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Review Article

Herbal products for the prevention and management of 5-fluorouracil-induced oral mucositis: A systematic review of preclinical evidence

Pocut Astari[1*], Dewi F. Suniarti[2] and Erik Idrus[2]

[1]Doctoral Program in Dentistry, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia; [2]Department of Oral Biology, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia

*Corresponding author: pocut.astari@ui.ac.id

Abstract

Oral mucositis is a painful and dose-limiting complication of chemotherapy, particularly in patients receiving 5-fluorouracil (5-FU). Herbal products have attracted increasing interest as supportive care candidates because of their antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective properties. This systematic review aimed to synthesize preclinical evidence on the effects and mechanisms of herbal products in 5-FU-induced oral mucositis models. A literature search was conducted in PubMed, Scopus, EBSCO, ScienceDirect, and ProQuest for studies published up to March 2026, following PRISMA guidelines. Eligible studies were in vitro studies, or studies with a clearly described in vitro component, that evaluated herbal extracts, multi-herbal formulations, or naturally derived plant-based compounds in 5-FU-induced oral mucositis models. Study reliability was assessed using the ToxRTool. Seven studies were included, comprising three in vitro-only studies and four combined in vitro–in vivo experimental studies published between 2014 and 2025. The evaluated products included Daiokanzoto, *Salvia miltiorrhiza*, Onchung-eum, anthocyanins from *Oryza sativa*, FITOPROT, cannabidiol, and Camellia tea saponin. Across the included studies, herbal products were reported to improve cell viability, reduce reactive oxygen species production, suppress inflammatory mediators, inhibit apoptosis, and promote epithelial repair. The main mechanisms involved the modulation of nuclear factor kappa-light-chain-enhancer of activated B cells signaling, caspase-3 activation, the Nrf2/Keap1/ARE pathway, mitochondrial dysfunction, and ferroptosis-related markers. All included studies were classified as reliable without restrictions, with ToxRTool scores ranging from 16 to 18. In conclusion, preclinical evidence suggests that herbal products may have protective effects against 5-FU-induced oral mucositis through antioxidant, anti-inflammatory, and cytoprotective mechanisms. However, standardized in vivo studies and clinical trials are needed before their therapeutic use can be recommended.

Key words: Oral mucositis, 5-fluorouracil, phytotherapy, reactive oxygen species, anti-inflammatory agents

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Introduction

Oral mucositis (OM) is a debilitating side effect commonly observed in patients undergoing chemotherapy, particularly those treated with 5-fluorouracil (5-FU), a widely used antimetabolite in oncology [1]. Clinically, OM presents as erythema, ulceration, pain, and functional impairment of the oral mucosa, significantly diminishing patients' quality of life and often necessitating modifications to cancer treatment regimens, such as dose reductions or therapy interruptions [2-

Received: April 30, 2025 - Accepted: June 9, 2026 - Published online: June 10, 2026

4]. The pathogenesis of 5-FU-induced OM is multifactorial and includes oxidative stress, inflammation, and epithelial apoptosis initiated by the overproduction of reactive oxygen species (ROS) and the subsequent activation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [5-8].

Current therapeutic options for OM remain largely palliative and insufficient. Although agents such as palifermin have received regulatory approval, their clinical applicability is constrained by cost and limited efficacy [6,9]. This has intensified interest in identifying alternative preventive and therapeutic approaches, especially those derived from natural products with antioxidant, anti-inflammatory, and epithelial protective properties.

Historically, herbal medicines have played a vital role in traditional health systems and are increasingly recognized for their pharmacological potential in modern supportive oncology care [10-13]. Various herbal plants such as *Curcuma longa*, *Bidens pilosa*, *Salvia miltiorrhiza*, *Camellia sinensis*, and *Oryza sativa* have been evaluated in preclinical models for their ability to mitigate 5-FU-induced mucosal injury through diverse mechanisms, including inhibition of inflammatory signaling pathways, modulation of oxidative stress responses, and promotion of epithelial regeneration [14-16]. However, despite growing interest in herbal and natural products for chemotherapy-induced OM, the available evidence remains fragmented. Previous reviews have generally discussed OM management in broader clinical or therapeutic contexts, with limited focus on in vitro evidence specific to 5-FU-induced mucosal injury. In addition, the molecular pathways targeted by herbal interventions have not been systematically synthesized across cell-based OM models. Therefore, a focused synthesis is needed to clarify which herbal agents have been investigated, which biological mechanisms have been reported, and which candidates may warrant further in vivo and clinical evaluation.

