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Moxibustion for the Treatment of Cancer and its Complications: Efficacies and Mechanisms

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Abstract

Cancer treatment remains a significant challenge for the medical community, and improved therapies are necessary to treat cancer and its associated complications. Current anticancer therapies often have significant side effects, underscoring the need for new treatment options. Moxibustion is a representative external therapy used in traditional Chinese medicine. This review examines clinical studies demonstrating moxibustion's ability to improve the efficacy of radiotherapy and chemotherapy and control tumor progression. Moxibustion can prevent and treat various complications of cancer, including cancer-related or therapy-induced gastrointestinal symptoms, myelosuppression, fatigue, pain, and postoperative lymphedema. has also been shown to enhance the quality of life for cancer patients. However, very few studies have investigated the underlying mechanisms for these effects, a topic that requires systematic elucidation. Evidence has shown that moxibustion alone or combined with chemotherapy can improve survival and inhibit tumor growth in cancer-bearing animal models. The anticancer effect of moxibustion is associated with alleviating the tumor immunosuppressive and vascular microenvironments. Additionally, the therapeutic effects of moxibustion may originate from the heat and radiation produced during the combustion process on acupoints or lesions. This evidence provides a scientific basis for the clinical application of moxibustion in anticancer treatment and reducing the side effects of cancer therapies and helps promote the precise application of moxibustion in cancer treatment.

Keywords

moxibustion, cancer, complications of cancer, chemotherapy, side-effect

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Introduction

Cancer is a major non-communicable disease that seriously affects human health, with an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths recorded worldwide in 2020.[1] The main anticancer therapies include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, amongst others.[2] However, while suppressing tumor growth, these therapies also affect normal cells, resulting in significant side effects, such as chemotherapy-induced anemia, nausea, vomiting, infection, fatigue, and peripheral neuropathy.[3,4] Therefore, numerous studies have focused on methods for increasing the efficacy of chemotherapy while reducing its side effects. Complications also arise from the tumor, including cancer-related pain, fatigue, pleural and

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abdominal effusion, intestinal obstruction, and fever. As attention to the physiological, psychological, and social well-being of cancer patients has increased, enhancing their quality of life has become a crucial aspect of the treatment process.

Moxibustion is one of the external therapies used in traditional Chinese medicine (TCM), which heats the acupoints by burning moxa or herbs on the acupoints, leading to therapeutic effects.[5] It has been found that moxibustion can relieve cancer complications, including adverse reactions after chemotherapy, such as gastrointestinal toxicity and myelosuppression, as well as cancer-related fatigue, pain, and postoperative lymphedema.[6] Moxibustion has also been shown to boost the anticancer effect of chemotherapy and improve the quality of life for patients.[7,8] Moxibustion can play an anticancer role through the thermal and radiation effects after burning. However, these effects and mechanisms have not been systematically summarized. Thus, this paper reviews moxibustion's clinical efficacy in reducing cancer therapy's toxicity, summarizes the current research status, and discusses the potential of moxibustion in inhibiting tumor growth from the aspects of improving tumor immune microenvironment and vascular normalization. Furthermore, we summarized the acupoint initiation and intrinsic regulation mechanisms. We hope to provide a scientific basis for the clinical application of moxibustion in cancer and promote the further application of moxibustion in cancer treatment.

Methods

Retrieval Strategy

A systematic search was conducted to retrieve relevant studies from the PubMed and Web of Science core collection databases from inception to October 2021. The search strategy involved the use of the medical subject headings terms and specific keywords: ["moxibustion" or "moxa"] and ["tumor" or "cancer" or "neoplas*" or "carcinoma*" or "malignan*"]. The search was limited to English and Chinese languages. Each database's search engine was used to filter out irrelevant studies. The initial search yielded 197 articles from PubMed and 142 from the Web of Science.

Research Selection

Duplicates within and between the 2 databases were identified and removed using NoteExpress software. Following the removal of 100 duplicate entries, 239 articles remained for evaluation. A detailed review of these articles' reference lists was undertaken to identify studies of relevance that fulfilled the predetermined inclusion criteria, initially based on the title and abstract, and subsequently corroborated by full-text review. These inclusion criteria comprised studies investigating the impact and underlying mechanisms of moxibustion intervention on tumors and their associated complications, encompassing clinical and animal experimental research. Intervention methods encompassed a variety of moxibustion methods, such as mild moxibustion, grain-moxibustion, ginger-partitioned moxibustion, and heat-sensitive moxibustion. Exclusion criteria involved articles devoid of an abstract or full text, those unrelated to the research topic as indicated in the title and abstract, along with case reports, protocols, reviews, and meta-analyses. The final selection comprised 19 clinical studies and 20 basic science studies. The first and third authors of this review selected the articles. The search process is graphically represented in Figure 1.

Data Extraction

The data from the 19 clinical and 20 basic science studies are shown in Tables 1 and 2, summarizing the clinical characteristics, actions, and mechanisms of moxibustion in cancer treatment. Data from the study design were collected and arranged using predetermined data extraction tables. Clinical study details encompass trial design, cancer type or related complications, study groups, intervention (including methods, acupoints, and moxibustion parameters), and respective outcomes. Similarly, details regarding the type of cancer model, intervention (methods, acupoints, and moxibustion parameters), and outcomes were collected for basic science research. The resolution of any disparities in the extracted data was achieved through author discussions. Any disagreement was resolved by discussion between the authors.

General Characteristics of Studies on Moxibustion Intervention in Cancers

Although few studies on moxibustion in cancer treatment were published before 2005, their number has steadily increased since then (Figure 2A). By region, China accounted for more than half of the research volume, and 14 other countries also had relevant studies, among which South Korea and the USA ranked second and third, respectively. In general, the use of moxibustion in cancer treatment has received increasing attention and recognition (Figure 2B).

The main tumor types that involved moxibustion treatment included breast, lung, gastric, and nasopharyngeal cancers. In addition to carcinoma in situ, metastatic cancers have also been studied. Moxibustion can be divided into direct and indirect moxibustion. In the direct form, heat stimulation is applied directly to the skin surface, while indirect moxibustion involves the placement of ginger, garlic, salt, or herbal cake between the burning moxa

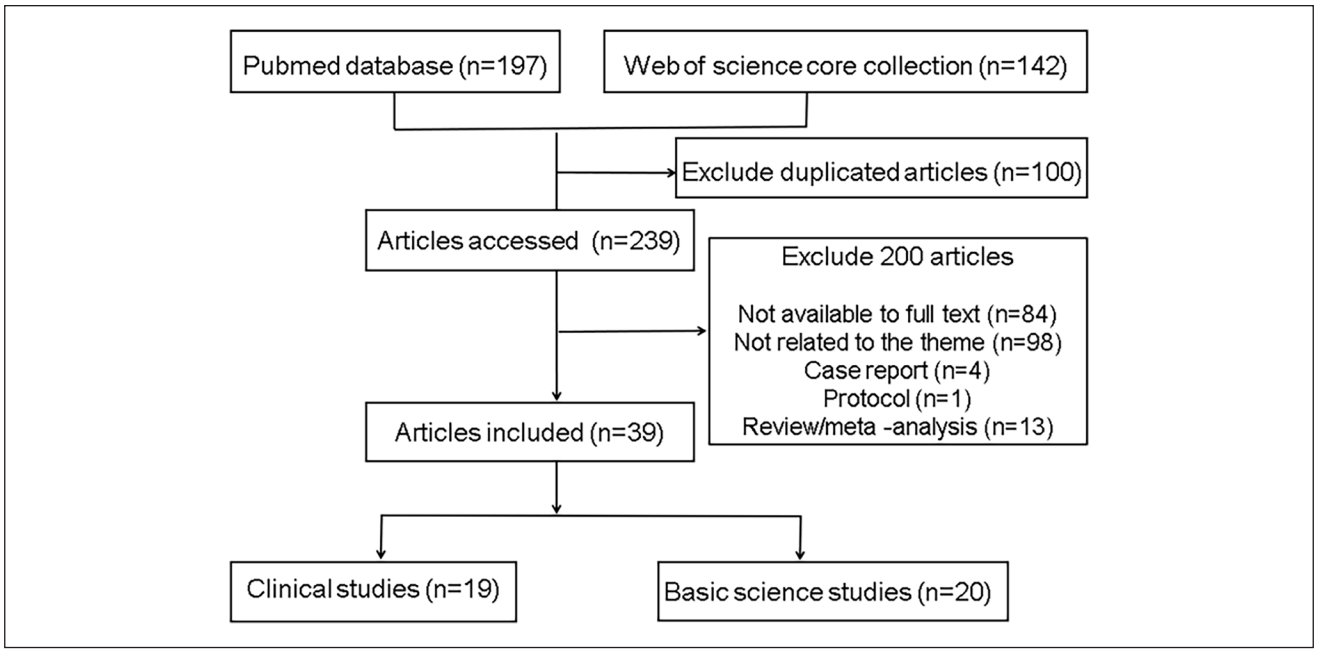

Figure 1. Flow chart of the search processes.

