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REVIEW ARTICLE

Use of cucurbitacins for lung cancer research and therapy

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Abstract

As the main substance in some traditional Chinese medicines, cucurbitacins have been used to treat hepatitis for decades in China. Currently, the use of cucurbitacins against cancer and other diseases has achieved towering popularity among researchers worldwide, as detailed in this review with summarized tables. Numerous studies have reported the potential tumor-killing activities of cucurbitacins in multiple aspects of human malignancies. Continuous research on its anticancer activity mechanisms also brings a glimmer of light to the treatment of patients with lung cancer. In line with the promising roles of cucurbitacins against cancer, through various molecular signaling pathways, it is justifiable to propose the use of cucurbitacins as a potential mainline chemotherapy before the onset and after the diagnosis of lung cancers. Here, this article mainly summarized the findings about the biological functions and underlying mechanisms of cucurbitacins on lung cancer pathogenesis and treatment. In addition, we also discussed the safety and efficacy of their application for further research and even clinical practice.

Keywords Traditional Chinese medicine · Cucurbitacins · Lung cancer · Treatment · Mechanisms

Introduction

Lung cancer is a worldwide public health problem and has been a major cause of mortality in recent years [1–3]. According to the report of global cancer statistics, there are approximately 2.1 million new cases of lung cancer diagnosed each year, and 1.8 million patients died of lung cancer in 2018 [4–6]. In clinical practice, the treatments that are available for lung cancer include surgical resection, radiotherapy and chemotherapy drugs [7, 8]. Specific treatment is mainly based on the diagnosis and clinical staging of patients [9]. However, the status quo is that the clinical screening of lung cancer is not accessible for each patient. As a result, patients are usually diagnosed at advanced stages. At the same time, the 5-year survival rate of lung cancer, which continues to decrease as the disease stage progresses, with comprehensive consideration of various factors, only varies from 4–17% [10, 11]. Even though some emerging therapeutic strategies, including targeted therapy and immunotherapy, have exhibited momentous clinical benefits [7, 10, 12], some patients do not show durable remission, and some tumor cells have been refractory to response with the anticancer drugs [10, 13, 14].

Therefore, to further prolong the life expectancy of these patients, and better improve their quality of life, the progress of research regarding more sophisticated diagnostic methods and more effective therapeutic drugs for early lung cancer needs to be sped up.

Cucurbitacins, natural products originally derived from Cucurbitaceae, have been shown to possess strong antitumor activity by modulating multiple signaling pathways in vivo and in vitro [15–17]. With several unique advantages, such as lower toxicity and fewer side effects, these compounds could more promptly be moved into clinical practice [18–20]. Currently, besides the Cucurbitaceae, cucurbitacins can also be extracted from various families of plants

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worldwide [18, 21]. In terms of structural composition, except for the nucleus skeleton of tetracyclic cucurbitane, cucurbitacins carry different oxygen-containing functional groups in different positions. There are approximately 12 different classes of cucurbitacins, divided from A to T with over 200 derivatives [21]. After years of accumulation, a growing contingency of researchers have confirmed their activity against several human pathological processes, for example, the anticancer effects, anti-inflammatory action, immunomodulatory capacities, etc. [15, 22–24]. Emerging evidence documents that cucurbitacin has a certain degree of inhibitory effect on a variety of tumors [25–27]. Nowadays, the research advancement of cucurbitacins in various human cancers have been reviewed in several papers [18, 28–32]. Especially, a recent review has summarized the potential anti-cancer properties in breast cancer [33]. However, the detailed biological functions and regulatory mechanisms of cucurbitacins in the occurrence and development of lung cancer are poorly summarized. Recently, its potent antagonized efficacy in lung cancer attracts the attention of researchers and has been well-identified in different experiments (Tables 1, 2). Therefore, as a promising antitumor drug, the detailed roles of cucurbitacins in lung cancer research and treatment are worthy of further research. To date, the major mechanisms of action involve apoptosis induction, cell cycle arrest, cytoskeleton regulation and so on [21, 34–38]. Although a large number of reports exist regarding the effective anticancer functions of cucurbitacins, their detailed mechanisms have not been fully elucidated so far.

In this article, we mainly summarize the application of cucurbitacins in lung cancers, focusing on the therapeutic functions and related biological mechanisms (Fig. 1). The isolated cucurbitacin components with attractive anticancer activity for lung cancer have been reported to include A, B, D, E, I, Q, IIa and their derivatives. Furthermore, the safety problems are also discussed for the purpose of clinical application in the future.

Cucurbitacin B

Cucurbitacin B (CuB) is one of the most active and popular cucurbitacins studied. It is widely distributed in a variety of plants, mainly in the form of glycosides. CuB and its derivatives, extracted from different parts of different plants, showed significant cytotoxicity to different lung cancer cells, including A549, SK-LU1 and so on [39, 40]. Although the roles of CuB have not yet been elucidated clearly, relevant mechanisms and targets that have been discovered deserve our attention.

Epidermal growth factor receptor (EGFR), which is normally overexpressed in various cancers, is a key target for lung cancer therapy, especially for non-small-cell lung cancer (NSCLC) [41–43]. For patients who carry a sensitizing mutation in EGFR, tyrosine kinase inhibitors (TKIs) are recommended first [6, 44, 45]. A recent study has found that CuB could directly suppress EGFR signaling through the lysosomal pathway both in vitro and in vivo, which is distinct from TKIs [46]. Consequently, CuB successfully impeded cell migration and invasion in the gefitinib-resistant (GR) NSCLC EGFR/ERK pathway. The CIP2A/PP2A/Akt axis was verified to play a dominant role in CuB-induced cell proliferation inhibition through a series of studies by Liu PF's group [46].

