



Herbal Medicine in Head and Neck Cancer: A Review of Randomized Controlled Trials

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Abstract

Head and neck cancer (HNC) is a significant global health issue, ranking as the seventh most common cancer worldwide in 2020. Standard treatments like surgery, radiotherapy, and chemotherapy often lead to adverse effects such as oral mucositis (OM) and gastrointestinal complications, which negatively impact patients' quality of life (QoL). The use of herbal medicine has emerged as a complementary approach to mitigate these side effects. This review aims to explore and assess the overview and outcomes of herbal medicine use in HNC patients through a review of randomized controlled trials (RCTs) studies. Articles were searched until to October 19, 2024, using two databases: PubMed and The Cochrane Library with the keywords and combinations of 'AND' and 'OR' to search for relevant studies. Out of 1,312 articles identified, 11 studies met the inclusion criteria. These studies were conducted in diverse regions, including Iran, Japan, Taiwan, India, China, Germany, and Brazil, with sample sizes ranging from 20 to 74 participants. Herbal medicine showed potential benefits in managing OM, improving gastrointestinal motility, and alleviating xerostomia. Herbal medicines demonstrate promising efficacy and safety profiles in managing HNC-related complications, such as OM, gastrointestinal issues, and QoL. These findings suggest the potential integration of herbal medicine into HNC management as an innovative and supportive care strategy.

Keywords: Head and neck cancer; Herbal medicine; Randomized controlled trials

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Introduction

Head and neck cancer (HNC) is a cancer originating from the upper human organs that develops with tumors in the oral cavity, nose, larynx, sinuses, pharynx, and salivary glands [1,2]. HNC ranked seventh as a cancer disease in 2020 with 931,931 cases and 467,125 deaths [3]. HNC has a major impact on patients, i.e., difficulty in swallowing, communication, and impact on the breathing system, which causes an increase in the health care process [4]. Treatment of HNC involves surgical management with non-invasive procedures such as chemotherapy and radiotherapy given to patients as adjunctive therapy not only after surgery, but also can be used before or as a definitive or palliative therapy [4]. Treatment of HNC involves surgical management with non-invasive procedures such as chemotherapy and radiotherapy, which may be administered not only as adjuvant therapy after surgery but also before surgery or as definitive or palliative therapy [4,5].

Radiotherapy and chemotherapy cause side effects in the form of mucositis in the oral cavity, which develops into inflammation as erosive or ulcerative lesions, so that it becomes a complication of therapy in as much as 40–80% of patients with cancer, which has an impact on the patient's quality of life (QoL) [6]. Traditional medicine is widely practiced in several countries, using herbal medicines as additional drugs to help treatment [7]. The increase of herbal medicine in epidemiological studies has been carried out especially in the consumption of raw fruits and vegetables against several types of cancer that show protective effects using the influence of macromolecular or micromolecular nutritional interventions to patients [8]. In addition, herbal remedies are widely used in some studies as they have effects on gastrointestinal motility using anti-inflammatory activity that helps treat cancer [9]. Therefore, this study aims to explore and assess the overview and outcomes of herbal medicine use in HNC patients through a review of randomized controlled trials (RCTs) studies.

Methods

Search criteria

This study is a review article of RCTs focusing on the use of herbal medicine in HNC. Articles were searched until October 19, 2024, using two databases: PubMed and The Cochrane Library with the keywords "herbal medicine" and "head and neck cancer" to identify relevant studies.

Eligibility criteria

In the context of study eligibility, the inclusion criteria consisted of (1) study type, RCTs; (2) study population, HNC patients; (3) intervention, herbal medicine; (4) study outcomes, all outcomes including effect, efficacy, and safety; and (5) accompanied by control. Articles that did not have access to the full-text or were in a language

other than English were excluded from the study.

Data handling and quality assessment

Data that have been obtained will be checked for duplication using automated tools from Mendeley. Authors independently extracted the data included in the study in table form using Microsoft Excel sheets (Microsoft Inc., Redmond, WA, USA), including (1) first author and year of publication; (2) study location; (3) objective; (4) number of samples, including the number of control and intervention groups; (5) age of samples; (6) control to participants; (7) intervention, including drug name, content, dose, and frequency of use; and (8) study outcomes. Two authors assessed the methodological quality of the studies using the Jadad scale [10-13]. All disagreements were resolved through discussion with the validator.

Results and Discussion

Included and excluded studies

A total of 1,312 articles were identified in the initial search using two databases. Of these, 1,274 articles were automatically excluded by the databases, including 1,119 articles that were not RCTs, 72 articles that were not available in full-text, and 3 articles that were not in English. Ultimately, 11 articles were included in the review. Figure 1 shows the flow of the article selection process.