cone and the skin surface. Several specialized moxibustion methods exist, such as thunder-fire, heat-sensitive, and electronic moxibustion. Electronic moxibustion, including infrared laser moxibustion, is a significant advancement in traditional practice. It addresses several limitations of traditional moxibustion, such as smoke production, ash and burn risks, and low efficiency. The most commonly used acupoint in clinical studies was *Zusanli* (ST36). Among the 19 clinical studies in our review, 11 utilized the acupoint ST36. In TCM, ST36 is believed to nourish *qi* and regulate the spleen and stomach functions. In addition, moxibustion was often used with acupuncture or drugs, especially chemotherapy drugs.

The Effects and Mechanism by Which Moxibustion Reduces the Toxicity of Cancer Therapies

Gastrointestinal (GI) Toxicity

GI toxicity is one of the most common adverse reactions experienced during chemotherapy. It includes chemotherapy-induced nausea and vomiting (CINV), diarrhea, and constipation. 5-Hydroxytryptamine (5-HT) receptor antagonists can alleviate acute CINV, yet they fail to effectively control about 30% of acute and 60% of delayed vomiting cases.[46] In one study, lung cancer patients in a control group were treated with a conventional antiemetic regimen with a 5-HT receptor antagonist, while the observation group was treated with moxibustion *Baihui* (GV20) and *Zhongwan* (CV12). The incidence of nausea and vomiting was assessed at intervals of 0 to 24, 24 to 48, 48 to 72, and 72 to 96 hours post-chemotherapy. The degree of nausea and vomiting in both patient groups was evaluated using the Index of Nausea, Vomiting, and Retching (INVR). The results showed that in the 4 observation periods (0-24, 24-48, 48-72, and 72-96 hours after chemotherapy), the incidence of nausea and vomiting, as well as the nausea scores, in the observation group were lower than those in the control group.[12] Research has found that mild moxibustion at ST36, *Guanyuan* (CV4), *Qihai* (CV6), and salt separation moxibustion at *Shenque* (CV8) effectively reduce chemotherapy-induced symptoms of nausea, vomiting, and constipation in breast cancer patients. The mechanism may be related to the down-regulation of pepsinogen I (positively correlated with gastric acid secretion), pepsinogen II (an indicator of chronic gastric mucosal inflammation), and gastrin-17, a non-invasive biological indicator of gastric mucosal structure.[15] In a study by Zhang et al, tropisetron was used as a control while the experimental group underwent ginger-separated moxibustion at ST36, Neiguan (PC6), Tianshu (ST25), and CV8 acupoints in addition to tropisetron. The results showed a significant improvement in the observation group's effectiveness, with the effectiveness rate increasing from 76.67% to 90% 24 hours post-chemotherapy and 83.33% to 96.67% 7 days after chemotherapy. This indicates that combining ginger-separated moxibustion and tropisetron was more effective in treating digestive tract side effects than using tropisetron alone.[13] According to the principle of selecting acupoints

Table 1. The Clinical Efficacy of Moxibustion on Tumor Patients.

Ref.	Trial design	Cancer type/ complication	Intervention group	Control group	Acupoints	Moxibustion parameters	Outcomes
Wang et al[9]	RCT	Breast cancer-related lymphedema	(A) Moxibustion (n = 24)	(B) Compression garments (n = 24)	LI14, LI13, SJ5, SI9, BL23, *Ashi* points	Moxa stick: 1.8 × 20 (cm), 5 cm from skin, 30 min, every 2 d; 4 wk	Up: total RPFS scores, behavior, sensory, emotional, and cognitive RPFS scores (self-control) Down: the circumference of the affected arm, VAS swelling score
Wang et al[10]	Controlled trial	Advanced gastric cancer	(A) Grain-moxibustion plus (B) (n = 30)	(B) Chemotherapy plus symptomatic treatment (n = 30)	ST36, BL21	5 mg, 9 pillars, once a day, 90 d	Up: general health condition Down: NLR, fatigue, nausea, vomiting, loss of appetite, diarrhea (self-control); fatigue, sleep disorder, loss of appetite, diarrhea (vs control group)
Li et al[11]	Controlled trial	Advanced malignant tumor with nausea and vomiting	(A) Haloperidol plus (B) (n = 65) (C) Moxibustion plus (B) (n = 63) (D) Moxibustion plus (A) (n = 68)	(B) Metoclopramide (n = 70)	ST36, CV4, CV6	20 min, twice a day, 2 wk	Up: FACT-G total scores, physiological and emotional scores Down: INVR score, HAMD score
Li and Li[12]	Controlled trial	Nausea and vomiting induced by cisplatin for lung cancer	(A) Moxibustion plus (B) (n = 29)	(B) 5-HT receptor antagonist (n = 29)	GV20, CV12	5 pillars, once a day, 3 d	Down: INVR, the incidence of nausea and vomiting, fatigue score
Zhang et al[13]	RCT	Nausea and vomiting after chemotherapy for lung cancer	(A) Ginger-partitioned moxibustion plus (B) (n = 30)	(B) Tropisetron (n = 30)	ST36, PC6, ST25, CV8	Moxa cone: 1 × 1 (cm), ginger slices: 2 × 3 × 0.3 (cm), 5 pillars, the degree is local flush, 20 min, once a day, 3 d	Up: WBC, Karnofsky functional status score, platelet count (7 d after chemotherapy) Down: gastrointestinal reaction (24 h/7 d after chemotherapy)
Jeon et al[14]	Randomized sham controlled trial	Anorexia in patients with metastatic cancer	(A) Moxibustion (n = 90)	(B) SM (n = 7)	CV12, CV8, CV4, ST36	40 min, 5 times per week, 2 wk	Down: anorexia-cachexia subscale of the FAACT questionnaire, EORTC QLQ-C30 questionnaire (fatigue, nausea, vomiting, pain, diarrhea)
Guo et al[15]	Controlled trial	Gastrointestinal reaction of breast cancer chemotherapy	(A) Mild moxibustion plus salt-separated Moxibustion (n = 24)	(B) Tropisetron hydrochloride (n = 24)	ST36, CV12, CV4, CV6, CV8	3 pillars, according to the degree of red halo on the moxibustion site,15 min, once a day, 7 d	Down: PG Ⅰ, PG Ⅱ, G-17 (serum), the score of nausea, vomiting, and constipation total scores
Zhang et al[16]	RCT	NSCLC	(A) Scar-producing moxibustion (n = 35)	(B) Black control (n = 35)	ST36, BL13	5 mg, once a day, 6 wk	Up: EORTC QLQ-C30 (global health status, quality of life, and function) Down: NLR, EORTC QLQ-C30
Lee and Yoon[17]	RCT	Pain in patients with metastatic cancer	(A) Moxibustion (n = 8)	(B) SM (n = 8)	CV4, CV12, three *Ashi* points	Moxa cone: 1.4 × 1.5 (cm), 150 mg; 10 min, once a day, 7 d	Down: total BPI score, BPI intensity score, BPI interference score
Lu et al[18]	Controlled trial	Qi deficiency-induced fatigue in breast cancer patients	(A) Thunder-fire moxibustion, plus chemotherapy (n = 30)	(B) Chemotherapy plus conventional nursing (n = 30)	BL20 to BL24 and to the abdominal part from CV12 to CV4	3 to 5 cm from skin, 30 min, once a day, 14 d	Up: WBC Down: BFI score, TCM syndrome score

