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Review Article

Cucurbitacin B From Cucurbitaceae Plants: Emerging Anticancer Mechanisms, Immunomodulatory Potential, And Translational Challenges

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Abstract

Cucurbitacin B (CuB), a highly oxidized cucurbitane-type triterpenoid predominantly isolated from Cucumis melo and Momordica charantia, has emerged as a multifaceted anticancer agent with expanding therapeutic implications beyond its classical STAT3 inhibitory activity. This mini review provides a comprehensive synthesis of recent advances (2022–2025) in CuB research, highlighting transformative discoveries that have reshaped its mechanistic landscape. Key developments include the identification of IGF2BP1, GRP78, and MTCH2 as direct covalent targets of CuB via its α, β-unsaturated ketone moiety, the discovery of ferroptosis and mitophagy as novel cell death mechanisms, and the demonstration of immunomodulatory effects encompassing M2 macrophage repolarization, cGAS-STING pathway activation, and PD-L1 downregulation—properties that synergize with immune checkpoint blockade therapy. Despite these promising mechanisms, clinical translation remains constrained by CuB's narrow therapeutic window, dose-limiting hepatotoxicity, poor aqueous solubility (log P ≈ 4.5), and low oral bioavailability (<5% in rats). Innovative nanotechnology-based delivery systems—including plant-derived nanovesicles, ROS-responsive nanocarriers, and biomimetic chemo-photothermal platforms—offer strategies to enhance tumor-specific accumulation while mitigating systemic toxicity. We propose a multi-pronged translational pathway integrating IGF2BP1/STAT3/PD-L1 expression-based patient stratification, nano delivery or prodrug formulation, combination with anti-PD-1/PD-L1 checkpoint inhibitors, and CuB-Cys metabolite monitoring as a pharmacokinetic/pharmacodynamic biomarker. These integrated approaches may enable CuB's transition from a traditional botanical remedy to a mechanistically guided, next-generation anticancer therapeutic.

Keywords: Cucurbitacin B; Cucurbitaceae; anticancer; STAT3; IGF2BP1; tumor microenvironment; ferroptosis; nanodelivery; pharmacokinetics; immunotherapy

Introduction

Cucurbitaceae, commonly known as the gourd family, encompasses over 900 species across approximately 95 genera, including economically and medicinally significant plants such as Momordica charantia L. (bitter gourd), *Cucumis melo* **L.** (melon), *Lagenaria siceraria* (bottle gourd), *Trichosanthes kirilowii* (snake gourd), and Cucurbita species (pumpkins and squashes) [1-3]. Throughout millennia of traditional medicine practice across Asian, African, and Latin American cultures, various Cucurbitaceae

plants have been employed for treating diverse ailments, ranging from diabetes and inflammation to malignancies [3,4,]. Modern phytochemical investigations have revealed that the therapeutic potential of these plants is largely attributable to a class of highly oxidized tetracyclic triterpenoids known as cucurbitacins, among which Cucurbitacin B (CuB) stands out as the most abundant and pharmacologically potent member [5,6].