The aim of this systematic review was to synthesize current in vitro evidence on the protective effects and underlying mechanisms of herbal plants and plant-derived compounds in the prevention and management of 5-FU-induced OM. These findings may help identify promising phytochemical candidates for future translational and clinical research.

Methods

Literature search strategy

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review aimed to investigate the use of herbal or natural products for the prevention or treatment of 5-FU-induced oral mucositis in in vitro oral mucositis models. A comprehensive literature search was conducted across five major electronic databases, namely PubMed, Scopus, EBSCO, ScienceDirect, and ProQuest, to identify relevant studies published up to March 2026. The search strategy included both free-text terms and Medical Subject Headings (MeSH), where applicable.

Boolean operators “AND” and “OR” were used to combine and refine the search terms. The following English keywords were used in various combinations: “oral mucositis,” “5-fluorouracil,” “5-FU,” “herbal,” “plant extract,” “natural product,” “antioxidant,” “in vitro,” “reactive oxygen species,” “ROS,” and “cytokine.” In addition, the reference lists of eligible articles were manually screened to identify additional relevant studies.

Eligibility criteria

Studies were included if they met the following criteria: (1) the study used an in vitro cell culture model relevant to oral mucositis, such as oral keratinocytes or mucosal cell lines exposed to 5-fluorouracil (5-FU) to simulate mucositis-like injury; (2) the intervention involved herbal extracts, multi-herbal formulations, or naturally derived plant-based compounds; (3) the outcomes included mucositis-related biological endpoints, such as cell viability, cell proliferation, oxidative stress, inflammatory cytokine expression, and cell death or apoptosis; and (4) the article was published in English in a peer-reviewed scientific journal between 2010 and 2026.

Studies were excluded if they met any of the following criteria: (1) non-English publications; (2) studies focusing on synthetic drugs, recombinant growth factors, or non-natural compounds; (3) in vivo or clinical studies without a clearly described in vitro component; and (4) studies

lacking a relevant mucositis injury model, such as experiments performed only on healthy or untreated cells without chemically induced mucosal damage. For studies that included both in vitro and in vivo components, only the in vitro findings were analyzed.

Screening, study selection, and data extraction

The eligibility assessment was conducted using a two-step screening process. First, titles and abstracts were reviewed to identify potentially relevant studies. Study selection was performed using Rayyan, a web-based platform for systematic review screening. Titles and abstracts were independently screened by the reviewers, and conflicts were resolved through discussion. Studies that appeared to meet the inclusion criteria were then assessed through full-text review. Three reviewers independently conducted the screening process, and any discrepancies were resolved by discussion and consensus. Data extraction was initially performed by one reviewer and focused on key study characteristics, including the cell line or model used, the type of 5-FU-induced injury, details of the herbal or natural intervention, such as source, concentration, and treatment protocol, and the primary outcomes measured.

The extracted data were subsequently reviewed and validated by all three reviewers to ensure accuracy and consistency. Any disagreements were resolved through discussion. Because of the diversity of interventions, experimental models, and outcome measurements across the included studies, a qualitative narrative synthesis was conducted.

Risk of bias assessment

The quality of the included in vitro studies was assessed using the ToxRTool, a toxicological data reliability assessment tool. This tool evaluates the internal validity and reliability of experimental studies using an 18-point scoring system across five domains: (1) test substance identification, (2) test system characterization, (3) study design description, (4) study result documentation, and (5) plausibility of the study design and data.

Each study received a total score ranging from 0 to 18. Based on the established ToxRTool criteria, scores of 15–18 were classified as high reliability (Category 1), 11–14 as moderate reliability (Category 2), and ≤10 as low reliability (Category 3). The risk of bias and reliability across domains were qualitatively summarized for each study. Any discrepancies between reviewers were resolved through discussion and consensus.

Results

Literature search

The comprehensive search across five databases identified 440 records, including 21 from PubMed, 24 from EBSCO, 51 from Scopus, 161 from ScienceDirect, and 183 from ProQuest. After duplicate records were removed, 357 records remained and were screened by title and abstract. During screening, 330 records were excluded because they were not relevant based on title and abstract review. A total of 27 reports were sought for retrieval; however, two reports could not be retrieved. Therefore, 25 reports were assessed for eligibility. Of these, 18 reports were excluded because the intervention was unidentified, the intervention used nanoparticles, the intervention did not use 5-FU, or the study was conducted only in animals. Finally, seven studies met the eligibility criteria and were included in the qualitative synthesis. The literature search and study selection process are presented in **Figure 1**.