(continued)

Table 1. (continued)

Ref.	Trial design	Cancer type/ complication	Intervention group	Control group	Acupoints	Moxibustion parameters	Outcomes
Zhou et al[19]	Controlled trial	Advanced malignant tumor	(A) Moxibustion plus (B) (n=30)	(B) Routine symptomatic scheme (n=30)	ST36	Moxa cone: 20×40 (mm); once a day, 12 d	Up: KPS (self-control) Down: TCM symptom score (lassitude, insomnia, poor appetite, spontaneous sweating, dizziness, vertigo)
Mao et al[20]	RCT	Cancer-related fatigue	(A) Infrared laser moxibustion (n=39)	(B) Sham laser moxibustion (n=39)	ST36, CV4, CV6	10.6 μm, 20 min, 3 times per week; 4 wk	Down: BFI-C score
Li et al[21]	Controlled trial	Colorectal cancer	(A) Heat-sensitive moxibustion plus chemotherapy (n=30)	(B) Chemotherapy plus medicant (n=30)	ST36, SP6	Once a day, 5 d for a course, 4 courses	Up: total effective rate of symptom improvement Down: the MDASI-C of reaction rate of uncomfortable symptoms/general activity (distress) and emotional distress (mood)
Zhang et al[22]	Controlled trial	NSCLC	(A) Moxibustion plus (B) (n=40)	(B) Chemotherapy (n=40)	BL17, BL19	3 pillars, once a day, 10 d	Up: CSF, IL-2 (serum) KPS score Down: TNF (serum)
Han et al[23]	Controlled trial	Breast cancer-related lymphedema	(A) Electronic moxibustion (n=10)	(B) Self-control	LI14, LI11, CTE5	30 min, twice per week, 8 wk	Up: flexion and internal rotation (8 wk) Down: EORTC QLQ-BR23 (arm symptoms, 5 wk)
Zhang et al[24]	RCT	NSCLC patients after chemotherapy	(A) Scarring moxibustion (n=35)	(B) Blank control (n=35)	ST3, BL13	9 pillars, once a day, 6 wk	Up: platelet count Down: NLR
Han et al[25]	RCT	Cancer-related fatigue	(A) Moxibustion (n=32)	(B) Usual care (n=32) (C) SM (n=32)	CV8, CV12, LI4, ST36	30 min; twice per week; 8 wk	Up: QLQ-C30 in terms of physical, emotional, and cognitive functions Down: BFI; FACT-F; QLQ-C30 (fatigue, dyspnea, appetite loss, diarrhea)
Chen et al[26]	Controlled trial	Ⅲ/Ⅳa stage nasopharyngeal carcinoma	(A) Moxibustion plus (B) (n=28)	(B) Chemotherapy plus radiotherapy (n=28)	CV8	Moxa cone: 1.5×2 (cm), 640 mg; 10 pillars, once a day, 30 times for a course	UP: -SH, SOD (plasma) (self-control) Down: MDA, MMS (plasma) (self-control) WBC, gastrointestinal symptoms, oral mucosa, and hair loss (vs control group)
Zhang et al[27]	RCT	Advanced malignant bone tumors	(A) Ginger-partitioned moxibustion plus (B) (n=32)	(B) AP plus tropisetron hydrochloride (n=32)	PC6, ST36, CV8, CV12	Moxa cone: 1×1 (cm), ginger slices: 2×3×0.3 (cm), 3 pillars, once a day, 30 min, 5 d	Up: KPS score, WBC, the number of 0 grade in digestive tract reaction Down: the number of Ⅲ/Ⅳ grade in digestive tract reaction

Abbreviations: Ref., reference; RCT, randomized controlled trial; up, up-regulated; down, down-regulated; RPFS, revised piper fatigue scale; VAS, visual analog scale; NLR, neutrophil-to-lymphocyte ratio; FACT-F, the Functional Assessment of Cancer Therapy-Fatigue; FACT-G, the Functional Assessment of Cancer Therapy-General; INVR, Index of Nausea, Vomiting, and Retching; HAMD, Hamilton depression rating scale; SM, sham moxibustion; FAACT, functional assessment of anorexia/cachexia therapy; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer 30-item core Quality of Life Questionnaires; PG, pepsinogen; G-17, gastrin-17; NSCLC, non-small cell lung cancer; BPI, Brief Pain Inventory; TCM, traditional Chinese medicine; WBC, white blood cell; KPS, Karnofsky Performance Scale; MDASI-C, the Chinese version of the MD. Anderson Symptom Inventory; BFI-C, the Chinese version of the Brief Fatigue Inventory; BFI, Brief Fatigue Inventory; CSF, colony-stimulating factor; IL-2, interleukin-2; TNF, tumor necrosis factor; EORTC QLQ-BR23, the European Organization for Research and Treatment of Cancer Breast-Cancer-Specific Quality of Life Questionnaire; -SH, sulfhydryl; SOD, superoxide dismutase; MDA, malondialdehyde; MMS, medium molecular mass; AP, adriamycin combined with cisplatin.

Table 2. The Mechanisms of Moxibustion Treating Cancer.

Ref.	Tumor model	Acupoints	Moxibustion parameters	Outcomes
Wang et al[8]	NSCLC	ST36	Moxa stick: 120 × 5 (mm), 42 ± 2°C, 1-1.5 (cm) from the skin, 5 times per week, 2 wk	TM vs T Up: Th1 cells, CD4 CD25 T cells, Tregs Down: size, tumor area, tumor weight, VEGF score TM vs TC Up: CD4T cells, Th2 cells, Cd69, Cd86, Cd20 Down: net body weight, VEGF score
Xue et al[28]	Breast Cancer	*Housanli*	6 mg, 3 pillars, once a day	MPTG vs PTG Up: survival rate; Down: tumor volume MTG vs TG Up: thymus index, spleen index, WBC, IL-2, INF-γ Down: IL-10, TGF-β1, HIF-1α, VEGFA, PD-1, PD-L1 MPTG vs TG Up: IL-2, INF-γ Down: IL-10, TGF-β1, PD-1, PD-L1, CD34, HIF-1α, VEGFA
Zhang et al[29]	NSCLC	ST36	2 mg, 5 pillars, once a day, 10 d	TM vs T Up: the integral of survival state on day Down: tumor volume, IL-6
Wang et al[30]	HCC	BL18	5 mg, 0 cm from skin, 5 pillars, every other day, 20 d (prevention group 1); 40 d (prevention group 2)	Prevention group 2 vs T Down: TSGF, TNF-α (serum)
Lu et al[31]	LLC	DU14, BL17, BL23, ST36	Moxa stick: 250 × 4 (mm), 3 min, 2 cm from skin, half once a day, 3 d, the other half, once a day, 5 d	CTX + M vs CTX Up: IL-12, TNF-α (spleen)
Lu et al[32]	S180 sarcoma	DU14, BL17, BL23, ST36	Moxa stick: 250 × 4 (mm), 3 min, 2 cm from skin, half, once a day, 3 d, the other half, once a day, 5 d	CTX + M vs CTX Up: WBC, spleen index (serum), IL-18 (PB)
Liu et al[33]	H22 liver cancer	DU14	1.5 mg, 0 cm from skin, 2 pillars, every other day, 6 d	TM vs T Down: $CD4^+CD25^+$Treg cell proliferation (in vitro)
Qiu et al[34]	H22 ascitic tumor	CV8	1.5 mg, 6 pillars, once every other day	TT + M vs TT, TT + M+C vs TT, TT + M vs TT + C Up: IL-2, IL-12, the kill rate of NK cells (serum) TT + M+C vs TT + C Up: IL-2, IL-12 (serum), survival time, the kill rate of NK cells
Pei et al[35]	H22 liver cancer	DU14	2 mg, 0 cm from skin, 2 pillars every other day, 6 d	TM vs T Up: IL-1β, IL-2 protein (cerebral cortex) Down: IL-6 mRNA, IL-6 protein (cerebral cortex) TM vs non-point group Up: IL-1β, IL-2; Down: IL-6 (cerebral cortex)
Chen et al[36]	EL-4 thymoma	DU14	1.5 mg, 0 cm from skin, 2 pillars, every other day, 6 d	TM vs T Up: TIL TM vs Con A group Up: TIL, $CD3^+$cells rates, $CD8^+$cells rates (TIL) TM vs non-point group Up: TIL; $CD3^+$cells rates, $CD4^+$cells rates, $CD8^+$cells rates (TIL) Down: $CD4^+/CD8^+$cells (TIL)
Huang et al[37]	LLC	ST36	1.5 mg, 30-35 s, 0 cm from skin, 3 pillars, once a day, 10 d	TM vs T Up: T lymphocyte proliferation rate, IL-2 Down: IL-10 (serum)
Hu et al[38]	NSCLC	ST36	0 cm from skin, 3/7 moxa cones, every other day, 3 wk	TM vs T Up: NK cells rates (spleens, tumor), tumor lysis Down: tumor weight

