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# Off-label use of sodium cantharidinate and vitamin B6 injection in cancer: a protocol for a systematic review and meta-analysis

Wenzhen Jin[1], Yibin Zhang[1], Shu Pang[1], Dongdong Yao[1] and Yiwen Huang[1*]

## Abstract

**Background** In China, sodium cantharidinate/vitamin B6 (SC/VB6) injection has been approved since 2002 for the treatment of lung cancer and primary liver cancer. In addition to these authorized indications, clinical application of SC/VB6 is also common in various other types of cancer. However, there is a lack of comprehensive understanding on this topic. Thus, this systematic review and meta-analysis aims to consolidate evidence regarding the efficacy and safety of off-label use of SC/VB6 in oncology.

**Methods** International databases including PubMed, Embase, Cochrane Library, Web of Science, and CINAHL Plus, as well as Chinese databases including China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Wanfang, will be searched from the inception to 31 December 2024. Comparative studies that evaluated the add-on effect of SC/VB6 to conventional cancer treatments against the use of conventional treatments alone will be considered in the scope of this review. The primary outcomes are objective response rate and performance status. Secondary outcomes are disease control rate (DCR), progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), and adverse events (AEs). Depending on heterogeneity, data will be synthesized using either the Mantel–Haenszel fixed-effect or the DerSimonian and Laird random-effect model. Subgroup analyses will be conducted for the following variables: type of cancer, study design, SC/VB6 dosage, treatment duration, and combined therapies, provided that each subgroup contains at least two studies. Sensitivity analyses will be performed on efficacy outcomes. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) will be utilized to appraise the overall quality of evidence.

**Discussion** This review will encompass both randomized controlled trials (RCTs) and cohort studies, thereby enabling us to synthesize and assess evidence across experimental and real-world observational settings. Our findings will contribute to a better understanding on the benefit-risk profile regarding the off-label use of SC/VB6 in oncology, guiding the trajectory of future research, and offering a robust scientific foundation to inform clinical and regulatory decision-making process.

**Systematic review registration** PROSPERO CRD42024504977.

**Keywords** Off-label use, Sodium cantharidinate/vitamin B6, Cancer, Systematic review, Meta-analysis

## Background

Cancer represents a heterogeneous group of diseases resulting from abnormal proliferation of cells that damage adjacent cells or organs and can spread to other parts of the body [1, 2]. Globally, cancer is a leading cause of premature death with rapid growth of incidence and

*Correspondence:
Yiwen Huang
yiwen.huang2@clinflash.com
[1] Scientific Affairs Department, Clinflash Healthcare Technology (Jiaxing) Co., Ltd, Room 813, 999 West Zhongshan Road, Huawen Plaza, Shanghai 200051, People's Republic of China

mortality rates in both developing and developed countries [3]. According to the GLOBOCAN cancer statistics, there was an estimated 19.3 million incident cases and 10 million deaths in 2020, of which female breast cancer corresponded to the highest incidence and lung cancer to the leading cause of cancer mortality [4]. About 23.7% and 30.2% of the GLOBOCAN 2020 estimates of cancer incidence and mortality occurred in China, respectively, accounting for an immense cancer burden of 4.6 million new cases and 3 million deaths [5, 6]. Despite that age-standardized incidence rate of all cancers was lower than that in the USA and UK (204.80 vs 362.20 and 319.90 per 100,000 population), China had a much higher cancer mortality rate (129.40 vs 86.30 and 100.50 per 100,000 population) [6]. Lung cancer, digestive cancer of the liver, stomach, and esophagus, and cervical cancer were the mainstay that accounted for 37.4% of all cancer mortality in China, compared to less than 12% in either the USA or UK [6].