Characteristics of included studies

This systematic review included seven studies [3,4,6,14,16-18] published between 2014 and 2025. Four studies [3,4,6,18] used combined in vitro and in vivo experimental models, whereas three studies [14,16,17] used in vitro-only experimental models. Overall, seven herbal or natural products were evaluated for their protective or therapeutic effects against 5-FU-induced oral mucositis. These included Daiokanzoto, a Kampo formulation containing *Rheum palmatum* and *Glycyrrhiza uralensis*; *S. miltiorrhiza*; Onchung-eum, a multi-herbal formulation; anthocyanins from *O. sativa*; and FITOPROT, containing curcuminoids from *C. longa* and extract from *Bidens pilosa*; cannabidiol from *Cannabis sativa*; and Camellia tea saponin

from *Camellia sinensis*. The main characteristics of the included studies are summarized in **Table 1**.

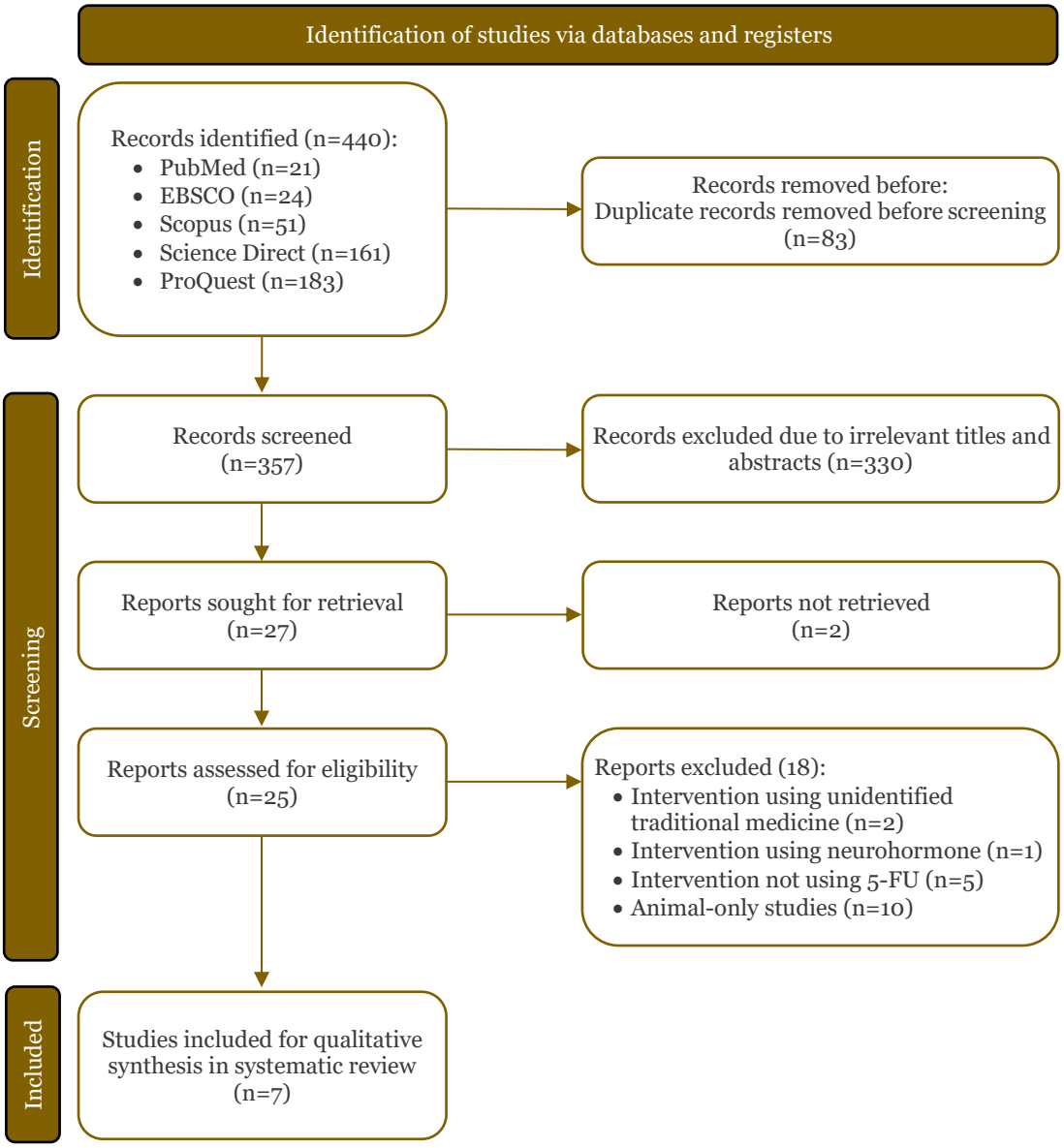

Figure 1. Literature searching and screening process.