(continued)

Table 2. (continued)

Ref.	Tumor model	Acupoints	Moxibustion parameters	Outcomes
Hau et al[39]	Breast cancer	the normal tissue around the tumor and the surface of the tested tumor	Moxa stick: 250 × 150 (mm), 10 min, 42.5°C-44°C, 0.2-1 cm from skin, treated daily with MT for 1, 2, 3, or 4 d	MT1/MT2/MT3/MT4 vs T Down: tumor volume MT2/MT3/MT4 vs T Down: the uptake of 86Rb-radioactive tracer MT3/MT4 vs T Up: mean survival time
Zhai et al[40]	H22 ascites hepatoma	CV4, CV12, DU14	1.5 mg, 0 cm from skin, 2 pillars, every other day, 10 d	CV4 vs T Up: cytotoxic activity of NK cells, lymphocyte transformation function, β-EP concentration (plasma) CV12 vs T Up: cytotoxic activity of NK cells, ACTH concentration (plasma) DU14 vs T Up: activity of M ϕ ADCC (enterocoelia), ACTH concentration (plasma)
Zhang et al[41]	S-180 cancer	CV4	100 mg, 5 pillars	TM vs T Up: intracellular drug levels; Down: P-170 protein
Zhai et al[42]	H22 ascites hepatoma	CV4	1.5 mg, 0 cm from skin, 2 pillars, every other day, 10 d	TM vs T Up: pituitary weight, adrenal weight Down: β-END (adrenal, plasma)
Zhai et al[43]	H22 ascites hepatoma	CV4	1.5 mg, 0 cm from skin, 2 pillars, every other day, 10 d	TM vs T Up: thermodynamic reserve, phosphorylation potential
Jia et al[44]	HCC	BL18	0.5 mg, 0 cm from skin, 5 pillars, every other day, 10 d (prevention group 1), 20 d (prevention group 2)	Prevention group 1 vs T Down: AFP (serum) Prevention group 2 vs T Down: Livin (liver)
Yan et al[45]	HCC	BL18	5 mg, 0 cm from skin, 3 pillars, every other day, 10 wk	Direct moxibustion 1 group, direct moxibustion 2 group vs T Up: $CD3^+$T cells (PB) Direct moxibustion 1 group, direct moxibustion 2 group, ginger moxibustion vs T Up: $CD4^+$T cells; $CD4^+/CD8^+$T cells (PB) Down: $CD8^+$T cells (PB)

Abbreviations: Ref., reference; NSCLC, non-small cell lung cancer; T, tumor group; TC, cisplatin group; TM, moxibustion group; CG, control group; TG, tumor group; MTG, moxibustion + tumor group; PTG, paclitaxel + tumor group; MPTG, moxibustion + paclitaxel + tumor group; LLC, Lewis lung cancer; HCC, hepatocellular carcinoma; CTX, cyclophosphamide; M, moxibustion group; WBC, white blood cell; PB, peripheral blood; NC, normal control group; TT, transplanted tumor group; TT + M, moxibustion treatment group; TT + C, chemotherapy group; TT + M + C, moxibustion plus chemotherapy group; TIL, tumor infiltrates lymphocytes; gMoxi, grain-sized moxibustion group; MT, moxibustion; MT1, treatment moxibustion for 1 time; MT2, treatment moxibustion for 2 times; MT3, treatment moxibustion for 3 times; MT4, treatment moxibustion for 4 times; CV4, Guanyuan group; CV12, Zhongwan group; DU14, Dazhui group; AFP, alpha-fetoprotein.

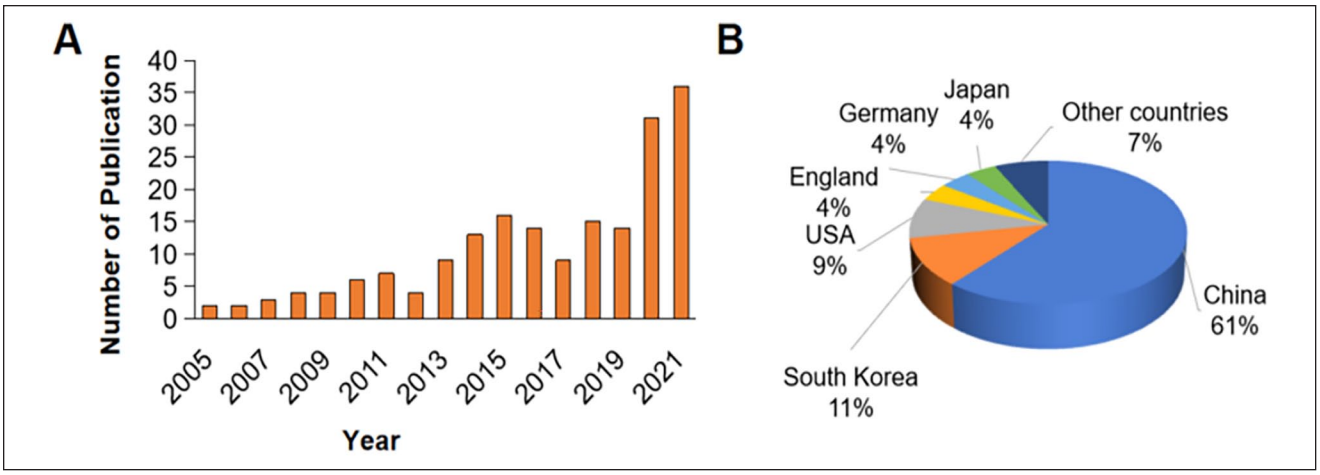

Figure 2. The number of studies published on moxibustion intervention in cancers has increased year by year in general, and China has the largest number of studies ,accounting for more than half.

based on integral-local combination, utilizing both abdominal and limb acupoints, such as ST25 and PC6, known to regulate digestive function.

Between 30% and 60% of patients with advanced cancer experience nausea and vomiting unrelated to radiation and chemotherapy. The synergistic effect of moxibustion on ST36, CV4, and CV6, combined with the central antiemesis drug metoclopramide and the antiemesis and antidepressant drug haloperidol, can reduce the INVR score, and reduce the Hamilton Depression Scale score when compared with the drug alone.[11] Anorexia is common in patients with metastatic cancer and is often associated with increased morbidity and mortality. A randomized sham-controlled trial reported patients with metastatic cancer anorexia treated with moxibustion at CV12, CV4, CV8, and ST36, while sham moxibustion was used as a control. It was found that the degree of anorexia and appetite loss was reduced according to the anorexia-cachexia subscale, with no occurrence of serious adverse events during the whole process.[14] The diameter of the mesenteric artery was widened, blood flow increased, and intestinal peristalsis was accelerated by thermal stimulation (41°C) from heat transfer control device at the umbilicus.[47] It was also found that after hot stupe application on the epigastrium (40°C), gastroenterogram showed that the electrical synergy between the stomach and intestine was enhanced, stimulating the electrical rhythm and effectively improving gastrointestinal peristalsis,[48] indicating that the generation of local thermal stimulation can regulate gastrointestinal function. However, the differences between heating and moxibustion, particularly their relative impacts on gastrointestinal function, require further investigation. The chemotherapy-induced gastrointestinal toxicity mechanism has been associated with gastrointestinal inflammation, intestinal microbiota, dysfunctional gastrointestinal motility and secretion, and intestinal neuropathy.[49] Despite these findings, there is still no direct evidence elucidating the mechanism by which moxibustion alleviates gastrointestinal reactions post-radiotherapy and chemotherapy, and it needs further investigation.