Traditional Chinese medicine (TCM) is often used in combination with chemoradiotherapy to reduce adverse effects, enhance treatment effectiveness, and improve patients' quality of life [7, 8]. As an adjunctive therapy for cancer, TCM can not only alleviate gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting) and cardiotoxicity brought about by anticancer treatments but also protect against chemotherapy-induced peripheral neuropathy and radiation-induced pneumonitis [9]. Mechanisms underlying the anti-tumor activities of TCM include oncogenes and tumor suppressor genes regulation, epigenetic modification, tumor microenvironment modulation, and metabolic reprogramming; furthermore, TCM can prevent local invasion and metastasis of cancer cells by targeting the signals involved in tumor epithelial-mesenchymal transition (EMT) [10, 11]. Recent advances in cancer research have shown that TCM can regulate tumor cell senescence, which is an irreversible cell cycle arrest state leading to permanent loss of proliferation capability, thus becoming a promising anticancer option due to the telomerase suppression characteristics [12].

Cantharidin, which is a bioactive ingredient extracted from Chinese blister beetles of meloid family (*Mylabris phalerata* and *Mylabris cichorii*), has been applied for treatment of various diseases for more than 2000 years [13, 14]. The anticarcinogenic activity of cantharidin mainly attributes to its inhibitory effect on protein phosphatases type 1 (PP1) and type 2A (PP2A) enzymes, thus eliciting a series of molecular actions to inhibit cancerous cells growth and metastasis and induce cell cycle arrest and apoptosis of the neoplasm, while strengthening the function of tumor suppressor proteins such as p53, in a broad spectrum of human cancer cell lines [13–17]. Sodium cantharidinate (SC), a semisynthetic derivative of cantharidin, preserves the unique anticancer activity but with reduced toxicity [18]. Preclinical findings showed that SC can, in a dose- and time-dependent manner, induce HepG2 cell apoptosis through LC3 autophagy pathway and inhibit human osteosarcoma MG-63 cell proliferation by inducing cell cycle arrest at the G0/G1 phase [19–21]. SC also stimulated dendritic cell maturation of patients with bladder carcinoma, thereby upregulating innate immunity even in the immunosuppressive tumor microenvironment [8, 22]. Furthermore, there was evidence on the synergistic effect of SC with chemotherapy to hamper growth of pancreatic and cervical cancer, respectively [18, 23].

Sodium cantharidinate/vitamin B6 (SC/VB6) injection is a compound agent that combines the pharmacological properties of both SC and vitamin B6 [24, 25]. Per 10-mL injection contains 0.1-mg SC and 2.5-mg vitamin B6. The combination with vitamin B6 allows to further lower the toxicity and adverse effects of SC [26]. First approved in China in 2002, SC/VB6 injection is indicated for the treatment of primary liver cancer and lung cancer. Compared to platinum-based chemotherapy alone, the addition of SC/VB6 significantly improved tumor response rate, quality of life, and clinical symptoms of patients with non-small-cell lung cancer (NSCLC) while reducing the risk of hematologic toxicity and gastrointestinal adverse reactions [27–29]. Auxiliary treatment with SC/VB6 also revealed prominent therapeutic effects and alleviated toxicities of chemotherapeutic agents in primary liver cancer [30, 31]. SC/VB6 injection has been included in the China National Reimbursement Drug List (NRDL), thereby facilitating broader accessibility and affordability.

Off-label drug use refers to the prescription of medicines beyond the scope of therapeutic indications, dosages, patient demographics, pharmaceutical formulations, or routes of administration that have been explicitly approved by regulatory agencies [32, 33]. In China, off-label use of therapeutic agents is a common practice that accounted for 47.64% of hospitalized patients [34]. When it comes to the field of oncology, physicians may frequently turn to off-label anticancer drugs to improve patient survival and quality of life, particularly for individuals with palliative and metastatic cancers who had exhausted standard lines of treatment [33, 35]. Fernandez et al. retrospectively reviewed 10-year treatment data of 684 oncology patients in a Spanish university hospital and found off-label treatments were mainly used for breast, gynecological, lung, and gastric cancers that shared the characteristics of high prevalence and/or mortality, with most of these off-label applications being supported by high levels of clinical evidence (2A or 2B) [35]. Similar findings were revealed in a systematic review of 23 studies [33], which also showed that the main reasons for

