



Research article

The prospect of *Xihuang* pill in the treatment of cancersZehui Chen^{a,*}, Zhiming Li^b, Shuo Yang^{a,**}, Yue Wei^b, Jing An^b^a Institute of Information on Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, 100700, China^b The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, 100029, China

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ABSTRACT

Background: *Xihuang* pill, a Traditional Chinese Medicine (TCM) prescription and a representative of *Huoxuehuayu* therapy (one of the TCM therapies to promote blood circulation and remove blood stasis), has been widely used in breast cancer treatments. Although some evidence suggests the efficacy and safety of the *Xihuang* pill in treating certain cancer, the overall efficacy of the *Xihuang* pill in other cancer treatment is uncertain.

Objective: This study aimed to summarize the current clinical literature and provided evidence support for addressing the research question of whether the *Xihuang* pill is safe and effective in the treatment of various cancers as *Huoxuehuayu* therapy, and possibly identify the clinical dosage range and therapeutic effect of *Xihuang* pills.

Method: Seven Chinese and English databases such as PubMed, CNKI, and Google Scholar were searched to collect the publications on *Xihuang* pill and cancer. Then the researchers extracted data from the articles that met the inclusion criteria and used SAS statistical program version 9.4 (by SAS Institute, Cary, North Carolina, USA) for statistical statistics.

Results: Our search identified 78 studies, including 69 RCTs (randomized control trials), 6 NRCCs (non-randomized concurrent control trials), and 3 BAS (before-after study), evaluating 3151 patients in total. The daily doses of *Xihuang* pills/capsule were between 2 g and 60 g, and duration between 2 weeks and 5 years, mostly used in the middle or late stage of cancer. The therapeutic effect of the *Xihuang* pill was mainly reflected in improving Complete Response (CR, a term from The Response Evaluation Criteria In Solid Tumors) or Partial Response (PR, a term from The Response Evaluation Criteria In Solid Tumors), reducing adverse reactions, promoting quality of life (QoL), regulating immunity, alleviating pain, prolonging survival, reducing metastasis and recurrence, reducing inflammation, regulating estrogen levels, decreasing hypercoagulative status, and reducing tumor markers.

Conclusion: *Xihuang* pill representing *Huoxuehuayu* therapy has a good prospect in the treatment of cancer.

1. Introduction

Cancer incidence and mortality are rapidly growing worldwide. In 2020, an estimated 19.3 million new cancer cases had been diagnosed worldwide, with around 10.0 million cancer deaths. In 2040, there will be an estimated 28.4 million cancer cases expected

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to happen globally [1]. Given its relapsing and fatal features, curing cancer seems to be insurmountable for the patients. Currently, common cancer therapeutics include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, treatment with curative intent by these methods is mainly eligible for patients with the localized disease or treatment-sensitive cancers, so their contributions to cancer curability are relatively limited [2]. Therefore, finding more safe and effective methods for cancer treatment has always been one of the focuses of researchers around the world.

It should be noticed that Traditional Chinese Medicine (TCM) has been taking advantage of treating cancer due to its various biological activities, including fitting well within the whole system and multi-target cancer treatment [3]. The diagnosis and treatment of tumors were discussed in the literature of ancient Chinese medicine, where there is a wealth of content [4]. Among them, the *Xihuang* pill was first recorded in ‘The Encyclopedia of Surgical Diagnosis and Treatment (外科证治全书)’ by Wang Hongxu in the Qing Dynasty (Fig. 1), which is traditionally used to treat “*Ru Yan*” (considered as breast cancer nowadays) and to treat breast cancer or other cancers in today [5–9]. It contains four Chinese herbal medicines: *Calculus Bovis* (from *Bos taurus domesticus* Gmelin), *Moschus* (from *Moschus berezovskii* Flerov), *Olibanum* (*Boswellia carterii* Birdw.), and *Myrrha* (from *Commiphora myrrha* Engl.) [10], which typically represents *Huoxuehuayu* therapy, one of the TCM therapies to promote blood circulation and remove blood stasis. In the previous study [11], we demonstrated that *Huoxuehuayu* therapy showed promise in cancer treatment, improving quality of life, addressing cancer-related symptoms, and reducing toxicity in a secure way. However, it is unsure that the secure dosage of herbs or prescription with *Huoxuehuayu* functions. Moreover, the *Xihuang* pill as an example of *Huoxuehuayu* therapy is lacking sufficient evidence to suggest it could also work for more cancer treatments. In this study, we tried to give a specific example of *Huoxuehuayu* therapy, the *Xihuang* pill, to discuss whether it is safe and effective in the treatment of various cancers and to explore the securely clinical dosage and comprehensively therapeutic effect of the *Xihuang* pill.