Indeed, it was also reported that CuB inhibited tumor growth and cell colony formation regardless of their EGFR expression in different studies [47–49]. Another possible reason for this attractive result might, in part, stem from the inhibitory effect of CuB on the downstream molecules of EGFR. Khan N et al. [48] revealed that CuB suppressed PI3K/Akt/mTOR and signal transducer and activator of transcription 3 (STAT3) signaling both in EGFR-mutant and EGFR-wild-type lung cancer cells, leading to growth inhibition along with G2-phase cell cycle blocking. As the downstream molecules of EGFR, STATs have been recognized as promising targets for cancer treatment as well [50]. Existing evidence indicated that Janus kinase (JAK)-STAT3 signaling played a significant role in promoting cancer progression, with effects on tumor cell proliferation, survival and invasion [51–53]. As early as 2004, it was found that CuB inhibited the JAK-STATs pathway in vitro and in vivo and induced apoptosis and tumor growth inhibition [54]. Li YM's group revealed that CuB suppressed cell proliferation and induced caspase-related apoptosis through the STAT3 pathway, along with cytochrome *c* release and Bcl-2 reduction. Upregulation and activation of STAT1, the important effector in IFN-γ signaling, further enhanced the antitumor effects of CuB [55]. Similar to STAT3, Akt is also closely related to cell survival and proliferation and is commonly overexpressed in cancer cells [56, 57]. Treatment with CuB was found to result in decreased viability and improved apoptosis of lung cancer cells by causing inhibition of PI3K/Akt/mTOR signaling pathway [48]. To sum up, CuB may provide an opportunity to overcome the common clinical problems of EGFR-TKI therapy in lung cancer, that is, poor sensitivity and drug resistance [41, 46]. Aside from the EGFR/Akt pathway mentioned above, CuB exhibited significant inhibitory effects on the migratory and invasive abilities of NSCLC cells in vitro and in vivo, with attenuation of the canonical Wnt/β-catenin signaling pathway [46, 58]. Given that the migration and invasion potentials in lung cancer often predict progression and recurrence [59, 60], CuB has good prospects in inhibiting the progression of lung cancer tumors and enhancing the treatment response.

Table 1 The anti-lung cancer activities of cucurbitacins in vitro

Type	Source	Cell lines	Active concentration	Biological outcomes	Related molecular	Refs
CuB	Purchased	H1975 H820	0.1, 0.2, 0.4 μM 0.05, 0.1, 0.2 μM	Growth and proliferation↓ Invasion and migration↓ Apoptosis↑	caspase-3,8, PRAP LAMP-1, EGFR, ERK CIP2A/PP2A/Akt	46
CuB	Purchased	A549	0.1, 1.0 μM	Proliferation↓ G2/M cell cycle arrest Apoptosis↑	caspase-3 and 9 cytochrome c cyclin B1, Bcl-2, STAT3	47
CuB	Purchased	A549, H1650	0.2, 0.4, 0.6 μM	Growth and colony↓ Apoptosis↑ G2-phase cell cycle arresst	AMPKα, PI3K/Akt/mTOR, 4EBP1, eIF-4E, p70S6K STAT3 sestrin-3	48
CuB	Purchased	H1299	0.1, 0.35 μM	Viability↓ Morphological change G2/M cell cycle arrest Apoptosis↑	p38 MAPK/Hsp27, F-actin, Rac, cdc42 ERK, STAT3, WAF1, cdc2p34, cyclin B1, D1, PCNA Bcl2, Bax, cytochrome c, caspase-3, 9, PARP, gelsolin, thiol, GSH	49
CuB	Unkown	A549, H1299	0.025–0.1 μM	Migration↓ (0.01–0.1 μM) Invasion↓ Stemness↓	canonical Wnt/β-catenin GSK-3, TCF-1, MMP-2, vimentin, MYC, Cyclin D1, VEGF, Survivin-FZD-7, E-Cadherin	58
CuB	Purchased	A549	0.05, 0.1, 0.2 μM	Proliferation↓ DNA-double strand breaks G2/M cell cycle arrest	ATM-Chk1-Cdc25C-Cdk1, Cyclin B1 ATM-p53-14–3-3-s ROS	61
CuB	L. graveolense Roxb	H1299	0.06, 0.6, 0.86 μM	Proliferation↓ Apoptosis↑	TSGs, Oncogenes, TPGs DNMTs, HDACs,HATs	64
DACE	Semisythesis from CuB	A549	0.5 μM, 1 μM	Growth and colony↓ G2/M cycle arrest Apoptosis↑ (1 μM)	F-actin, caspase-3, Cyclin B1, survivin STAT3, PI3K/AKT ERK, EGFR, Ras, Raf	40
CuE	Purchased	A549	0.25, 1, 2.5 μM	Proliferation↓	Wnt/β-catenin, cyclin D1, cyclin E, Menin	70
CuE	Purchased	95D	0.05, 0.2,1 μM	Proliferation↓ MMP depolarization Apoptosis↑ Autophagy↑ Regulating cytoskeleton	ROS PTEN, AKT/mTOR Bcl-2, Bcl-xL, capase-3, 7, 9, PARP LC3II, p62, Beclin-1, ULK F-actin	71
CuE	Purchased	H2030-BrM3, PC9-BrM3	0.05, 1 μM	Viability↓ (IC_{50} = 0.146/0.187 μM) Migration and invasion↓ Brain metastatic↓	YAP, GTIIC reporter, CTGF, CYR61, EREG, ERK	72
CuI	Unkown	A549	0.1-10 μM	Proliferation↓ (10 μM) Apoptosis↑ (10 μM)	JAK/STAT3	75
CuI	Purchased	A549	0.1–10 μM	/	STAT1, STAT3	76
CuI	Purchased	NSCLC-derived CD133-positive cells	0.1, 0.15 μM	Proliferation↓ Apoptosis↑ Differentiation↑ Sensibilization	STAT3 survivin, Bcl-2,Bcl-xl,Capsase-3	77
CuI	Goya	A549	0.0625–4 μM	Growth↓	PAK1	80