off-label antineoplastic drug use were "lack of approved indication for specific tumor type (9–46%)" and "modified drug application (10–40%)." While off-label drug use allows for more knowledgeable clinical practice on therapeutic alternatives [34], the appropriateness still remains controversial and attributes to factors that include uncertainty for a favorable benefit-risk ratio, limited evidence to support clinical decision-making, increased out-of-pocket costs for patients, and ethical concerns about lack of informed consents [33, 36]. Nevertheless, a complete prohibition of off-label drug use could have detrimental effects on the development of discipline and the well-being of patients; therefore, it is imperative to analyze the efficacy and safety profiles of off-label anticancer medications through evidence-based approaches to ensure that the legitimate rights and interests of all stakeholders, encompassing physicians, pharmacists, nurses, and patients, are effectively safeguarded [36].

SC/VB6 injection has been used as off-label antitumor medication in various types of digestive cancers like gastric [37, 38], colorectal [39, 40], esophageal [41, 42], and pancreatic [43]. In patients with gastric cancer, the combination of SC/VB6 with the XELOX regimen could offer better therapeutic benefits while mitigating the adverse effects of leukopenia, nausea, and vomiting associated with the XELOX regimen [44]. Similarly, SC/VB6 in conjunction with the FOLFOX regimen can favorably relieve gastrointestinal reactions and hepatic dysfunction associated with the use of the FOLFOX regimen alone for treatment of gastric cancer [45]. A meta-analysis of 1825 patients with advanced digestive system neoplasms from 24 trials showed that compared to conventional medical treatment alone, the combination with SV/VB6 was more effective in terms of improving the overall tumor response rate ($OR = 2.25$, 95% $CI = 1.83–2.76$, $P < 0.00001$), disease control rate ($OR = 2.41$, 95% $CI = 1.85–3.15$, $P < 0.00001$), and performance status ($OR = 2.75$, 95% $CI = 2.13–3.55$, $P < 0.00001$) while alleviating the adverse effects caused by chemotherapy [30].

For non-digestive tumors, SC/VB6 injections are used off-label alongside chemotherapy for breast [46, 47] and ovarian cancers [48, 49] and chemoradiotherapy for cervical [50, 51] and nasopharyngeal cancers [52, 53]. Preclinical studies showed that SC effectively inhibits breast cancer cell proliferation, invasion, and migration, inducing G0/G1 cell cycle arrest and apoptosis via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin (PI3K-Akt-mTOR) pathway [54, 55]. SC also shifts the metabolic phenotype of breast cancer cells from glycolysis to mitochondrial oxidative phosphorylation by modulating the protein phosphatase 5-p53 axis [54]. These findings suggest that SC is a potential therapeutic candidate for breast cancer, targeting both metabolism and pro-apoptotic signaling pathways. SC not only inhibits the growth of cervical cancer cells but also enhances their sensitivity to cisplatin by suppressing PTP nonreceptor type 1 (PTPN1), whose overexpression correlates with advanced clinical stages, higher lymph node metastasis risk, and poorer tumor differentiation [23]. Additionally, SC triggers apoptosis in human cervical cancer Hela cells and alters the expression of apoptosis-related genes like Bcl-2/Bax and Caspase-3 in a dose-dependent manner, underscoring its promise as a cervical cancer therapeutic [56]. Although no preclinical study has directly assessed SC's anti-tumor effects in both ovarian and nasopharyngeal carcinoma, cantharidin has been shown to reduce invasion, migration, and adhesion in the highly metastatic HO-8910PM ovarian carcinoma cell line, possibly due to the downregulation of the nuclear factor-kappa B (NF-κB) P65 subunit and vascular endothelial growth factor (VEGF) [57]. Cantharidic acid, the hydrolysis product of cantharidin, induces apoptosis in human nasopharyngeal carcinoma cells through p38-mediated upregulation of caspase activation [58].

