Cinnamomum osmophloeum and Oral Mucositis

Subjects: Biology
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Definition

Cinnamon plants (Cinnamomum spp.) are of the genus Lauraceae, native to South and Southeast Asia, and are generally used as food flavors and traditional medicinal plants. *Cinnamomum osmophloeum*, commonly known as indigenous cinnamon or pseudocinnamon, is endemic to Taiwan's natural hardwood forests.

1. Introduction

Cinnamon plants (Cinnamomum spp.) are of the genus Lauraceae, native to South and Southeast Asia, and are generally used as food flavors and traditional medicinal plants. *Cinnamomum osmophloeum*, commonly known as indigenous cinnamon or pseudocinnamon, is endemic to Taiwan's natural hardwood forests [1]. Major components of the essential oils extracted from *C. osmophloeu*m leaves explored by high-performance liquid chromatography (HPLC) are as follows: α-pinene, camphene, benzaldehyde, β-pinene, 3-pheayl pionaldehyde, cis-cinnamaldehyde, trans-cinnamaldehyde, isobornylacetate, eugenol, and cinnamil acetate [2]. The essential oils extracted from C. osmophloeum leaves comprise 101 volatile compounds, as identified by GC/MS analysis, including monoterpenoids, sesquiterpenoids, alcohols, phenols, aldehydes, ketones, esters, acids, and other miscellaneous compounds. It was demonstrated that the linalool chemotypes present in C. osmophloeum were as follows: linalool, trans-cinnamyl acetate, camphor, cinnamaldehyde, 3-phenyl-2-propenal, caryophyllene, coumarin, bornyl acetate, limonene, α-(+)-pinene, estragole, and caryophyllene oxide [3]. In several studies (both in vitro and in vivo), C. osmophloeum has been applied as an alternative natural therapy to treat certain compromised and uncompromised diseases [3][4][5][6][7].

Oral mucositis (OM) is known as the inflammation of oral mucosa, usually occurring as an adverse side-effect of chemotherapy and/or radiation therapy (radiotherapy), and is manifested as atrophy, swelling, erythema, and ulceration [8]. OM occurrence in the hospital might increase costs and deteriorate oral health quality of life [9][10][11]. Hence, oral care treatments, including nutritional care, pain control, oral cleansing, palliation of a dry mouth, bleeding handling, and medicinal interventions have been introduced to decrease the severity of OM after cancer therapy [12]. Patients receiving radiotherapy to head and neck areas are at a significant risk of developing oral mucositis. The risk is lower (less than 50% or little risk) in patients with prolonged chemotherapy, patients receiving surgery, and patients with radiotherapy to non-head and neck areas [10][13]. The underlying pathophysiology of OM is divided into five phases: (1) initiation, (2) primary damage response, (3) signaling and amplification, (4) ulceration (symptomatic phase), and (5) healing [14][15][16]. The first phase (initiation stage) happens after exposure to radiotherapy or chemotherapy. It consists of two events: DNA breakdown and the generation of reactive oxygen species (ROS). DNA strand breakdowns lead to direct injury and death of the cells, and reactive oxygen species play a role as key initiators and mediators of downstream biological events. During the second phase (primary damage response), activator transduction pathways are stimulated by the DNA breaks strand, which can lead to the activation of several transcription factors, including p53 and nuclear factor kappa-B (NF-κB). NF-κB works as a controller for the expression of a broad range of genes, and produces a series of mediators, including pro-inflammatory cytokines and both pro- and anti-apoptotic cellular changes. During phase III (signal amplification stage), pro-inflammatory cytokines deliver a positive reaction to enhance and accelerate the process of wound healing. During phase IV (ulceration phase, also called symptomatic phase), it is common for the mucosal surface to become re-infected with bacteria. Bacterial invasion stimulates macrophage accumulation to conceal additional amounts of pro-inflammatory cytokines. During phase V (healing stage), signals from the connective tissue to the bordering epithelium can activate the migration, propagation, and differentiation of cells, resulting in healed mucosa. A number of biomaterials explored for OM therapy perform their principal mechanisms linked to pathophysiology by depressing pro-inflammatory cytokines. In addition to anti-inflammation, antioxidant, antifungal, antibacterial, and immunomodulator mechanisms of action have been reported [17]. As one of the encouraging biomaterials, C. osmophloeum might be a potential alleviator of OM.