Table 1 (continued)

Type	Source	Cell lines	Active concentration	Biological outcomes	Related molecular	Refs
CuI	Purchased	A549	0.3, 0.4 μM	Proliferation↓ (0.2, 0.3, 0.4 μM) Apoptosis↑ Pro-death autophagy↑	LC3IILC3I ERK/mTOR/STAT3	81
CuI	Unkown	A549	0.05, 0.1, 0.2 μM	Proliferation↓ Apoptosis↑	PI3K/Akt/p70S6K LDH, caspase-3,9	82
CuA	Purchased	A549	40, 100, 200 μM	Proliferation↓ Apoptosis↑ Morphology change G2/M cell cycle arrest	PI3K/Akt/mTOR	83
CuD	Ecballium elaterium	NSCLC-N6	1.93–9.68 μM	Proliferation↓ G1 phase cell cycle arrest Apoptosis↑	Cdk1	85
CuD	Purchased	H1299	0.019–0.39 μM	Proliferation↓ Morpahological change G2/M cell cycle arrest Apoptosis↑	survivin, Bcl-2, Bax, caspase-3,8,9, PARP cyclin A1, B, D, cdc2, cdc 25c ErB3, ErB2, PI3K, Akt, ERK, STAT3, p38 MAPK, JNK, NF-κB	86
CuQ	Purchased	A549	10 μM	Apoptosis↑	STAT3, ERK	54
CuIIa	H. amalils Diell	H1299	17.77, 88.86 μM	Growth↓ Apoptosis↑ Cell cycle progression↓	F-actin, RhoA, survivin, PRAP Histone H3	90
CuIIa	Purchased	A549	50, 60, 70 μM	Growth↓ (40-80 μM) apoptosis↑ G2/M cell cycle arrest	EGFR, Raf, MEK, ERK STAT3, survivin, cyclin B1,	91

↑Promoting

↓Inhibiting

Table 2 The anti-lung cancer activities of cucurbitacins in vivo

Type	Administration Route	Model	Active concentration	Biological outcomes	Related molecular	Refs
CuB	Unkown	H1975 xenograft model	0.5 mg/kg	Tumor growth↓	CIP2A, EGFR	46
CuB	Intraperitoneal	H1299 xenograft model	1 mg/kg	Tumor growth↓	STAT3, WAF1, cyclin B1, Cdk1, Bcl2, Bax, caspase-3	49
CuB	Intraperitoneal	NKK-induced lung cancer mice	0.1, 0.2 mg/kg	Tumorigenesis↓	Wnt/β-catenin MMP-2, E-Cadherin, Cyclin D1, Cox-2, PCNA, VEGF	58
CuB	Unkown	NKK-induced lung cancer mice	0.1,0.2 mg/kg	Tumorigenesis↓	PNCA, TSGs, Oncogenes, TPGs, DNMTs, HDACs	64
CuE	Intraperitoneal	H2030-BrM3 cell murine model	0.2 mg/kg	Brain metastatic↓ Survival time↑	YAP	71
CuI	Intraperitoneal	A549 xenograft model	1 mg/kg	Tumor growth↓		75
CuI	Intraperitoneal	NSCLC-derived CD133-positive-Xenograft Model	1 mg/kg	Tumor growth↓ Metastasis↓ Sensibilization Survival↑		77
CuQ	Intraperitoneal	A549 xenograft model	1 mg/kg	Tumor growth↓	STAT3	54
CuIIa	Intravenous	Lewis lung carcinoma mouse model	5, 10, 15 mg/kg	Tumor size↓		90