2. Materials and methods

2.1. Evidence acquisition

We used Chinese databases, including CNKI Database, Wanfang Database, VIP Database, and China Biology Medicine disc (CMB disc), and English databases, including PubMed, Google Scholar, and Web of Science to perform electronic searches for publications on *Xihuang* pill and cancer. Our search included Chinese or English language entries from inception until July 2022 and incorporated the following keywords: *Xihuang/cancer/tumor* in all fields. The search formula of relevant literature was listed in Table 1. Only human studies were eligible for inclusion; case reports, editorials, letters, commentaries, and reviews were excluded. Repeatedly published research, research based on extractive or components of the *Xihuang* pill, the use of other herbal medicine combination therapy, unclear diagnosis, and treatment period were also excluded. The initial search resulted in 728 publications. After title and abstract screening, 123 studies remained, and 78 were finally selected for the present review after full-text screening (Fig. 2).

3. Results

We identified 78 studies on clinical aspects of *Xihuang* pills/capsules in treating cancer, including 11 specific types of cancer and

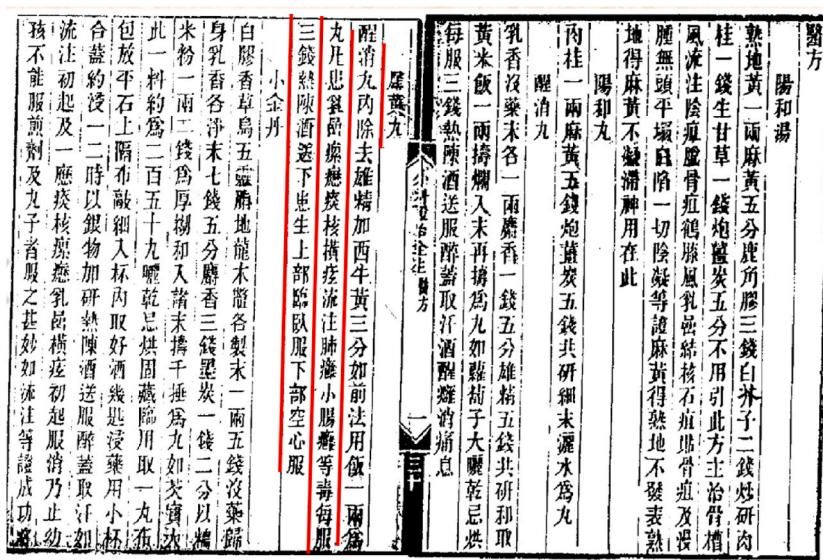


Fig. 1. *Xihuang* pill recorded in The Encyclopedia of Surgical Diagnosis and Treatment (外科证治全书)*. *The picture derives from Guoyi Diancang Database <http://v2.gydc.ac.cn:82/>.

Table 1
Search formula of relevant literature.

Search mode	Search fomula
#1	cancer
#2	malignant neoplasm
#3	carcinoma
#4	malignant tumor
#5	#1 or #2 or #3 or #4
#6	Xihuang pill
#7	Xihuang capsule
#8	Xihuang wan
#9	#6 or #7 or #8
#10	#5 and #9

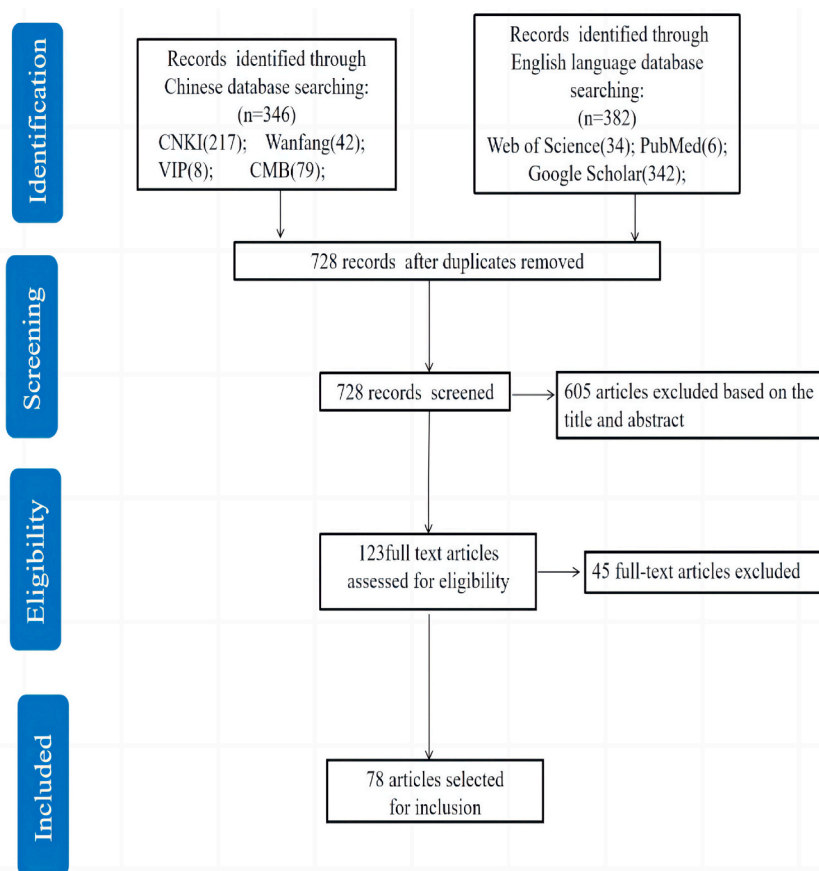


Fig. 2. Summary of the flow of our literature search.