Quality assessment

The included studies were assessed for their methodological quality using the modified Jadad scale, with scores ranging from 0 to 5. A score of 3 or more classified the study as high quality, based on the following criteria: description of the study as randomized along with details of the randomization method, description of the study as double-blind, details of the double-blinding procedure, and information on dropouts or withdrawals [10-13]. Among the 11 identified studies, three studies achieved the highest Jadad score of 5 [14-16], two Jadad score of 4 [5,17], and three Jadad score of 3 [6,9,18], indicating excellent methodological quality who also demonstrated strong adherence to appropriate randomization and blinding procedures. This suggests that these trials were well-designed and reported, with minimal risk of bias. Table 1 presents the quality assessment of the studies based on the Jadad scale.

Study distribution by country

A total of 11 articles that met the inclusion criteria were conducted in various countries, Iran (n=3), Japan (n=2), Taiwan, Republic of China (n=2), India (n=1), China (n=1), Germany (n=1), and Brazil (n=1). Figure 2 display a world map of the study distribution by country.

Characteristic included studies

The sample size ranged from 20 to 74 participants.

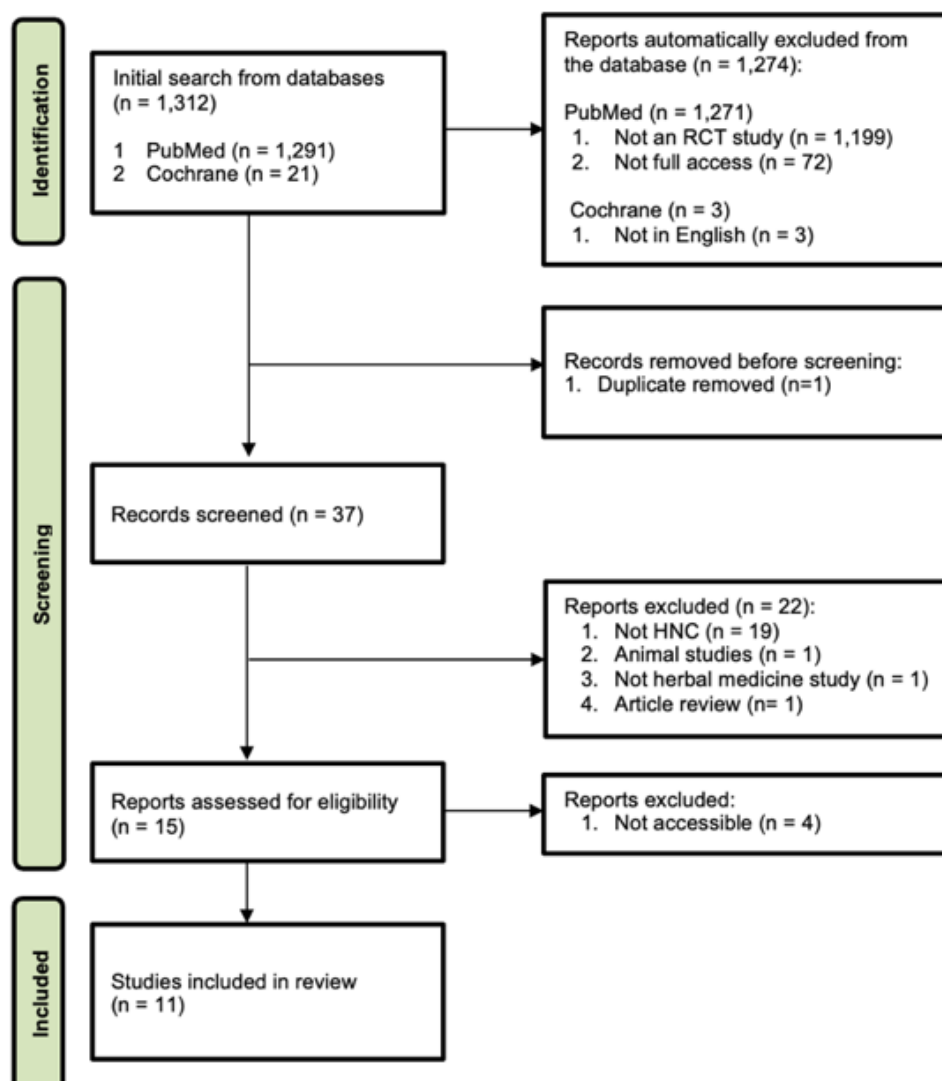


Figure 1. The flow of article selection process



Figure 2. World map of the study distribution by country

Table 1. Quality assessment of included studies based on the modified jadad scale