↑Promoting

↓Inhibiting

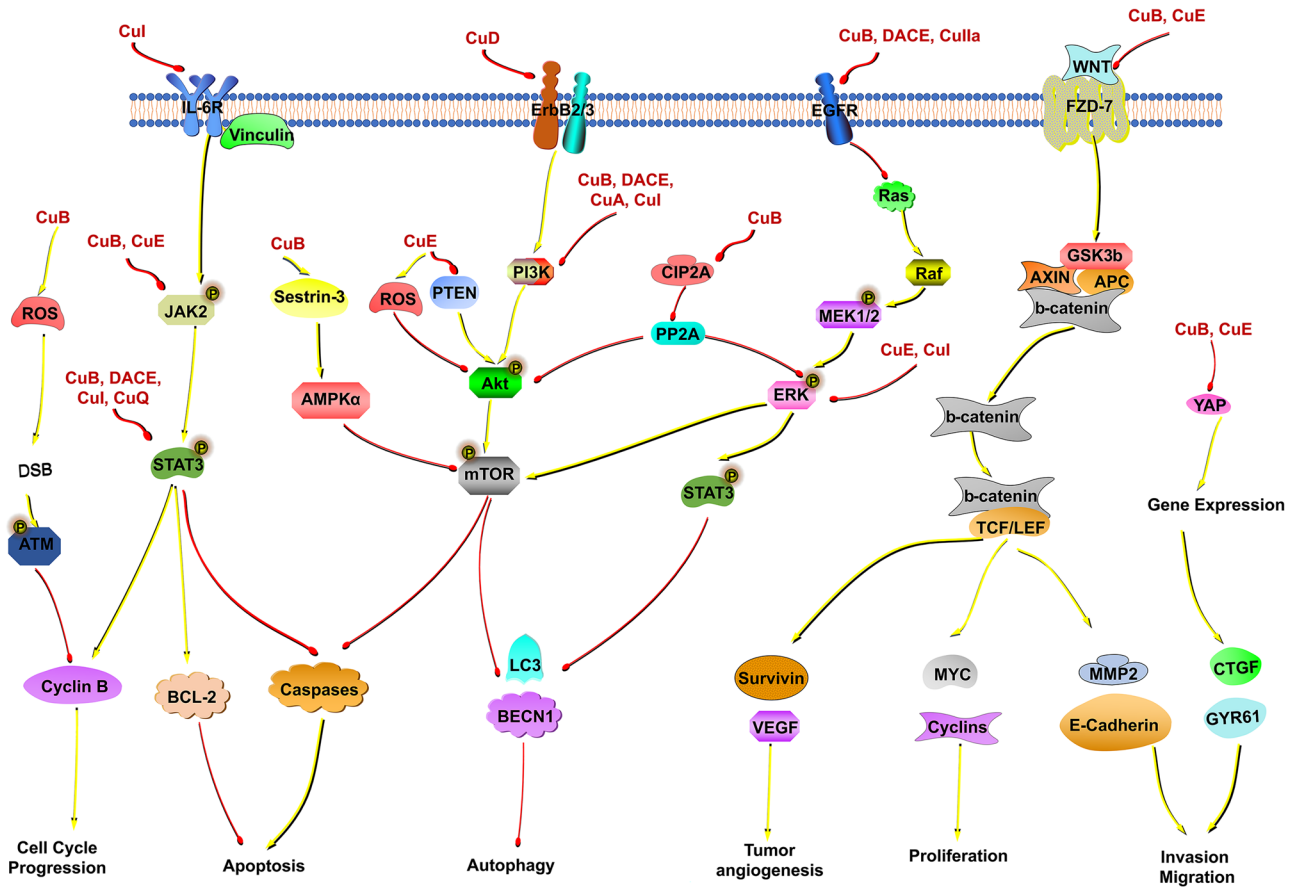

Fig. 1 Overview of the effects of the natural compound cucurbitacins on aberrant signaling pathways in lung cancer research and therapy

It is worthy to note that EGFR-wild-type and EGFR-mutant NSCLC cells exhibited differential expression of sestrin-3 with the treatment of CuB [48]. In Khan N's studies, the connection between sestrin-3 and the AMPKα/mTOR1 axis was verified, which was partly involved in the CuB-induced growth attenuation in H1659 (EGFR-mutant). The elevated protein and mRNA expression of sestrin-3 resulted in inhibition of the mTOR1 complex and its downstream molecules through phosphorylation of AMPKα. This provided a novel sight for a potential treatment mechanism of CuB. The role that CuB-induced setrin-3 downregulation played in A549 cells (EGFR-mutant) was not clearly explained. Recent research unveiled the role of sestrin-3 in cellular redox balance as an antioxidant against the production of ROS, which was ignored by Khan N. As a result, it was speculated that the inhibition of sestrin-3 may be related to an increase in ROS production as a potential anticancer mechanism of CuB. In fact, ROS production was observed in A549 cells by Guo J [61], which was consistent with the putative results. Nevertheless, validation is still needed in further research, along with mechanistic insight into the different effects of CuB on sestrin-3. As was evident in Guo J's experiments, CuB induced DNA damage along with the promotion of the ATM-Chk1-Cdc25C-Cdk1 cascade in A549 mediated by reactive oxygen species (ROS) formation, which induced G2/M cell cycle arrest [61].

As a redox regulator of tumor pathophysiology, ROS upregulation promotes cancer occurrence and development and is therefore proposed to be a promising target [62, 63]. Beyond that, intracellular thiols and glutathione (GSH) are other redox regulators in cancer cells. CuB was tested to see if it could interrupt the cellular redox balance in NSCLC cells through the downregulation of protein thiols and the GSH/GSSG ratio starting from a 0.1 μM concentration [49], but no marked change in ROS was observed at 3 h. Given that ROS formation was observed after 24 h of CuB treatment [61], it was suggested that the effects on ROS may be lagging, and CuB may interact directly with thiols. In addition, the cytotoxicity of CuB based on thiols and GSH specifically manifested as a reduction in cell viability and induction of G2/M cell cycle arrest and mitochondrial apoptosis. Furthermore, the epigenetic analysis indicated that CuB suppressed the activities of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) and facilitated histone

acetyltransferases (HATs), which led to the upregulation of some key tumor suppressor genes (*p16*, *p21*) and concurrent downregulation of some key tumor promoter genes (*hTERT*) [64]. However, CuB negatively regulated the protein expression pertaining to oncogenes (c-MYC, K-RAS) in H1299 without significant alteration of the mRNA expression. Hence, it provides a novel perspective for the chemotherapeutic potential of CuB for patients with cancer.