Off-label SC/VB6 is also clinically used in conjunction with chemotherapy for hematologic malignancies such as acute leukemia [59, 60] and non-Hodgkin's lymphoma (NHL) [61, 62]. In vitro studies showed that cantharidin effectively reduces cell viability and colony formation, induces apoptosis and G2/M cell cycle arrest, and promotes acute myeloid leukemia (AML) cell differentiation via the nuclear receptor Nur77 pathway, which includes Nur77 mitochondrial translocation and Bcl-2 conformational change [63]. In NOD/SCID mice, cantharidin has demonstrated anti-leukemic effects featuring extended survival, reduced white blood cells (WBC), increased red blood cells (RBC), decreased hepatomegaly and splenomegaly, and improved histopathology [63]. Furthermore, SC partially reverses multidrug resistance in K562/AO2 leukemia cells to adriamycin by increasing intracellular adriamycin concentration and decreasing P-gp and Bcl2 expression over time [64]. In xenograft mouse models derived from human lymphoma-resistant cells, cantharidin enhances vorinostat's tumor growth inhibition and reverses vorinostat resistance by raising ROS levels and blocking IL-2Rα signaling [65].

However, there is still a lack of comprehensive understanding on the off-label use of SC/VB6 in oncology, particularly concerning the benefit-risk profiles in cancer types other than those of the digestive system. Thus, it is necessary to undertake a systematic review and meta-analysis to address this knowledge gap and provide evidence-based support for the judicious clinical application of SC/VB6 in oncology.

### Objective

The objective of this study is to compile and assess the aggregated evidence regarding the off-label use of SC/VB6 in oncology. The following questions will be addressed:

- Does the addition of SC/VB6 to conventional cancer therapies further enhance their clinical efficacy?
- Is SC/VB6 effective in mitigating the adverse reactions associated with conventional cancer therapies?

## Methods

This protocol has been registered in the PROSPERO database (CRD42024504977) and adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) statement (Additional file 1) [66].

### Eligibility criteria

#### *Types of studies*

Comparative studies that include randomized controlled trials (RCTs), quasi-RCTs, and cohort studies with either prospective or retrospective design will be included to the scope of this systematic review and meta-analysis. Case series, cross-sectional studies, case reports, and expert opinions will be excluded along with nonclinical experiments owning to the inadequate levels of evidence provided by these study types. Letters and conference abstracts without sufficient available data are not eligible. Furthermore, comparative studies without pre-specified outcomes or with the sample size of less than 10 participants will also be excluded [67, 68]. Besides, we will only consider studies in Chinese or English.

#### *Types of participants*

Patients who were histologically or cytologically diagnosed with solid tumors or hematological malignancies will be included, regardless of age, gender, and ethnicity. This review will specifically address the off-label use of SC/VB6 in cancer treatment, excluding patients with lung cancer or hepatocellular carcinoma, as these indications have already been approved by the China National Medical Products Administration (NMPA). To obtain sufficient evidence on the clinical use of SC/VB6 in each specific type of cancer, studies that did not differentiate data between different malignancies will be omitted. Patients who received SC/VB6 mainly for treatment of concurrent malignant ascites, pleural effusion, or metastatic tumors will also be excluded from the analysis.

#### *Types of interventions/exposure*

Patients in the experimental/exposure group should receive SC/VB6 in combination with conventional anticancer treatments, such as radiotherapy, chemotherapy, targeted therapy, or any combination of these modalities, without limitations on dosage, frequency, and treatment duration.

#### *Types of comparators*

Patients in the control group should receive conventional anticancer treatments, such as radiotherapy, chemotherapy, targeted therapy, or any combination of these modalities. This review will include studies where SC/VB6 was used with conventional treatment in the experimental/exposure group, compared to the same conventional treatment as a control group, ensuring a balanced comparison.

#### *Types of outcomes*

The primary outcomes are objective response rate (ORR) and performance status (PS).