multiple types of cancer. Twenty-five studies reported in treating breast cancer (32%) [12–36] (Table 2), 14 lung cancer (17.9%) [6, 37–49] (Table 3), 11 cervical cancer (14.1%) [5,50–59] (Table 4), 6 esophagus cancer (7.6%) [60–65] (Table 5), 5 liver cancer (6.4%) [8,66 = 69], (Table 6), 3 pancreatic cancer (3.8%) [66–68] (Table 7), 3 ovarian cancer (3.8%) [7,69,70] (Table 7), 2 gastric cancer (2.5%) [9,71] (Table 7), 2 colon cancer (2.5%) [72,73] (Table 7), 2 nasopharynx cancer (2.5%) [74,75] (Table 7), 1 bladder cancer (1.2%) [76] (Table 7), and 4 multiples of cancer (5.1%) [77–80] (Table 8). Among 78 studies, 69 types of research were RCTs, 6 NRCCs, and 3 BAS (Fig. 3, Fig. 4).

3.1. The stage of cancer treated by Xihuang pills/capsule

Among 78 studies, 11 types of cancer were mentioned to be treated by *Xihuang* pills/capsules in various stages. Stage III (57 studies) and IV (50 studies) were the major target periods for the application of *Xihuang* pills/capsules, in contrast to Stage 0 (1 study) and I (9 studies). At the initial stage, bladder cancer was reported to be treated with *Xihuang* pills (Fig. 5).

Table 2
General study characteristics of included studies for Breast Cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Chen [12]	II-IV	RCT	50	<i>XH</i> + chemotherapy	chemotherapy	1 g/bid	6	improve CR/PR, reduce adverse reactions, prolong survival
Hong et al. [13]	II-IV	RCT	42	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	18	improve CR/PR, QoL, prolong survival
Jia et al. [14]	Advanced	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	8	alleviate pain
Jin et al. [15]	I-IV	RCT	30	<i>XH</i> + chemotherapy	chemotherapy	3 g/tid	12	improve CR/PR, regulate immunity
Li et al. [16]	I-III	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	1 g/bid	48	improve QoL, reduce tumor marker, regulate estrogen levels
Mao et al. [17]	II-III	RCT	34	<i>XH</i> + chemotherapy, surgery	chemotherapy, surgery	2 g/bid	5 years	improve CR/PR, QoL, lessen metastasis and recurrence
Peng et al. [18]	II-III	RCT	46	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	2 g/bid	12	improve CR/PR, regulate immunity, reduce adverse reactions
Qi et al. [19]	III-IV	RCT	48	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	3 g/bid	12	improve CR/PR, regulate immunity, prolong survival
Qian et al. [20]	II-IV	RCT	45	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	3 g/bid	12	improve CR/PR, QoL, reduce adverse reactions
Wang [21]	III-IV	RCT	64	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	12	improve CR/PR, QoL, prolong survival, reduce tumor marker
Wang [22]	III	RCT	15	<i>XH</i> + chemotherapy	chemotherapy	2 g/bid	24	reduce adverse reactions
Wang et al. [23]	IV	RCT	57	<i>XH</i> + endocrine therapy	endocrine therapy	3 g/bid	12	improve CR/PR, prolong survival, reduce tumor marker, regulate immunity
Wang [24]	II-IV	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	1 g/bid	6	improve CR/PR, prolong survival, reduce adverse reactions
Wang [25]	Advanced	RCT	49	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	8	improve CR/PR, regulate immunity, reduce tumor marker, improve hypercoagulative status
Wu et al. [26]	III	RCT	39	<i>XH</i> + chemotherapy	chemotherapy	2 g/bid	18	improve CR/PR, regulate immunity, reduce adverse reactions
Wu [27]	II-IV	RCT	45	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	regulate immunity, reduce adverse reactions and inflammation
Xu et al. [28]	III-IV	RCT	55	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	regulate immunity
Xu et al. [29]	III-IV	RCT	55	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	improve QoL, reduce inflammation
Xu et al. [30]	III-IV	RCT	55	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	improve CR/PR, reduce adverse reactions, prolong survival
Yue et al. [31]	III	RCT	39	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	18	improve CR/PR, regulate estrogen levels
Zhang et al. [32]	I-III	RCT	45	<i>XH</i> + chemotherapy	chemotherapy	2 g/bid	12	improve QoL, reduce adverse reactions
Zhang et al. [33]	II-IV	BAS	32	<i>XH</i> + chemotherapy	chemotherapy	1.5 g/bid	8	improve QoL, reduce adverse reactions, regulate immunity
Zhang et al. [34]	Advanced	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	1.5 g/bid	9	improve CR/PR, QoL, reduce tumor marker, alleviate pain
Zhou et al. [35]	II-IV	RCT	22	<i>XH</i> + radiotherapy	radiotherapy	1 g/bid	6	improve QoL, regulate immunity
Zhou et al. [36]	III	RCT	44	<i>XH</i> + chemotherapy	chemotherapy	1 g/bid	6	improve CR/PR, reduce tumor marker, reduce adverse reactions

