+
Water Grass Decoction Oral Administration + Gargle Solution	Antioxidant, Immunoregulator, Anti-inflammation, Antimicrobial, Analgesic	Bubali Cornu, Callicarpae macrophyllae folium	+	+
Weleda Ratanhia Mouthwash and Tooth Gel	Anti-inflammation, Antibacterial, Lesion healing	Ratanhia roots extraction		+
Yarrow Distillate Mouthwash	Anti-inflammation, Antibacterial	Yarrow plant		+
Yellow Five Decoction Mouthwash	Anti-toxic, Immunoregulator, Anti-inflammation, Wound healing	Phellodendri Chinensis Cortex, Forsythiae fructus, Verbenae officinalis herba, Borneolum, Galla chinensis, Catechu		

[Table/Fig-1]: Herbal agents used in oral mucositis.

According to WHO oral toxicity scale, the severity of mucositis can be divided into four stages- Grade 1 presents with soreness with or without erythema; Grade 2 happens when patients have erythema or ulcer, but still able to swallow solid food; Grade 3 occurs when the patient has extensive erythema and ulcer and cannot swallow food; Grade 4 is an extensive mucositis so that alimentation is not possible [6].

Many herbal agents have been inaugurated for the treatment of oral mucositis. Most of herbs evaluated in this review showed positive preventive, therapeutic or both effects on oral mucositis. Among them Hangeshashinto, Chamomile, Honeysuckle and Forsythiae Powder, QLD, and Traumeel S with both preventive and therapeutic benefits studied more compared to others, therefore, the results seem to be more reliable.

Medicinal herbs help improve oral mucositis via several routes such as anti-inflammatory, immunomodulatory, antitoxic, antiseptic, sedative and wound healing effects with most of them having anti-inflammatory and immunomodulatory properties to some extent. The underlying mechanism is thought to be down regulation of proinflammatory cytokines like IL-1, IL-6, IL-8, and TNF- α , and up regulation of anti inflammatory cytokines such as IL-4, IL-13, IL-10, and TGF- β . Among single herbal compounds aloe vera, Camila, Catechu, Evodiae fructus, Rhodiola algida, and Kangfuxin, exert their immunoregulatory effects via cytokine regulation. Meanwhile, some herbal combinations like Chrysanthemi flos Plus Gardeniae Fructus, Clear-the-Stomach Powder, Clear the Ying Level Decoction, Clear Wind Heat Tea, Eight Treasure Tea,

Generate the Pulse Powder, Honeysuckle and Forsythiae Powder, Jade Woman Decoction, Lonicerae flos Plus Glycyrrhizae are demonstrated to have cytokine regulatory effects.

Focusing on single active compounds may perform modestly, but the technique could not be used for the multidimensional complexity of herbal prescriptions. It seems that, the special effects of every single herb are required to be recognized on a molecular basis and subsequently herbal combinations should be assessed.

CONCLUSION

Taking together, even though herbal remedies seem to have lower side effects and better accessibility than chemical agents, prescription of herbal medicine to treat oral mucositis depends on availability, administration route, patient compliance and also comprehensive knowledge regarding their properties. Our knowledge of herbal mechanisms, particularly in multi-herbal combination therapy, however, is quite restricted; therefore, standard concepts for this kind of treatment do not exist and acceptance by conventional oncologists is still low. Although some findings could improve the character of aliveness in the patients, further written reports are required to reach a fuller apprehension of the underlying mechanisms of the long-term effects of herbal agents to standardize the protocols for developing the efficacy.

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