	S. Shah., et al (2021) [5]	S. Kia., et al (2021) [14]	S. Moriyama., et al (2018) [6]	Cheng, et al (2022) [19]	Ameri A, et al (2016) [20]	Rezaeipour N., et al (2017) [17]	Martins A, et al (2023) [15]	Nishino T, et al (2017) [9]	Zejun X, et al (2015) [18]	Klopp R, et al (2005) [21]	Lin K, et al., (2014) [16]
Was the study described as random	1	1	1	1	1	1	1	1	1	1	1
Was the randomization scheme described and appropriate?	1	1	1	1	0	0	1	1	1	0	1
Was the study described as double-blind?	1	1	0	0	0	1	1	0	0	0	1
Was the method of double blinding appropriate?	1	1	0	0	0	1	1	0	0	0	1
Was there a description of dropouts and withdrawals?	0	1	1	*	1	1	1	1	1	0	1
Overall Jadad Score	4	5	3	2	2	4	5	3	3	1	5

*study protocol

Research on herbal medicine related to mucositis has been conducted in India [5], Iran [14,17,20], Japan [6], Taiwan [19], and Brazil [15]. Furthermore, research on herbal medicine related to gastrointestinal issues has been conducted in Japan [9] and China [18]. In addition, studies on the safety and therapeutic efficacy of herbal medicine has been conducted in Germany to evaluate the effect of adding standardized mistletoe extracts to the common side effect of radiotherapy and chemotherapy [22]. Another study in Taiwan has explored the safety and therapeutic efficacy of *Tianwang Buxin* Mini-pills (TWBXM) for the prevention of acute radiation therapy (RT) toxicity in patients with HNC [16]. Table 2 displays the characteristics of the included studies.

This review has provided an overview of studies exploring herbal medicine in HNC organized by the following benefits: mucositis, gastrointestinal, safety, and therapeutic efficacy.

Herbal medicine related to mucositis

The management of HNC includes surgery followed by non-invasive procedures such as RT or chemotherapy [26]. In the management of RT in the head and neck area, oral mucositis (OM) is a common occurrence that can produce clinical manifestations [27,28]. General manifestations of mucositis include pain, ulceration, erythema, soreness, dryness, and white patches [5]. Several randomized controlled trials have evaluated the effectiveness of curcumin-based interventions for the prevention of Radiotherapy-induced oral mucositis (RIOM). In a study conducted in India, benzydamine (0.15%) as a control compared to intervention using curcumin mouthwash (0.1%) shows that though both mouthwashes were not able to completely prevent the onset of RIOM and reduce the severity of RIOM, use of curcumin mouthwash was able to significantly delay the onset of RIOM [5]. This

outcome is attributed to the multiple pharmacological properties of curcumin in preventing RIOM, including its analgesic, antipyretic, immunomodulatory, antineoplastic, antifungal, and antibacterial properties [29].

Similarly, a study in Iran compared placebo capsules twice daily after meals with mostly sugar content (manufactured by Sobhan Daru CO, Tehran, Iran) as a control with curcumin nanomicelle capsules of 80 mg administered twice daily after meals until week 7 in patients undergoing RT and/or chemotherapy [14]. The results demonstrated that nanomicelle curcumin capsules are effective on prevention and treatment of HNC radiotherapy and especially chemotherapy-induced OM [14]. These findings are consistent with previous studies on the effectiveness of curcumin in the prevention and treatment of RIOM, which showed reduced severity, slowed progression, accelerated healing, anti-inflammatory, antioxidant, and antimicrobial effects [30,31].

Beyond curcumin, Traditional Chinese Medicine (TCM) formulations have also been investigated. A protocol study in Taiwan evaluated the effect of *Zi-Yin-Liang-Ge-San* (ZYLGS) powder (containing Rx. *Scutellariae*, Rx. *Glycyrrhizae*, Hb. *Dendrobii*, Rx. *Ophiopogonis*, and Hb. *Menthae Haplocalycis*) 4 g (per bag) each time, thrice daily, from the first day of RT until the completion of RT, while control group received RT without allocated intervention [19]. The intervention showed promising efficacy in reducing OM incidence and severity [19]. The modern study of pharmacological activities of ZYLGS components supports these findings. Rx. *Scutellariae*, Rx. *Glycyrrhizae* and Hb. *Menthae Haplocalycis* possess positive effects on oral epithelial damage by mechanisms that may inhibit oxidative stress and inflammation and thus prevent bacterial dysbiosis [32]. Hb. *Dendrobii* has been shown to modulates macrophage activity through the NF- κ B pathway which has been shown to act as an