Table 1. Characteristics of the included studies

Author (year)	Country	Study design	Objective of study
Yoshida *et al.* (2014) [17]	Japan	In vitro experimental study	To investigate the effect of Daiokanzoto (TJ-84) on 5-FU-induced human gingival cell death and reactive oxygen species production.
Kim *et al.* (2017)[3]	Japan	In vitro and in vivo experimental study	To evaluate the protective effect of *Salvia miltiorrhiza* on the 5-FU-induced oral mucositis model.
Park *et al.* (2018)[18]	South Korea	In vitro and in vivo experimental study	To evaluate the effects of Onchung-eum on 5-FU-induced oral mucositis (OM) in cell and animal models.
Tancharoen *et al.* (2018) [4]	Thailand	In vitro and in vivo experimental study	To investigate the immunomodulatory effect of anthocyanins from *Oryza sativa* extracts on 5-FU-induced oral mucositis.

Author (year)	Country	Study design	Objective of study
Dos Santos Filho *et al.* (2018) [14]	Brazil	In vitro experimental study	To evaluate the chemopreventive effects of FITOPROT against 5-FU-induced cellular toxicity in an oral mucositis model.
Li *et al.* (2022) [6]	China	In vitro and in vivo experimental study	To investigate the protective effect of cannabidiol on 5-FU-induced oral mucositis through nuclear factor erythroid 2–related factor 2 (Nrf2) / Kelch-like ECH-associated protein 1 (Keap1)/ Antioxidant Response Element (ARE) signaling pathway.
Likitsatian *et al.* (2025) [16]	Thailand	In vitro experimental study	To evaluate the protective effect of Camellia tea saponin against 5-FU-induced ferroptosis and inflammation in human keratinocytes.

Risk of bias assessment

Quality assessment using the ToxRTool showed that all included studies were classified as reliable without restrictions (**Table 2**). Total scores ranged from 16 to 18 out of 18, indicating high overall methodological reliability. Five studies [4,6,14,16,17] achieved the maximum score of 18, one study [3] scored 17, and one study [18] scored 16. The mean total score was 17.57, suggesting consistently high reliability across the included studies. Across the five assessment domains, the mean scores were 3.93 for test substance identification, 3.00 for test system characterization, 5.79 for study design description, 2.86 for study result documentation, and 2.00 for plausibility of study design and data. These findings indicate that the included studies generally provided clear descriptions of the test substances, experimental systems, study designs, results, and biological plausibility.

Preclinical evidence on herbal products for 5-fluorouracil-induced oral mucositis

The synthesized findings from seven preclinical studies that explored the protective effects of various herbal plants and their bioactive compounds against 5-FU-induced OM are presented in **Table 3**. All studies utilized either in vitro or in vivo models, with consistent evidence supporting the antioxidant, anti-inflammatory, and cytoprotective properties of herbal extracts in alleviating OM symptoms. The herbal products were administered at varying concentrations and treatment regimens, either before or during 5-FU exposure. Overall, protective effects against 5-FU-induced cellular injury were reported, including improved cell viability, reduced oxidative stress, suppressed inflammatory mediators, inhibited apoptosis, and enhanced wound healing. The main mechanisms were characterized by reduced ROS production, inhibition of NF-κB signaling, suppression of caspase-3 activation, modulation of the Nrf2/Keap1/ARE pathway, and regulation of ferroptosis-related markers.

Cannabidiol demonstrated a significant chemopreventive effect by alleviating OM severity, reducing ROS overproduction, promoting epithelial proliferation, and suppressing apoptosis [6]. The mechanistic pathway involved activation of the Nrf2/Keap1/ARE axis, with an inhibition experiment confirming its central role [6]. *S. miltiorrhiza* extract also showed protective effects by enhancing cell proliferation, scavenging free radicals, and downregulating NF-κB and caspase-3 expression. These molecular changes led to decreased inflammatory responses and reduced cell death in both cell and animal models [3]. Similarly, Onchung-eum, a multi-herb Korean traditional medicine, reduced epithelial damage, inhibited cell death, and decreased expression of pro-inflammatory cytokines, NF-κB, and caspase-3 [18]. These effects suggest its potential utility in preventing OM through anti-inflammatory and regenerative mechanisms [18].