CuB (molecular formula: $C_{32}H_{44}O_8$; molecular weight: 556.69 Da) is predominantly isolated from the pedicels of *Cucumis melo* L. (sweet melon), the fruits of *Momordica charantia*, and various *Cucurbita species* [5,7]. In traditional Chinese medicine, the dried pedicels of *Cucumis melo* (known as "Guadi") have been documented in the *Bencao Gangmu* (Compendium of Materia Medica, 1596 CE) for the treatment of jaundice and hepatic disorders, conditions now understood to involve pathways that CuB modulates at the molecular level [7,8]. The compound features a characteristic cucurbitane skeleton with multiple hydroxyl groups and a unique α,β-unsaturated ketone moiety that serves as a Michael acceptor, enabling covalent interactions with cysteine residues of target proteins [9,10]—a chemical property that underpins much of its biological activity and represents a key mechanistic insight discovered only recently. The anticancer potential of CuB has attracted escalating scientific interest over the past decade. A landmark study by Liu et al. (2022) from Peking University's State Key Laboratory of Natural and Biomimetic Drugs identified IGF2BP1 as a direct covalent target of CuB through the α, β-unsaturated ketone reacting with Cys253 of IGF2BP1, representing the first definitive target deconvolution for this natural product [11]. Subsequent investigations have unveiled an expanding repertoire of anticancer mechanisms, including STAT3 pathway inhibition [12-15], ferroptosis induction [16,17], mitophagy activation [7], cGAS-STING pathway stimulation [18,19], and synergistic enhancement of immune checkpoint blockade therapy [20,21]. These discoveries collectively position CuB as a multifaceted anticancer agent with particular promise in the era of immunotherapy and combination treatment strategies. Despite these advances, the clinical translation of CuB remains hindered by its narrow therapeutic window, dose-limiting hepatotoxicity, poor aqueous solubility, and unfavorable pharmacokinetic profile [5,22]. Recent efforts to address these limitations through nanotechnology-based delivery systems, structural derivatization, and synergistic combination regimens have yielded encouraging results but have not yet achieved the breakthrough needed for clinical adoption [23-26]. This Mini Review aims to provide a comprehensive and timely synthesis of the most recent advances (2022–2025) in CuB research, with particular emphasis on newly identified molecular targets, emerging anticancer mechanisms beyond classical STAT3 inhibition, immunomodulatory effects in the tumor microenvironment, innovative delivery strategies, and the translational challenges that must be overcome for clinical realization. By integrating these multidimensional perspectives, we seek to offer novel insights into how CuB might be repositioned from a traditionally employed botanical extract toward a mechanistically guided, next-generation anticancer therapeutic.

Chemical Structure and Biosynthetic Origin of Cucurbitacin B

Structural Characteristics and Functional Moieties

CuB belongs to the cucurbitacin family, characterized by a highly oxidized cucurbitane tetracyclic triterpenoid skeleton (19(10→9β)-abeo-10α-lanostane) [5,27]. The molecule features several pharmacologically critical structural elements: (i) a 23-en-25-ol side chain with a 22-en-24-ol fragment that contributes to membrane permeability; (ii) an α, β-unsaturated ketone at C-2/C-3 that acts as a Michael acceptor for covalent binding to nucleophilic cysteine residues in target proteins [9,10]; and (iii) multiple hydroxyl groups at C-16, C-24, and C-25 that influence solubility and hydrogen-bonding interactions. The α, β-unsaturated ketone moiety is particularly significant, as it enables CuB to form irreversible covalent adducts with proteins such as IGF2BP1 and MTCH2, a property that distinguishes CuB from reversible inhibitors and underlies its potent biological effects [11,20].

Biosynthetic Pathway in Cucurbitaceae Plants

CuB is biosynthesized in Cucurbitaceae through the mevalonate-dependent triterpenoid pathway, beginning with 2,3-oxidosqualene cyclization by cucurbitadienol synthase to form the cucurbitane skeleton [28]. Subsequent oxidation, acetylation, and hydroxylation steps—mediated by cytochrome P450 monooxygenases (CYP450s) and acetyltransferases—generate the diverse array of cucurbitacin variants, including CuB, CuE, CuD, and CuI [28,29]. Liu et al. (2025) recently provided a detailed analysis of the bitterness, biosynthesis, and chemical transformation of cucurbitane-type triterpenoids in Momordica charantia, highlighting how the bitter taste receptors (TAS2Rs) detect these compounds and how the biosynthetic machinery is regulated at the transcriptional level [28]. The co-evolution of cucurbitacin biosynthesis and bitter taste perception in Cucurbitaceae represents a fascinating example of plant defense chemistry that paradoxically renders these compounds medicinally valuable to humans.