Table 2. Characteristic included studies

First Author and Years	Country	Objective	Samples	Age	Control	Intervention		Outcome
						Name and Frequency	Ingredients	
Herbal medicine related to mucositis								
S. Shah, et al (2021) [5]	India	Compare the effectiveness and safety of curcumin 0.1% (freshly prepared using the nanoparticle method) and benzydamine mouthwash 0.15% on radiation-induced OM (RIOM) among 74 head and neck cancer patients scheduled to receive radiotherapy (RT).	74 patients (35 control, 33 treatment, and the remaining 6 not described in the article).	54.34 ± 13.78 (26-96 years).	Benzydamine mouthwash (0.15%) containing (benzydamine hydrochloride BP 0.15% w/v, aqueous base QS, brilliant blue, and tartrazine yellow).	Curcumin mouthwash (0.1%) nanoparticles powder with a frequency of 10 mL of mouthwash three times a day for 7 days without mixing it with water and not eating or drinking for 30 minutes after gargling until week 6.	1 gram curcumin (<i>Curcuma longa</i> L.) powder, 1.5 grams sodium benzoate, 1 mL clove oil, and 1 L drinking water.	The use of curcumin mouthwash (0.1%) was able to significantly prevent the onset of RIOM for up to 2 weeks in 50% of patients.
S. Kia, et al (2021) [14]	Iran	This study aimed to investigate the effects of nanomicelles curcumin on OM-related to chemotherapy and head and neck radiotherapy.	50 patients (25 control, 25 treatment).	55.96 ± 1.10 years.	Placebo capsule twice daily after meals with mostly sugar content (manufactured by Sobhan Daru CO, Tehran, Iran).	Curcumin nanomicelle capsules of 80 mg twice daily after meals until week 7.	<i>Curcuma longa</i> L.	Curcumin nanomicelles capsules are effective in preventing and treating OM associated with radiotherapy and chemotherapy and may be an acceptable alternative to current palliative and local treatments. The pain level in the treatment group was lower than that in the control group at week seven. The incremental gradient of NRS in the

S. Moriyama, et al (2018) [6]	Japan	The aim of this study was to investigate the impact of the use of two Kampo medicines on OM, tongue coating bacteria, and gingiva condition in patients with esophageal cancer undergoing chemotherapy.	24 patients were divided into three groups: 7 were given <i>Daiokanzoto</i> to sherbets (TJ-84), 7 were given <i>Hangeshashinto</i> sherbets (TJ-14), and 10 were used as control.	64.7 ± 7.7 (52-81 years)	The patient is not given anything.	Two Kampo drugs in sherbet form <i>Daiokanzoto</i> sherbets (TJ-84) and <i>Hangeshashinto</i> sherbets (TJ-14) frequency i.e., Kampo drug formula consumed three times a day between meals during chemotherapy	Kampo formula, distilled water. The content in <i>Daiokanzoto</i> sherbet (TJ-84; <i>Rheum palmatum</i> L. and <i>Glycyrrhiza uralensis</i> Fisch [24]); while in <i>Hangeshashinto</i> (TJ-14; <i>Pinelliae Tuber</i> , <i>Scutellariae Radix</i> , <i>Zingiberis Rhizoma</i> , <i>Ginseng Radix</i> , <i>Glycyrrhizae Radix</i> , <i>Zizyphi Fructus</i> , and <i>Coptidis Rhizoma</i> [25]).	<i>Daiokanzoto</i> administration is effective in relieving gum inflammation and reducing periodontopathogen bacteria levels in patients with esophageal cancer. <i>Daiokanzoto</i> reduces the secretion of proinflammatory cytokines (IL-6 and CXCL8) in LPS-stimulated oral epithelial cells and gingival fibroblasts and inhibits the catalytic activity of matrix metalloproteinases.
Cheng, et al (2022) [19]	Taiwan	The objective of this study is to determine whether a Traditional Chinese Medicine (TMC) based prescription named the <i>Zi-Yin-Liang-Ge-San</i> (ZYLGS) powder, when used alongside RT, can improve OM in patients with head and neck cancer compared to radiotherapy alone.	40 patients (20 treatment group and 20 control group)	Patients aged 20–75 years	Radiotherapy without allocated intervention	6 weeks of RT and ZYLGS, 4 g (per bag) each time, thrice daily, from the first day of RT until the completion of RT.	ZYLGS containing Rx. <i>Scutellariae</i> , Rx. <i>Glycyrrhizae</i> , <i>Hb. Dendrobii</i> , Rx. <i>Ophiopogonis</i> , and <i>Hb. Menthae Haplocalycis</i>	ZYLGS offers a promising therapeutic approach for the prevention and treatment of OM.

