Post-print of a Clinical Study on Clove Guanshitong Lozenge Alone and in Combination with Fugui Guanshitong Granules for Advanced Esophageal Cancer

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Abstract

Background: Traditional Chinese medicine has become an important therapeutic option for advanced esophageal cancer patients who are ineligible for surgery, radiotherapy, or chemotherapy, or who have experienced disease progression following chemotherapy. This study aims to investigate the clinical efficacy of Dingxiang Guanshitong Hanhua Pills used alone and in combination with Fugui Guanshitong Granules, in order to improve the quality of life of advanced esophageal cancer patients and provide an effective treatment protocol for the TCM management of esophageal cancer.

Objective: To evaluate the effects of Dingxiang Guanshitong Hanhua Pills alone and combined with Fugui Guanshitong Granules on survival rate and quality of life in esophageal cancer patients after 6 weeks of treatment.

Methods: A total of 109 advanced esophageal cancer patients admitted to nine centers (including the First Affiliated Hospital of Henan University of Chinese Medicine, Linzhou Traditional Chinese Medicine Hospital, and Jiaxian Traditional Chinese Medicine Hospital) between January 2020 and April 2021 were enrolled. Using block randomization, patients were divided into three groups: control group, test group 1, and test group 2, with 40 cases in each group. The control group received Danggui Buxue Tang combined with Guizhi Renshen Tang granules; test group 1 received Dingxiang Guanshitong Hanhua Pills combined with Fugui Guanshitong Granules; test group 2 received Dingxiang Guanshitong Hanhua Pills alone for a 6-week treatment course. Survival rates after 6 weeks of treatment, as well as quality of life (QOL) scores, performance status (KPS) scores, and TCM syndrome scores (dysphagia, retrosternal pain,

vomiting mucus, appetite loss, fatigue) before and after treatment were compared among the three groups, and safety was evaluated.

Results: After 6 weeks of treatment, survival rates were 72.7% in the control group, 88.6% in test group 1, and 86.8% in test group 2. There was no statistically significant difference in survival rates among the three groups (^{2}=4.036, P=0.133). No interaction effect between group and time was observed for QOL scores, KPS scores, or TCM syndrome scores (Pinteraction>0.05). The main effect of group was not significant for QOL scores, KPS scores, or TCM syndrome scores (Pbetween-group>0.05). The main effect of time was significant for QOL scores, KPS scores, and TCM syndrome scores (Ptime<0.05). An interaction effect between group and time was observed for vomiting mucus scores (Pinteraction<0.05). Furthermore, after 6 weeks of treatment, patients in test group 2 had lower scores for appetite loss and vomiting mucus compared with test group 1, with statistically significant differences (P<0.05). Adverse events across the three groups included diarrhea, fever, dry mouth, sore throat, inability to eat, and pulmonary infection, with no severe related complications. There was no statistically significant difference in the incidence of adverse events among the three groups (^{2}=0.063, P=0.969).

Conclusion: All three treatment regimens can alleviate clinical symptoms and improve quality of life in advanced esophageal cancer patients, and Dingxiang Guanshitong Hanhua Pills alone demonstrates superior efficacy for appetite loss and vomiting mucus compared with both Danggui Buxue Tang combined with Guizhi Renshen Tang granules and Dingxiang Guanshitong Hanhua Pills combined with Fugui Guanshitong Granules.

Full Text

Clinical Observation of Dingxiang Guanshitong Hanhua Pills Alone and Its Combination with Fugui Guanshitong Granules in the Treatment of Advanced Esophageal Cancer

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Abstract

Background: Traditional Chinese medicine (TCM) has become an important therapeutic option for patients with advanced esophageal cancer who are unable to undergo surgery, radiotherapy, chemotherapy, or have experienced disease progression following chemotherapy. This study investigates the clinical effects of Dingxiang Guanshitong Hanhua Pills used alone and in combination with Fugui Guanshitong Granules, aiming to improve quality of life and provide an effective TCM treatment protocol for advanced esophageal cancer.