Table 3
General study characteristics of included studies for Lung Cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Zeng et al. [37]	Advanced	NRCC	40	XH + chemotherapy	chemotherapy	1–2g/ bid	6	improve CR/PR, reduce adverse reactions
He et al. [38]	IV	RCT	36	XH + chemotherapy	chemotherapy	1.5 g/ bid	8	improve CR/PR, reduce adverse reactions
Chen et al. [6]	Advanced	RCT	29	XH + chemotherapy	chemotherapy	1 g/ bid	6	improve CR/PR, reduce adverse reactions
Chi et al. [39]	Medium and Advanced	RCT	55	XH + morphine	morphine	2 g/ bid	2	alleviate pain
Guo et al. [40]	III-IV	RCT	30	XH + chemotherapy	chemotherapy	3 g/ bid	8	improve CR/PR, QoL, reduce adverse reactions
He et al. [41]	III-IV	RCT	40	XH + chemotherapy	chemotherapy	3 g/ bid	3	improve QoL, reduce tumor marker
Liu et al. [42]	III-IV	RCT	25	XH + chemotherapy	chemotherapy	2 g/ bid	16	improve CR/PR, regulate immunity, reduce adverse reactions
Du et al. [43]	III-IV	RCT	32	XH + chemotherapy	chemotherapy	1 g/ bid	16	alleviate symptoms
Wu et al. [44]	Medium and Advanced	RCT	49	XH + chemotherapy	chemotherapy	2 g/ bid	2	improve QoL, reduce adverse reactions, alleviate pain
Xiao et al. [45]	Medium and Advanced	RCT	30	XH + radiotherapy, chemotherapy	chemotherapy, radiotherapy	20 g/ tid	8	improve CR/PR, QoL, reduce adverse reactions
Xu et al. [46]	Medium and Advanced	RCT	40	XH + heteropathy	heteropathy	20 g/ tid	8	improve PFS, OS, reduce adverse reactions
Yan et al. [47]	III-IV	RCT	50	XH + oxycodone hydrochloride	oxycodone hydrochloride	3 g/ bid	2	improve QoL, alleviate pain, reduce adverse reactions
Zhang et al. [48]	III-IV	RCT	30	XH + chemotherapy	chemotherapy	2 g/ bid	6	improve CR/PR, QoL, reduce adverse reactions
Zhang et al. [49]	I-III	NRCC	20	XH + chemotherapy	chemotherapy	2 g/ bid	24	improve CR/PR, reduce adverse reactions

3.2. The daily doses and duration of *Xihuang* pills/capsule for cancer treatment

In terms of the daily dose, 32 studies indicated the daily dose of *Xihuang* pills/capsules was 6 g, including 2 g/tid, 3 g/bid, and 6 g/qd. Twenty-one studies showed the usage of *Xihuang* pills/capsule was 4 g/day and 2 g/day for 13 studies. The maxim daily doses of *Xihuang* pills/capsule reached 60 g, which was recorded in 2 studies, treating lung cancer. Regarding the treatment period, most studies revealed the duration was ≤ 12 weeks (6 weeks for 20 studies, 8 weeks for 11 studies, 12 weeks for 18 studies), while 12 studies demonstrated the treatment period was ≥ 16 weeks (16 weeks for 2 studies, 18 weeks for 4 studies, 24 weeks for 4 studies, 48 weeks for 1 study), and one treatment of breast cancer was maintained for five years (Fig. 6).

3.3. The therapeutic effect of *Xihuang* pills/capsules

We summarized the outcome of RCTs studies and non-RCTs, comparing the control group and trial group or before and after treatment. Radiotherapy, chemotherapy, heteropathy, analgetic, and endocrine therapy were used in the control group, and *Xihuang* pills/capsules combined with which were applied in the trial group. According to the outcomes of included studies, improving CR or PR was demonstrated in 47 studies, and *Xihuang* pills/capsule show promise in reducing adverse reactions (38 studies) and promoting QoL (37 studies). In addition, improving immunity (20 studies) and alleviating pain (13 studies) were also reported as the effectiveness of *Xihuang* pills/capsules. Typically, it was conducive to applying *Xihuang* pills/capsules to prolong survival (10 studies) and reduce metastasis and recurrence (2 studies) (Fig. 7).

4. Discussion

Xihuang pill is composed of *Bovis Calculus Sativus*, *Moschus*, *Boswellia carterii* Birdw. (Frankincense), and *Commiphora myrrha* (Nees) Engl. (Myrrha), with ratio 1:1:37:37 [10]. Involving three kinds of blood-stasis removing herbs (*Huoxuehuayu* function) and one kind