Anthocyanins from *O. sativa* might be effective in mitigating OM symptoms by suppressing NF-κB activation, reducing inflammatory cytokines, and restoring epithelial tissue structure. Both in vitro and in vivo findings highlighted its role in modulating key inflammatory signaling pathways [4].

Table 2. Quality assessment of the selected articles according to the ToxRTool in vitro criteria

Author (year)	Test substance identification (4)	Test system characterization (3)	Study design description (6)	Study result documentation (3)	Plausibility of study design and data (2)	Total score	Reliability categorization
Yoshida *et al.* [17]	4	3	6	3	2	18	Reliable without restrictions
Kim *et al.* [3]	4	3	5.5	2.5	2	17	Reliable without restrictions
Dos Santos Filho *et al.* [14]	4	3	6	3	2	18	Reliable without restrictions
Park *et al.* [18]	3.5	3	5	2.5	2	16	Reliable without restrictions
Tancharoen *et al.* [4]	4	3	6	3	2	18	Reliable without restrictions
Li *et al.* [6]	4	3	6	3	2	18	Reliable without restrictions
Likitsatian *et al.* [16]	4	3	6	3	2	18	Reliable without restrictions
Mean score	3.93	3.00	5.79	2.86	2.00	17.57	-
Score range	3.5–4	3–3	5–6	2.5–3	2–2	16–18	-

Summary rows were added to complement the individual study assessments and provide an overview of the distribution of scores across the evaluated reliability domains. Overall, the included studies showed high reliability, with a mean total score of 17.57 out of 18, and all studies were categorized as reliable without restrictions.

Table 3. Experimental characteristics and key findings of herbal products in 5-fluorouracil-induced oral mucositis models

Author (year)	Groups of interventions	Cell line	Dose of 5-FU	Herbal extract	Concentration	Treatment regimen	Main findings	Key mechanism
Yoshida *et al.* (2014) [17]	1. Control (untreated) 2. 5-FU only 3. 5-FU + TJ-84 (250–1000 µg/mL) 4. TJ-84 only 5. 5-FU + NLRP3 inhibitor (zVAD-FMK or siRNA)	Sa3 human gingival epithelial cell line	5 mg/mL	Daiokanzoto (TJ-84)	250–1000 µg/mL	TJ-84 pre-incubated for 1 h before 5-FU treatment; 5-FU exposure for 24 h.	TJ-84 reduced 5-FU-induced cell death and improved cellular protection.	Reduced ROS, NO, LDH release, mitochondrial depolarization, and partially inhibited NLRP3/caspase-1 inflammasome activation.
Kim *et al.* (2017)[3]	1. Normal 2. Control (5-FU) 3. Positive Control (Benzydamine HCl) 4. SM + 5-FU	Detroit 562 (human pharyngeal cells)	10 µM	*Salvia miltiorrhiza* (SM)	1, 5, 10, 50, 100 µg/mL	co-treated with 5-FU for 48 h.	SM improved cell proliferation and reduced 5-FU-induced cellular injury.	Reduced ROS, TUNEL-positive cells. NF-κB expression, and caspase-3 activation.
Park *et al.* (2018)[18]	1. Normal (vehicle) 2. Control (5-FU) 3. Positive Control (Benzydamine HCl) 4. OCE + 5-FU	Detroit 562 (human pharyngeal cells)	10 µM	Onchung-eum (OCE)	1, 5, 10, 50, 100 µg/mL	48 h co-treatment with 5-FU.	OCE increased cell viability and reduced 5-FU-induced inflammatory injury.	Suppressed ROS, NF-κB, caspase-3, TNF-α, and IL-1β expression.

