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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 drugs have 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 plants such as *Chamomile, royal jelly, Calendula officinalis* and *salvadora perisca* in oral mucositis induced by either chemotherapy or radiotherapy. Some herbal drugs are proved to have potential efficacy in decreasing both incidence and severity of oral mucositis in clinical studies. The molecular targets modulated by herbal drugs are various including scavenging reactive oxygen species (ROS), Inhibition of 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 pharmacologic activity.

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 induced 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, submandibular and pharyngeal area such as those who have squamous cell carcinoma in the head and neck region commonly have oral mucositis [3].

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Combination of radiotherapy and chemotherapy is associated with a risk of around 100% [2]. Oral mucositisis a painful condition that significantly affects patients' quality of life [4]. The severe case is associated with ulcerated mucosa and secondary infection which may lead 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 forms. 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 drugs that have been used for oral mucositis management focusing on different therapeutic pathways that are targeted by these medicinal plants.

Pathophysiology of Oral Mucositis: Oral mucositis induced by antineoplastic via 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-κB (NF-κB) [18]. It an important factor that up regulates expression of pro inflammatory cytokine such as tumor necrosis factor α (TNF- α), Interleukin 1β (IL-1β), and Interleukin 6 (IL-6). Those cytokines amplify tissue damage [19, 20]. Tissue damage is deteriorated with activation of matrix metalloproteinase as a result of activated pro inflammatory molecules [21, 22]. All these process led to formation of ulcers in the mucosa. The healing phase of oral mucositis initiated by signaling pathways starting in endothelial cell with specific growth factor that control renewal of epithelial cell proliferation and differentiation. Keratinocyte growth factor (KGF) is one of the key molecules that regulates communication between endothelial and epithelial cells. It is associated with triggering epithelial cells 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 and his collegues [9] reported that topical preparation of Chamomile decrease the incidence and severity of oral mucositis induced by 5-flurouracil in hamster. It has been reported that Chamomile ointment decreases severity of oral mucositis by decreasing pro inflammatory cytokine [25]. These results were further evaluated in clinical studies. One of these studied use Cammomile extract as infusion. Cammomile infusion decreased incidence and severity of mucositis when used as adjuvant therapy with cryotherapy in patient under 5-fluorouracil and leucovorin protocols. Moreover the toxic profile of Cammomile infusion showed a wide margin of safety [13]. Results of another randomized, controlled, Phase II Clinical Trial pointed out that Cammomile mouthwash (containing 1% *C. recutita* extract) can be associated with reduction in incidence, intensity, and duration of mucositis in patients undergoing allogenic Hematopoietic Stem Cell Transplantation HSCT [26].

Calendula officinalis: *Calendula officinalis* is a member of asteraceae family. Extract of *C. officinalis* flowers contains 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 [11]. Clinically, *C. officinalis* 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* L. (*S. persica*) [27]. *S. 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-fuorouracil in rats. The mechanism underlying this effect may be multi-factorial 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 accelerate 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 immunomodulatry effect 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 [37]. Similarly, Using Hangeshashinto (TJ-14) enables patients under chemo-radiotherapy to complete their treatment course and preserve their nutritional status during treatment periods [38]. Results from random placebo controlled study revealed that Hangeshashinto is effective in treating mucositis in colorectal cancer patients under different chemotherapeutic protocols [39].