Objective: To evaluate the effects of Dingxiang Guanshitong Hanhua Pills alone and combined with Fugui Guanshitong Granules on survival rate and quality of life in patients with esophageal cancer after 6 weeks of treatment.

Methods: A total of 109 patients with advanced esophageal cancer admitted to nine centers (including the First Affiliated Hospital of Henan University of Chinese Medicine, Linzhou Hospital of Traditional Chinese Medicine, and Jiaxian Hospital of Traditional Chinese Medicine) between January 2020 and April 2021 were enrolled. Using block randomization, patients were allocated to three groups: control group (n=36), experimental group 1 (n=35), and experimental group 2 (n=38). The control group received Danggui Buxue Decoction combined with Guizhi Renshen Decoction Granules; experimental group 1 received Dingxiang Guanshitong Hanhua Pills combined with Fugui Guanshitong Granules; and experimental group 2 received Dingxiang Guanshitong Hanhua Pills alone. All treatments were administered for 6 weeks. Survival rate at 6 weeks, quality of life (QOL) scores, Karnofsky Performance Status (KPS) scores, and TCM syndrome scores (dysphagia, retrosternal pain, mucus vomiting, appetite loss, fatigue) were compared before and after treatment, with safety evaluations conducted.

Results: After 6 weeks, survival rates were 72.7% in the control group, 88.6% in experimental group 1, and 86.8% in experimental group 2, with no statistically significant difference among the three groups (^{2}=4.036, P=0.133). No interaction effect between group and time was observed for QOL scores, KPS scores, or TCM syndrome scores (P_{interaction}>0.05). The main effect of group was not significant for these outcomes (P_{intergroup}>0.05), while the main effect of time was significant (P_{time}<0.05). A significant interaction effect between group and time was found for mucus vomiting scores (P_{interaction}<0.05). After 6 weeks, appetite loss and mucus vomiting scores in experimental group 2 were significantly lower than those in experimental group 1 (P<0.05). Adverse events across the three groups included diarrhea,

fever, dry mouth, sore throat, inability to eat, and pulmonary infection, with no serious complications reported. The incidence of adverse events did not differ significantly among groups (^{2}=0.063, P=0.969).

Conclusion: All three treatment regimens alleviated clinical symptoms and improved quality of life in patients with advanced esophageal cancer. Dingxiang Guanshitong Hanhua Pills alone demonstrated superior efficacy in treating appetite loss and mucus vomiting compared to both Danggui Buxue Decoction combined with Guizhi Renshen Decoction Granules and the combined regimen of Dingxiang Guanshitong Hanhua Pills with Fugui Guanshitong Granules.

Keywords: Esophageal neoplasms; Advanced esophageal cancer; Spleen-kidney yang deficiency, stubborn phlegm and stagnant blood syndrome; Dingxiang Guanshitong Hanhua Pills; Fugui Guanshitong Granules; Chinese medical formula; Clinical study

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Introduction

Esophageal cancer ranks as the sixth most common malignant tumor in China, with approximately 300,000 new cases annually, accounting for 55.3% of global cases [1-2]. Current treatment approaches primarily integrate Chinese and Western medicine, combining TCM with surgery, radiotherapy, chemotherapy, ion stent implantation, and photodynamic therapy to significantly improve patient quality of life and prolong survival [3]. For patients with advanced esophageal cancer who cannot undergo surgery, radiotherapy, chemotherapy, or have experienced post-chemotherapy disease progression, TCM has become an important therapeutic alternative. Characterized by holistic concepts, syndrome differentiation, and individualized treatment, TCM offers cost-effective and convenient administration. To identify optimal treatment protocols and improve survival and quality of life for advanced esophageal cancer patients, Professor Zheng Yuling' s research team developed Dingxiang Guanshitong Hanhua Pills based on extensive clinical experience and TCM theory, targeting the common pattern of spleen-kidney yang deficiency with stubborn phlegm and stagnant blood in advanced esophageal cancer [4]. Preliminary clinical observations by our research group found that either the combination of Fugui Guanshitong Granules with Dingxiang Guanshitong Hanhua Pills or Dingxiang Guanshitong Hanhua Pills alone could improve clinical symptoms and quality of life. Building on this, we conducted a randomized, controlled, prospective study to evaluate the clinical efficacy and safety of Dingxiang Guanshitong Hanhua Pills alone and in combination with Fugui Guanshitong Granules for advanced esophageal cancer, aiming to enhance patient quality of life and provide an effective TCM treatment protocol.