2. Medical-Biological Activities of *C. osmophloeum*

Table 1. Beneficial biological activities of *C. osmophloeum*.

Bioactivity	Chemical Identification	C. osmophloeum Parts	Constituent (s)	Study	Mechanisms	Reference
Anti-inflammatory effect	LC-MS/MS	Leaves	Kaempferitrin	In vitro	Down-regulate the extracellular LDL-R (chronic inflammation-related diabetes mellitus)	Ku et al., (2017) [18]
	GC-MS	Twigs	Trans-cinnamaldehyde, caryophyllene oxide, L-borneol, L-bornyl acetate, eugenol, β-caryophyllene, E-nerolidol, and cinnamyl	In vitro	Suppressing nitric oxide synthesis by LPS-stimulated macrophages	Tung et al. (2008) [19]
	GC-MS	Leaves	Trans-cinnamaldehyde,(-)-aromadendrene, caryophyllene oxide, T-cadinol, and α-cadinol	In vitro	Suppressing nitric oxide production by LPS-stimulated macrophages	Tung et al. (2010) [20]
	GC-MS and HPLC	Leaves	Cinnamaldehyde	In vitro	Cinnamaldehyde inhibits LPS-mediated pro-inflammatory cytokine production	Chao et al. (2008) [21]
	TLC	Leaves	NA	In vitro	Inhibition of the production of NO and cytokines (TNF-a and IL-12), from LPS/IFNc-activated macrophages	Fang, Rao & Tzeng (2005) [22]
	CC, HPLC, TLC, ESIMS, and GC-MS	Twigs	Kaempferol glycosides	In vitro	Nitric oxide production inhibitory activities	Lin & Chang(2012) [23]
	GC-MS	Leaves	Linalool and cinnamaldehyde	In vivo	Inhibition of the expression of molecules in both TLR4 and NLRP3 signaling pathways	Lee et al. (2018) [24]
	GC-MS	Leaves	21 compounds were identified	In vitro	Inhibition of IL-1â and IL-6 production	Chao et al. (2005) [25]
Antibacterial activity	GC	Leaves	Cinnamaldehyde	In vitro	Bactericidal	Chang, Chen & Chang (2001) [26]
	GC-MS	Leaves	Cinnamaldehyde, cinnamic acid, cinnamyl alcohol, and cinnamyl acetate	In vitro	Bacterial inhibition	Chang et al. (2008) [27]
	GC-MS	Leaves	Cinnamaldehyde	In vitro	NA	Cheng et al. (2006) [28]