ORR, defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period, is delineated by the sum of complete response (CR) and partial response (PR) [69–71]. PS is assessed using the Karnofsky performance score (KPS) [72], with significant clinical improvement defined as an increase of $\geq 20$ points after treatment [52], improvement as a 10-point increment, stability as an increase or decrease of $< 10$ points, and decline as a decrease of $\geq 10$ points [27].

Secondary outcomes include disease control rate (DCR), progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), and adverse events (AEs).

DCR is delineated by the sum of CR, PR, and stable disease (SD) [30, 73, 74]. For long-term outcomes, the focus is on the PFS rate, DFS rate, OS rate, and the respective hazard ratios (HRs) associated with PFS, DFS, and OS. PFS is defined as the time from the date of randomization/initiation of treatment until the date of objective disease progression or death from any cause [70, 71]. DFS is defined as the time from the date of randomization/initiation of treatment until the date of disease recurrence or death from any cause [70, 71]. OS is defined as the time from the date of randomization/initiation of treatment until death due to any cause [70, 71].

Proportion of participants experiencing each of the following treatment toxicities, including leucopenia, neutropenia, thrombocytopenia, anemia, myelosuppression, nausea and vomiting, diarrhea, anorexia, gastrointestinal reaction, hepatorenal toxicity, hand-foot syndrome, oral mucositis, cardiotoxicity, neurotoxicity,

skin reaction, phlebitis, and alopecia, will be assessed. If available, toxicities will be further categorized according to severity grades and by the scale used (e.g., grades 1–4 for the World Health Organization [WHO] scale [75] and 1–5 for the Common Terminology Criteria for Adverse Events [CTCAE] v5.0 scale [76]). To maximize safety data capture, studies that either did not provide a severity grading or lacked reporting of a specific toxicity scale will not be disregarded; instead, these will be accounted for the overall event category. AEs not defined in this protocol but were otherwise reported in the included studies will also be extracted and analyzed in a post hoc manner to avoid missing any relatively rare or unexpected safety signals.

## Search strategy

### *Electronic searches*

Published studies will be identified by searching the international databases including PubMed, Embase, Cochrane Library, Web of Science, and CINAHL Plus, as well as Chinese databases including China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Wanfang from the inception to the 31 December 2024. PubMed, the most widely used electronic database in systematic reviews of life sciences, offers early online ahead of print publications [77, 78]. Embase, similar to PubMed in biomedical citations coverage, has added 300,000 conference abstracts annually since 2009 [78]. The Cochrane Library is renowned for its systematic reviews, while Web of Science offers a multidisciplinary approach to literature across science and biomedicine [79]. CINAHL Plus is important for systematic reviews in nursing and allied health, often used for TCM searches [80–83]. To enhance the identification of TCM-related studies, we selected three comprehensive Chinese biomedical databases—CNKI, CBM, and Wanfang—commonly utilized in meta-analyses on SCV/B6 injections [28, 29].

The literature search will be restricted to English and Chinese languages using a combination of subject wording and free text terms such as "disodium cantharidinate," "sodium cantharidinate," "disodium cantharidinate and vitamin B6," "disodium cantharidinate/vitamin B6," "aiyishu," "neoplasms," "cancer," "tumor," "carcinoma," and "malignancy." The detailed search strategy for each database is attached as Additional file 2.

### *Searching other resources*

Bibliographic search of relevant reviews, guidelines, and meta-analysis will be conducted to identify additional studies that were not covered by electronic database search.

The Chinese Clinical Trial Registry (ChiCTR; http://www.chictr.org.cn/) and ClinicalTrials.gov (www.clinicaltrials. gov) will also be searched for ongoing or completed RCTs with unpublished data.