Distribution Across Cucurbitaceae Species

CuB is found across multiple Cucurbitaceae genera, with concentration varying significantly by species, tissue type, and developmental stage. The highest concentrations are typically found in the roots and pedicels of Cucumis melo, the fruits and leaves of Momordica charantia, and the stems of Ecballium elaterium [5,27]. Borecka and Karaś (2025) conducted a comprehensive review of the nutritional and health-promoting properties of edible parts of selected Cucurbitaceae plants, noting that while cucurbitacins are present in edible tissues, their concentrations are substantially lower than in medicinal parts, explaining the dual nutritional-pharmacological nature of these plants [3].

Anticancer Mechanisms of Cucurbitacin B

Classical STAT3 Pathway Inhibition

The inhibition of the JAK2/STAT3 signaling cascade has long been recognized as the primary anticancer mechanism of CuB [5,12]. STAT3, constitutively activated in over 70% of human cancers, promotes tumor cell survival, proliferation, angiogenesis, and immune evasion through transcriptional regulation of downstream

genes including BCL-2, Cyclin D1, VEGF, and MMP-9 [12,13]. CuB disrupts this pathway by inhibiting JAK2 phosphorylation, thereby preventing STAT3 nuclear translocation and target gene expression [12,14]. Recent studies have expanded our understanding of CuB-STAT3 interactions across multiple cancer types. Liu et al. (2022) demonstrated that CuB inhibits the IL-6/STAT3 axis through the lncRNA XIST/miR-let-7c regulatory network in lung cancer, revealing a previously unrecognized epigenetic dimension of STAT3 modulation [15]. Zhang et al. (2022) showed that CuB controls M2 macrophage polarization—a critical component of the immunosuppressive tumor microenvironment—via JAK2/STAT3 inhibition in colorectal cancer, thereby linking STAT3 suppression to immune remodeling [30]. Zeng et al. (2024) discovered that CuB induces ferroptosis in NSCLC through STAT3 targeting, establishing a novel connection between STAT3 inhibition and iron-dependent cell death [16]. Lv et al. (2025) reported that CuB suppresses glioblastoma through a STAT3/ROS/ER stress cascade, demonstrating that STAT3 inhibition converges with oxidative stress and ER stress to drive multi-pathway cell death [14]. These findings collectively illustrate that STAT3 inhibition by CuB extends beyond direct transcriptional suppression to encompass epigenetic regulation, metabolic reprogramming, and immunological remodeling.

Novel Target Identification: IGF2BP1, GRP78, and MTCH2

IGF2BP1 as a Covalent Target

The identification of IGF2BP1 (Insulin-like Growth Factor 2 mRNA-Binding Protein 1) as a direct covalent target of CuB by Liu et al. (2022) at Peking University represents a paradigm shift in understanding CuB's mechanism of action [11]. Using chemical proteomics with a CuB-derived molecular probe, the authors demonstrated that CuB covalently modifies Cys253 of IGF2BP1 through its α, β-unsaturated ketone moiety, inducing allosteric conformational changes that destabilize IGF2BP1-mRNA interactions and promote the degradation of oncogenic transcripts including c-MYC, β-ACTIN, and PTEN [11]. Critically, IGF2BP1 stabilization is a hallmark of multiple cancers, and its disruption by CuB not only inhibits tumor cell proliferation but also reprograms the tumor immune microenvironment by downregulating PD-L1 expression and enhancing $CD8^+$ T cell infiltration [11]. This dual oncogenic-immune regulatory function positions IGF2BP1 as a therapeutically superior target compared to STAT3, as it simultaneously addresses tumor intrinsic signaling and immune evasion.

GRP78-FOXM1-KIF20A Cascade

Wei et al. (2022) identified an alternative CuB target axis in conjunctival melanoma, demonstrating that CuB induces G2/M cell cycle arrest through the GRP78-FOXM1-KIF20A pathway [31]. GRP78 (Glucose-Regulated Protein 78), a master regulator of the unfolded protein response (UPR), interacts with CuB to suppress FOXM1 transcription factor activity and its downstream effector KIF20A (a mitotic kinesin), leading to mitotic catastrophe [31]. This finding underscores CuB's capacity to engage multiple targets across different cancer contexts.