Author(s)	Country	Study Objective	Patients	Inclusion range	Artificial saliva (Hypozalix)	Herbal compound (4 g sachets), administered three times daily for four weeks	<i>Malva sylvestris</i> and <i>Alcea digitialis</i>	Outcome
Ameri A, et al (2016) [20]	Iran	To evaluate the efficacy of an herbal compound (containing <i>Malva sylvestris</i> and <i>Alcea digitialis</i>) compared to artificial saliva (Hypozalix) in managing dry mouth (xerostomia) in head and neck cancer patients undergoing radiotherapy.	62 patients with radiation-induced xerostomia (41 male and 21 female).	32 completed in the experimental group and 30 in the control group				Both groups showed significant improvement in dry mouth symptoms, measured by the Visual Analog Scale (VAS). The herbal compound group showed significantly greater VAS improvement at the 4-week mark compared to the Hypozalix group
Rezaei N, et al (2017) [17]	Iran	To evaluate the efficacy of <i>Alcea digitialis</i> , <i>Alf</i> , and <i>Malva sylvestris</i> L. in preventing radiation-induced mucositis in patients with head and neck cancer.	23 patients, 13 males and 10 females (12 in the herbal group and 11 in the placebo group)	17–65 years	Placebo group received Avicel-based placebo sachets,	Herbal compound, 4 g sachets, three times daily for seven weeks	<i>Alcea digitialis</i> and <i>Malva sylvestris</i>	Drug containing <i>A. digitialis</i> and <i>M. sylvestris</i> can be beneficial to prevent radiation-induced mucositis and decrease the severity and complications of this condition.
Martins A, et al (2023) [15]	Brazil	To assess the effect of a mucocathesive herbal medicine (FITOPROT, containing curcuminoids and <i>Bidens pilosa</i> extract) combined with photobiomodulation (PBM) and a Preventive Oral Care Program (POCP) compared to PBM and POCP alone in treating radiotherapy-induced OM (ROM) and improving QoL in patients undergoing head and neck cancer treatment.	52 participants with head and neck cancer (pre-dominance of male patients)	Mean age: 57.08 years (±11.20)	PBM and POCP (Group 1, 27 participants)	PBM + POCP + FITOPROT (Group 2, 25 participants), mouthwash twice a day	20 mg/ml curcuminoids (<i>Curcuma longa</i> L.) and 40% glycerinated <i>Bidens pilosa</i> L. extract	Both groups showed control over ROM severity and stabilized QoL. No statistically significant differences between groups in ROM evaluation, adherence, or QoL metrics.