Myelosuppression

Severe infectious complications, including neutropenia due to chemotherapy, are a major cause of morbidity and mortality in cancer patients. Granulocyte colony-stimulating factor (G-CSF) is often used as a preventive measure to reduce the incidence and duration of chemotherapy-induced leukopenia.[50] However, G-CSF therapy is not always effective and cannot fundamentally stimulate the proliferation of hematopoietic stem/progenitor cells (HSPCs). A systematic review based on 6 randomized clinical trials demonstrates the superiority of moxibustion over drug therapies in treating chemotherapy-induced leukopenia, however, the quality of these studies is very low.[51] For instance, 7-day ginger moxibustion at ST36, ST25, PC6, and CV8 after chemotherapy increased the white blood cell (WBC) and platelet counts in patients with lung cancer[13]; other studies found similar results.[18,52] It was also found that ginger moxibustion at *Dazhui* (GV14), *Geshu* (BL17), and *Pishu* (BL20) has a better effect on the treatment of leukopenia after chemotherapy, improving impaired heart, lung, and renal function resulting from chemotherapy in comparison with Chinese patent medicine.[53] These results suggest that ginger moxibustion is beneficial for managing chemotherapy-induced myelosuppression, and the BL17 acupoint is commonly used in this treatment.

Research into the mechanism of moxibustion in treating myelosuppression after chemotherapy has made significant progress. It has been shown that BL17 moxibustion can increase peripheral blood leukocytes in rats treated with cyclophosphamide and enhance the ability of macrophages to induce granulocyte-macrophage colony-stimulating

factor (GM-CSF), rapidly promoting the proliferation of HSPC.[54] Acupuncture and moxibustion at ST36, *Shenshu* (BL23), BL17, and GV14 can regulate bone marrow cell cycling in myelosuppression models and may promote the synthesis, repair, replication, and proliferation of cellular DNA.[55] The same group also used GV14 and BL17 in the moxibustion group and ST36 and *Sanyinjiao* (SP6) in the acupuncture group and measured the number of WBCs and the activity of serum colony-stimulating factor (CSF). It was found that both acupuncture and moxibustion increased the WBC numbers and serum CSF activity in mice with myelosuppression, with similar results observed in the sera of the corresponding clinical study subjects.[56,57]

These pieces of evidence suggest that moxibustion has a good synergistic effect in cancer patients during chemotherapy, and may be safe and effective for chemotherapy-induced GI side effects and myelosuppression, but further clinical research is needed.

Cancer-Related Fatigue (CRF)

CRF is a type of fatigue induced by cancer or cancer treatment and is present throughout cancer development, progression, and treatment.[58] The mechanisms involved in CRF are complex, and the effectiveness of drug interventions can be limited.[59] In TCM, moxibustion is often used for treating weak patients as it is considered suitable for increasing energy, and many studies have shown that moxibustion is beneficial for chronic fatigue.[25,60] Compared with sham laser moxibustion, 10.6 μm infrared laser moxibustion at ST36, CV4, and CV6 has been shown to reduce the score on the Chinese version of the Brief Fatigue Inventory (BFI), which is used for the evaluation of fatigue symptoms in cancer patients. This technique can simulate the effect of moxibustion while avoiding the disadvantages of traditional moxibustion, such as smoke, unpleasant smell, and difficulties in dosage control.[20] In addition to infrared laser moxibustion, thunder-fire moxibustion can reduce the BFI score in breast cancer patients.[18] In patients with breast cancer-related lymphedema (BCRL), the overall score and the behavior, sensation, mood, and cognition scores on the Revised Piper Fatigue Scale were improved after moxibustion treatment.[9] These pieces of evidence indicate that moxibustion may be beneficial for CRF.

The pathogenesis of CRF is multifactorial, including changes in the inflammatory response, neuroendocrine system, cortisol rhythm, and immune response.[61,62] Moxibustion has been found to alleviate fatigue by regulating inflammatory cytokines and neurotransmitters in the hippocampus, such as 5-HT and dopamine, and reducing serum malondialdehyde levels.[63,64] Additionally, moxibustion at CV4 and ST36 has been shown to decrease levels of corticotropin-releasing hormone in the hypothalamus. It also reduces adrenocorticotropic hormone and corticosterone levels in the plasma, increasing progranulin mRNA and protein expression in the hippocampus. These results suggest that moxibustion can alleviate the behavioral symptoms of chronic fatigue syndrome by regulating the hypothalamic-pituitary-adrenal (HPA) axis and upregulating the precursor protein of hippocampal granules.[65] The underlying mechanism of moxibustion in alleviating fatigue may involve the modulation of inflammatory factors, the HPA axis, and antioxidant activity. However, the specific mechanism by which moxibustion targets CRF may differ from the general mechanism of fatigue reduction. Additionally, the precise mechanism by which moxibustion relieves CRF remains unclear, highlighting the need for further investigation by scholars in the relevant field.

Cancer Pain

Pain is a common complication, especially in advanced stages of cancer.[66] The "3-step drug analgesic method" recommended by the World Health Organization is often used as a standard guideline in treating cancer pain, and opioid analgesia is a vital medication.[67,68] However, the effectiveness of opioid analgesics varies,[69] and they can lead to adverse reactions such as nausea, vomiting, and constipation.[70]

It was found that the total Brief Pain Inventory (BPI) score and the scores of subsets, including the pain intensity and pain interference, decreased after moxibustion treatment compared with patients with metastatic cancer who received sham moxibustion. After adjusting for opioid consumption, the significant results persisted, indicating that moxibustion may be a beneficial treatment option for cancer pain in patients with metastatic cancer.[17] The curative effect of acupressure before moxibustion at *Ashi*, Zhangmen (LR13), and Qiuxu (GB40) was also observed in 36 patients with primary liver cancer pain.[71] However, there is a lack of research on the mechanisms of moxibustion in the treatment of cancer pain.

Breast Cancer-Related Lymphedema

Breast cancer-related lymphedema (BCRL) is considered one of the most serious complications of breast cancer surgery, with a 10-year cumulative incidence of 41.1%, according to several studies.[72,73] Commonly used treatments for BCRL include combined decongestant therapy, drug intervention (diuretic or dehydration), and lymphatic surgical reconstruction.[74] However, these methods fail to address the underlying issue causing lymphedema. It was shown that electronic moxibustion at *Binao* (LI14), GB40, and *Waiguan* (TE5) could reduce arm symptoms, improve varus and internal flexion rotation, and improve the quality of life in patients with BCRL.[23] Compared with patients treated with compression garments, moxibustion could reduce the swelling score of the affected arm.[9,24] The *Ashi* or local acupoints were mostly selected.[23,75]

In summary, the above studies indicate that moxibustion can treat GI symptoms such as nausea and vomiting, anorexia induced by cancer or cancer therapy, myelosuppression after chemotherapy, and cancer-related fatigue, pain, and lymphedema after breast cancer surgery.

Moxibustion Improves the Quality of Life in Cancer Patients

Over the past 20 years, cancer patients' health-related quality of life (HRQOL) has received increasing attention. The US Food and Drug Administration uses HRQOL as one of the reference indicators for the approval of new cancer drugs, and many studies also use HRQOL as the primary endpoint of tumor efficacy.[76] Several lines of evidence have demonstrated that moxibustion can improve the quality of life of tumor patients. In a study investigating the efficacy of moxibustion as an intervention for anorexia in patients with metastatic cancer, significant improvements were observed in various symptoms and quality-of-life measures. Specifically, patients in the moxibustion-treated group had lower scores in the European Organization for Research and Treatment of Cancer 30-item core Quality of Life Questionnaires (EORTCQLQ-C30) for fatigue, nausea and vomiting, pain, and diarrhea, as well as lower scores for anorexia and cachexia in the functional assessment of anorexia/cachexia therapy questionnaire. These findings suggest that moxibustion can effectively alleviate these symptoms and reduce cachexia, ultimately improving the overall quality of life in patients with metastatic cancer.[14] Wheat grain moxibustion combined with chemotherapy and symptomatic treatment of advanced gastric cancer can improve the EORTCQLQ-C30 scores regarding fatigue, nausea, vomiting, anorexia, and diarrhea, while the health score is higher.[10] In patients with advanced malignant tumors, the Karnofsky Performance Scale (KPS) scores were higher in patients with moxibustion at ST36 than those before treatment, while the TCM symptom scores in terms of fatigue, insomnia, loss of appetite, spontaneous sweating, and dizziness were lower than the control group.[19] In a randomized controlled trial (RCT) examining the prevention of nausea and vomiting after chemotherapy for lung cancer using ginger moxibustion, the KPS scores were also higher than those of the control group.[13] Studies have also shown that combining moxibustion and anti-nausea drugs has obvious advantages in treating refractory nausea and vomiting while improving the overall Functional Assessment of Cancer Therapy-General score and the physiological and emotional scores.[77] In conclusion, moxibustion can effectively improve patients' overall quality of life.