MTCH2 and PD-1 Immunotherapy Enhancement

Xu et al. (2025) from Nanjing University of Chinese Medicine identified MTCH2 (Mitochondrial Carrier Homolog 2) as another covalent target of CuB in breast cancer [20]. CuB covalently modifies MTCH2, triggering mitochondrial membrane permeability alteration, mtDNA release, cGAS-STING pathway activation, and type I interferon production, which collectively enhance the response to anti-PD-1 immunotherapy [20]. This represents the first demonstration that a natural product can directly target a mitochondrial carrier protein to activate innate immunity and synergize with immune checkpoint blockade.

Cell Cycle Arrest and Apoptosis Induction

CuB consistently induces G2/M phase cell cycle arrest across diverse cancer cell lines, with IC50 values typically ranging from 0.1 to 50 nM depending on the cancer type [5,6,32]. Alafnan et al. (2022) confirmed that CuB exerts anticancer effects in prostate cancer PC3 cells through JAK/STAT downregulation, accompanied by apoptosis induction (caspase-3/9 activation, Bax/Bcl-2 ratio increase) and G2/M arrest [32]. Li et al. (2024) revealed that CuB suppresses HCC progression through ATM-dependent DNA damage response, demonstrating that CuB activates the ATM-Chk2-Cdc25C-Cdk1 axis to enforce G2/M arrest, providing a mechanistic link between genotoxic stress and cell cycle control [33]. Huang et al. (2023) demonstrated ROS-dependent apoptosis induction in colorectal cancer cells, showing that CuB generates oxidative stress that triggers both mitochondrial apoptosis (cytochrome c release, caspase cascade) and ER stress-mediated cell death (CHOP, ATF4 upregulation) [34]. These findings confirm that CuB's cytotoxic effects involve integrated stress responses converging on apoptotic execution.

Autophagy and Mitophagy Regulation

The relationship between CuB and autophagy has revealed complex, context-dependent outcomes. Yin et al. (2025) demonstrated that CuB from Cucurbitaceae plants treats pancreatic cancer via inducing PINK1/Parkin-dependent mitophagy, simultaneously inhibiting glycolysis through HIF-1α/GLUT1 axis suppression and enhancing immune function through $CD8^+$ T cell and NK cell activation [7]. This tripartite mechanism-mitophagy induction, glycolysis inhibition, and immune enhancement-represents a novel multi-target therapeutic paradigm for pancreatic cancer, a malignancy notoriously resistant to conventional chemotherapy.

Song et al. (2025) further demonstrated that CuB inhibits HIF-1α through ZFP91 regulation in NSCLC, indirectly suppressing tumor glycolysis-a metabolic adaptation essential for cancer cell survival under hypoxic conditions [35]. The convergence of mitophagy induction and glycolysis inhibition suggests that CuB targets the metabolic-flexibility axis that cancer cells exploit for survival, representing a conceptually innovative approach to cancer therapy.

Ferroptosis and Other Emerging Cell Death Modalities

Ferroptosis

Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation accumulation, has emerged as a significant mechanism of CuB action. Zeng et al. (2024) demonstrated that CuB targets STAT3 to induce ferroptosis in NSCLC, revealing that STAT3 inhibition downregulates SLC7A11 (the core component of system Xc^-) and glutathione peroxidase 4 (GPX4), thereby disabling the cellular antioxidant defense system and enabling iron-dependent lipid peroxidation [16]. Bakar-Ates and Ozkan (2024) showed that co-treatment of CuB with the ferroptosis inducer erastin synergistically enhanced ferroptosis in breast cancer cells through altered iron-regulating proteins (increased TFRC, decreased FTH1) and elevated lipid peroxidation [17], suggesting that CuB-erastin combination may represent a viable therapeutic strategy for ferroptosis-resistant tumors.