Herbal medicine related to gastrointestinal complications

Nishino T, et al (2017) [9]	Japan	Determine the effect of TJ-100 after esophagectomy in patients with esophageal cancer.	40 patients (20 treatment: 17 males, 2 females 20 controls: 16 males, 4 females)	Median treatment 68.0 (61-74 years), control 60.5 (55-67 years)	None	Herbal medicine <i>Daikenchuto</i> (TJ-100) at a dose of 15 g/day (5g, 3 times a day) after surgery until 21 days post-operatively.	<i>Kankyo</i> (Dried ginger; <i>Zingiber officinale</i>), <i>Sansho</i> (Japanese pepper; <i>Zanthoxylum piperitum</i>), <i>Ninjin</i> (ginseng; <i>Panax ginseng</i>), and <i>Koui</i> (<i>Saccharum granorum</i>)	39 patients were observed; 1 patient was not observed due to unresectable surgery. Weight loss of the TJ-100 group < control (3.6% vs. 7.0%, $p = 0.014$). Recovery of gastrointestinal function (flatulence, defecation, oral intake), length of postoperative hospitalization, and serum albumin levels were not significantly different. CRP levels decreased less in the TJ-100 group (4.9 mg/dL vs. 6.9 mg/dL on day 3), but not statistically significant. TJ-100 may restore gastrointestinal motility, minimize weight loss, and may suppress excessive inflammatory reactions associated with surgery.
Zejun X, et al (2015) [18]	China	Determine the clinical effects of modified <i>Dachengqi Tang</i> (DCQT) in promoting gastrointestinal motility in postoperative esophageal cancer patients.	60 people (30 treatment: 23 males and 7 females (9 patients undergoing intrathoracic anastomosis and 21 patients undergoing cervical anastomosis); 30 controls: 24 males and 6 females (6 patients undergoing intrathoracic anastomosis and 24 patients undergoing cervical anastomosis).	Average of the treatment group: 60 ± 3 years (49-67 years), control group: 60 ± 7 years (42-77 years).	Normal saline (150 mL solution) was administered via nasogastric infusion at 37°C using a thermostat at a rate of 80-100 drops per minute.	Modified DCQT, 150 mL, was administered once daily for the first three postoperative days (starting 24 hours after enteral nutrition). The intervention was performed by the same method as the control.	<i>Dahuang</i> (<i>Radix Et Rhizoma Rhei Palmati</i>) 10 g, <i>Mangxiao</i> (<i>Natrii Sulfas</i>) 5 g, <i>Houpu</i> (<i>Cortex Magnoliae Officinalis</i>) 15 g, <i>Zhishi</i> (<i>Fructus Aurantii Immaturus</i>) 15 g, <i>Danggui</i> (<i>Radix Angelicae Sinensis</i>) 15 g, <i>Huangqi</i> (<i>Radix Astragali Mongolici</i>) 15 g, <i>Chishao</i> (<i>Radix Paconiae Rubra</i>) 15 g, and <i>Wuyao</i> (<i>Radix Linderae Aggregatae</i>) 10 g.	Modified DCQT showed shorter time to first bowel sound, flatulence, and defecation, less total amount of gastric drainage, significantly decreased plasma motilin (MTL) and vasoactive intestinal peptide (VIP) levels, and no significant side effects, except for one patient who developed mild diarrhea and recovered after therapy was stopped. Modified DCQT effectively improves decreased gastrointestinal motility in esophageal cancer postoperative patients by increasing MTL and reducing VIP.

Herbal medicine related to safety and therapeutic efficacy

Klopp R, et al (2005) [22]	Germany	Evaluating the common side effects of radiotherapy and chemotherapy from the effect of adding standardized mistletoe extracts	Male patients (20 people); 10 treatment, 10 control)	Average age 60 years	Radiotherapy and chemotherapy with mistletoe extract supplementation	Subcutaneous administration of standardized mistletoe extract (Viscum album, Iscador®) in the abdominal area based.	Extracts of mistletoe (<i>Viscum album</i>)	Improved microperfusion in target tissues, reduced immune system side effects due to radiotherapy and chemotherapy, faster restitution of microperfusion function in the treatment group, and no serious side effects of mistletoe administration.
Kao-Shin Lin et al., (2014) [16]	Taiwan	To explore the safety and therapeutic efficacy of <i>Tianwang Buxin</i> Mimi pills (TWBXM) for the prevention of acute RT toxicity in patients with HNC.	73 patients with HNC (38 in the TWBXM group, 35 in the placebo group), 12 female and 61 male patients	Majority of participants were above 50 years old with minimum age of 18 years old	Placebo group receiving a placebo treatment alongside RT	TWBXM (3 g, three times daily, during and up to one month after RT).	Ingredients include 13 herbs such as <i>Radix Ginseng</i> , <i>Rehmanniae Radix</i> , <i>Salvia Miltiorrhiza</i> , <i>Radix Scrophulariae</i> , <i>Poria cocos</i> (Schw.) Wolf, <i>Schisandra sphenanthera</i> , <i>Radix Polygalae</i> , <i>Radix Platycodonis</i> , <i>Radix Angelica Sinensis</i> , <i>Asparagus cochinchinensis</i> , <i>Ophiopogonis Radix</i> , <i>Platycladus orientalis</i> , and <i>Zizipus jujuba Mill. Var. spinosa</i> .	TWBXM maintained hemoglobin levels better than placebo and demonstrated safety, though significant improvements in radiation-associated toxicities like OM were not observed

immune modulator to regulate gastrointestinal mucosal barrier function [33,34]. Meanwhile, *Rx. Ophiopogonis* stimulates lymphocyte proliferation and enhances immune responses [35]. According to TCM theory, these herbs collectively benefit qi, promote the production of body fluids, and are reported to have cardiovascular, anti-inflammatory and anticancer effects [34,36,37].