Bioactivity	Chemical Identification	C. osmophloeum Parts	Constituent (s)	Study	Mechanisms	Reference
Antifungal activity	GC-MS	Leaves	Cinnamaldehyde	In vitro	NA	Wang, Chen & Chang (2005) [29]
Antioxidant activities	ESIMS	Twigs	Kaempferol-7-O-rhamnoside	In vitro	NA	Chua, Tung, & Chang (2008) [30]
	GC-MS and GC−FID	Leaves	Alloaromadendrene	In vitro	NA	Yu et al. (2014) [31]
	GC-MS and GC-FID	Leaves	Trans-cinnamaldehyde	In vitro	NA	Yeh et al. (2013) [32]
	GC-MS and GC-FID	Leaves	Trans cinnamaldehyde	In vivo	Expression of antioxidative-related genes was pointedly affected by essential oils from C. osmophloeum.	Hsu et al. (2012) [33]
Antidyslipidemic activity	HPLC	Leaves	Kaempferol and kaempferitrin	In vivo	Cholesterol-lowering activity	Lin et al. (2011) [34]
Anti-hyperglycemic and antioxidant activities	A modified vanillin-H_2SO_4 assay A modified acid-butanol assay The $AlCl_3$ method	Twigs	Proanthocyanidin and tannin contents	In vitro	CoTE has PTP1B inhibitory activity to improve insulin or leptin resistance	Lin et al. (2016) [35]
Hepatoprotective effects	NA	Leaves	trans-cinnamaldehyde, ()-aromadendrene, T-cadinol, or R-cadinol	In vivo	The modulation of anti-inflammatory activities (decreased the aspartate aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor-R (TNF-R), and interleukin 6 (IL-6) levels in serum)	Tung et al. (2011) [6]
Pancreas Protective Effect and Hypoglycemic activity	GC/MS	Leaves	Linalool	In vivo	1. Decreased pancreatic values of thiobarbituric acid reactive substances and activities of superoxide dismutase and glutathione reductase 2. Decreased pancreatic levels of interleukin-1β and nitric oxide	Lee et al. (2013) [3]
Prevent Cardiac Hypertrophy	HPLC	Leaves	Cinnamaldehyde	In vivo	The protective role of cinnamaldehyde related to the ERK1/2 signaling pathway.	Yang et al. (2015) [7]

Bioactivity	Chemical Identification	C. osmophloeum Parts	Constituent (s)	Study	Mechanisms	Reference
Treatment of renal interstitial fibroblasts	NA	Leaves	Cinnamaldehyde	In vitro	Inhibit high glucose-induced hypertrophy (decreased cell size; cellular hypertrophy index; and protein levels of collagen IV, fibronectin, and α-smooth muscle actin).	Chao et al. (2010) [4]
Anticancer (liver and oral cancer)	TLC, CC and HPLC	Heart wood and roots	Lignan Esters	In vitro	Tumor cell growth inhibition	Chen et al. (2010) [36]
Anti-diabetes	TLC	Twigs	Kaempferol glycosides CO-1 and CO-2	In vitro	Enhanced adiponectin secretion, and activation of the insulin signaling pathway	Lee et al. (2009) [37]
Anti-hyperuricemia effect	GC-MS	Leaves	Cinnamaldehyde	In vivo	Acts as a xanthine oxidase inhibitor and reduces the serum uric acid levels	Wang et al. (2008) [2]
Anxiolytic properties	HPLC	Leaves	Linalool	In vivo	Reduced the amount of 5-HT, DA and NE and increased the level of dopamine in striatum	Cheng et al. (2014) [38]
Wound Repair Promoter and Antioxidant	NA	Leaves	NA	In vitro and in vivo	Inhibited tyrosinase activity and reduced melanin content	Lee et al. (2015) [39]
Anti-inflammatory and anti-cancer properties	NA	Barks	NA	In vivo	The growth inhibition of NO, TNF-, and IL-12, and tumor cell proliferation	Rao et al. (2007) [40]
Hypolipidemic effects	NA	Leaves	S-(þ)-linalool	In vivo	Inhibited lipid accumulation through downregulation of 3T3-L1 adipocyte differentiation	Cheng et al. (2018) [41]
Effect on the human immune system	HS-GC/MS and HPLC	Leaves	Cinnamaldehyde	In vivo	Cytokines modulatory effect	Lin et al. (2011) [42]
Potential skin-whitening and protective agent	NA	Leaves	Cinnamaldehyde and cinnamylacetate	In vitro	Neutralized the IBMX-induced increase in melanin content in B16-F10 cells by inhibiting tyrosinase gene expression at the level of transcription	Lee et al. (2015) [39]