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
Korean red ginseng	Radiation-induced oral mucositis in rat	Decrease severity of oral mucositis in rats	Inhibition of keratinocyte apoptosis [29]
Hippophae rhamnoides 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]
Zizyphus jujuba 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 *Carum carvi* L.	Oral mucositis induced by 5-fluorouracil in golden hamster	Improve healing of oral mucositis in golden hamster	Antibacterial [32]
Salvadora persica extract	Oral mucositis induced by 5-fluorouracil in rats	Decrease incidence and severity of oral mucositis in rats	Oral hygiene Induction of KGF [12]
Clandula officinals	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
Pinelliae ternatae Rhizoma	5
Scutellariae baicalensis Radix	2.5
Glycyrrhizae uralensis Radix	2.5
Zizyphi jujubae Fructus	2.5
Gin seng Radix	2.5
Coptidis Rhizoma	1
Zingiberis officinalis Recens Rhizoma	2.5

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 [40 - 42]. 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 enzyme *e.g.*, glutathione peroxidase, glutathione reductase, SOD and catalase. Scavenging ROS and activation of antioxidant enzyme is considered as the main pharmacologic targets modulated by many herbal drugs this may attributed to many antioxidant substances such as polyphenol and flavonoid. For example *Calendula officinalis* decreases the intensity of radiotherapy - induced oral mucositis[14]. The effects of this medicinal plant are mostly related to its antioxidant compositions such as polyphenols, carotenoids andtriterpenes. The main flavonoid in *C. officinals* is quercetin this compound has potent antioxidant activities [14, 43].

In the same manner, *Hippophae rhamnoides* exerts a prophylactic 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 [44].

Similarly, the antioxidant polyphenol particularly oleuropeine and hydroxytyrosol found in topical olive leaf extract is responsible for its healing activity of oral mucositis induced by 5-fluorouracil [8, 11].

Zizyphus jujuba is an herb that is widely distributed in Europe and South-eastern Asia. The main active constituents in this herb are cyclopeptide alkaloids, flavonoids, sterols, jujuboside A, jujuboside B, lauric acid, and triterpenoid and saponins [45]. Topical and systemic forms of *Zizyphus jujuba* hydro-alcoholic extract are associated with reduced intensity of oral mucositis of golden hamster undergoing 5-FU consumption mainly due to anti-oxidant effect as measured as low level of MDA and increased activity of SOD on mucosa [31].

Anti-inflammatory: As discussed in the pathophysiology section above, induction of pro inflammatory cytokines such as (TNF- α), Interleukin 1β (IL-1β), and Interleukin 6 (IL-6) play an important role in amplification of tissue injury through activation NF-κB and matrix metalloproteinase [19, 20]. Targeting these pro inflammatory 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* reduce the tissue levels of IL-1β and TNF-α [25, 30, 33]. Other herbal drugs block inflammatory cascade and decrease the formation of prostaglandin. Honey has an anti-inflammatory effect, it inhibits prostaglandin level in both plasma and mucosa tissue [35]. The Japanese herbal combination hangeshashinto enable patients to complete chemo-radiation therapeutic course partially due to its anti-inflammatory activity [46]. Kono and his colleagues 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, baicalein, 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 as those patients are already neutropenic due chemotherapy [49]. *Salvadora persica* Linn. provide a protection against variety of microorganism [50-53]. The reported antiseptic effect of *S. persica* is attributed to its phyto-constituents such as Vitamin C, salvadorine, salvadourea, 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_4 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, topical form of *Carum carvi* L. (caraway) is associated with reduced intensity of oral mucositis due to impart appropriate antibacterial activity of its terpinene contents [32].

Inhibition of Keratinocyte Apoptosis: Radiotherapy induced apoptosis is one of the important molecular events 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 pro-apoptotic factor Bax [58]. Inflammatory molecules that released during progress of mucositis often share in apoptosis induction in mucositis [59]. Korean red ginseng inhibit caspase induced opotosis in oral mucosa of irradiated rats [29], *Artemisia asiatica* is an herbal drug that have anti-apoptotic effect. *Artemisia asiatica* reduced the expression of cytochrome c, cleaved caspase-3 and nuclear factor-kappa B (NF-κB) induced by cisplatin. Moreover it induces the expression of Antiapototic 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^+ 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 fibro-blast 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 and his collegues [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 multicenter randomized studies are needed to clarify efficacy and safety of different herbal products as therapeutic option for oral mucositis.

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