Izabella TS et al. [40] synthesized a new derivation of CuB, namely, 2-deoxy-2-amine-cucurbitacin E (DACE). DACE has an amino moiety in C2 instead of the hydroxyl group, compared to CuB, which brings out a nucleophilic, basic and hydrogen bond donor/acceptor group. In addition, the mechanism of action was changed along with an optimized solubility and bioavailability via the alteration of hybridization from sp3 to sp2 in C2. In the presence of DACE, the activation of the EGFR, STAT3, PI3K/Akt and ERK pathways was inhibited in A549 cells, similar to the inhibition seen with CuB. Of note, the Ras/Raf/MEK pathway was considered a key signaling pathway of DACE-induced cytotoxicity in vitro and in vivo. As illustrated in various NIH3T3 model cell lines, DACE exhibited selectivity toward malignant cells that were transduced with RAF or RAS.

Cucurbitacin E

Cucurbitacin E (CuE) is a well-known antifeedant, and shows strong antitumor activity in various cancers both in vitro and in vivo [65–68]. A recent study from Cheng SE's group has identified CuE as a promising STAT3 inhibitor that displays attractive cytotoxicity on human lung cancer A549 cells [69]. In this article, CuE successfully inhibited ATPγS-induced expression of COX-2 mRNA and PGE_2 generation through its downregulation of STAT3, which provided a new prospective treatment for chronic lung pathologies.

In addition, with regard to mechanisms in lung cancer research, increasing studies have demonstrated that CuE attenuated cell proliferation mediated by inhibition of the Wnt/β-Catenin signaling axis along with upregulation of the tumor suppressor Menin [70]. In addition, with the activation of caspase family proteins, Unc-51-like kinase 1 (ULK-1) phosphorylation and BECN1 upregulation in 95D cancer cells, CuE treatment induced apoptosis and autophagy by weakening the Akt/mTOR pathway. Further results were obtained when an accumulation of LC3II and CuE-induced cytotoxicity were enhanced by pretreatment with the autophagy inhibitors chloroquine and bafilomycin. Moreover, it is noteworthy that these functions were mediated by ROS generation [71]. One recent study indicated that CuE inhibits the migration and invasion of H2030-BrM3 and PC9-BrM3 cells through the Yes-associated protein (YAP) signaling pathway, among which, both H2030-BrM3 with KRAS mutation and PC9-BrM3 with EGFR mutation are prone to metastasize. Especially in the H2030-BrM3 murine model, CuE successfully reduced brain metastasis through the downregulation of YAP. In addition to these direct effects, CuE also had a negative impact on YAP modulation by interfering with the EGFR/MAPK/ERK axis [72]. It was reported that the EGFR/MAPK/ERK pathway influenced CTGF and CYR61 expression, the downstream genes of the Hippo/YAP pathway [73]. Altogether, this research provided new insight for the treatment of metastatic lung cancer.

Cucurbitacin I

Cucurbitacin I (CuI), also called JSI-124, was first extracted from plants that belonged to cucurbitaceae and was also found in cruciferae [67, 74]. The first time that CuI was thought to be a possible agent for lung cancer treatment was when its anticancer activity was identified in A549 cells and in a xenograft model where it was identified as a targeted JAK/STAT3 inhibitor [75]. By screening the NCI Structural Diversity Set comprising a library of 1,992 compounds, Blaskovich MA et al. [75] uncovered that CuI was highly selective for the JAK/STAT3 signaling pathway by functioning on STAT3 DNA-binding activity precisely and had no obvious effect on other oncogenic pathways such as Akt, ERK1/2 and JNK. For example, CuI treatment of human lung adenocarcinoma Calu-1 cells, which lack constitutive STAT3 activation, showed no clear impact on cellular apoptosis in vitro or on corresponding xenograft tumor growth. On account of its pharmacological targeting of STAT3, subsequent research on CuI against lung cancer was mainly focused on the modulation of STAT signaling. Like CuB, CuI dose-dependently blocked STAT3 signaling but promoted STAT1 signaling, possibly by disrupting actin filaments [76]. The findings indicated that the actin filaments physically interacted with STAT3 in A549 cells and thus regulated STAT3 phosphorylation through two different signaling complexes, the IL-6 receptor complex and the focal adhesion complex. Meanwhile, actin filaments could also significantly promote STAT1 dephosphorylation by physically interacting with STAT1. Thus, these data demonstrated the interesting roles of CuI on the actin filament-mediated STAT signaling regulation. In addition, the compound CuI also displays anticancer stem cell properties, especially in NSCLC-derived CD133 + cells by deactivating the STAT3 signaling. CuI successfully inhibited the proliferation of CD133 + cells and promoted their differentiation into CD133- cells with lower tumorigenicity and radio-resistance, to significantly improve the therapeutic effects [77].

To date, apart from STAT3, other recent works reported that CuI could act as an inhibitor of p21-activated kinase 1 (PAK1), which can promote proliferation and invasion in multiple solid tumors [78, 79]. CuI treatment resulted in A549 cell growth arrest by blocking phosphorylated PAK1 [80]. CuI was also verified to promote pro-death autophagy by inhibiting ERK activation and the downstream STAT3 phosphorylation level in A549 cells [81]. Based on autophagy induction, the triggered cell death and apoptosis with CuI treatment have been enhanced to some extent. In fact, similar to the findings from Blaskovich MA's group [75], they also further revealed that CuI treatment had no remarkable effect on the PI3K/Akt signaling cascade. However, CuI inhibits p-ERK expression, and this is absolutely the opposite of Blaskovich MA's results. Comparing the details of the two experiments, the discrepancy may arise from the distinct duration of CuI treatment. Nevertheless, there were no explanations regarding CuI-induced phosphorylation of ERK at early timepoints.