In Japan, a study compared the control group without herbal treatment, with intervention of two Kampo medicine, *Daiokanzoto* sherbet (TJ-84; *Rheum palmatum* L. and *Glycyrrhiza uralensis* Fisch [24]); and *Hangeshashinto* (TJ-14; *Pinelliae Tuber*, *Scutellariae Radix*, *Zingiberis Rhizoma*, *Ginseng Radix*, *Glycyrrhizae Radix*, *Zizyphi Fructus*, and *Coptidis Rhizoma* [25]) [5]. Although there was no significant difference in the onset of oral mucositis among the three groups, the tongue coating index, gingival index (GI), plaque index, and the number of total bacteria, *F. nucleatum* and *C. rectus*, were decreased during chemotherapy [5]. These findings are similar to a previous study that showed antimicrobial activity of *Hangeshashinto* against 19 oral bacteria, including *F. nucleatum* and *P. gingivalis* [38]. In addition, anthraquinones present in *Daiokanzoto*-containing rhubarb-derived molecules- exhibit potent antibacterial activity against several oral bacterial pathogens [39–41], which may explain the reduction of *F. nucleatum* and *C. rectus* observed in this study [5].

Xerostomia or dry mouth is another debilitating side effect commonly associated with RT in HNC patients [42]. An Iranian study has been conducted with the control group using artificial saliva (HypoZalix) compared with the intervention of an herbal compound containing *Malva sylvestris* and *Alcea digitata* [20]. Patients who received the herbal formulation 4 g sachets, administered three times daily for four weeks showed a significant difference between the grade of dry mouth before and after intervention, but no change was observed for the grade of dry mouth in the HypoZalix group [20]. A similar study in Iran used a control placebo group that received Avicel-based placebo sachets compared to the intervention herbal compound (*A. digitata* and *M. sylvestris*) 4 g sachets, three times daily for seven weeks [17]. The study shows that not only the severity of mucositis and the average of MPS were significantly lower in the drug group compared with the control group, but also, they were invariant during the study and showed no uptrend [17]. *A. digitata* and *M. sylvestris* are Persian medicine recommendations, both are mucilaginous plants that have well-documented emollient, laxative, anti-inflammatory, and pain relief properties [43,44]. Recent studies have also shown antioxidant, anti-inflammatory, antimicrobial, and beneficial effects for improving dry mouth [45–48]. In Brazil, a randomized controlled study was conducted to evaluate the effectiveness of a mucoadhesive herbal medicine, FITOPROT (containing curcuminoids and *Bidens pilosa* extract), in combination with PBM

and a preventive oral care program POCP, compared to PBM and POCP alone, for the treatment of ROM and the improvement of QoL in patients undergoing HNC treatment. Participants in the control group received PBM and POCP, while those in the intervention group received PBM, POCP, and FITOPROT mouthwash administered twice daily. The findings indicated that the addition of FITOPROT was associated with better control of ROM severity and stabilization of QoL in HNC patients [15]. The therapeutic effects of FITOPROT can be attributed to the biological activities of its components, particularly curcuminoids derived from *C. longa* and bioactive compounds from *Bidens pilosa*, both of which possess anti-inflammatory, antimicrobial, antioxidant, and anti-neoplastic properties [49–51].

In summary, herbal interventions, including curcumin-based therapies, TCM, Kampo medicines, Persian medicine from *A. digitata* and *M. sylvestris*, and FITOPROT mouthwash, show promising benefits as complementary approaches offering improved management of OM, xerostomia, and overall oral health in patients with HNC.

Herbal medicine related to gastrointestinal

Esophageal cancer with esophageal resection is one of the most invasive surgical procedures with a high incidence of morbidity and mortality [52]. Studies have been conducted in Japan comparing a no-treatment control group with an intervention group receiving Daikenchuto (TJ-100), a traditional herbal medicine containing *Kan-kyo* (Dried ginger; *Zingiber officinale*), *Sansho* (Japanese pepper; *Zanthoxylum piperitum*), *Ninjun* (ginseng; *Panax ginseng*), and *Koui* (*Saccharum granorum*) administered at a dosage of 15 g/day (5 g, 3 times a day) until 21 days postoperatively. The result indicated Daikenchuto (TJ-100) promoted the recovery of gastrointestinal motility, minimizing body weight loss, and might suppress the excess inflammatory reaction related to surgery [9]. In Japan, the traditional herbal formula Daikenchuto (TJ-100) has been widely used to manage postoperative ileus [53]. Daikenchuto (TJ-100) has been investigated the most extensively, its main effects are the acceleration of gastrointestinal transit, an increase in intestinal blood flow, and an anti-inflammatory effect [9].