Bioactivity	Chemical Identification	C. osmophloeum Parts	Constituent (s)	Study	Mechanisms	Reference
Anti-inflammatory effect in intestine	GC/MS	Leaves	Linalool	In vivo	The suppression of the TLR4 pathway by CO and partly by the inhibitory effect of CO on the activity of xanthine oxidase	Lee et al. (2015) [43]
Anti-tumor	NA	Leaves	Trans-cinnamaldehyde	In vitro	Trans-cinnamaldehyde triggers suicidal death oferythrocytes, i.e., cells devoid of mitochondria and gene expression.	Theurer et al. (2013) [44]
Dietary supplements and treatment of hyperuricemia and gout	GC-MS and GC-FID	Leaves	Cinnamaldehyde	In vitro	The xanthine oxidase inhibitory activity	Huang et al. (2018) [45]
Anti-hyperglycemic and antioxidant activities	(MALDI/MS) (RP-HPLC) /MS/MS	Twigs	Proanthocyanidin	In vitro	The proanthocyanidins in CoTE mainly consisted of (epi)catechin and contained at least one A-type linkage. The inhibitory activity of α-glucosidase and α-amylase	Lin et al. (2016) [46]

NA: Not available; LC: liquid chromatography; MS: mass spectrometry; GC: gas chromatography; HPLC: high-performance liquid chromatography; TLC: thin layer chromatography; CC: column chromatography; ESIMS: electrospray ionization mass spectrometry; GC-FID: gas chromatography−flame ionization detection; MALDI: matrix-assisted laser desorption/ionization; RP: reverse phase.

3. Potential Use of *C. osmophloeum* for the Treatment of Oral Mucositis (OM)

The current protocols of medicine for chemotherapy are associated with oral mucositis. Cytarabine, high-dose 5-fluororacil, alkylating agents, and platinum-based compounds are highly associated with the incidence of oral mucositis. Actinomycin D, amsacrin, bleomycin, busulfan, capecitabine, carboplatin, chlorambucil, cisplatin, cytarabine, docetaxel, doxorubicin, etoposide, floxuridine, ifofsamide, irinotecan, leucovorin, methotrexate, mitoxantron, oxaliplatin, paclitaxel, plicamycin, tioguanin, vinblastine, vincristine, vindecine, and vinorelbine (the protocol can be combined) are the medicines used for chemotherapy and are reported to lead to the development of oral mucositis [47][48]. In order to prevent oral mucositis, the Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) help clinics by comprising Clinical Practice Guidelines for Oral Mucositis [49]. The recommendations are comprised of basic oral care, growth factors and cytokines, anti-inflammatory agents, laser and other light therapy, cryotherapy, and natural and miscellaneous agents (Table 2). Köstler et al. provided several experimental approaches to treat oral mucositis; they included locally applied non-pharmacological methods, anti-inflammatory and mucosa protectant agents, cytokines, granulocyte colony-stimulating factor (G-CSF, filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF, molgramostim), antiseptic agents, corticosteroids, mouth-coating agents, and dexpanthenol [48].

Table 2. Interventions to prevent oral mucositis (clinical practice guidelines) proposed by the Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO).

Intervention	Protocol	Population	Evidence of Effectiveness
Basic oral care	Tooth brushing, flossing, and one mouth rinse	All age groups and across all cancer treatment modalities	Not strong evidence
Growth factors and cytokines	Palifermin (keratinocyte growth factor-1)	Patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation for hematological malignancies	Strong evidence
Anti-inflammatory agents	Benzydamine mouthwash	Patients with head and neck cancer receiving moderate-dose radiation therapy (up to 50 Grays), without concomitant chemotherapy	Strong evidence
Laser and other light therapy	Low-level laser therapy (LLLT)	Patients receiving high-dose chemotherapy for HSCT with or without total body irradiation	Strong evidence
Cryotherapy	The placement of ice chips in the mouth	Patients receiving bolus dosing of 5-fluorouracil	Strong evidence
Natural and miscellaneous agents	Systemic zinc supplements administered orally (antioxidant effect)	Patients with oral cancer undergoing radiotherapy or chemoradiation	Not strong evidence