To sum up, the studies above show that moxibustion aids in tumor regression and enhances patient survival while mitigating adverse reactions to chemotherapy, such as nausea, vomiting, constipation, and myelosuppression. It can also treat fatigue, pain, and postoperative lymphedema associated with cancer or cancer treatment and improve cancer patients' overall quality of life. Moxibustion has also effectively treated other cancer-related complications such as sleep disorders, postoperative bladder dysfunction, and malignant pleural effusion.[78,79] However, these studies were published in Chinese journals not indexed by PubMed or Web of Science. Therefore, more high-quality evidence is needed to evaluate the significance of moxibustion in tumor treatment. Furthermore, the mechanisms underlying the effects of moxibustion on cancer and its complications are yet to be fully elucidated, and this represents an important area of research for the future.

Effects and Mechanisms of Moxibustion Enhancement of the Antitumor Efficacy of Cancer Therapies

Enhancing Antitumor Efficacy

There is evidence that moxibustion at CV8 combined with radiotherapy and chemotherapy has a specific therapeutic effect on patients with stage III or stage IVa nasopharyngeal carcinoma. Patients receiving salt-partitioned moxibustion at CV8 demonstrated higher 5-year nasopharyngeal tumor and lymph node-local control rate, as well as 5-year survival rates, compared to those receiving conventional treatment.[26] At the same time, moxibustion was also found to improve the overall level, immune function, and physical condition of cancer patients, effectively controlling tumor development.[22] In basic research studies, moxibustion also improved the survival of tumor-bearing mice. For instance, it was found that moxibustion combined with paclitaxel improved the survival rate of the mice compared with the paclitaxel-only group, and moxibustion could increase both the survival rate and overall survival of mice with breast cancer tumors,[28] could prolong the survival time of mice with H22 liver cancer,[8,34,39] and increase the survival status score in LLC mice.[29] Combined moxibustion therapy also controlled tumor growth in mice with non-small cell lung cancer (NSCLC) and breast cancer tumors and those with metastatic cancer.[8,28,39,80]

Antitumor Mechanism

Improving the tumor immune microenvironment. The immune function of cancer patients is impaired due to both the progression of the tumor itself and the effects of long-term radiotherapy and chemotherapy treatment, leading to immunosuppression.[81] This seriously affects the ability of the immune system to monitor and attack tumor cells, resulting in the escape of tumor cells and leading to the progression of the disease. Protecting the immune function of tumor patients is thus very important in antitumor therapy.

In addition to the tumor microenvironment's local immune response, the tumor's immune response also includes all the immune cell lineages of the peripheral immune system, the bone marrow, blood, spleen, and draining lymph nodes to form an immune network that continuously intersects during tumor development.[82] Studies have shown that patients with various types of tumors have increased hematopoietic stem cells, pluripotent progenitor cells, and granulocyte large monocyte progenitor cells in their peripheral blood,[83] indicating the mobilization of these cells into proliferation and differentiation toward monocytic and granulocytic lineages. This leads to the expansion of immature immunosuppressive neutrophils, also known as polymorphonuclear myeloid-derived suppressor cells, monocytes or monocytic myeloid-derived suppressor cells, and macrophages in the periphery and intratumoral regions. These cells are then recruited to immune organs or tumor tissues, which may contribute to immunosuppression and the development of the tumor microenvironment. The study found that early dynamics in peripheral blood immune cell subsets reflect changes in the tumor microenvironment and capture antitumor immune responses.[84] Integrated dynamics of peripheral blood cell counts, predominantly neutrophil-lymphocyte ratio (NLR) dynamics, and eosinophil level changes predicted clinical outcomes.[85,86] Many immune tissue alterations were observed in the peripheral blood of tumor patients. Surgical resection or cytokine blockade in multiple tumor models could restore numerous peripheral immune perturbations.[87] However, the link between changes in peripheral blood immunity and the tumor microenvironment has not been systematically elucidated, and future studies are needed to provide mechanistic insights into how peripheral immune recombination is driven. Many studies of moxibustion on antitumor have detected immune cells in peripheral blood. The antitumor mechanism of moxibustion, particularly its influence on peripheral blood immune changes, warrants further exploration.

Studies have found that moxibustion can enhance antitumor activities by acting on different types of immune cells in the tumor microenvironment. NLR is the ratio of neutrophil count to lymphocyte count in the peripheral blood, and this inflammatory indicator has been independently correlated with the prognosis of gastric cancer.[88] Grain-sized moxibustion at ST36 and *Weishu* (BL21) can improve the NLR and reduce diarrhea, loss of appetite, fatigue, and nausea/vomiting while improving patients' overall health and prognosis with advanced gastric cancer.[77] In a recent RCT study, scar moxibustion at ST36 and *Feishu* (BL13) of NSCLC patients reduced the NLR and enhanced the adaptive immune function.[52]

Infiltrating T lymphocytes are the main cells involved in the antitumor immune response. They differentiate into $CD4^+$ helper T (Th) cells, $CD8^+$ cytotoxic T cells (CTLs), and regulatory T cells (Tregs) under the stimulation of various cytokines. $CD8^+$CTLs are the most important effector cells to recognize and clear tumor cells. In $CD4^+$T cells, Th1 cells activate $CD8^+$CTLs by releasing interferon-γ (IFN-γ), and IFN-γ promotes the recruitment of $CD8^+$CTLs to the tumor and the maintenance of $CD8^+$CTLs function.[89] Both moxibustion and ginger moxibustion increased the $CD4^+$T cell levels and the ratio of $CD4^+/CD8^+$ T cells in rats with precancerous liver lesions.[45] Cisplatin combined with moxibustion promoted the infiltration of $CD8^+$ CTLs, $CD4^+$ T cells, and Th1 cells, as well as enhancing the gene expression of CD69 (a major marker of T cell activation) and the related cytokine IFN-γ in Lewis lung cancer (LLC) mice.[8] In sarcoma-transplanted tumors, moxibustion also promoted the expression of CD4 and CD8 in the tumor microenvironment.[80] Blocking the tumor-induced Th1/Th2 drift and transforming it into a Th1 direction can prevent tumor development. Grain-sized moxibustion can regulate immune function in tumor-bearing mice, promoting Th1 cytokine production and adjusting the Th1/Th2 imbalance.[37] CV8 moxibustion could also promote the secretion of IL-2 by Th1 cells and mediate the antitumor immune response in hepatocellular carcinoma mice.[34] Cisplatin combined with moxibustion increased the number of Th1 cells in LLC mice tumor tissue.[8] Programed death-1 (PD-1) is an important co-inhibitory molecule discovered in recent years. Generally, PD-1 is expressed in immune cells such as T lymphocytes, while its ligand Programed death ligand-1 (PD-L1) is expressed in tumor cells.[90] The interaction between PD-1 and PD-L1 promotes immunosuppression, ultimately leading to tumor immune escape. Moxibustion combined with paclitaxel significantly inhibited weight loss in breast cancer-bearing mice and increased their survival rate. Notably, moxibustion combined with paclitaxel inhibited PD-1/PD-L1 expression, indicating that the combination therapy may inhibit tumor growth through the PD-1/PD-L1 signaling pathway.[28]