Pyroptosis

Yuan et al. (2021) demonstrated that CuB triggers TLR4/NLRP3/GSDMD-dependent pyroptosis in NSCLC [36]. While this study predates the 2022–2025 window emphasized in this review, it established a foundational connection between CuB and inflammatory cell death that has informed subsequent investigations of CuB's immunomodulatory properties, particularly the cGAS-STING pathway activation studies discussed in Section 4.

Immunomodulatory Effects and Tumor Microenvironment Remodeling

M2 Macrophage Polarization Inhibition

Tumor-associated macrophages (TAMs), particularly the M2-polarized subset, constitute a major immunosuppressive component of the TME and correlate with poor prognosis across multiple cancer types [30,37]. Zhang et al. (2022) demonstrated that CuB inhibits M2 macrophage polarization via JAK2/STAT3 targeting in colorectal cancer, thereby reversing the immunosuppressive TME and suppressing metastasis [30]. Wu et al. (2024) extended this finding to osteosarcoma, showing that CuB modulates M2 macrophage differentiation through the PI3K/AKT pathway, attenuating tumor progression [37]. These findings reveal that CuB's anti-metastatic effects extend beyond direct tumor cell killing to encompass TME remodeling, a conceptually important shift from cytotoxic-centric to microenvironment-centric therapeutic thinking.

Enhancement of Anti-Tumor Immunity via cGAS-STING Pathway

The cGAS-STING pathway, a cytosolic DNA-sensing mechanism that triggers type I interferon production and innate immune activation, has emerged as a critical mediator of CuB's immunomodulatory effects. Xu et al. (2025) demonstrated that CuB covalent targeting of MTCH2 causes mitochondrial membrane damage and mtDNA release, activating the cGAS-STING cascade and promoting IFN-β production, which in turn enhances cytotoxic T lymphocyte (CTL) infiltration and sensitizes tumors to anti-PD-1 therapy [20]. Luo et al. (2025) independently confirmed that CuB induces STING-dependent DNA damage pathway activation, enhancing immunotherapy efficacy in osteosarcoma [18]. Yin et al. (2023) demonstrated proteomic-level changes in cisplatin-resistant ovarian cancer cells treated with CuB, including activation of DNA damage response pathways that may similarly engage STING-mediated immune sensing [19]. These findings collectively establish a novel mechanistic framework: CuB induces tumor cell DNA damage (via ATM activation) and mitochondrial damage (via MTCH2 targeting), releasing nuclear and mitochondrial DNA fragments that activate the cGAS-STING pathway, thereby transforming immunologically "cold" tumors into "hot" tumors susceptible to immune checkpoint blockade therapy. This mechanism positions CuB as a potential STING agonist with the unique advantage of dual damage source activation (nuclear + mitochondrial DNA release).

Synergy with Immune Checkpoint Inhibitors

The immunomodulatory properties of CuB have direct implications for combination with immune checkpoint inhibitors. Liu et al. (2022) demonstrated that CuB-mediated IGF2BP1 allosteric regulation downregulates PD-L1 expression and enhances $CD8^+$ T cell infiltration in hepatocellular carcinoma, providing preclinical evidence for CuB + anti-PD-1/PD-L1 combination therapy [11]. Xu et al. (2025) showed that CuB targeting MTCH2 in breast cancer stimulates PD-1 immunotherapy response through mtDNA-cGAS-STING type I IFN cascade [20]. Yin et al. (2025) reported that CuB enhances immune function in pancreatic cancer models through NK cell and $CD8^+$ T cell activation [7]. These three independent lines of evidence converge on a unified paradigm: CuB renders tumors more immunologically visible and responsive through multiple mechanisms—PD-L1 downregulation, cGAS-STING activation, M2 macrophage repolarization, and direct CTL/NK cell enhancement-making it a uniquely positioned candidate for combination immunotherapy strategies. The convergence of these immunological effects across different tumor types and mechanistic pathways suggests that CuB's immunomodulatory capacity may be a generalizable property rather than a cancer-type-specific phenomenon, which significantly broadens its potential clinical applicability.