## Study selection

Records retrieved from the database searches will be imported to a reference manager to automatically eliminate duplicates. Study selection will be conducted independently by two reviewers (Y. D. D., J. W. Z.). First, they will assess the titles and abstracts to identify studies that are relevant. Full-text articles will be retrieved for detailed inspection. Any inconsistencies between the two reviewers will be resolved by consultation with other members of the study team. Studies retained after full-text screening will be considered eligible for inclusion to this systematic review and meta-analysis. The study selection process and the reasons for exclusion will be summarized in a PRISMA flow diagram [84].

## Data extraction and management

### *Data extraction*

Two independent reviewers (Y. D. D., J. W. Z.) will extract data using a standardized form. All records will be fully checked against the original article by a third reviewer (PS) to ensure accuracy and completeness of data. Disputes will be addressed through discussion within the study team. In the case of uncertainties or the lack of sufficient data, authors of the included studies will be contacted through e-mail with a maximum of three attempts to obtain the necessary information [85, 86].

### *Data items*

Data relevant to the research questions outlined above will be collected. The following data will be extracted from each study:

- General information: First author, publication year, and country
- Study characteristics: Study design (such as randomization and blinding), multi-center (yes/no), and study period
- Patient characteristics: Sample size, age, sex, type of cancer, tumor stage, pathologic type, and KPS
- Treatment details: SC/VB6 and conventional anticancer treatments (such as treatment name, dosage, frequency, route of administration, number of cycles, and duration)
- Outcomes: Primary and secondary outcomes, evaluation criteria, and time of assessment

### Risk-of-bias assessment

Risk of bias will be assessed using the revised Cochrane risk-of-bias tool (RoB 2; available at https://www.riskofbias.info/) for RCTs and quasi-RCTs and the Risk Of Bias In Non-randomized Studies-of Interventions, Version 2 (ROBINS-I V2, available at https://www.riskofbias.info/welcome/robins-i-v2) for comparative cohort studies, as applicable. The ROB2 will be administered at outcome level in six domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall risk of bias; each separate domain will be rated as having a low risk of bias, some concerns, or high risk of bias. The ROBINS-I V2 will examine three additional domains to those of RoB2: confounding, selection of participants, and classification of intervention, which involve a risk-of-bias judgement of low, moderate, serious, critical, or no information.

Two reviewers (Z. Y. B., H. Y. W.) will independently assess the methodological quality of the included studies. In the event of discrepancies, they will be resolved by consultation with other members of the study team. Should the information provided is insufficient for a comprehensive evaluation, the authors of the studies may be contacted to solicit further details.

### Data synthesis

Data synthesis will be conducted using Review Manager (RevMan) 5.4.1 (Cochrane Collaboration) and supplemented with R software (R Foundation for Statistical Computing; version 4.2.3).

#### *Effect size measures*

The estimate of effect will be expressed as risk ratio (RR) along with its 95% confidence interval (CI) for dichotomous data and mean difference (MD) with a 95% CI for continuous data. When the same outcome is measured using different scales across studies, standardized MD (SMD) with a 95% CI will be employed to facilitate a meaningful comparison. Survival data, including OS, DFS, and PFS, will be measured using HR with a 95% CI. If survival data or its 95% CI was not directly provided, the values will be estimated from the Kaplan–Meier curves using methods described by Tierney and colleagues [87].

#### *Effect size models*

Forest plots will be generated for each outcome, displaying the summary effect, standard error, and corresponding *P*-value along with a 95% CI. The Mantel–Haenszel fixed-effect model will be employed for meta-analysis if no significant heterogeneity is observed between the studies (i.e., $P \geq 0.1$ and $I^2 \leq 50\%$); otherwise, the DerSimonian and Laird random effect model will be used when there is evidence of significant heterogeneity (i.e., $P < 0.1$ or $I^2 > 50\%$).

The minimum number of studies to perform meta-analyses is two studies per outcome. A narrative summary of the results will be provided for outcomes on which a meta-analysis is not possible.