1. Methods

1.1 Study Subjects From January 2020 to April 2021, 120 patients with advanced esophageal cancer were recruited from nine centers including the First Affiliated Hospital of Henan University of Chinese Medicine, Linzhou Hospital of Traditional Chinese Medicine, and Jiaxian Hospital of Traditional Chinese Medicine. Using block randomization, patients were divided into three groups: control, experimental group 1, and experimental group 2, with 40 patients each. The study protocol was approved by the Ethics Committee of Henan Province Hospital of Traditional Chinese Medicine [Approval No.: 2019 Hospital Ethics Review (36)].

1.1.1 Inclusion Criteria

(1) Pathologically confirmed esophageal cancer diagnosis; (2) Advanced-stage patients ineligible for surgery, radiotherapy, chemotherapy, or with post-chemotherapy disease progression; (3) No restrictions on gender or age; (4) Expected survival >20 days; (5) Karnofsky Performance Status (KPS) score $ $40; (6) Able to take oral medication before treatment; (7) Normal blood routine and cardiac, hepatic, and renal function; (8) Signed informed consent.

1.1.2 Exclusion Criteria

(1) Pregnant or lactating women; (2) Patients with psychiatric disorders unable to cooperate with treatment; (3) Drug allergies; (4) Severe hepatic, renal, cardiac, or hematopoietic system diseases; (5) No definitive pathological diagnosis; (6) Participation in other clinical studies; (7) Conditions that might complicate enrollment or follow-up, such as unstable work or living environments.

1.1.3 Exclusion Criteria for Analysis

(1) Cases without any evaluable records after medication; (2) Subjects who met inclusion criteria but failed to complete the trial for any reason, including voluntary or involuntary withdrawal. Reasons for exclusion should be documented, with case report forms retained for review.

1.2 Diagnostic Criteria

1.2.1 Western Medicine Diagnostic Criteria

(1) All patients had a definitive pathological diagnosis of esophageal cancer, staged according to the 8th edition TNM classification of the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) implemented in 2017 [5]; (2) Histological type: squamous cell carcinoma; (3) Pathological grading (G): Gx (grade cannot be determined)

was classified as G1; G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated), and G4 (undifferentiated) were classified as G3 for squamous cell carcinoma staging.

1.2.2 Traditional Chinese Medicine Diagnostic Criteria TCM syndrome differentiation was based on the "Eleventh Five-Year" national planning textbook *Oncology in Traditional Chinese Medicine* [6] and clinical diagnostic criteria for spleen-kidney yang deficiency with stubborn phlegm and stagnant blood syndrome in esophageal cancer established by Professor Zheng Yuling' s team. Main symptoms: inability to swallow food; choking sensation; vomiting of clear saliva or foam; pale and swollen tongue with little coating; deep, thin or weak pulse. Accompanying symptoms: pale complexion; fatigue and shortness of breath; aversion to cold; facial or bilateral lower limb edema; irregular bowel movements. Diagnosis required two of the first three main symptoms plus two of the five accompanying symptoms, confirmed by two physicians with senior professional titles.

1.3 Treatment Methods

1.3.1 Control Group The control group received Danggui Buxue Decoction combined with Guizhi Renshen Decoction Granules (Sichuan Xinlüse Co., Ltd.), the recommended primary formula for esophageal cancer in the *Guidelines for TCM Diagnosis and Treatment of Tumors: ZYYXH/T136~156-2008* [7] issued by the China Association of Chinese Medicine. Composition: Astragalus membranaceus. Dosage: one dose daily, three times daily for 6 weeks.