Author (year)	Groups of interventions	Cell line	Dose of 5-FU	Herbal extract	Concentration	Treatment regimen	Main findings	Key mechanism
Tancharoen *et al.* (2018) [4]	1. Control 2. 5-FU only 3. 5-FU + 0.5 mg/mL 4. 5-FU + 1 mg/mL 5. ANT only	Human oral keratinocytes	10 µg/mL	Anthocyanins (ANT) from *Oryza sativa*	0.5–1 mg/mL	Cells were pretreated with 1 mg/mL ANT-rich extract and exposed to 5-FU (10 µg/mL) for 1 h and 2 days.	ANT protected oral keratinocytes from 5-FU-induced growth inhibition.	Inhibited NF-κB p50/p65 activation and modulated inflammatory responses.
Dos Santos Filho *et al.* (2018) [14]	1. Control 2. 5-FU 3. FITOPROT 4. FITOPROT + 5-FU	HaCaT (keratinocytes) and SCC-4 cancer cells	10 µg/mL	FITOPROT (Curcuminoids from *Curcuma longa* and *Bidens pilosa* extract)	0.00031–0.01% (for HaCaT); 0.00031–0.125% (for SCC-4)	HaCaT: Pretreated with FITOPROT for 24h, then FITOPROT + 5-FU for 24h; SCC-4: co-treatment with FITOPROT + 5-FU for 24h.	FITOPROT protected HaCaT cells from 5-FU-induced damage but enhanced cytotoxicity in SCC-4 cells.	Reduced oxidative stress, mitochondrial dysfunction, cytochrome c release, inflammatory cytokines, and modulated Nrf2, TNF-R1, Ki-67, and NF-κB expression.
Li *et al.* (2022) [6]	1. Vehicle 2. 5-FU 3. 5-FU + CBD	Human oral keratinocytes	10 µg/mL	Cannabidiol (CBD)	0.5, 2.5, 5 µM	12h CBD pretreatment, then 5-FU 12h.	CBD protected human oral keratinocytes from 5-FU-induced oxidative damage, inflammation, and apoptosis.	Activated the Nrf2/Keap1/ARE pathway, increased HO-1 and NQO1, and reduced TNF-α and IL-6
Likitsatian *et al.* (2025) [16]	1. Control 2. 5-FU 3. 5-FU + TS (various doses) 4. Erastin 5. Erastin + TS	HaCaT (human keratinocyte cell line)	5 µg/mL	Camellia tea saponin (TS)	3.13, 6.25, 12.5, 18, 25 µg/mL	24 h incubation with 5-FU ± TS; dose-response and time-course assays.	TS reduced 5-FU-induced cellular injury and promoted cell viability.	Reduced ROS, lipid peroxidation, labile iron pool, IL-6, and TNF-α, while restoring GSH and GPX-4 activity.

5-FU: 5-fluorouracil; ANTs: anthocyanins; ARE: antioxidant response element; CBD: cannabidiol; FITOPROT: mucoadhesive formulation with curcuminoids from *Curcuma longa* and *Bidens pilosa*; GPX4: glutathione peroxidase 4; GSH: glutathione; HaCaT: human adult low calcium high temperature keratinocytes; HO-1: heme oxygenase-1; HOK: human oral keratinocytes; IL: interleukin; Keap1: Kelch-like ECH-associated protein 1; Ki-67: marker of proliferation Ki-67; LDH: lactate dehydrogenase; ML385: Nrf2 pathway inhibitor ML385; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; NO: nitric oxide; NQO1: NAD(P)H quinone dehydrogenase 1; Nrf2: nuclear factor erythroid 2–related factor 2; OCE: Onchung-eum; ROS: reactive oxygen species; SCC-4: squamous cell carcinoma-4 oral cancer cells; siRNA: small interfering RNA; SM: *Salvia miltiorrhiza*; TNF-α: tumor necrosis factor-alpha; TNF-R1: tumor necrosis factor receptor 1; TS: tea saponin.

Camellia tea saponin exhibited protective effects against 5-FU-induced keratinocyte damage by regulating ferroptosis and oxidative stress [16]. The compound restored glutathione peroxidase 4 activity, reduced ROS and lipid peroxidation, and suppressed pro-inflammatory cytokine release, positioning it as a potential adjunct in OM management [16]. The mucoadhesive formulation FITOPROT, containing curcuminoids from *C. longa* and extracts of *B. pilosa*, showed marked reduction in ROS levels, restored mitochondrial function, and normalized inflammatory signaling (Nrf2, TNF-R1, and NF-κB). It also enhanced cell proliferation and demonstrated selective cytotoxicity against carcinoma cells [14]. Daiokanzoto, a Kampo formulation, significantly reduced 5-FU-induced gingival cell death by inhibiting mitochondrial ROS production and nitric oxide levels [17]. Although NLRP3 inflammasome activation was partially involved, the primary mechanism appeared to be the suppression of oxidative stress [17].