In addition, some inconsistent functions of CuI on PI3K/Akt/mTOR modulation have been found recently. When CuI acts at a very low concentration (50 nM), it could markedly attenuate the phosphorylated AKT and p70S6K pathway, at last leading to cell growth inhibition of human NSCLC A549 cells [82]. These contradictory results might be due to different standards; one considered the level of phosphorylation only, while the other chose the ratio of phosphorylation to dephosphorylation or dephosphorylation only, which needs to be well-clarified in further studies.

Other cucurbitacins

In addition to CuB, CuE and CuI mentioned above, other independent research teams have discovered cucurbitacin compounds that also have pivotal functions against the pathological behaviors of human lung cancers, including cucurbitacin A, D, E, Q, IIa, etc.

Cucurbitacin A (CuA), mainly isolated from Cucumis species with a narrow distribution, is identified as a potential PI3K/Akt/mTOR signaling suppressor in A549 cells [64]. Specifically, CuA treatment blocked the cell cycle progression in a dose- and time-dependent manner, triggering cell proliferation inhibition and apoptosis induction in A549 lung cancer cells [83].

Cucurbitacin D (CuD) is one of the most common derivatives from Cucurbitaceae and has strong antitumor properties [54, 67, 84]. Jacquot C. and her group found that CuD triggered CDK1 overexpression at the transcriptional level, leading to G1-phase cell cycle arrest, succedent apoptosis induction, and eventually irreversible growth inhibition in NSCLC-N6 cells [85]. In addition, Ku JM et al. [86] further explained the molecular mechanisms behind CuD's actions against lung cancer. In H1299 cells, CuD administration obviously induced cell apoptosis incidence by increasing the apoptosis markers (cleaved caspases and increased proapoptotic protein Bcl-2). Further exploration indicated that CuD inhibited ErbB3 signaling, which could bind many downstream signaling proteins correlated with cancer progression and prognosis. More importantly, it was worth noting that trichosanthes, the main derivatives from CuD, successfully inhibited the growth of patient-derived tumor cells [86, 87].

Cucurbitacin Q (CuQ) has been discovered as a more selective inhibitor that disrupts STAT3 without significant effects on other carcinogenic biomarkers in A549 cells, especially JAK [54]. However, more in-depth studies are needed to further clarify its specific role in disrupting STAT3 signaling.

Cucurbitacin IIa (CuIIa), also called hemslecin A, is the major bioactive cucurbitacin in *Hemsleya amabilis* and has been verified to have antitumor effects in different cancers, including lung cancer [88, 89]. Unlike the other cucurbitacins, CuIIa could not cause death in H1299 cells by regulating the JAK/STAT3 pathway [90]. However, a recent kinase inhibition assay indicated that CuIIa could directly act as a potential EGFR-TKI with an IC_{50} value of 1.455 nM [91]. Due to its evident antagonistic effects on EGFR oncogenic signaling, CuIIa successfully induced cell apoptosis and cell-cycle arrest in A549 lung cancer cells [91]. In addition, the CuIIa homolog, CuIIb, could also exhibit more potent activity against A549 cells [92].

Characterization of the concentration and structure

Collectively, the effective concentration of cucurbitacins in vitro ranges from 10 nM ~ 200 μM [58, 83]. At the nanomolar level, it was reported that CuB inhibited tumor cells stemness and angiogenesis via the canonical Wnt/β-catenin axis [70], induced ATM-dependent DBS through ROS [61] and regulated epigenetic alteration, although it was clearly stated that STAT3 did not change significantly. CuI had an impact on the PI3K/Akt/p70S6K pathway [82] and PAK1 beginning at a 50 nM concentration [80]. In addition, CuE was declared to augment the level of ROS [71] and inhibit the YAP signaling pathway [72]. It was worth noting that the lagging effects on ROS mentioned above compared to the interaction between thiol and CuB may be due to its insignificant impact at high concentrations of CuB [61]. These cucurbitacins functioned on different targets at 0.1 to 1 μM, while CuA blocked the PI3K/Akt/mTOR axis from 40 μM, CuQ inhibited STAT3 with an IC_{50} of 3.77 ± 1.7 μM in A549 cells [54], and CuIIa attenuated EGFR from 40 μM [91]. However, another study showed that CuA could inhibit the cell proliferation of A549 cells

with an IC_{50} of 0.4 ± 0.013 μM [93]. On account of insufficient evidence, further research may be needed to ascertain whether CuA functions at a lower dose.

Given the characteristics of these cucurbitacins, the different active concentrations may partly derive from structural differences such as highly oxidized tetracyclic triterpenoids. A lanostane skeleton with multiple substituents, including hydroxyls at C-16 and C-20, carbonyls at C-11 and C-22, and a methyl at C-9 rather than C-10 in lanostane, along with an unsaturated double bond at position 5 was the common structure. Among these cucurbitacins that exhibited antitumor activity in lung cancer, the discrepancies were mainly embodied in C-1, 2, 3, 2 3, 24, and 25. Compared with others, CuB seems to have the most typical traits, which represented the majority of substitutions. Lang KL et al. pointed out that the cytotoxic potency of cucurbitacins in A549 cells was related to multivariate factors, among which, the electrophilicity of molecules played a pivotal role, according to multivariate SAR and QSAR analyses of cucurbitacin derivatives. The derivatives that carried an amino (compound 32, also known as DACE) or bromine (compound 34) at C-2 exhibited the most potent cytotoxicity, among 43 compounds, in A549 cells. On this foundation, further studies that focused on DACE proposed that the double bond, along with the amino substitution that formed a conjugated structure, and the Michael acceptor (α, β-unsaturated ketone) in the side chain should be noticed [40]. Likely, CuIIa, whose conjugated 23,24 olefinic bond was saturated, functioned at high concentrations, which supported the importance of the Michael acceptor. Meanwhile, CuIIa was unable to inhibit phosphorylation of STAT3 in A549 cells even though it could promote the expression of STAT3 in H1299 cells due to the absence of a 23, 24 double bond. Notably, the special side chain of CuIIa made its combination with EGFR more stable [90]. According to Sun J's study, the absence of 3-carboxy in CuQ, which was replaced by a hydroxyl, led to higher selectivity towards STAT3 without any obvious effects on JAK2, while the presence of 11-hydroxyl in CuA eliminated its anti-STAT3 activity [54]. Furthermore, Lang and his group hinted at the importance of a 25-acetoxy group [93], which seemed limited after considering the cytotoxicity of CuI and CuD.