Table 4
General study characteristics of included studies for Cervical cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Bao et al. [5]	II-III	NRCC	40	<i>XH</i> + chemotherapy	chemotherapy	1 g/tid	8	improve CR/PR, QoL, reduce adverse reactions
Chang [50]	III-IV	RCT	25	<i>XH</i> + radiotherapy	radiotherapy	1 g/bid	4	reduce adverse reactions
Chen et al. [51]	II-IV	RCT	77	<i>XH</i> + chemotherapy+3D-CRT	chemotherapy+3D-CRT	3 g/bid	6	reduce adverse reactions, prolong survival
Li et al. [52]	II-III	RCT	45	<i>XH</i> + radiotherapy	radiotherapy	1 g/bid	8	improve CR/PR, reduce adverse reactions
Peng et al. [53]	III-IV	RCT	93	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	1.5 g/bid	8	improve CR/PR, reduce adverse reactions, lessen metastasis and recurrence
Qiu et al. [54]	II-III	RCT	52	<i>XH</i> + radiotherapy	radiotherapy	2 g/bid	3	improve CR/PR, reduce adverse reactions, prolong survival
Sang et al. [55]	I-III	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	reduce adverse reactions, regulate immunity
Shao [56]	I-III	RCT	41	<i>XH</i> + chemotherapy	chemotherapy	3 g/tid	12	improve CR/PR, reduce adverse reactions, tumor marker
Shi [57]	III-IV	RCT	48	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	improve CR/PR, regulate immunity
Wang et al. [58]	III-IV	RCT	50	<i>XH</i> + chemotherapy	chemotherapy	3 g/tid	12	improve CR/PR, QoL, regulate immunity, reduce tumor marker
Zhang [59]	III-IV	RCT	39	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	12	improve QoL, reduce tumor marker, prolong survival

Table 5
General study characteristics of included studies for Esophagus cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Cheng et al. [60]	Advanced	RCT	18	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	improve CR/PR, reduce adverse reactions
Ma et al. [61]	II-IV	RCT	40	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	2 g/bid	24	improve CR/PR, reduce adverse reactions
Shao et al. [62]	Medium and Advanced	RCT	30	<i>XH</i> + chemotherapy	chemotherapy	1.5 g/tid	3	improve CR/PR and QoL
Xu et al. [63]	I-III	RCT	30	<i>XH</i> + radiotherapy	radiotherapy	2 g/bid	4	improve CR/PR and QoL
Xue [64]	I-III	RCT	34	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	1.5 g/bid	6	improve CR/PR and QoL, reduce adverse reactions
Zhang et al. [65]	Medium and Advanced	RCT	106	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	2 g/tid	12	improve QoL, reduce adverse reactions

of heat-clearing and detoxicate herb, the *Xihuang* pill has many beneficial effects such as heat-clearance and detoxification, activating blood circulation to dissipate blood stasis, and disintegrating scleroma, which was recorded to treat furunculosis, scrofula, and neoplasms in ancient China [85], and is still used today, especially for the treatment of *Ruyan* (Traditional Chinese medical diagnosis of breast cancer). Although breast cancer is the most common targeting cancer for the *Xihuang* pill, we witnessed *Xihuang* pill can be widely used to treat 11 types of cancer including lung, liver, ovarian, colon, nasopharynx, etc. We believed the *Xihuang* pill has a curative effect on different kinds of cancer, which means that it has good popularization in tumor treatment.

Compared with the initial stage of cancer, advanced cancer meets the dilemma of limited therapies, the constitution of patients, and the cachexia caused by invasion cancer. According to our results, the *Xihuang* pill became a promising option for the treatment of middle and advanced cancers and was used more often. This finding has not been focused on before because most studies are inclined to discuss the therapeutic effect of the *Xihuang* pill but not its targeting stage or dosage of it. The main therapeutic approach for

Table 6
General study characteristics of included studies for Liver.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Cheng [8]	Advanced	BAS	23	<i>XH</i> + heteropathy + acesodyne		3 g/bid	18	improve QoL, alleviate pain, reduce adverse reactions
Feng et al. [81]	II-III	RCT	49	<i>XH</i> + chemotherapy	chemotherapy	1–2g/bid	8	improve CR/PR, reduce adverse reactions, alleviate renal or hepatic impairment
Liu et al. [82]	II-III	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	2	improve CR/PR and QoL, prolong survival
Wu et al. [83]	Advanced	RCT	70	<i>XH</i> + TACE	TACE	3 g/bid	2	improve CR/PR, prolong survival
Zhang [84]	III	BAS	28	<i>XH</i> + heteropathy		3 g/bid	6	reduce adverse reactions, alleviate hepatic impairment