Discussion

This systematic review evaluated seven in vitro studies that investigated the potential of herbal and natural products in preventing or managing 5-FU-induced OM. Overall, the evidence suggests that various plant-derived compounds exert protective effects against mucosal injury through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. The 5-FU is a chemotherapeutic agent that interferes with DNA and RNA synthesis, targeting rapidly proliferating cancer cells. However, this cytotoxic effect also impacts normal rapidly dividing cells, particularly the basal epithelial cells of the oral mucosa, leading to OM, one of the most common and distressing side effects in cancer patients [19-22]. The development of OM from 5-FU occurs in a complex, multistage process. The initial phase involves the generation of ROS that cause direct DNA damage and lipid peroxidation in oral epithelial cells [23,24]. This oxidative stress activates the transcription factor NF-κB, which upregulates proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, further amplifying mucosal injury [12,25]. Following the inflammatory phase, signal amplification cascades intensify the damage through upregulation of matrix metalloproteinases (MMPs) and additional cytokines, contributing to epithelial thinning, ulceration, and pain [21,22,26]. Mitochondrial dysfunction also plays a role by promoting apoptosis via caspase activation, while suppressing cellular energy production and regeneration [20,25].

Histopathological evidence from both in vitro and in vivo models confirms epithelial cell detachment, nuclear fragmentation, and reduced mitotic figures in tissues exposed to 5-FU [8,20,26,27]. Furthermore, studies using immortalized human keratinocytes (HaCaT) and human oral keratinocytes (HOK) cell lines demonstrate significant reductions in cell viability, increases in ROS generation, and elevated levels of inflammatory markers following 5-FU exposure [14,16,23,26,28]. Altogether, 5-FU-induced OM is primarily driven by its cytotoxic action on epithelial cells, accompanied by excessive ROS generation, proinflammatory cytokine release, mitochondrial damage, and apoptosis. This pathophysiological understanding underscores the need for protective strategies that can target these molecular pathways to mitigate OM severity [12,19,23,29,30].

In the context of 5-FU-induced OM models, the use of cell lines plays a crucial role in elucidating the mechanisms of mucosal injury and evaluating potential therapeutic interventions, including herbal remedies. Several studies have employed various human epithelial or keratinocyte cell lines, such as HOK, human pharyngeal cells (Detroit 562), gingival cells (Sa3), and HaCaT, to mimic the oral mucosal environment in vitro. These models allow for controlled investigation of cytotoxicity, oxidative stress, inflammatory responses, and healing mechanisms relevant to oral mucositis. A study used oral keratinocytes to assess the protective effect of anthocyanins from *O. sativa* against 5-FU-induced inflammation [4]. They found that anthocyanin treatment restored cell proliferation and suppressed NF-κB activation in vitro, supporting the use of oral keratinocytes as a suitable model for studying anti-inflammatory and wound-healing agents [4]. Similarly, other studies used human pharyngeal cells to evaluate the effects of herbal formulations such as Onchung-eum and *S. miltiorrhiza*, respectively [3,18]. These studies demonstrated the ability of these cell lines to reflect oxidative and inflammatory damage induced by 5-FU, as well as to assess the potential of herbal extracts to promote epithelial recovery [3,18]. Other models include HaCaT cells, which have been employed in studies

involving Camellia tea saponin and FITOPROT formulations [14,16]. These models effectively demonstrated 5-FU-induced ferroptosis, mitochondrial dysfunction, and inflammatory cytokine release, which were ameliorated by the herbal interventions via pathways such as Nrf2/Keap1/ARE signaling and restoration of glutathione peroxidase 4 activity [14,16]. These in vitro models using oral-related cell lines provide a robust platform to simulate the pathogenesis of oral mucositis and evaluate the efficacy of natural compounds. They offer reproducibility, ethical advantages, and mechanistic insights, making them indispensable tools in mucositis research.

In the context of the potential effect on OM, the included studies consistently demonstrate that several herbal extracts exert protective effects through antioxidant, anti-inflammatory, anti-apoptotic, and regenerative mechanisms, offering viable adjunctive or alternative therapies to current pharmacological options. Cannabidiol, a non-psychoactive cannabinoid, was found to significantly alleviate 5-FU-induced OM in both mice and human oral keratinocytes through modulation of oxidative stress and inflammatory responses via the Nrf2/Keap1/ARE pathway. Cannabidiol restored epithelial thickness, decreased ulceration, and inhibited apoptosis, suggesting its utility as a novel therapeutic agent targeting the redox signaling network and epithelial regeneration pathways in OM management [6]. Similarly, anthocyanins extracted from *O. sativa* showed significant anti-inflammatory effects. Anthocyanin-rich extracts downregulated the nuclear translocation of NF-κB p50 and p65 subunits, thereby reducing the expression of pro-inflammatory cytokines in both in vivo and in vitro OM models. These findings underscore the immunomodulatory capacity of anthocyanins, reinforcing the value of polyphenolic compounds in maintaining mucosal integrity during chemotherapy [4].