1.3.2 Experimental Group 1 Experimental group 1 received Dingxiang Guanshitong Hanhua Pills combined with Fugui Guanshitong Granules: (1) Dingxiang Guanshitong Hanhua Pills (Sichuan Xinlüse Co., Ltd., prepared as pills by the pharmacy of Henan Province Hospital of Traditional Chinese Medicine; Batch No.: 20200801), an empirical formula originally named Guanshitong Hanhua Pills, composed of Syzygium aromaticum, Aquilaria sinensis, Panax ginseng, Rehmannia glutinosa, Cinnamomum cassia, and Asarum sieboldii. Administration: one pill sublingually, three times daily for 6 weeks. (2) Fugui Guanshitong Granules (Sichuan Xinlüse Co., Ltd.), originally named Fuzheng Guben Tongye Granules, composed of processed Aconitum carmichaelii and Dioscorea opposita. Dosage: one dose daily, three times daily for 6 weeks.

1.3.3 Experimental Group 2 Experimental group 2 received Dingxiang Guanshitong Hanhua Pills alone, with the same dosage and administration as above. All medications were dispensed and recorded by the pharmacy of Henan Province Hospital of Traditional Chinese Medicine according to each subject' s visit sequence. At each follow-up, the quantity of medication taken and returned

by subjects was recorded. Considering the poor physical condition and short survival time of advanced esophageal cancer patients, concurrent basic treatments such as nutritional support and symptomatic therapy were permitted with the investigators' knowledge.

1.4 Outcome Measures

1.4.1 Baseline Data Collection Baseline data included gender, age, esophageal cancer course, allergy history, smoking history (smoking cessation: $ $2 years before enrollment; smoking: $ $1 cigarette/day for >6 months; both smoking and cessation counted as smoking history), alcohol consumption history (alcohol cessation: $ $2 years before enrollment; drinking: $ $1 time/week for >6 months; both drinking and cessation counted as alcohol history), surgical resection history, chemotherapy history, radiotherapy history, targeted therapy history, immunotherapy history, coronary heart disease history, hypertension history, and diabetes history.

1.4.2 Primary Outcome Measures Primary outcomes included 6-week survival rate, Quality of Life (QOL) score [8] (total score 60: <20=very poor, 21-30=poor, 31-40=fair, 41-50=good, 51-60=very good; higher scores indicate better quality of life), Karnofsky Performance Status (KPS) score [8] (total score 100; higher scores indicate better quality of life), and TCM syndrome score [9] (appetite loss, mucus vomiting, dysphagia, retrosternal pain, and fatigue were scored as Grade III=3, Grade II=2, Grade I=1, Grade 0=0; total score 15; lower scores indicate better quality of life).

1.4.3 Safety Evaluation Safety evaluation included vital signs (heart rate, respiration, blood pressure, temperature), laboratory tests (blood routine, urine routine, liver function, renal function, electrocardiogram), and adverse event records.

1.4.4 Toxicity and Side Effects Toxicity and side effects related to treatment were recorded, including gastrointestinal reactions, bone marrow suppression, hepatic and renal function damage, and neurotoxicity.

1.5 Follow-up Follow-up was conducted through regular outpatient visits or electronic communication, with weekly follow-ups for 6 weeks, using 2-week intervals as nodes. Observed indicators were recorded at each time point (baseline, 2 weeks, 4 weeks, 6 weeks) as shown in Table 2 .

1.6 Statistical Methods Statistical analysis was performed using SPSS 25.0 software. Normally distributed measurement data were expressed as ($\bar{x}\pm s$) and compared among the three groups using one-way ANOVA. Non-normally distributed measurement data were expressed as M(P_{25}, P_{75}) and compared using

Kruskal-Wallis H test. Count data were expressed as percentages and analyzed using ^{2} test or Fisher' s exact test. Generalized estimating equations were used to compare QOL scores, KPS scores, and TCM syndrome scores among the three groups at different time points. P<0.05 was considered statistically significant.

2. Results

2.1 Comparison of Baseline Data Among Three Groups A total of 109 patients with advanced esophageal cancer were included: 36 in the control group, 35 in experimental group 1, and 38 in experimental group 2. No statistically significant differences were observed among the three groups in gender, age, disease course, allergy history, smoking history, alcohol history, surgical resection history, chemotherapy history, radiotherapy history, targeted therapy history, immunotherapy history, coronary heart disease history, hypertension history, or diabetes history (P>0.05), as shown in Table 1 .