#### *Assessment of heterogeneity*

Heterogeneity will be assessed using the chi-squared ($\chi^2$) test and the inconsistency index ($I^2$) value. Statistically significant heterogeneity is revealed when $P < 0.1$ of $\chi^2$ test or $I^2 > 50\%$ [88]. Alternatively, $P \geq 0.1$ and $I^2 \leq 50\%$ indicate no significant heterogeneity across the included studies.

#### *Reporting bias*

Reporting bias will be examined using a funnel plot for any meta-analysis with a minimum of 10 studies. Visual inspection of funnel plot asymmetry, in conjunction with Egger's regression test, will be conducted to assess potential publication bias [89, 90].

#### *Subgroup analysis*

We plan to conduct subgroup analyses according to the type of cancer for both efficacy and safety outcomes, provided that each subgroup includes a minimum of two studies. Furthermore, we will assess the impact of study design (RCT, cohort studies), SC/VB6 dosages (< 50 ml/day, ≥ 50 ml/day), treatment duration (divided into two subgroups by pooling estimates defined by the median days) [91, 92], and combined therapies (radiotherapy, chemoradiotherapy, chemotherapy [including DP, TP, FP, TEC, CHOP, SOX, nedaplatin, XELOX, FOLFOX, capecitabine, raltitrexed + oxaliplatin, others]) on clinical efficacy.

The challenges anticipated when conducting subgroup analyses, and strategies to manage these challenges, are described as follows:

Firstly, there can be inconsistent reporting of SC/VB6 dosage units (ml vs. mg) across the included studies. Given that the product label of SC/VB6 injection specifies a 0.05 mg SC dose in 5 ml per injection, the daily dosages from various studies will be standardized to ml/day based on this label specification.

Secondly, while uncommon, some studies may lack details on SC/VB6 dosage and/or treatment duration (either the number of days treated per cycle and/or number of treatment cycles). For these cases, three attempts

to contact the authors via email will be made to secure the necessary SC/VB6 treatment information. If no response is received, these studies will be excluded from the subgroup analysis.

Thirdly, SC/VB6 dosage threshold is established based on a previous meta-analysis that distinguished between low (< 50 ml/day) and high (≥ 50 ml/day) dosages [28]. If significant heterogeneity ($P < 0.1$ or $I^2 > 50\%$) is detected within either subgroup, a more granular classification, such as increments of 10 ml/day, may be implemented, as used in a meta-analysis of off-label SC/VB6 use in digestive tumors [30]. Studies with dosages ranging from < 50 ml/day to ≥ 50 ml/day (e.g., 20–60 ml/day) will be excluded from subgroup analysis due to inadequate data for evaluating the effect of dosage variations on clinical outcomes.

A meta-analysis on SC/VB6 as an adjunct to platinum-based chemotherapy for NSCLC showed that the treatment duration was typically 10–15 days across 1–4 cycles [28]. While this duration was common for chemotherapy adjuncts, it varies when SC/VB6 was combined with chemoradiotherapy or radiotherapy, often spanning 21 days or 6–7 weeks [50, 52, 53]. Studies on SC/VB6 as an adjunct to chemotherapy sometimes reported varying durations per cycle, ranging from 7 to 8 days to 21 days or longer and extending up to 6–8 cycles [37, 40, 46, 49]. To account for this variability, subgroups are categorized based on the cumulative days of SC/VB6 treatment (days/cycle × number of cycles). Data handling for heterogeneity and diverse treatment durations will mirror the approaches applied to SC/VB6 dosages.

#### *Sensitivity analysis*

Sensitivity analyses will be performed on efficacy outcomes by deleting individual study at each turn to evaluate the reliability and robustness of the results. The differences between the recalculated effects and the original ones will be compared.

### Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) will be utilized to appraise the overall quality of evidence as high, moderate, low, or very low [93]. We will construct a summary of findings table to encapsulate the quality of the primary outcomes in aspects of the five domains in the GRADE: risk of bias, consistency, directness, precision, and publication bias.

### Dissemination

The results of this study will be disseminated through publication in a peer-reviewed journal.