Table 7
General study characteristics of included studies for Pancreatic cancer, Ovarian cancer, Gastric cancer, Colon cancer, Nasopharynx Cancer, Bladder Cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Pancreatic cancer								
Yang et al. [66]	Medium and Advanced	RCT	20	<i>XH</i> + morphine	morphine	2 g/bid	4	improve QoL, alleviate pain,
Zhang et al. [67]	II-IV	RCT	16	<i>XH</i> + chemotherapy	chemotherapy	6 g/qd	6	improve CR/PR and QoL, reduce tumor marker and adverse reactions
Zhu et al. [68]	Advanced	RCT	17	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	8–24	improve QoL, reduce adverse reactions
Ovarian cancer								
Cheng et al. [7]	Advanced	RCT	35	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	12	improve CR/PR, reduce adverse reactions
Guan et al. [69]	III-IV	RCT	35	<i>XH</i> + chemotherapy	chemotherapy	3 g/tid	12	improve CR/PR and QoL, regulate immunity, reduce adverse reactions
Zhang [70]	III-IV	RCT	45	<i>XH</i> + chemotherapy	chemotherapy	3 g/tid	12	improve CR/PR and QoL, regulate immunity, reduce adverse reactions
Gastric cancer								
Jiang [9]	IV	RCT	20	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	6	improve CR/PR and QoL
Zhu et al. [71]	Advanced	RCT	40	<i>XH</i> + chemotherapy	chemotherapy	2 g/bid	12	improve CR/PR, regulate immunity, prolong survival
Colon cancer								
Li et al. [72]	Advanced	RCT	35	<i>XH</i> + chemotherapy	chemotherapy	1 g/bid	6	improve CR/PR and QoL, reduce adverse reactions
Zhang et al. [73]	IV	RCT	60	<i>XH</i> + chemotherapy	chemotherapy	2 g/tid	6–12	reduce tumor marker and adverse reactions
Nasopharynx Cancer								
Ren et al. [74]	Advanced	RCT	30	<i>XH</i> + chemotherapy, radiotherapy	chemotherapy, radiotherapy	2 g/bid	12	improve CR/PR and QoL, regulate immunity
Zhang et al. [75]	III-IV	RCT	40	<i>XH</i> + radiotherapy	radiotherapy	1–2g/bid	2	improve QoL, regulate immunity, reduce adverse reactions
Bladder Cancer								
Wang et al. [76]	0-I	RCT	28	<i>XH</i> + chemotherapy	chemotherapy	3 g/bid	12	lessen recurrence, reduce adverse reactions

advanced cancer is combined surgery with neoadjuvant chemotherapy, targeted therapy, or immunotherapy [86], which also brings many side effects such as multi-drug resistance, fatigue, weakened immune system, and gastrointestinal side effect [87]. *Xihuang* pill is used frequently in the middle and late stage with the above-mentioned therapy for cancer treatment, which may play the role of enhancing effect and reducing toxicity.

Table 8
General study characteristics of included studies for Multiple Cancer.

Ref.	Stage	Research Type	Number of patients	Control group	Trial group	Daily dose	Treatment Period (week)	Outcome
Chen et al. [77]	Advanced	RCT	24	XH + radiotherapy	radiotherapy	3 g/tid	3	alleviate pain
Huang et al. [78]	Advanced	NRCC	47	XH + heteropathy	heteropathy	3 g/bid	3	improve QoL
Liu et al. [79]	Medium and Advanced	RCT	40	XH + acesodyne	acesodyne	2 g/bid	2	alleviate pain, reduce adverse reactions
Yang [80]	IV	RCT	24	XH + morphine	morphine	2 g/bid	2	improve QoL, alleviate pain

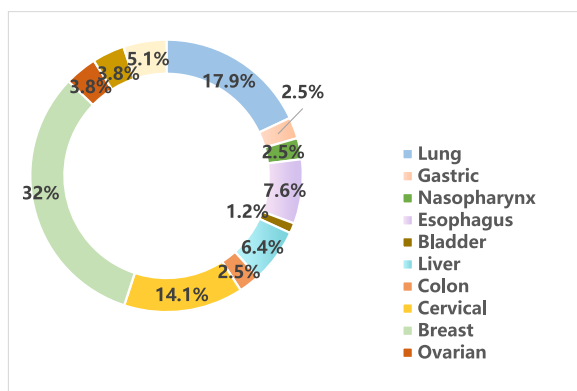


Fig. 3. The proportion of different cancer types in the included studies.

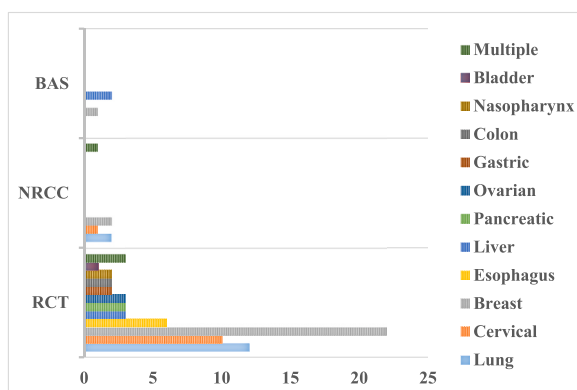


Fig. 4. Different categories of studies in treating cancer by *Xihuang* pills/capsules.

In addition, we paid special attention to the dosage of *Xihuang* pills because the safe dosage of drugs with *HuoxueHuayu* function is still unclear. Based on the Chinese Pharmacopoeia edition 2020 [88], the regular dose of the *Xihuang* pill is 3 g at a time, twice a day. Only 29 (37.1%) studies showed that the dosage of *Xihuang* pills was following the pharmacopoeia instructions, most of the studies were based on self-prescribed doses and did not exceed the standard dose, which means the clinical use of the *Xihuang* pill is relatively cautious. We should emphasize that the maximum dose of the *Xihuang* pill was 60 g/day, treating stage III lung cancer in 2 studies without records of adverse reactions. However, more evidence is needed to determine whether this dose is optimal, safe, and generally applicable to other cancer treatments.