Daiokanzoto, a traditional Kampo formulation, demonstrated efficacy in reducing 5-FU-induced human gingival cell death primarily through inhibition of mitochondrial ROS production. While activation of the NLRP3 inflammasome was partially involved in OM pathogenesis, the study emphasized that oxidative stress was the major contributor to cytotoxicity. Daiokanzoto effectively attenuated both oxidative and inflammatory pathways without involving NF-κB signaling, suggesting a unique mechanistic profile [17]. The polyherbal formula Onchung-eum also proved effective in reducing ROS levels, NF-κB expression, and caspase-3 activity. The formulation significantly promoted epithelial repair in 5-FU-induced hamster models, highlighting its dual antioxidant and anti-apoptotic potential. This study emphasized the relevance of traditional herbal combinations in OM therapy by modulating critical inflammation-related signaling cascades [18].

A more recent approach involved Camellia tea saponins, which mitigated 5-FU-induced damage in keratinocytes by inhibiting ferroptosis and related oxidative and inflammatory markers. The treatment preserved glutathione levels, enhanced glutathione peroxidase 4 activities, and decreased ROS and lipid peroxidation levels. These effects reflect a promising protective role for saponins against ferroptotic pathways that contribute to OM [16]. *S. miltiorrhiza* extract was also effective in decreasing 5-FU-induced ROS generation, inhibiting NF-κB and caspase-3, and promoting cell viability in pharyngeal cells. Its ability to scavenge free radicals and suppress pro-inflammatory mediators highlights its potential as a natural chemoprotective agent against mucosal damage [3]. Lastly, FITOPROT, a mucoadhesive formulation containing curcuminoids from *C. longa* and extract from *B. pilosa,* offered significant cytoprotection. It restored proliferation (via Ki-67), reduced ROS, prevented mitochondrial dysfunction, and downregulated inflammatory cytokines and NF-κB [14]. These findings validate FITOPROT's multifaceted mechanism involving both antioxidant and anti-inflammatory activities [14].

Overall, these studies reveal that various herbal compounds target different stages of OM pathogenesis, ranging from oxidative stress and inflammation to apoptosis and 5-FU-induced impaired regeneration. The pathways frequently modulated include NF-κB, Nrf2/Keap1, ferroptosis regulators, and mitochondrial ROS signaling. However, while preclinical evidence is compelling, future clinical trials are needed to confirm efficacy, optimize dosing, and assess safety in humans.

This systematic review supports the potential role of herbal agents in 5-FU-induced oral mucositis, but several limitations should be considered. All included studies were preclinical and

used in vitro and/or in vivo models, limiting direct translation to clinical practice. Blinding, randomization, and power calculations were not consistently reported, and standardization or chemical characterization of herbal extracts was sometimes limited. Heterogeneity in herbal formulations, concentrations, treatment durations, cell lines, and outcome measurements also limited direct comparison across studies. Although antioxidant and inflammatory pathways were examined, mechanistic evaluations remained relatively narrow. Further standardized experimental studies and well-designed clinical trials are needed to confirm efficacy, safety, optimal dosing, and clinical applicability.

Conclusion

This systematic review highlights the significant potential of herbal plants in the prevention and management of 5-FU-induced oral mucositis. Across in vitro and in vivo studies, a variety of plant-derived compounds, including cannabidiol, anthocyanins, curcuminoids, saponins, and traditional polyherbal formulations, demonstrated consistent protective effects against oxidative stress, inflammation, and epithelial damage central to OM pathogenesis. Most of the interventions exerted their effects through modulation of key molecular pathways, including NF-κB and Nrf2/Keap1/ARE, inhibition of mitochondrial ROS generation, suppression of pro-inflammatory cytokines, and restoration of mucosal integrity. These findings align with the current understanding of OM as a multistage, multifactorial condition, further validating phytotherapy as a rational and promising approach. Despite robust preclinical evidence, clinical research remains limited. Future studies should prioritize randomized controlled trials to assess the efficacy, safety, and optimal administration routes of these herbal agents in cancer patients. Standardization of extract composition, dosage, and treatment duration will be essential to translate these findings into clinical practice. Ultimately, integrating phytotherapeutic strategies may offer an accessible, cost-effective, and well-tolerated adjunct to conventional oral mucositis management.

Ethics approval

Not required

Acknowledgments

The authors would like to acknowledge the academic support provided during the preparation of this review article.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

All data supporting the findings of this systematic review were derived from the studies included and cited in this article. No new primary data were generated or analyzed.

Declaration of artificial intelligence use

The authors did not use generative AI tools for manuscript writing or data analysis. Rayyan was used only as a screening management tool to support the study selection process. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

How to cite

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