The study of *C. osmophloeum* and/or its constituents in OM are limited. In one study, the effect of cinnamaldehyde on oral mucositis and an evaluation of the salivary total antioxidant capacity of gamma-irradiated rats were carried out. The saliva samples were taken from the rats in triplicate [50]. In order to evaluate the consequences and severity of mucositis, the conditions of the oral cavity were assessed by using Parkin's clinical scale, where 0 represents normal mucosa, 0.5 indicates normally pink mucosa, 1 stands for minor red mucosa, 2 is severe red mucosa, 3 is local desquamation, 4 describes exudation and crust around less than half of the lip area, and 5 characterizes exudation and crust for more than half of the lip area [51]. The authors concluded that the clinical effects in the intervention group seemed to be due to the antioxidant, antibacterial, and anti-inflammatory effects of cinnamaldehyde. It is noteworthy to mention that through anti-inflammation and antioxidant mechanisms, cinnamaldehyde would delay the onset of oral mucositis. Moreover, alteration in the oral microflora of existing bacteria in the fourth phase (ulceration phase) could exacerbate the severity of mucositis, whereas cinnamaldehyde alleviated oral mucositis via its antibacterial properties [50]. A recent investigation reported the effect of cinnamon bark fractions (an essential oil and an aqueous extract) on Candida albicans growth inhibition (growth, biofilm formation, and adherence properties) and oral epithelial cells (barrier integrity and inflammatory response) [52]. The anti-adherence and anti-inflammatory properties of proanthocyanidins, a family of polyphenols containing flavan-3-ol oligomers and polymers, are used to treat oral infections [52][53]. The two pro-inflammatory cytokines, IL-6 and IL-8, which serve as important cytokines in the development of oral mucositis, were reduced by an aqueous extract enriched with proanthocyanidins of the cinnamon fraction. This shows that the cinnamon presented in the study may be a promising agent in the alleviation of oral mucositis [52].

Other biomaterials or herbal products, such as Aloe vera, Acacia catechu, Chamomile, Hangeshashinto, indigowood root (Isatis indigotica Fort.), honey, Traumeel S, water grass decoction, and Weleda Ratanhia, also showed similar effects on the alleviation of OM via anti-inflammation activities [17][54][55][56][57][58][59][60][61][62][63]. The bioactive properties of the yarrow plant (Achillea mileofolium), honey, Callendula officinalis flowers, Hipophae rhamnoides L. plant, Chamomile, and Aloe vera were associated with antioxidant, anti-inflammatory, antibacterial, and wound healing effects of oral mucositis therapy (Table 3) [55][56][57][63][64][65][66][67][68]. Similar to the advantages of the medical-biological activities of these herbal agents, *C. osmophloeum* would provide an identical mechanism for relieving oral mucositis.

Table 3. Bioactive properties of natural agents for oral mucositis therapy.

Natural Agents	Bioactivity	References
Yarrow Plant (Achillea millefolium)	Anti-bacterial and anti-inflammatory effect	Mirazandeh et al. (2014) [64]