Apart from the daily dose of *Xihuang* pills, the treatment period of *Xihuang* pills was also summarized to assess the medication safety. Due to the categories of studies (RCTs), the duration was limited to about 20 weeks in most cases. Even at the maximum dose (60 g/day), it did not exceed 8 weeks. Notably, two studies revealed that the *Xihuang* pill could be used as a supplement for 1 year or more, and the outcome of 5 consecutive years of use was tracked. The optimal duration of immunotherapy and chemotherapy treatment for cancer patients is unknown [89,90], while the *Xihuang* pill is usually combined with such therapies, which is difficult to

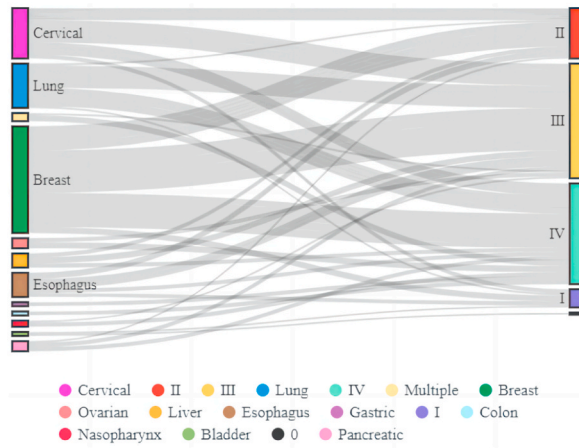


Fig. 5. The staging of different cancer treated by *Xihuang* pills/capsules.

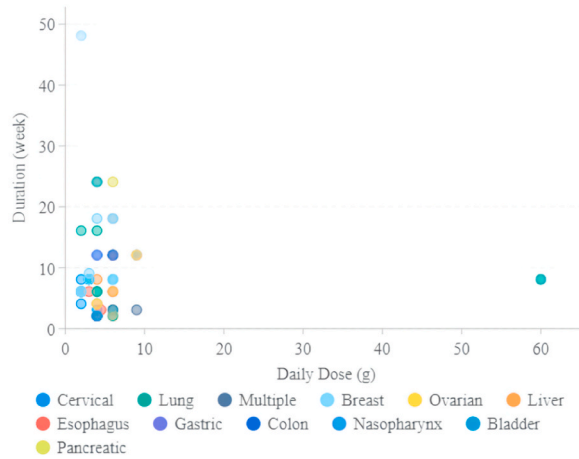


Fig. 6. The daily doses and duration of *Xihuang* pills/capsule for cancer treatment.

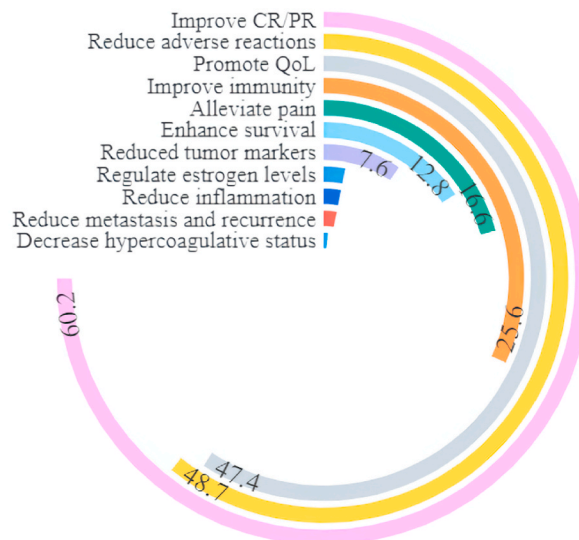


Fig. 7. The proportion of literature related to the therapeutic effect of *Xihuang* pills/capsule.

evaluate the ideal treatment period. Meanwhile, without regular therapies, long-time intake of the *Xihuang* pill as a complementary therapy is acceptable for patients with cancer in China. Although there is rarely compelling evidence to demonstrate the beneficial effects of *Xihuang* pills on cancer patients when taken for a long time, according to the results of the current studies, *Xihuang* pills seem harmless to cancer patients when taken in small doses for a long time.

Xihuang pill combined with chemotherapy in comparison with chemotherapy alone could significantly enhance the tumor response, improve QoL, alleviate toxicity induced by chemotherapy [91], decrease hypercoagulability [92], regulate immunity, reduce tumor markers [10], and relieve the side effects of modern therapies [93], which is convinced by previous studies. We tried to summarize the specific effects of *Xihuang* pills more comprehensively than just those mentioned above. In terms of side effects, *Xihuang* pills enable to alleviate myelosuppression (leukopenia, anemia, thrombocytopenia), gastrointestinal reactions (nausea, vomiting, diarrhea, constipation, anorexia), renal or hepatic impairment, skin lesions (hand-foot syndrome, pruritus, alopecia), neurological reactions (dizziness, somnolence, insomnia, blurry vision), and has an analgesic effect. The treatment for cancer-related pain remains largely unchanged, so most patients with cancer-related pain are managed using opioids [94]. While in patients responding to strong opioids, long-term use of opioids will lead to many undesired side effects such as constipation, tolerance, and addiction [95]. We found that *Xihuang* pills could achieve the same or better pain relief as opioids and avoid the possibility of addiction, which provides a viable replacement for opioids. However, *Xihuang* pills should be used with caution in pregnant women because excessive *Huoxuehuayu* therapy may lead to abortion [96]. For non-pregnant women with cancer, 2 studies referred that *Xihuang* pills can not only improve the symptoms of hectic fever and night sweat but also regulate estrogen equalization. Besides that, *Xihuang* pills also have a positive effect on the prognosis of tumor treatment, reflected in extending survival by 1–2 years (10 studies) and reducing the 5-year recurrence and metastasis rate (2 studies), which was not mentioned in the previous review. Despite the relative lack of evidence, We believe that the *Xihuang* pill, the representative medicine for *Huoxuehuayu* therapy, tends to inhibit tumor metastasis and recurrence to prolong the lifetime in the treatment of tumors, which is relatively safe under the condition of rational use (Fig. 8).