Natural killer (NK) cells are innate lymphocytes with strong antitumor activities in clearing malignant cells and limiting tumor metastasis.[91] Death receptor-mediated apoptosis and perforin/granzyme-mediated NK cell cytotoxicity also limit primary tumor growth.[92] Moxibustion at CV8 can improve the killing rate and activities of NK cells in H22-transplanted tumors.[34] Grain-sized moxibustion at ST36 increased the proportion of NK cells in the spleen and tumor by inhibiting adrenergic signaling in NSCLC and promoting the antitumor immune functions of NK cells.[38] Moxibustion at CV12 and CV4 in xenograft mice with liver tumors improved the cytotoxic activity of NK cells.[42]

In the early stages of tumor development, M1 macrophages kill and eliminate tumor cells, producing cytokines to recruit and activate other immune effector cells. With tumor development, the evolution of the tumor microenvironment can transform infiltrating macrophages into M2

macrophages with tumor-promoting and immunosuppressive functions. Tumor-associated macrophages stimulate the production of specific cytokines, including macrophage colony-stimulating factor (M-CSF), IL-4, IL-13, IL-10, and prostaglandin E2. These cytokines play significant roles in tumor growth promotion.[93] It was found that moxibustion can reduce the concentrations of serum IL-4 and IL-10 in the sarcoma microenvironment and down-regulate the expression of the IL-10 gene in the transplanted tumor.[80] In breast cancer mice, moxibustion on ST36 reduced the serum IL-10 level,[28] suggesting that moxibustion may reduce immunosuppression by modulating the polarization of tumor-associated macrophages.

Improving tumor vascular normalization. Tumor angiogenesis is characterized by a high degree of disorder, distortion, dilation, uneven thickness, excessive branching, low pericyte coverage, loose binding to TECs, and elevated interstitial fluid pressure. These features lead to vascular collapse and reduced blood flow, forming an anoxic tumor microenvironment.[94] Vascular endothelial growth factor (VEGF) has been identified as the most critical angiogenic factor in angiogenesis and vascular abnormalities leading to tumor progression. Anti-angiogenic therapy with low-dose anti-VEGF receptor 2 antibodies can induce tumor vessel normalization, reduce hypoxia, and promote tumor $CD8^+$T lymphocyte infiltration, ultimately improving the tumor immunosuppressive microenvironment and enhancing tumor immunity.[28,95]

Moxibustion primarily employs localized warmth and heat stimulation to warm *qi* and blood, thus promoting overall well-being. The warming effect of moxibustion primarily pertains to the correlation between warm and hot stimulation and its associated impacts, including alterations in blood components, enhancement of hemorheology, regulation of vasomotor function, and inhibiting inflammatory factors.[96] In LLC mice, moxibustion alone and moxibustion combined with cisplatin increase microvascular tumor density and pericyte coverage, reducing the expression of VEGFA in tumor tissues, and promoted vascular normalization and $CD8^+$T cell infiltration, thus exerting an antitumor effect.[8] Hypoxia-inducible factor-1 alpha (HIF-1α) is a key transcription factor in cancer progression and targeted cancer therapy. HIF-1α acts and has different functions depending on the presence or absence of oxygen. Overexpression of HIF-1α and activation of its downstream genes enhance cell survival, reprograming metabolism, promotion of invasion and metastasis, maintenance of cancer stem cells, and the promotion of genetic instability and resistance to treatment.[97] Moxibustion combined with paclitaxel significantly down-regulated HIF-1α and VEGFA in breast cancer, suggesting that moxibustion can inhibit tumor progression by inhibiting tumor angiogenesis.[28]

The mechanisms underlying the antitumor effect of moxibustion are complex. While studies have shown that moxibustion can promote tumor immunity and vascular normalization, by regulating various immune cells and factors related to vascular normalization within the tumor microenvironment. As a result, moxibustion can directly combat cancer and enhance the effectiveness of conventional therapies.

Initiation and Transmission Mechanism of Moxibustion Action

Modern moxibustion is a therapeutic intervention that primarily involves generating heat from the combustion of moxa strips/leaves coupled with infrared radiation. While moxibustion at specific acupoints has not been extensively studied in cancer research, previous studies have reported on the mechanisms of moxibustion action. Moxibustion generates heat, which can promote the infiltration of immune cells into tumors, improve hypoxia in tumors, and induce the normalization of tumor-associated blood vessels. Moxibustion can be used in treating tumors in 2 ways: local tumor moxibustion and moxibustion at specific acupoints. Both methods utilize the thermal effect of moxibustion, but the underlying mechanisms differ.

Moxibustion can cause constriction of blood vessels at the site of treatment while promoting dilation of surrounding blood vessels, thus increasing blood flow through peripheral arteries and enhancing microvascular permeability.[98] Utilizing moxibustion for tumor treatment typically requires maintaining the temperature of moxa sticks within the range of 39°C to 46°C. Research suggests that temperatures in this range can increase local blood circulation in the tumor area, enhancing oxygen transfer and reducing tumor hypoxia. Moxibustion can kill tumor cells by inhibiting DNA repair and damaging tumor-associated blood vessels.[99] By inhibiting the production of VEGF in tumors, heat therapy can inhibit the proliferation of vascular endothelial cells and thus allows the remodeling of the extracellular matrix.[100] When the local temperature of the tumor reaches 43°C to 46°C, the tumor cells' physiological structure changes, leading to apoptosis or necrosis.[101] Moxibustion might also modulate the activity of immune cells in the tumor microenvironment through thermal effects. After heat stimulation, researchers found a significant reduction in tumor cell proliferation in breast tumors, an increase in the number of activated dendritic cells in dendritic nodes, and an increase in the infiltration of T cells, NK cells, and B cells into the tumors.[102] Temperatures above 40°C enhanced the cytotoxic actions of NK cells against tumor cells and inhibited their activity.[103] Moxibustion at the tumor site can inhibit tumor proliferation.

In most clinical and experimental studies on tumors, moxibustion is usually applied to the corresponding acupoints. Local thermal stimulation from moxibustion can activate local Langerhans cells (LC) at acupoints, leading to changes in the morphology and quantity of LC. The differential immunological effects of infrared irradiation and its associated heat in vivo have also been observed. For example, 41°C heat stimulation significantly increased the expression of Toll-like receptor 3 and Toll-like receptor 4.[104] Under the stimulation of heat and Toll receptors, LCs migrate into draining lymph nodes and mature into highly efficient antigen-presenting cells. Naive T lymphocytes in the lymph nodes undergo clonal expansion after recognizing the presented antigen, and they differentiate into antigen-specific effector T lymphocytes and memory T lymphocytes. Some memory T lymphocytes circulate through the body and activate the systemic immune system.[105] After moxibustion on local acupoints, local transient receptor potential vanilloid-1 (TRPV1) receptors in the acupoints can be activated.[106] This type of stimulation could trigger a supraspinal reflex through afferent nerve fibers and ascend to the brain via a single pathway of the lateral thalamic tract of the spinal cord, which conveys a warm pain sensation. This signal is then transmitted from the brain to the tumor site via the spinal cord.[107] The nerve impulses induced by the activation of TRPV1 receptors by moxibustion may be transmitted to the hypothalamus. This results in alterations within the hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-gonadal axis, and the HPA axis.[106] The local sensation of moxibustion stimulation in the acupuncture point area activates the corresponding immune cells and specific receptors in the acupuncture point area, which transmits the thermal stimulation signal of moxibustion to the distant target organs or even to the whole body via nerves and body fluids, eventually causing a series of cascade effects in the target organs and the whole body. This may be the mechanism by which moxibustion fights tumors through thermal stimulation.

Moxa can emit both visible and infrared radiation when combusted. It has a wide spectral range with several general bands seen in the region between 0.6 and 5.6 μm and many spectral peaks in the near-infrared, mid-infrared, and far-infrared regions.[108] Molecules in the human body absorb energy from the infrared and convert it into heat, thereby improving blood circulation and cell and enzyme activity. When tissues are irradiated with near-infrared radiation, the skin reflects relatively little light, allowing the photons to penetrate the blood vessels, lymphatic vessels, nerve endings, and subcutaneous tissues up to 10 mm in depth, followed by tissue absorption.[109] Photochemistry-based cancer therapy, including near-infrared photoimmunotherapy (NIR-PIT), aims to target cancer cell surface antigens and induce immunogenic cell death, which can lead to the rapid maturation of nearby immature dendritic cells and initiate an antitumor immune response.[110] Other studies have also found that NIR-PIT can kill tumor cells and specific host cells that promote the tumor immunosuppressive microenvironment and can thus be used in combination with other therapies to enhance the therapeutic effect.[111] These NIR applications in tumor therapy inspire studying the antitumor effects of moxibustion.

