

# Natural Remedies Target Different Therapeutic Pathways in Oral Mucositis Induced by Cancer Chemo or Radiotherapy

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## Abstract

Oral mucositis (OM) is an inflammatory condition affecting oral mucosa. The etiology of this type of inflammation is associated with exposure to radiotherapy or chemotherapeutic drugs. Herbal drug has been used to induce healing of different types of gastrointestinal ulcers. The role of medicinal plant in cancer therapy induced oral mucositis has been investigated extensively. Preclinical studies refer to healing activity of some medicinal plant such as *Chamomile*, royal jelly, *Calendula officinalis* and *Salvadora perisca* in oral mucositis induced by either chemotherapy or radiotherapy. Some herbal drug is proved to have potential efficacy in decreasing both incidence and severity of oral mucositis in clinical studies. The molecular targets that is modulated by herbal drug is various including scavenging reactive oxygen species (ROS), inhibition inflammatory cascade, prevention of keratinocyte apoptosis and induction of some growth factors. This review illustrates the common herbal drugs that have been used for oral mucositis management focusing on different therapeutic pathways that are implicated in this process.

**Keywords:** Oral mucositis; Herbal remedies; Antioxidant; Anti-inflammatory; Keratinocyte apoptosis; KGF

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## Introduction

Oral mucositis is an inflammatory condition that affects mucosa of the oral cavity. The etiology of this type of inflammation is associated with exposure to radiotherapy or chemotherapeutic drugs [1,2]. Patients under chemotherapeutic protocols that are associated with bone marrow-suppression are at high risk of oral mucositis. Approximately 60-100% of those patients may encounter oral mucositis, patients who need radiotherapy directed at the oral, sub mandibular and pharyngeal area such as those who have squamous cell carcinoma in the head and neck region commonly have oral mucositis [3]. Combination of radiotherapy and chemotherapy is associated with a risk of around 100% [2]. Oral mucositis is a painful condition that significantly affects patients' quality of life [4]. The sever cases is associated with ulcerated mucosa and secondary infection which may led to life-threatening sepsis.

Herbal drugs have been used to induce healing of different types of gastrointestinal ulcers such as gastric ulcer, aphthous

stomatitis, ulcerative colitis and oral mucositis [5-8]. The role of medicinal plants in cancer therapy induced oral mucositis has been investigated extensively. Preclinical studies refer to healing activity of some medicinal plants like *Chamomile*, royal jelly, *Calendula officinalis* and *salvadora perisca* in oral mucositis [9-12]. Recently, some of medicinal plants products are formulated in various dosage form. These preparations have been proved to be effective in prevention of oral mucositis in patients under chemo or radiotherapy [13-15]. This review illustrates the common herbal drug that has been used for oral mucositis management focusing on different therapeutic pathways that are targeted by medicinal plants.

## Pathophysiology of oral mucositis

Anti-neoplastic drugs induce direct epithelial cell injury starting with DNA strand breaks concurrently with production of reactive oxygen species (ROS) [16] especially in early stage of oral mucositis which results in consumption of large quantities of antioxidants molecules including glutathione [17]. Degraded DNA strand

and ROS activate nuclear factor- $\kappa$ B (NF- $\kappa$ B) [18]. It is an important factor that upregulates expression of proinflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), Interleukin 1 $\beta$  (IL-1 $\beta$ ), and Interleukin 6 (IL-6). These cytokines amplify tissue damage [19,20]. Tissue damage is deteriorated with activation matrix metalloproteinases as a result of activated proinflammatory molecules [21,22]. All these processes led to formation of ulcers in the mucosa. The healing phase of oral mucositis is initiated by signaling pathways starting in endothelial cells with specific growth factors that control renewal of epithelial cell proliferation and differentiation. Keratinocyte growth factor (KGF) is one of the key molecules that regulated communication between endothelial and epithelial cells. It is associated with triggering epithelial cell growth and differentiation [23].