We tried to answer the question of whether the effect of the *Xihuang* pill on cancer treatment varies according to the type of cancer through relative literature, even though breast cancer is the most frequently treated cancer. Network pharmacology-based identification predicted that the potential therapeutic targets of *Xihuang* pills might be VEGFA, EGFR [97], IL-17, toll-like receptor, and tumor necrosis factor signaling pathways [98] (Akt/mTOR pathway [99], MEKK1/SEK1/JNK1/AP-1 pathway [100]), which can be found in most cancer. Hence, it is difficult to assess which cancer *Xihuang* pill is better for treatment. We surmised that the therapeutic effect of the *Xihuang* pill on different cancers may be similar due to its multi-target properties.

5. Suggestions for future research

We confronted some limitations based on published literature so that our conclusion might be conserved, and further research is deeply needed. First, the dosage forms of *Xihuang* pills included in the literature were divided into capsules and pills. Even though the



Fig. 8. Target cancer and effectiveness of the *Xihuang* Pill.

ingredients and compatibility ratios are the same among the two types, in the theory of TCM formulations, different dosage forms will lead to certain differences in drug effects, reflected in the duration and the speed of effectiveness. Therefore, it will be beneficial to learn potential differences in dosage forms for the treatment of cancer patients. Second, we attempted to explore the possible differences in the targeting effect of the *Xihuang* pill on different tumors, such as improving CP or PR of breast cancer or prolonging the survival time of lung cancer. But unfortunately, due to the inclusion of a few references, *Xihuang* pills treat more types of cancer, and the experimental results do not have a certain tendency. Similarly, the included literature suggests that the *Xihuang* pill is mainly used for the treatment of stage III-IV cancer. We are not sure whether publication bias leads to rare literature in the initial stage of treatment of the *Xihuang* pill, and therefore the difference in treatment effect of different stages cannot be obtained. Besides, we found that there was a great span in the dosage and time of *Xihuang* pill application, and there was no significant difference in the therapeutic effect, so the optimal dosage and treatment time of the *Xihuang* pill could not be determined. In future studies, we need more evidence on the efficacy of the *Xihuang* pill in treating different tumor stages (especially the initial stage) and different tumor types (especially tumors other than breast cancer). Third, treatment based on syndrome differentiation is one of the distinctive features of TCM. *Xihuang* pills are used to treat patients with the syndrome of blood stasis and heat toxicity. In this study, almost all literature did not indicate that patients with cancer undergo TCM syndrome differentiation, as long as they met the cancer diagnosis. Based on the treatment effect, we speculated that cancer patients had the syndrome of blood stasis and heat toxicity, especially in patients with advanced cancer, which needs more compelling evidence in the future.

6. Conclusion

In conclusion, the highlight of this study is to provide relatively comprehensive insight into the application of *Xihuang* pills in cancer treatment. *Xihuang* pill has a therapeutic effect on various kinds of cancer, and the therapeutic effect may not be different in terms of tumor stage and types, which is reflected in enhancing the tumor response, reducing adverse reactions/toxicity induced by modern therapies, promoting QoL, alleviating pain, prolonging survival, lessening metastasis and recurrence, reducing inflammation, regulating estrogen levels, improving hypercoagulable status, and decreasing tumor markers. The optimal dose and duration of *Xihuang* pills have not yet been determined. Given the present study, the *Xihuang* pill is generally applicable and safe in the treatment of middle and advanced cancer, demonstrating the safety and effectiveness of *HuoxueHuayu* therapy in the treatment of tumors.

Author contribution statement

Zehui Chen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Shuo Yang: Conceived and designed the experiments.

Jing An: Analyzed and interpreted the data.

Yue Wei: Analyzed and interpreted the data.

Zhiming Li: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Consent for publication

The authors all agreed for publication of this paper.

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Declaration of interest's statement

The authors declare no competing interests.

Abbreviations

CR Complete Response
BAS before-after study

NRCC	non-randomized concurrent control trial
OS	Overall Survival
PFS	progression-free survival
PR	Partial Response
QoL	Quality of life
RCT	randomized control trial
TACE	Transhepatic Arterial Chemotherapy And Embolization
TCM	Traditional Chinese Medicine
XH	Xihuang pill or capsule
3D-CRT	3 dimensional conformal radiation therapy

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