2.2 Comparison of 6-Week Survival Rates Among Three Groups After 6 weeks of treatment, survival rates were 72.7% (26/36) in the control group, 88.6% (31/35) in experimental group 1, and 86.8% (33/38) in experimental group 2. No statistically significant difference was found among the three groups (^{2}=4.026, P=0.133).

2.3 Comparison of QOL Scores Before and After Treatment No interaction effect between group and time was observed for QOL scores (P_{interaction}>0.05). The main effect of group was not significant (P_{intergroup}>0.05), while the main effect of time was significant (P_{time}<0.05). QOL scores at 4 and 6 weeks were significantly higher than baseline and 2-week scores in all three groups, and 6-week scores were significantly higher than 4-week scores (P<0.05), as shown in Table 2 .

2.4 Comparison of KPS Scores Before and After Treatment No interaction effect between group and time was observed for KPS scores (P_{interaction}>0.05). The main effect of group was not significant (P_{intergroup}>0.05), while the main effect of time was significant (P_{time}<0.05). KPS scores at 6 weeks were significantly higher than 4-week scores in all three groups (P<0.05), as shown in Table 3 .

2.5 Comparison of TCM Syndrome Scores Before and After Treatment No interaction effect between group and time was observed for overall TCM syndrome scores (P_{interaction}>0.05). The main effect of group was significant (P_{intergroup}<0.05), and the main effect of time was significant (P_{time}<0.05). TCM syndrome scores at 2, 4, and 6 weeks were significantly lower than baseline, with scores at 4 and 6 weeks lower than at 2 weeks, and 6-week scores lower than 4-week scores (P<0.05), as shown in Table 4 .

A significant interaction effect between group and time was found for mucus vomiting scores (P_{interaction}<0.05), but not for appetite loss, dysphagia, retrosternal pain, or fatigue scores (P_{interaction}>0.05). The main effect of group was significant for appetite loss and mucus vomiting scores (P_{intergroup}<0.05), and the main effect of time was significant for appetite loss, mucus vomiting, dysphagia, and retrosternal pain scores (P_{time}<0.05). After 6 weeks, appetite loss and mucus vomiting scores in experimental group 2 were significantly lower than those in experimental group 1 (P<0.05).

At 2 weeks, appetite loss, mucus vomiting, and retrosternal pain scores were significantly lower than baseline in all three groups (P<0.05). At 4 weeks, appetite loss, mucus vomiting, dysphagia, and retrosternal pain scores were significantly lower than baseline, with appetite loss and mucus vomiting scores also lower than at 2 weeks (P<0.05). At 6 weeks, appetite loss, mucus vomiting, dysphagia, retrosternal pain, and fatigue scores were significantly lower than baseline, with appetite loss, mucus vomiting, and dysphagia scores lower than at 2 weeks (P<0.05), as shown in Table 5 .

2.6 Safety Evaluation Adverse events across the three groups included diarrhea, fever, dry mouth, sore throat, inability to eat, and pulmonary infection. The vast majority were considered unrelated to the study medications, and no serious complications occurred. The incidence rates were 19.4% (7/36) in the control group, 17.1% (6/35) in experimental group 1, and 18.4% (7/38) in experimental group 2, with no statistically significant difference among groups (^{2}=0.063, P=0.969).

Discussion

For ethical considerations, this study did not include a placebo control group but instead used the esophageal cancer treatment recommended in the *Guidelines for TCM Diagnosis and Treatment of Tumors: ZYYXH/T136~156-2008* [7] as the control. TCM formulas have evolved into various internal and external preparations—including decoctions, wines, pills, powders, and ointments —through accumulated clinical experience. Pills are particularly suitable for chronic or debilitating conditions. Dingxiang Guanshitong Hanhua Pills, as a pill formulation, are appropriate for cancer patients with relatively stable pathomechanisms who have not undergone surgery, radiotherapy, or chemotherapy. Pills can be taken long-term, and sublingual administration allows the medication to reach the lesion directly, increasing drug concentration. Additionally, pills offer convenient administration and cost-effectiveness [10]. This study innovatively combines TCM concepts with clinical research by applying Dingxiang Guanshitong Hanhua Pills to treat advanced esophageal cancer, providing new insights for investigating the mechanisms of TCM in esophageal cancer treatment.