### Evidence for efficacy of traditional medicine in oral mucositis

**Chamomile:** There are two types of chamomile, German Chamomile (*Chamomilla recutita*) and Roman Chamomile (*Chamaemelum nobile*). The main active constituents of chamomile flowers are terpenoids and flavonoids [24]. Pavesi et al. [9] reported that topical preparation of Chamomile decreases the incidence and severity of oral mucositis induced by 5-fluorouracil in hamster. It has been reported that Chamomile ointment decreases severity of oral mucositis by decreasing proinflammatory cytokines [25]. These results were further evaluated in clinical studies. One of these studies used *Chamomile* extract as infusion. *Chamomile* infusion decreased incidence and severity of mucositis when used as adjuvant therapy with cryotherapy in patients under 5-fluorouracil and leucovorin protocols. Moreover, the toxic profile of *Chamomile* infusion showed a wide margin of safety. Results of another randomized, controlled, Phase II Clinical Trial pointed out that *Chamomile* mouthwash (containing 1% *C. recutita* extract) can be associated with reduction in incidence, intensity, and duration of mucositis in patients undergoing allogeneic Hematopoietic Stem Cell Transplantation HSCT [26].

**Calendula officinalis:** *Calendula officinalis* is a member of Asteraceae family. Extracts of *C. officinalis* flowers have active constituents that have different pharmacological activity such as bactericidal, antiseptic, anti-inflammatory, and antioxidant [11]. Topical *Calendula officinalis* extract formulated as gel accelerated the healing of oral mucositis induced by 5-fluorouracil (5-FU) in hamsters. Clinically, Calendula mouthwash ameliorated the severity of radiotherapy induced oral mucositis in patients with head and neck cancer [14].

**Salvadora persica:** Miswak (*Salvadora persica* L.) is the most widely used chewing stick for oral hygiene in middle-eastern and eastern African cultures, which is prepared from the roots or stems of *Salvadora persica* [27]. *Salvadora persica* accelerates healing of ulceration induced by ethanol, indomethacin and cold restraint stress in rats [28]. Recently, *Salvadora persica* aqueous extract was found to decrease incidence of oral mucositis induced by 5-fluorouracil in rats. The mechanism underlying this effect may be multifactorial including preservation of oral hygiene as well as increasing level of KGF in mucosa tissues [12]. Different herbal remedies that showed promising results in preventing or accelerating healing of oral mucositis are summarized in **Table 1**.

**Herbal remedies combination:** Traditional Japanese herbal medicine prescribes herbal remedies that contain different medicinal plants such as Daiokanzoto (TJ-84) and Hangeshashinto. The composition of Hangeshashinto is illustrated in **Table 2**. The herbal combination Daiokanzoto has an anti-inflammatory and immunomodulatory effect that suggesting possible benefits in treating oral mucositis. It has been reported that Daiokanzoto exerts some activity in decreasing apoptosis in gingival cells (SA3 cell line) exposed to 5-fluorouracil through inhibition of ROS release from mitochondria [29]. Similarly, Using Hangeshashinto (TJ-14) enables patients under chemoradiotherapy to complete their treatment course and preserve their nutritional status during treatment periods. Results from random placebo controlled study revealed that Hangeshashinto is effective in treating mucositis in colorectal cancer patients under different chemotherapeutic protocols.

### Molecular targets modulated by traditional medicine

**Antioxidant:** Chemotherapy and radiotherapy is associated with release of ROS which play a pivotal role in initiating cascade that end in tissue damage. Moreover, ROS have a direct toxicity to mucosal cells. Hence, scavenging ROS could limit the progress of mucositis cascade and ameliorates tissue damage. In normal cells ROS level is managed by balance between ROS and antioxidant enzymes, glutathione peroxidase, glutathione reductase, SOD, and catalase. Scavenging ROS and activation of antioxidant enzymes is considered as the main pharmacologic targets that are modulated by many herbal drugs as they contain many antioxidant substances such as polyphenols and flavonoids. For example *Calendula officinalis* decreases the intensity of radiotherapy-induced Oral mucositis via its antioxidant properties [14]. The effects of this medicinal plant are mostly related to its chemical compositions such as polyphenols, carotenoids and triterpenes. The main flavonoid in *C. officinalis* is quercetin this compound has potent antioxidant activities. *Hippophae rhamnoides* is another medicinal plant that exerts a prophalactic effect against methotrexate induced oral mucositis [30]. The *H. rhamnoides* leaf extract has potent antioxidant activity due to the bioactive phenolic constituents, such as quercetin-3-O-galactoside, quercetin-3-O-glucoside, kaempferol and isorhamnetin. Similarly, the main constituent in olive leaf extract is the antioxidant polyphenol particularly oleuropein and hydroxytyrosol [31-35]. Topical olive leaf extract improve healing effect of 5-fluorouracil induced oral mucositis through antioxidant activity measured as MDA mucosa content [8]. *Zizyphus jujuba* is an herb that is widely distributed in Europe and Southeastern Asia [36-40]. The main active constituents in this herb are cyclopeptide alkaloids, flavonoids, sterols, jujuboside A, jujuboside B, lauric acid, and triterpenoid and saponins [41]. Topical and systemic forms of *Zizyphus jujuba* hydroalcoholic extract are associated with reduced intensity of Oral mucositis of golden hamster undergoing 5-FU consumption mainly due to antioxidant effect as measured as low level of MDA and increased activity of SOD on mucosa of [42].