Safety and efficiency

The toxicity of cucurbitacins and related derivatives has been reported for a long time. Garg S et al. concluded that CuB caused some poisoning events up until 2018 [18]. In addition, six other kinds of cucurbitacins were recognized as acutely toxic, with the exception of CuE, which was an irritant, according to the Laboratory Chemical Safety Summary Datasheet (LCSS). The median lethal dose (LD50) of CuB in mice was 14 mg/kg (oral route), 2.73 mg/kg (intramuscular route), and 1 mg/kg (subcutaneous route) [94]. The experiments performed in mice with lung tumors found that low doses of CuB, such as 0.1 mg/kg (intraperitoneal), successfully impeded tumor growth. It was confusing that no toxicity reaction was observed in H1299 xenograft mice with 1 mg/kg intraperitoneal CuB [49], which may depend on the purity of CuB or differences in the model. Furthermore, it was reported that the IC50 of CuB against 16-HBE, a kind of human bronchial epithelial-like cell, was 4.23 ± 0.81 μM, which was much higher than its active concentration in lung cancer cells [46]. With regard to CuD, it exhibited similar LD50 values in rats as CuB, namely, 8.2 mg/kg (oral), 3.4 mg/kg (subcutaneous), and 1.3 mg/kg (intraperitoneal) [95]. However, the active dose for lung cancer in vivo remains unclear. CuA, I, Q, and IIa lacked relevant toxicity data in mice, although there were no side effects mentioned in the A549 xenograft model or in a Lewis lung carcinoma mouse with 1 mg/kg intraperitoneal CuQ [54] or 15 mg/kg intravenous CuIIa, respectively [90]. However, one kind of adverse reaction, edema, was reported in an A549 xenograft model [75] but not in an NSCLC-derived CD133-positive-xenograft model [77]. Ultimately, it was attractive that CuE could inhibit brain metastasis and improve the survival time of H2030-BrM3 murine cells after 0.2 mg/kg intraperitoneal CuE [72], whose LD50 was as high as 340 mg/kg (oral) [96]. All in all, the active dose and lethal dose of different types of cucurbitacin are not the same, which may be associated with the diversity in structure.

Cucurbitacins are originally derived from Chinese traditional herbal plants that are used in dietary supplements and in medicine [97]. These compounds have shown various bioactivities against human disorders with the development of modern science and technology. On account of their attractive anti-inflammatory, anti-tumor and hepatoprotective effects, several Chinese medical patents based on cucurbitacins have been approved by the China Food and Drug Administration as an adjuvant treatment strategy for patients with chronic hepatitis and primary liver cancer [98]. Similarly, hemsleyadine tablets, which contain CuIIa and IIb as the main ingredients, have been used clinically to treat bacillary dysentery, enteritis and acute tonsillitis for a period of time [99, 100]. In Italy, a topical preparation for treating mono- or bilateral exudative otitis media in children, called Sinuclean Nebules, is already on the market. It is a saline solution with 45 mg of various cucurbitacins from *Ecballium elaterium*, including CuB, CuD, CuI and CuE [101]. In addition, a clinical trial examining the effect of CuB in patients with lung cancer indicated that oral use of CuB at 120 μg three times a day, i.e. approximately 6 μg/kg after conversion according to the standard human weight of 60 kg [102], can effectively decrease the frequency of immature myeloid cells (imCs); this may represent a deficiency of

antitumor immunity in advanced patients [103]. And there were no serious adverse reactions reported in these patients. Nevertheless, because of this trial did not directly explore the anti-tumor effects of CuB, more clinical trials were needed to explore whether the dose in cells and animals can provide similar clinical benefit in lung cancer patients. As illustrated in Table 2, the experimental dose range of most cucurbitacins in mouse is 0.1–1 mg/kg. According to the conversion formula recommended by the practice guidance [102], Human Equivalent Dose (mg/kg) = Animal dose (mg/kg) × (Animal Km ÷ Human Km), the human equivalent dose range is 0.008–0.081 mg/kg, i.e. 8–81 μg/kg, which may be used as the recommended dose for future clinical trials evaluating the anti-tumor functions of cucurbitacins. In addition, Km in the conversion formula is a correction factor that is calculated by dividing the average body weight of species to its body surface area. As reported by US Food and Drug Administration, the Km values in mouse and human are 3 and 37, respectively. Evidently, these evaluations will shed more light on how to properly treat infections or cancer with cucurbitacins without inducing apparent and serious adverse effects at recommended concentrations. Even so, more investigations on the clinical application of cucurbitacin-based therapies are required to reveal the details regarding their safety and efficacy.