In addition to findings from Japan, a study in China evaluated the clinical effects of modified *Dachengqi Tang* (DCQT) formula which includes multiple herbal components such as *Dahuang* (*Radix Et Rhizoma Rhei Palmati*), *Mangxiao* (*Natrii Sulfas*), *Houpu* (*Cortex Magnoliae Officinalis*), *Zhishi* (*Fructus Aurantii Immaturus*), *Danggui* (*Radix Angelicae Sinensis*), *Huangqi* (*Radix Astragali Mongolici*), *Chishao* (*Radix Paeoniae Rubra*), and *Wuyao* (*Radix Linderae Aggregatae*) in promoting gastrointestinal motility in postoperative esophageal cancer patients [18]. This formula was administered via nasogastric infusion to postoperative esophageal cancer patients

and compared with a saline control. The results indicated that DCQT significantly improved gastrointestinal motility by increasing motilin (MTL) levels and reducing vasoactive intestinal peptide (VIP), both of which are critical in regulating gut function [18].

These findings suggest that specific herbal formulas may offer supportive benefits in enhancing postoperative gastrointestinal recovery, with potential mechanisms involving both motility stimulation and anti-inflammatory effects.

Herbal medicine related to safety and therapeutic efficacy

A study in Germany evaluated the common side effects of radiotherapy and chemotherapy compared to when standardized mistletoe extract is added to the combination. The control group used radiotherapy and chemotherapy without mistletoe extract supplementation compared with subcutaneous administration of standardized mistletoe extract (*Viscum album*, Iscador®) in the abdominal area, which demonstrated microhematological and immunological success [22]. Several studies have shown therapeutically relevant immunomodulation may be induced by administration of mistletoe extract [21,54]. The noticeable changes in blood flow and the immune function of white blood cells suggest that the overall health of cancer patients may improve because of better blood circulation and stronger defense mechanism [22]. In Taiwan, a study explored the safety and therapeutic efficacy of *Tianwang Buxin* Mini-pills (TWBXM) with ingredients include 13 herbs *Radix Ginseng*, *Rehmanniae Radix*, *Salvia Miltiorrhiza*, *Radix Scrophulariae*, *Poria cocos* (Schw.) Wolf, *Schisandra sphenanthera*, *Radix Polygalae*, *Radix Platycodonis*, *Radix Angelica Sinensis*, *Asparagus cochinchinensis*, *Ophiopogonis Radix*, *Platycladus orientalis*, and *Zizipus jujuba* Mill. *Var. spinosa*. for the prevention of acute RT toxicity in patients with HNC, with group receiving a placebo treatment alongside RT compared to TWBXM (3 g, three times daily, during and up to one month after RT) demonstrated the safety and efficacy of TWBXM applied in the HNC patients receiving RT [16]. It prevented the decrease of Hgb in HNC patients undergoing RT treatment, as well, 1-month-post-RT treatment [16]. TWBXM has been used for centuries for the treatment of anemia, OM, xerostomia, and mouth ulcers in TCM. The study results are in line with studies that have revealed the potential effectiveness of TCM on the treatment of RT-related toxicities in HNC patients [16,55].

Strength and limitation

Although several previous reviews have investigated the use of herbal medicines in HNC, this study provides a novel perspective by specifically focusing on RCTs and offering a more up-to-date and comprehensive analysis. The main strength of this article lies in the inclusion of

RCTs, which represent the highest level in the hierarchy of evidence and therefore, provide more reliable and valid results. In addition, we conducted a quality assessment of the included studies using the Jadad Scale, a standardized and widely accepted tool that evaluates methodological rigor based on randomization, blinding, and withdrawals. Nevertheless, this review has limitations. First, we limited our literature search to two databases. Second, this review was unable to examine articles published in languages other than English that provided information on herbal medicine, which may have resulted in the exclusion of some studies in this topic area. To address the limitations identified in this review, future studies should consider a broader range of literature searches with additional databases. By considering these aspects, future reviews may provide a stronger understanding of the role of herbal medicine in HNC.

Conclusions

This review provides a comprehensive synthesis of RCTs investigating the role of herbal medicine in the management of HNC, focusing on four main domains: mucositis, gastrointestinal symptoms, safety, and therapeutic efficacy. The findings highlight the potential benefits of various herbal formulations, such as curcumin-based products, TCM, Persian medicine, and Kampo medicine in alleviating treatment-related complications, particularly OM and gastrointestinal dysfunction. Furthermore, certain herbal interventions demonstrated promising immunomodulatory and supportive effects during radiotherapy and chemotherapy, indicating a broader therapeutic value. Therefore, further exploration is needed to integrate herbal medicine into HNC management and pave the way for innovative and supportive care strategies according to patient needs.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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