**Anti-inflammatory:** As discussed in the pathophysiology section above, induction of proinflammatory cytokines such as (TNF- $\alpha$ ), Interleukin 1 $\beta$  (IL-1 $\beta$ ), and Interleukin 6 (IL-6) play an important role in amplification of tissue injury through activation NF- $\kappa$ B and

**Table 1** Evidence of different herbal remedies efficacy in preventing or retarding oral mucositis induced by chemotherapy.

Plant name	Oral mucositis Model	Results	Proposed Mechanism	Ref
Korean red ginseng	Radiation-induced oral mucositis in rat	Decrease severity of oral mucositis in rats	Inhibition of keratinocyte apoptosis.	[29]
<i>Hippophae rhamnoides</i> extract	Oral mucositis induced in rats with methotrexate.	Decrease incidence and severity of oral mucositis in rats	Antioxidant and anti-inflammatory	[30]
Topical olive leaf Extract	Oral mucositis induced by 5-fluorouracil in golden hamster	Improve healing of oral mucositis in golden hamster	Antioxidant	[8]
<i>Zizyphus jujuba</i> extract	Oral mucositis induced by 5-fluorouracil in golden hamster	Improve healing of oral mucositis in golden hamster	Antioxidant and anti-inflammatory	[31]
Hydroalcoholic extract of <i>Carum carvi</i> L	Oral mucositis induced by 5-fluorouracil in golden hamster	Improve healing of oral mucositis in golden hamster	Antibacterial	[32]
<i>Salvadora persica</i> extract	Oral mucositis induced by 5-fluorouracil in rats	Decrease incidence and severity of oral mucositis in rats	maintaining oral hygiene and induction of KGF	[12]
<i>Clandula officinalis</i>	Oral mucositis induced by 5-fluorouracil in hamster	Improve healing of oral mucositis in golden hamster	Antioxidant	[11-14]
Royal jelly (3%, 10% and 30%) ointments	Oral mucositis induced by 5-fluorouracil in hamster	Improve healing of oral mucositis in golden hamster	Antioxidant Anti-inflammatory	[10-33]
Honey	Clinical studies on radiochemotherapy induced mucositis in head and neck cancer patients.	Significant reduction in grade 4 mucositis	Anti-inflammatory	[34,35]

**Table 2** Composition of Hangeshashinto [36].

Name of herb	Dry weight (g) per day
<i>Pinelliae ternatae</i> Rhizoma	5
<i>Scutellariae baicalensis</i> Radix	2.5
<i>Glycyrrhizae uralensis</i> Radix	2.5
<i>Zizyphi jujubae</i> Fructus	2.5
<i>Ginseng</i> Radix	2.5
<i>Coptidis rhizoma</i>	1
<i>Zingiberis officinalis Recens</i> Rhizoma	2.5

matrix metalloproteinase [43-45]. Targeting these proinflammatory cytokines may be an important part of the pharmacological activity of some medicinal herbs such as *chamomile* and *Hippophae rhamnoides*. *Chamomile*, *royal jelly* and *Hippophae rhamnoides* reduced the tissue levels of IL-1 $\beta$  and TNF- $\alpha$ . Other herbal drugs block inflammatory cascade and decrease the formation of prostaglandin. Honey has an antiinflammatory effect, it inhibits prostaglandin level in both plasma and mucosa tissue. The Japanese compound hangeshashinto enable patients to complete chemoradiation therapeutic course partially due to its antinflammatory activity [46]. Kono et al. explained that hangeshashinto reduce PGE2 production in human oral keratinocyte. They suggested that this anti-inflammatory action is due to presence of active ingredient that inhibit inflammation such as [6]-shogaol, [6]-gingerol, wogonin, baicalin, baicalin, and berberine [47].