No statistically significant difference was found among the three treatment regimens in terms of survival rate (P>0.05). However, time showed significant main

effects on QOL scores, KPS scores, and TCM syndrome scores across all three groups ($P<0.05$). Post-treatment QOL and KPS scores changed over time, with pairwise comparisons revealing significant improvements in QOL scores following all three treatment protocols. TCM syndrome scores also decreased over time, with all three regimens showing significant efficacy in improving appetite loss, dysphagia, retrosternal pain, mucus vomiting, and fatigue. Between-group comparisons revealed that experimental group 2 was superior to the control group in improving appetite loss and mucus vomiting. Regarding safety, although experimental groups 1 and 2 had lower adverse event rates than the control group, the difference was not statistically significant ($P>0.05$), and no serious complications occurred. These findings indicate that all three treatment regimens effectively improved clinical symptoms and quality of life, with experimental group 2 showing more pronounced clinical improvements, possibly because continuous medication administration increased patient discomfort in the other groups, resulting in no significant differences between experimental group 1 and the control group.

Modern pharmacological studies demonstrate that Syzygium aromaticum (clove) induces tumor cell apoptosis by upregulating pro-apoptotic and downregulating anti-apoptotic protein expression [11]. Clove extracts enhance fluorescence magnetic nanoparticle-mediated cancer cell apoptosis, with significant cell proliferation reduction observed after 24 hours and further dose-dependent reduction after 48 hours [12]. Aquilaria sinensis (agarwood) possesses anti-tumor, analgesic [13], and antioxidant [14] activities. Ginsenosides may inhibit tumor angiogenesis by reducing vascular endothelial growth factor [15] and exert anti-tumor effects through multiple pathways including suppression of angiogenesis, promotion of tumor cell apoptosis, induction of cell cycle arrest, and reversal of drug resistance [16]. Rehmannia glutinosa (prepared rehmannia) exhibits pharmacological activities including anti-aging, anti-tumor, lipid and glucose regulation, antibacterial effects, anti-gastric ulcer, antidepressant, and hepatoprotective effects [17]. Cinnamomum cassia (cinnamon) demonstrates anti-tumor properties while enhancing immunity, with anti-radiation and anti-mutagenic effects [18]. Asarum sieboldii (asarum) exhibits multiple pharmacological activities, with α-asarone inhibiting human esophageal cancer cell proliferation by regulating mitochondrial apoptosis pathway gene expression and controlling lung cancer cell proliferation, demonstrating anti-cancer potential [19]. Asarum also shows immunomodulatory and anti-inflammatory effects both in vivo and in vitro, with its volatile oil possessing antipyretic and analgesic properties [20]. Curcuma longa (turmeric) demonstrates anti-tumor effects by inducing apoptosis and autophagy, inhibiting tumor cell growth, invasion, and metastasis, thereby suppressing early tumor dissemination and recurrence and improving prognosis [21]. Panax notoginseng (notoginseng) and its total saponin extracts exert anti-tumor effects by inhibiting precancerous cell malignant transformation, cancer cell proliferation, and metastasis, while also protecting against myocardial and cerebral ischemia, promoting neural stem cell proliferation after cerebral ischemia, and exhibiting anti-inflammatory, antibacterial, and anti-aging effects

[22]. Sargassum (seaweed) demonstrates anti-tumor effects primarily through inhibiting tumor cell proliferation and inducing apoptosis, with known anti-metastatic and anti-angiogenic activities in vivo [23-24].

Thus, the main components of Dingxiang Guanshitong Hanhua Pills all exhibit varying degrees of anti-tumor, anti-inflammatory, antioxidant, and immunomodulatory effects, pharmacologically validating its efficacy in treating esophageal cancer. This study utilized repeated measures data, which meets the application requirements for linear mixed models and generalized estimating equations (GEE). For small sample sizes, GEE provides more stable results. Due to the COVID-19 pandemic, some patients had missing data, and the relatively small sample size resulted in non-normal distribution and numerous missing values, making GEE analysis more appropriate.