Natural Agents	Bioactivity	References
Manuka Honey (Leptospermum scoparium)	Wound healing and anti-microbial	Hawley et al. (2013) [63]
Weleda Pflanzen-Zahngel and Weleda Ratanhia-Mundwasser	Anti-inflammatory, anti-bacterial, and lesion healing	Tiemann et al. (2007) [61]
Calendula officinalis flowers	Anti-inflammatory, anti-bacterial, and anti-oxidant	Babaee et al. (2013) [65]
Honey and coffee	Antioxidant, anti-microbial, and anti-inflammatory	Raeessi et al. (2014) [54]
Aloe vera	Anti-inflammatory, bactericidal, and wound healing	Sahebjamee et al. (2015) [62]
Hangeshashinto: Pinelliae tuber, Scutellariae Radix, Glycyrrhizae Radix, Zizyphi Fructus, Ginseng Radix, Zingiberis Processum rhizoma, and Coptidis rhizome	Anti-inflammatory	Aoyama et al. (2014) [58]
Indigowood Root (Isatis indigotica Fort.)	Anti-inflammatory	You et al. (2009) [60]
Topical Honey	Anti-inflammatory, anti-microbial, and wound healing	Khanal et al. (2010) [66]
Hippophae rhamnoides L. plant	Anti-oxidant, anti-ulcerogenic, anti-inflammatory, anti-microbial, and proinflammatory cytokine Antagonist	Kuduban et al. (2016) [67]
Honey from the clover plant Trifolium alexandrenum	Anti-microbial	Rashad et al. (2009) [69]
Qingre Liyan decoction	Anti-oxidant and anti-inflammatory	Lambros et al. (2014) [70]
Hangeshashinto	Anti-inflammatory and anti-microbial	Kono et al. (2014) [56]
Chamomile	Anti-inflammatory, anti-bacterial, and antifungal	Fidler et al. (1996) [55]
Rhodila algida	Anti-oxidant and immunostimulant	Loo et al. (2010) [71]
Qingre Liyan Decoction	Enhancing body immunity and promoting salivary EGF	Wu et al. (2007) [72]
Chamomile	Anti-inflammatory, anti-bacterial, and anti-fungal	Pourdeghatkar et al. (2017) [57]
Pure Honey	Anti-bacterial and anti-inflammatory	Motallebnejad et al. (2008) [68]
Aloe vera	Anti-inflammatory, anti-bacterial, and anti-fungal	Puataweepong et al. (2009) [73]
Aloe vera and vitamin E	Antioxidant, anti-inflammatory, and healing properties	Cuba et al. (2015) [74]
Traumeel S	Anti-inflammatory	Sencer et al. (2012) [75]
Chamomilla recutita	Anti-inflammatory	Braga et al. (2015) [76]
Wild chamomile (Matricaria recutita L.)	Anti-inflammatory, anti-bacterial, and anti-fungal	Mazokopakis et al. (2003) [56]

According to antibacterial mechanisms, several studies demonstrated bacterial changes due to radiotherapy and/or chemotherapy [76]. The bacteria were Gemella haemolysans, Streptococcus mitis [77], Escherichia coli, Pseudomonas aeruginosa, Enterobacter sp., Klebsiella pneumonia [78], Staphylococcus aureus, Staphylococcus epidermidis, Parvimonasmicra, Fusobacterium nucleatum, Treponema denticola, C. glabrata, C. kefyr [79], and Porphyromonas gingivalis [80]. Among these bacteria, C. osmophloeum has been confirmed to possess the antibacterial properties of Pseudomonas aeruginosa, Staphylococcus aureus, and Staphylococcus epidermidis (Figure 1) [26].

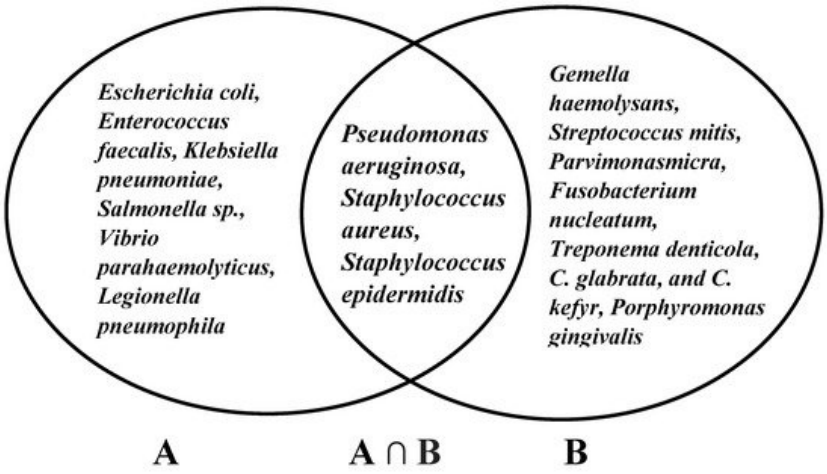

Figure 1. Antibacterial properties of *C. osmophloeum* (**A**) and bacterial infection of oral mucositis (**B**).