**Oral hygiene:** Maintaining Oral hygiene is very important in

patients receiving chemotherapy [48]. Those patients are of high risk of secondary infection which may be life threatening due to chemotherapy induced neutropenia [49]. *Salvadora persica* L provide a protection against variety of microorganism [50-53]. The reported antiseptic effect of *S. persica* is attributed to its phytoconstituents such as vitamin C, salvadorine, salvadorea, alkaloids, trimethylamine, cyanogenic glycosides, tannins, saponins and salts mostly as chlorides [54-57]. Moreover, it has been reported that *S. persica* aqueous extract contains potential antimicrobial anionic compound such as CL, SO<sub>4</sub> and SCN [27]. The use of *S. persica* was associated decrease in incidence and severity of oral mucositis induced by 5- fluorouracil in rats. This may impart due to maintaining oral hygiene and induction of growth factor expression such as KGF [12]. Similarly *Carum carvi* L. (*caraway*) in topical form appear to be associated with reduced intensity of OM. This may be due to impart appropriate antibacterial activity of its terpinene contents [32].

**Inhibition of keratinocyte apoptosis:** Radiotherapy induced apoptosis is one of the important molecular event in oral mucositis. Radiation induces activation of caspase 3. The activated caspase 3 cleave the RNA-binding protein HuR and subsequently promotes the expression of the proapoptotic factor Bax [58]. Inflammatory molecules that released during progress of mucositis often share in apoptosis induction [59]. Korean red ginseng KRG inhibit caspase induced opotosis in oral mucosa of irradiated rats [29], *Artemisia asiatica* is a herbal drug that have

antiapoptotic effect. *Artemisia asiatica* reduced the expression of cytochrome c and cleaved caspase-3 and nuclear factor-kappa B (NF- $\kappa$ B) induced by cisplatin. Moreover it induces the expression of antiapoptotic gene Bcl-2 [29].

**Analgesic effect:** Some medical herbs have analgesic effect. This effect is potentially important in oral ulcerative mucositis which is very painful. Processed Ginger extract contains two analgesic compounds namely [6]-gingerol and [6]-shogaol. These constituents inhibit voltage-activated Na<sup>+</sup> currents. Moreover, they inhibit the stimulant-induced release of substance P and action potential generation in cultured rat sensory neurons [60].

**Induction of growth factor:** Healing process is initiated by signaling pathways that target proliferation and differentiation of epithelial cells. Various types of growth factor are incorporated in different interaction to stimulate epithelial cell growth [61]. The most promising growth factor that regulates growth and proliferation of epithelial cell is the fibroblast growth factors (FGFs). Keratinocyte growth factor (KGF) is the most potent growth factors that induce epithelial growth and proliferation. Palifermin the generic name

of KGF is the first compound approved by the FDA to reduce oral mucositis in patients receiving HSCT [62]. Limited studies investigated the role of herbal remedies in induction of growth factor. *S. persica* enhances expression of KGF in mucosal tissues of 5- fluorouracil treated rats [12]. On the other hand, Watanabe et al. [33] reported that royal jelly couldn't increase the release of KGF from HPdLFs cells.

## Conclusion

Herbal remedies are effective as alternative therapy for oral mucositis. Data collected from both animal and clinical studies suggest herbal remedies as adjuvant therapy for oral mucositis induced by chemo or radiotherapy. Herbal drugs modulate different therapeutic pathways such as scavenging ROS, inhibiting inflammatory processes, inhibiting keratinocyte apoptosis and maintaining oral hygiene in addition to analgesic effect of some product. I think that extensive studies are needed to clarify the main constituent that target different therapeutic option for oral mucositis.

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