Pharmacokinetics, Toxicity, and Safety Profile

Pharmacokinetic Properties and Metabolic Fate

CuB exhibits unfavorable pharmacokinetic properties characterized by poor aqueous solubility (log P ≈ 4.5), low oral bioavailability (< 5% in rats), rapid systemic clearance, and extensive first-pass metabolism [5,22]. Dai et al. (2022) provided a comprehensive review of CuB pharmacokinetics, noting that the compound undergoes rapid phase I metabolism (hydrolysis, oxidation) and phase II conjugation (glucuronidation, sulfation), resulting in short plasma half-life and limited tissue exposure [5]. Liu et al. (2024) elucidated the metabolic fate of CuB using LC-MS/MS-enabled profiling, identifying major phase I metabolites

(hydrolysis products at C-16 and C-25 acetyl groups) and phase II conjugates (glucuronides and sulfates) in vivo [38]. Importantly, they identified CuB-Cys (cysteine conjugate) as a major metabolite formed through Michael addition of cysteine to the α, β-unsaturated ketone, representing a detoxification pathway that also constitutes a potential biomarker for CuB exposure monitoring [38]. Zhang et al. (2025) compared the pharmacokinetic profiles of three triterpenoids after oral administration of a cucurbitacin tablet versus a nanosuspension formulation, demonstrating that the nanosuspension significantly improved AUC and Cmax for CuB, providing quantitative evidence that nanotechnology-based formulation can address CuB's bioavailability limitations [39].

Toxicological Concerns and Hepatotoxicity

CuB's toxicity profile presents a significant translational bottleneck. The compound exhibits dose-dependent hepatotoxicity, with mechanism studies revealing that CuB induces cholestatic liver injury through bile acid transport disruption and ER stress in hepatocytes [5,40]. Dai et al. (2024) conducted network pharmacology combined with experimental verification to explore CuB's cholestatic liver injury mechanism, identifying bile acid homeostasis disruption, oxidative stress, and inflammatory cascade activation as the primary hepatotoxicity pathways [40]. Interestingly, Wang et al. (2024) demonstrated that CuB ameliorates AKT-driven fatty liver disease in mice by suppressing AKT/mTORC1 and LXRα/SREBP1 lipogenic pathways [41], suggesting a paradoxical dual effect: hepatotoxicity at anticancer doses versus hepatoprotective effects at sub-therapeutic doses. This dose-dependent bidirectional hepatic effect necessitates careful therapeutic window definition and dosing strategy optimization for clinical translation. Ji et al. (2022) employed metabolomics profiling to characterize AKT/c-Met-induced hepatocellular carcinogenesis and CuB's inhibitory effects, revealing that CuB's anti-HCC activity involves modulation of bile acid metabolism, lipid metabolism, and amino acid metabolism—metabolic pathways that are also implicated in its hepatotoxicity, underscoring the intimate mechanistic connection between CuB's anticancer efficacy and toxicological risk [42].

Strategies to Improve Bioavailability and Reduce Toxicity

Several strategies have been pursued to overcome CuB's pharmacokinetic and toxicological limitations. Shang et al. (2023) developed triazolyl derivatives of CuB targeting IGF2BP1 that exhibit improved pharmacokinetic properties and maintained anticancer efficacy against NSCLC, representing the most successful structural optimization approach to date [43]. The triazolyl modification preserves the α, β-unsaturated ketone for IGF2BP1 covalent binding while altering peripheral structural elements to modulate solubility and metabolic stability. Li et al. (2025) demonstrated that CuB alleviates DSS-induced ulcerative colitis by improving gut microbiota disorder, suggesting that microbiome modulation may represent an indirect strategy for managing CuB-related gastrointestinal toxicity [44]. Nanotechnology-based approaches, discussed in Section 6, offer additional avenues for bioavailability improvement and toxicity reduction through targeted delivery and controlled release mechanisms.