Therefore, moxibustion may kill tumor cells through thermal effects, reshape the immune and vascular microenvironment, and act on cancer cell surface antigens through radiation effects to induce immunogenic cell death, while initiating the host's anti-immune response to augment tumor treatment. This may be a potential mechanism for the antitumor effect of moxibustion.

Discussion and Conclusions

As a non-invasive external treatment method in TCM, moxibustion therapy is utilized to manage various types of cancer and associated complications. Compared with drug therapy, surgical therapy, and various complementary and alternative therapies, moxibustion has many advantages, such as no trauma, potential curative effect, better patient treatment experience, higher acceptance, and convenience, and it can be practiced at home. The clinical studies scrutinized in this review suggest that moxibustion can enhance the efficacy of radiotherapy and chemotherapy, contributing to the control of tumor progression and improvement of patient survival. Moreover, moxibustion can prevent and alleviate cancer-related complications, including gastrointestinal symptoms caused by cancer or cancer treatment, myelosuppression, CRF, cancer pain, and postoperative lymphedema, thus promoting a better quality of life for cancer patients (Figure 3). Nevertheless, more high-quality RCTs on moxibustion for cancer and its complications are necessary, along with well-defined standards for selecting acupoints, intervention time, and course of moxibustion each time. Although animal models of various cancer complications have become more sophisticated, there are few studies on the direct mechanism of moxibustion intervention.

Moxibustion operates by delivering heat and radiation produced during combustion to specific acupoints or areas of the lesion. The anticancer mechanism of moxibustion primarily involves mitigating tumor-induced immunosuppression and enhancing the vascular microenvironment, critical areas of interest in cancer research. Based on current research, it's posited that the local conduction mechanism of moxibustion at acupoints may involve the stimulation of local immune cells and the temperature receptor TRPV1. Following this stimulation, signals are transmitted via afferent nerves to the hypothalamus, which impacts the endocrine system and subsequently activates the immune system. In the local tumor site, moxibustion has been observed to suppress abnormal proliferation of vascular endothelial cells, increase pericellular coverage and microvascular density, and alleviate hypoxia, thus normalizing tumor blood

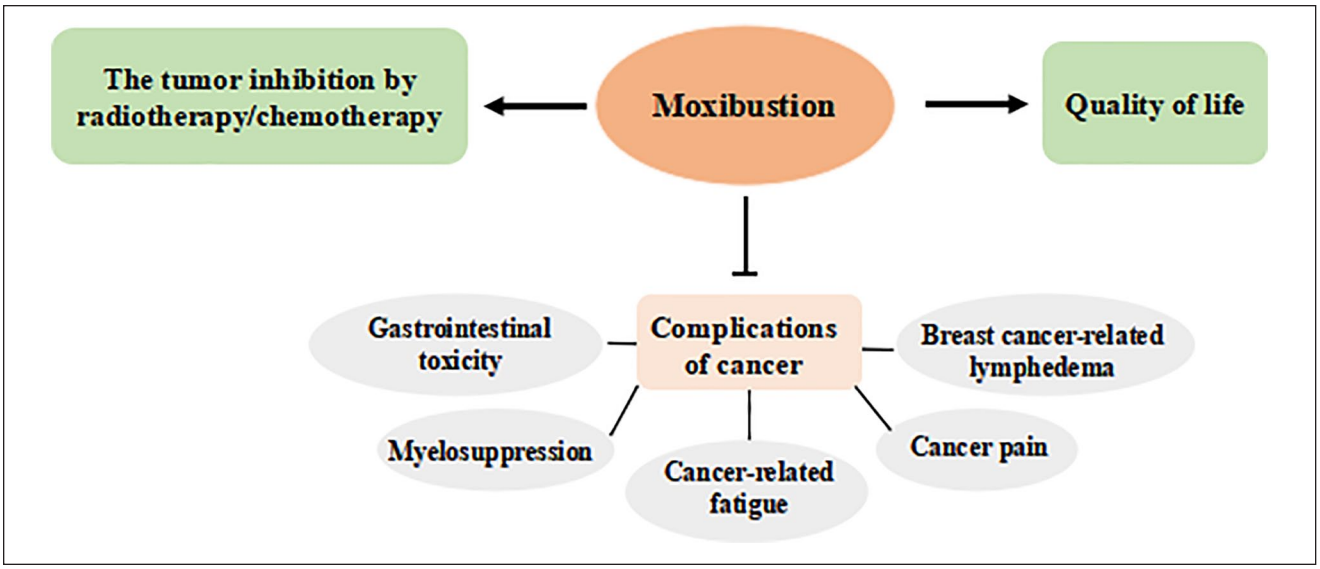

Figure 3. The benefits of moxibustion in cancer patients. Inhibit ⊣, Promote→.

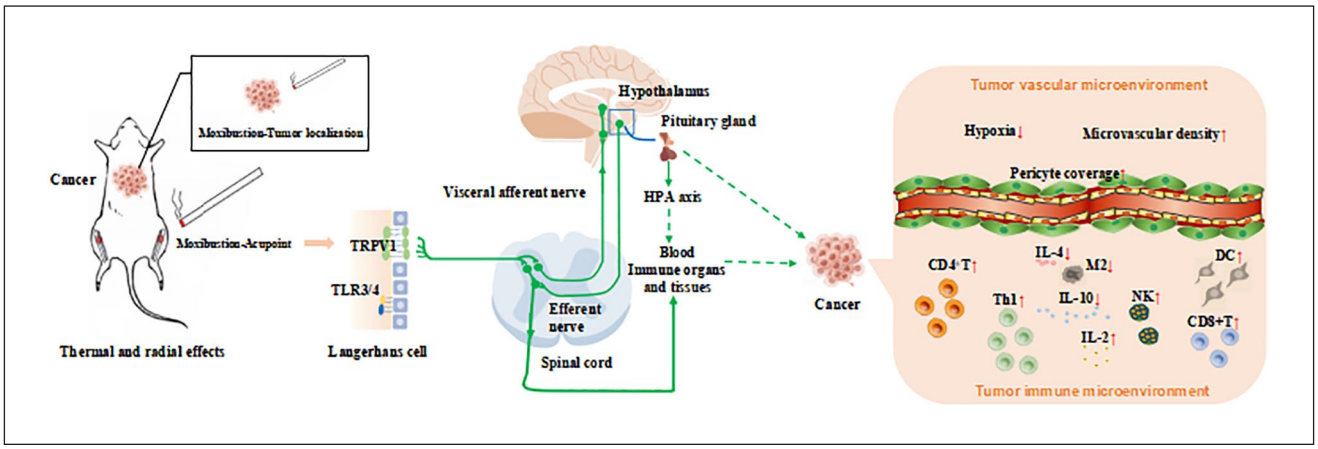

Figure 4. Potential mechanisms involved in moxibustion for combating cancer.

vessels. Concurrently, moxibustion can positively modulate tumor immune cytokines and improve the immunosuppressive microenvironment. In summary, moxibustion at tumors site may directly influence the tumor microenvironment. However, whether moxibustion at tumor site can also trigger a series of reactions through local transmission to the entire body and target organs, similar to the acupoints, is a question that requires further research and elucidation (Figure 4).

To sum up, moxibustion can enhance the therapeutic effect of cancer treatment and reduce the complications of cancer, especially the side effects of radiotherapy and chemotherapy. It is playing an increasingly important role in cancer treatment. Its mechanism needs more in-depth research and is worthy of widespread clinical application.

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The article presented here was carried out in collaboration between all the authors. Zhifang Xu and Jiaqi Wang conceived and designed the study. Shanshan Lu, Bin Wang, Shanshan Li, Suhong Zhao, Yuanzhen Yang and Yiting Feng searched the literature and analyzed the data, Yi Guo provided modification suggestions, Shanshan Lu, Jiaqi Wang, Bin Wang and Zhifang Xu wrote the article. All authors read and approved the final version of the manuscript.

Declaration of Conflicting Interests

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Data Availability

The data used to support the findings of this study are included within the article.

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