Flavanoid-rich fractions containing kaempferitin in Bauhinia forficata leaves have been investigated and shown to be effective ingredients for preventing the intestinal toxic effects of irinotecan chemotherapy. It was stated that kaempferitin, as one of the major active contents of *C. osmophloeum*, has been tested to prevent or reduce the severity of intestinal mucositis [18][81]. The chemotherapy drug 5-Fluororacil possesses side effects (i.e., induces mucositis manifestations in oral and gastrointestinal after chemotherapy). *Chimonatus Nitens* var. salicifolius aqueous extract contains three flavonoid contents: quercetin, kaempferol, and rutin, which might have an anti-inflammatory effect on gastrointestinal mucositis [82]. Kaempferol, cinamic acid, and nine other constituents obtained in mucoadhesive propolis agent have been proven to be effective in reducing radiation-induced oral mucositis. A clinical study of 24 patients revealed that mucositis only developed in two patients and each developed grade 1 mucositis and grade 2 mucositis, respectively; however, in the remaining 20 patients, mucositis did not develop [83].

Previous studies investigated the potential of *C. osmophloeum* to reduce oral mucositis. Nonetheless, *C. osmopohloeum*, which is a species of cinnamon, faces challenges in its use as an oral treatment. In addition, this review has several limitations. First, there are limited data on the medical-biological effects of *C. osmophloeum* and its potential use in oral mucositis therapy. Secondly, the reported events related to oral stomatitis allergy induced by cinnamon should be a concern [84][85][86]. In summary, *C. osmophloeum* and its constituent are anticipated to be effective and efficient in reducing the severity of OM by preventing secondary bacterial infection through their bactericidal activity, preventing the development of the second phase of OM (the primary damage response) or interrupting the third phase in which pro-inflammatory cytokines could enhance and accelerate the process of wound healing (Figure 2).

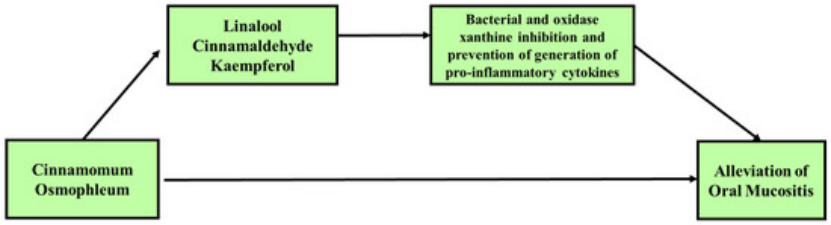

Figure 2. Proposed potential use of *C. osmophloeum* in the alleviation of oral mucositis (OM)**.** *C. osmophloeum* ameliorated oxidative stress and pro-inflammation through its constituents. Several studies have investigated the anti-inflammation, antibacterial, and antioxidant activities. The review of medical-biological activities showed that *C. osmophloeum* and its constituents inhibit the pro-inflammatory response. *C.*

osmophloeum potentially prevents the second phase of oral mucositis (the primary damage response) or may intercept in the third phase, with pro-inflammatory cytokines providing a positive reaction to enhance and accelerate the process of wound healing. *C. osmophloeum* was also confirmed to be bactericidal and inhibit bacteria which can reduce the severity of oral mucositis or secondary bacterial infection.

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Keywords

C. osmophloeum;biological activities;oral mucositis;cinnamaldehyde;linalool