Nanotechnology-Based Delivery Systems

Plant-Derived Nanovesicles

Chen et al. (2022) pioneered a novel approach by utilizing cucumber-derived nanovesicles as natural carriers for CuB delivery to NSCLC [45]. These plant-derived nanovesicles, isolated from Cucumis sativus L. through differential centrifugation, inherently contain CuB and other cucurbitacins, offering a biomimetic delivery platform that leverages the plant's own biosynthetic and packaging machinery [45]. This approach circumvents several limitations of synthetic nanocarriers: (i) natural membrane composition enhances biocompatibility; (ii) intrinsic CuB loading eliminates the need for external drug encapsulation; and (iii) plant vesicle surface proteins may facilitate tissue-specific uptake. This study represents a conceptual innovation in natural product delivery—using the source plant's own vesicular transport system as the delivery vehicle.

ROS-Responsive and Stimuli-Sensitive Nanocarriers

Pang et al. (2022) developed a ROS-responsive nanococktail for co-delivery of paclitaxel and CuB in gastric cancer treatment, featuring self-amplified drug release triggered by the elevated ROS environment characteristic of tumor tissues [23]. The ROS-responsive design exploits the intrinsic oxidative stress in tumor microenvironments to achieve selective drug release, thereby reducing systemic exposure and enhancing tumor-specific cytotoxicity. Chen et al. (2025) developed glycyrrhetinic acid-modified liposomes co-loaded with doxorubicin and CuB for synergistic HCC treatment, utilizing glycyrrhetinic acid as a hepatocyte-targeting ligand that enhances liver-specific accumulation [46]. These stimuli-responsive and actively targeted designs represent increasingly sophisticated strategies to reconcile CuB's potent anticancer activity with its narrow therapeutic window.

Biomimetic and Chemo-Photothermal Synergistic Systems

Leng et al. (2022) developed biomimetic CuB-polydopamine nanoparticles for synergistic chemo-photothermal therapy of breast cancer [24]. The polydopamine core provides photothermal conversion capability under near-infrared (NIR) irradiation, while the CuB payload delivers chemotherapy, creating a dual-modality treatment that achieves synergistic tumor ablation with reduced individual treatment doses [24]. This chemo-photothermal combination is particularly relevant for CuB, as the photothermal component can induce additional tumor cell damage at lower CuB doses, potentially expanding the therapeutic window.

Future Perspectives and Clinical Translation Challenges

From Single-Target to Multi-Target Paradigm

The evolution of CuB mechanistic understanding—from STAT3 as a singular primary target to the identification of IGF2BP1,

GRP78, and MTCH2 as additional covalent targets [11,20,31]—reflects a broader paradigm shift in natural product pharmacology: polypharmacology as an asset rather than a liability. CuB's multi-target engagement, while complicating mechanistic dissection, may confer therapeutic advantages over single-target agents, particularly in cancer therapy where pathway redundancy and compensatory signaling often limit the efficacy of targeted monotherapies [5,27]. Future research should systematically catalog CuB's covalent target repertoire through unbiased chemical proteomics and assess the therapeutic contribution of each target using genetic (CRISPR-based target validation) and pharmacological (structure-activity relationship) approaches.

Combination Therapy Strategies

The immunomodulatory properties of CuB, particularly its capacity to activate the cGAS-STING pathway, downregulate PD-L1, and repolarize M2 macrophages [11,18,20,30], strongly advocate for combination strategies with immune checkpoint inhibitors. Preclinical evidence from three independent studies supports CuB + anti-PD-1 combination efficacy in hepatocellular carcinoma, breast cancer, and pancreatic cancer [11,7,20]. However, the hepatotoxicity risk at anticancer doses [40] necessitates careful dosing optimization, potentially employing metronomic dosing schedules or nanodelivery systems that preferentially accumulate in tumor tissues while sparing the liver.