In summary, Dingxiang Guanshitong Hanhua Pills alone, combined with Fugui Guanshitong Granules, and Danggui Buxue Decoction combined with Guizhi Renshen Decoction Granules all alleviated symptoms and improved quality of life in patients with advanced esophageal cancer, with Dingxiang Guanshitong Hanhua Pills alone showing more pronounced clinical improvements. Both monotherapy and combination therapy with Dingxiang Guanshitong Hanhua Pills may improve survival rates to some extent and are suitable for patients with advanced esophageal cancer, demonstrating safety and efficacy worthy of clinical promotion. However, this study has limitations including small sample sizes at some centers and short observation periods. Future multi-center, large-sample randomized controlled trials are needed to validate these findings. The specific mechanisms of Dingxiang Guanshitong Hanhua Pills in treating advanced esophageal cancer remain unclear and will be further explored through animal experiments.

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Author Contributions

Yuling Zheng: Study conception, design, and feasibility analysis. **Yaling Zhang, Huaimin Liu, Yanchao Xu, Xiaolin Jia, Junsai Li, Wenlong He, Xinduo Tong, Shanwen Qin, Lihan Zhang:** Data collection. **Yaling Zhang:** Study implementation, data collation, statistical analysis, results interpretation, and manuscript drafting. **Yuling Zheng, Huaimin Liu:** Manuscript revision, quality control, and final approval. All authors take

responsibility for the overall content and supervision of the study.

Conflict of Interest

This article has no conflict of interest.

References

[1] Liu ZC, Li ZX, Zhang Y, et al. Interpretation of the 2020 global cancer statistics report [J]. Journal of Multidisciplinary Cancer Management, 2021, 7(2): 1-13. DOI: 10.12151/JMCM.2021.02-01.
[2] Yuan HY, Jiang YF, Tan YT, et al. Global cancer incidence and mortality: current status and changing trends [J]. Cancer Research on Prevention and Treatment, 2021, 48(6): 642-646. DOI: 10.3971/j.issn.1000-8578.2021.20.1533.
[3] Zheng YL, Chen YL. Review of research on TCM treatment of esophageal cancer [J]. Journal of Oncology in Traditional Chinese Medicine, 2020, 2(3): 1-4. DOI: 10.19811/j.cnki.ISSN2096-3258.2020.03.001.
[4] Zheng YL. A Chinese medicine buccal pill for treating middle and advanced esophageal cancer: CN202011047671.5 [P]. 2021-09-24.
[5] Li HM, Sun HB, Zheng Y, et al. Interpretation of the 8th edition AJCC/UICC TNM staging for esophageal and esophagogastric junction cancers and main contents of the Chinese version [J]. Chinese Journal of Clinical Thoracic and Cardiovascular Surgery, 2017, 24(2): 87-92. DOI: 10.7507/1007-4848.201701022.
[6] Zhou DH. Oncology in Traditional Chinese Medicine [M]. Beijing: China Press of Traditional Chinese Medicine, 2011.
[7] China Association of Chinese Medicine. Guidelines for TCM Diagnosis and Treatment of Tumors: ZYYXH/T136~156-2008 [M]. Beijing: China Press of Traditional Chinese Medicine, 2008: 17-20.
[8] Sun Y. Internal Medicine Oncology [M]. Beijing: People' s Medical Publishing House, 2001.
[9] Zheng XY. Guidelines for Clinical Research of New Chinese Medicines: Trial Implementation [M]. Beijing: China Medical Science and Technology Press, 2002.
[10] Wang WS, Yang XY. Analysis of advantages of Chinese medicine pills in tumor treatment [J]. Inner Mongolia Journal of Traditional Chinese Medicine, 2017, 36(19): 97-98. DOI: 10.3969/j.issn.1006-0979.2017.19.058.
[11] Das A, K H, S K D K, et al. Evaluation of therapeutic potential of eugenol-a natural derivative of syzygium aromaticum on cervical cancer [J]. Asian Pac J Cancer Prev, 2018, 19(7): 1977-1985. DOI: 10.22034/APJCP.2018.19.7.1977.
[12] Khan FA, Akhtar S, Almohazey D, et al. Extracts of clove (Syzygium aromaticum) potentiate FMSP-nanoparticles induced cell death in MCF-7 cells [J]. Int J Biomater, 2018, 2018: 8479439. DOI: 10.1155/2018/8479439.
[13] Xiong LY, Ji GX, Lin L, et al. Study on effective analgesic parts and material basis of Aquilaria sinensis [J]. Lishizhen Medicine and Materia Medica Research, 2014, 25(8): 1842-1844. DOI: 10.3969/j.issn.1008-0805.2014.08.017.