## Discussion

SC/VB6 injection has demonstrated a favorable benefit-to-risk profile in a spectrum of clinical studies that evaluated its efficacy and/or safety in the treatment of solid tumors and hematologic malignancies [27–31]. However, there are very few systematic reviews that provide clinical evidence for the application of SC/VB6 beyond its approved indications (i.e., lung cancer and primary liver cancer). With the exception of digestive cancers, the off-label use of SC/VB6 for other cancer types has not been systemically investigated. To the best of our knowledge, this study represents the first comprehensive analysis of the efficacy and safety profiles associated with the off-label use of SC/VB6 in oncology.

When administered in combination with conventional cancer treatments, SC/VB6 has been shown to enhance clinical efficacy while simultaneously mitigating the toxic effects associated with chemoradiotherapies [27–31]. Accordingly, we will include comparative clinical studies that evaluated the add-on effect of SC/VB6 to conventional cancer treatments against the use of conventional treatments alone. This review will encompass both RCTs and cohort studies, thereby enabling us to synthesize and assess evidence across experimental and real-world observational settings. We have incorporated subgroup analysis into the design of this study, which will allow us to investigate the efficacy and safety of SC/VB6 within each specific cancer type. A meta-analysis on digestive tumors indicated that SC/VB6 at dosages of 20, 30, 40, and 50 ml/day significantly improved ORR compared to conventional treatment alone; additionally, combining SC/VB6 with XELOX, capecitabine, or gimeracil and oteracil potassium capsules also demonstrated increased ORR over chemotherapy alone [30]. Another meta-analysis encompassing 19 trials totaling 1428 patients with advanced NSCLC showed a significant improvement in both ORR and KPS with SC/VB6, irrespective of dosage (< 50 ml/day vs. ≥ 50 ml/day), treatment duration (≤ 10 days vs. > 10 days), and chemotherapeutic regimen (GP, DP, TP, NP, and others) [28]. Given these promising results, this study will conduct subgroup analyses on SC/VB6 treatment modalities, including dosages, duration, and combination therapies, to determine if similar trends will be observed in off-label use of SC/VB6, particularly for non-digestive tumors. This systematic review and meta-analysis aims to elucidate the current landscape of off-label use of SC/VB6 in oncology. We hope that the findings of our study will contribute to a better understanding on the benefit-risk profile of SC/VB6, guiding the trajectory of future research, and offering a robust scientific foundation to inform clinical and regulatory decision-making process.

**Abbreviations**

| | |
|---|---|
| AE | Adverse event |
| CBM | Chinese Biomedical Literature Database |
| CI | Confidence interval |
| CNKI | China National Knowledge Infrastructure |
| CR | Complete response |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | Disease control rate |
| EMT | Epithelial-mesenchymal transition |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| HR | Hazard ratio |
| ICTRP | International Clinical Trials Registry Platform |
| KPS | Karnofsky performance score |
| MD | Mean difference |
| NDRL | National Drug Reimbursement List |
| NMPA | National Medical Products Administration |
| NSCLC | Non-small cell lung cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| PFS | Progression-free survival |
| PP1 | Protein phosphatases type 1 |
| PP2A | Protein phosphatases type 2A |
| PR | Partial response |
| PRISMA-P | Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols |
| PS | Performance status |
| RCT | Randomized controlled trial |
| RR | Risk ratio |
| SC | Sodium cantharidinate |
| SD | Stable disease |
| SC/VB6 | Sodium cantharidinate/vitamin B6 |
| SMD | Standardized mean difference |
| TCM | Traditional Chinese medicine |
| WHO | World Health Organization |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02826-y.

Additional file 1. PRISMA-P 2015 Checklist

Additional file 2. Search Strategy

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**Authors' contributions**
YWH is the guarantor of the review. WZJ and YWH defined the research question. YBZ, SP, and DDY developed the search strategy and determined inclusion and exclusion criteria. WZJ and YBZ created the first draft of this manuscript, and all authors reviewed and approved the final manuscript.

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## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
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**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note