In addition, to elucidate the underlying biological functions of cucurbitacins, specific and sensitive detection methods need to be developed. Evaluating the pharmacokinetics and pharmacodynamics would afford information on the development of cucurbitacin-based therapy. As early as 2006, a group from Canada established a promising method for quantitative analysis of CuI in rat plasma based on liquid chromatography/mass spectrometry (LC–MS) [104]. Subsequently, other cucurbitacin compounds have been quantitatively analyzed with LC–MS methods in the plasma of different species [105, 106], for example, rhesus monkeys [99]. In addition, Wang Z's group conducted several experiments to test the pharmacokinetic parameters of CuB and CuE in rat plasma by UHPLC-MS/MS [98, 107], and they found that the absolute oral bioavailability of CuB and CuE was very low (only approximately 10%). Surprisingly, with a high volume of distribution, these compounds were widely distributed in several organs including the lung, spleen and kidney [105]. However, the major pathways of CuB metabolism still require detailed clarification.

Bioavailability is another barrier to the use of plant-derived chemopreventive agents [17, 108–110]. Scientists put forward some attempts seeking the optimum carrier to improve the bioavailability of cucurbitacins. Micelles, including poly(ethylene oxide)-block-poly(ε-caprolactone) (PEO-b-PCL) and poly(ethylene oxide)-block-poly (α-benzyl carboxylate ε-caprolactone) (PEO-b-PBCL), were evaluated as the solubilizers and delivery vehicles for CuI and CuB [111, 112]. These drug conjugates make CuI and CuB more soluble, thus ameliorating their antitumor activity. Moreover, Lv Q and his group reported another similar mucoadhesive buccal film micelle as an effective carrier for CuB delivery [113]. Recently, a novel phospholipid complex carried CuB and not only ameliorated its permeability but also improved the targeted killing effect on cholangiocarcinoma cells to a certain extent [114]. According to the latest research, polymer nanoparticles modified with collagen peptides (CuB-MMs-CPs) have been developed to evidently increase the cellular uptake and transportation of CuB. The animal experiment involving rapid-growing rats further verified the significantly increased tumor inhibition caused by CuB-MMs-CPs [115]. In summary, choosing nanomicelles as a potential cucurbitacin carrier could be an effective strategy to overcome the difficulties in bioavailability.

To date, although there is a certain theoretical basis for the safety and efficacy of cucurbitacin-based therapy, these studies provide only limited information due to a lack of reliable clinical evidence. Thus, more studies are needed as a reference for its approval for extensive clinical application.

Perspective on cucurbitacins

As novel compounds extracted from a number of plant families all over the world, cucurbitacins have been used in the diet and in medicine for a long time. For instance, Goya containing CuI grows in Okinawa, Japan, while *Ibervillea sonorae*-containing CuIIb is a kind of traditional Mexican medicine [116]. Referring to earlier research, the anti-lung cancer activity of CuD from *Sloanea zuliaensis* was first reported around 2003 [117]. After that time, CuB and its derivatives, which were isolated from different plants, also showed significant cytotoxicity against different lung cancer cells [93, 118, 119].

Currently, finding novel intervention strategies for lung cancer that can overcome treatment failure in the clinic is becoming urgent [120, 121]. Natural agents with emerging cytotoxicity tend to attract more attention, due to their economic superiority and multitarget effects compared to synthetic products. A number of plant-derived molecules have been selected for further research, including cucurbitacins [20, 29, 122]. Abou-Salim MA et al. [123] designed innovative nitric oxide-donating cucurbitacin-inspired estrone analogs (NO-CIEAs) and suggested that NO-CIEAs exhibited more potent sensitization activity to cancer chemotherapy. More evidence has indicated that CuB and CuD derivatives both exhibited significant synergistic anticancer effects on human lung cancers in vivo and in vitro when used in combination with known chemotherapy drugs, such as paclitaxel [124] and cisplatin [86, 125]. It was remarkable that the cucurbitacins could

function even at 0.005 μM, further ensuring the safety of the treatment. In addition, targeting of STAT3 signaling by CuI significantly enhanced the chemoradiosensitivity in CD133-positive cells isolated from patients with lung cancer [77]. Above all, further investigation of these issues may help identify more promising strategies to enhance the benefits of therapeutic response in the treatment of patients with lung cancer.

Conclusion

As novel natural tetracyclic triterpenoid compounds, cucurbitacins display a wide range of biological effects. Moreover, with significant cytotoxic properties, cucurbitacins possess very potent effects toward a number of cancer cells. Herein, we summarized the pharmacological principles and mechanisms of action of different cucurbitacins in lung cancer research. Furthermore, the possibility of cucurbitacins actually entering clinical use for the treatment of lung cancer is also discussed in this article. The compounds CuA, B, D, E, I, Q and IIa were well-summarized as potential anticancer agents with different mechanisms in lung cancer. They successfully inhibited tumor growth and induced cell apoptosis and cell cycle arrest, with no obvious toxicity for normal lung tissues. Furthermore, these compounds could impair cell migration, which occurs in aggressive malignancy and has a negative influence on the chemotherapy response. The evidence mentioned above highlights the preponderance of cucurbitacins as promising agents for lung cancer prevention, based on existing favorable evidence of their safety and efficacy. Nevertheless, for use in clinical practice, more clinical trials focused on cucurbitacins as mainline targeted anticancer therapies for lung cancer, either as independent effectors or as supplements, are warranted.

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Availability of data and materials All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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