[14] Tian CP, Song YL, Xu HT, et al. Comparative study on chemical composition analysis and antioxidant and antibacterial activities of agarwood essential oil extracted by supercritical and steam distillation [J]. China Journal of Chinese Materia Medica, 2019, 44(18): 4000-4008. DOI: 10.19540/j.cnki.cjcmm.20190629.302.
[15] Li YT, Tang YW. Ginsenoside Rg3 inhibits vasculogenic mimicry formation in gastric cancer SGC7901 cells by suppressing Wnt/β-catenin pathway in vitro [J]. Chinese Journal of Cancer Biotherapy, 2019, 26(5): 518-523. DOI: 10.3872/j.issn.1007-385x.2019.05.006.
[16] Li GM, Li Y. Current status of pharmacological research on ginsenosides [J]. Chinese Journal of Clinical Pharmacology, 2020, 36(8): 1024-1027. DOI: 10.13699/j.cnki.1001-6821.2020.08.024.
[17] Chen JP, Zhang KX, Liu Y, et al. Research progress on chemical constituents and pharmacological effects of Rehmannia glutinosa [J]. Chinese Traditional and Herbal Drugs, 2021, 52(6): 1772-1784. DOI: 10.7501/j.issn.0253-2670.2021.06.028.
[18] Wu CE, Wang RP, Teng YH. Research progress on active components and anti-tumor effects of Cinnamomum cassia [J]. Lishizhen Medicine and Materia Medica Research, 2015, 26(8): 1985-1987. DOI: 10.3969/j.issn.1008-0805.2105.08.073.
[19] Wang BY, Zhang FF, Han QQ, et al. Effects of α-asarone on mitochondrial apoptosis pathway in esophageal cancer Eca-109 cells [J]. Herald of Medicine, 2018, 37(1): 31-35. DOI: 10.3870/j.issn.1004-0781.2018.01.008.
[20] Wu H, Wen XY, Yan P, et al. Research progress on chemical constituents and pharmacological effects of Asarum sieboldii [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2021, 27(4): 186-195. DOI: 10.13422/j.cnki.syfjx.20202353.
[21] Jiang LH, Yin KX, Ge MH. Research progress on anti-tumor effects and related mechanisms of curcumin [J]. Jiangsu Medical Journal, 2018, 44(7): 830-834. DOI: 10.19460/j.cnki.0253-3685.2018.07.030.
[22] Huang YD, Cheng JX, Shi Y, et al. Research progress on chemical constituents, chromatographic analysis, extracts, and pharmacological activities of Panax notoginseng in recent five years [J]. China Journal of Chinese Materia Medica, 2022, 47(10): 2584-2596. DOI: 10.19540/j.cnki.cjcmm.20211220.202.
[23] Schneider T, Ehrig K, Liewert I, et al. Interference with the CXCL12/CXCR4 axis as potential antitumor strategy: superiority of a sulfated galactofucan from the brown alga Saccharina latissima and fucoidan over heparins [J]. Glycobiology, 2015, 25(8): 812-824. DOI: 10.1093/glycob/cwv022.
[24] Xiao QH, Chen ZX, Zheng Q, et al. Research progress and clinical application of anti-tumor pharmacological effects of seaweed [J]. China Foreign Medical Treatment, 2020, 39(19): 196-198. DOI: 10.16662/j.cnki.1674-0742.2020.19.196.

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