Structural Derivatization and Precision Medicine

The triazolyl CuB derivatives developed by Shang et al. (2023) targeting IGF2BP1 represent a promising direction for structural optimization [43]. Future derivatization strategies should prioritize: (i) preserving the α,β-unsaturated ketone for covalent target engagement; (ii) modulating peripheral structural elements to improve pharmacokinetic properties; (iii) introducing targeting moieties (e.g., folate, peptides) for cancer cell-specific delivery; and (iv) generating prodrug forms that release active CuB selectively in tumor microenvironments. Additionally, precision medicine approaches that stratify patients based on IGF2BP1, STAT3, and PD-L1 expression levels in their tumors could optimize CuB therapeutic efficacy by matching drug mechanism to patient molecular profile.

Regulatory and Manufacturing Challenges

CuB's natural product origin presents standardization challenges: batch-to-batch variation in plant-derived material, variable CuB content depending on source species and harvest conditions, and the complexity of quality control for a compound with multiple pharmacologically active structural features [5,27]. These challenges necessitate: (i) establishing defined minimum purity standards for pharmaceutical-grade CuB; (ii) developing validated analytical methods for simultaneous quantification of CuB and its major metabolites; (iii) exploring sustainable production through plant cell culture or synthetic biology approaches; and (iv) defining regulatory pathways for a natural product-derived multi-target anticancer agent within current drug approval frameworks.

Conclusion

Cucurbitacin B, a highly oxidized cucurbitane-type triterpenoid from Cucurbitaceae plants, has undergone a remarkable conceptual evolution over the past four years—from a STAT3 inhibitor with limited mechanistic understanding to a multi-target, multi-mechanism anticancer agent with immunomodulatory properties that may synergize with contemporary immunotherapy approaches. The identification of IGF2BP1, GRP78, and MTCH2 as direct covalent targets [11,20,31], the discovery of ferroptosis [16,17] and mitophagy induction [7] as novel cell death mechanisms, the demonstration of cGAS-STING pathway activation [18,20] and M2 macrophage repolarization [30,37] as immunomodulatory effects, and the development of innovative delivery systems [23,24,45,46] collectively represent a transformative expansion of CuB's therapeutic narrative.

However, the path to clinical translation remains challenging. CuB's narrow therapeutic window, hepatotoxicity, poor bioavailability, and standardization difficulties constitute formidable barriers that must be addressed through integrated strategies combining structural derivatization, nanotechnology-based delivery, rational combination therapy, and precision patient stratification. The convergence of CuB's multi-target anticancer mechanisms with its immunomodulatory capacity in the era of cancer immunotherapy creates a uniquely promising—if technically demanding—opportunity for clinical development.

We propose that the most viable translational pathway for CuB involves: (1) IGF2BP1/STAT3/PD-L1 expression-based patient selection; (2) nanodelivery or prodrug formulation to enhance bioavailability and reduce hepatotoxicity; (3) combination with anti-PD-1/PD-L1 checkpoint inhibitors to leverage CuB's TME remodeling effects; and (4) monitoring of CuB-Cys metabolite as a pharmacokinetic/pharmacodynamic biomarker. This multi-pronged approach, informed by the mechanistic insights reviewed herein, may finally enable this ancient botanical remedy to fulfill its modern therapeutic promise.

List of Abbreviations

CuB, Cucurbitacin B; STAT3, Signal Transducer and Activator of Transcription 3; JAK, Janus Kinase; IGF2BP1, Insulin-like Growth Factor 2 mRNA-Binding Protein 1; ROS, Reactive Oxygen Species; ER, Endoplasmic Reticulum; HIF-1α, Hypoxia-Inducible Factor 1-alpha; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; STING, Stimulator of Interferon Genes; cGAS, cyclic GMP-AMP Synthase; M2, Type 2 Macrophage; TAM, Tumor-Associated Macrophage; TME, Tumor Microenvironment; IC50, Half-Maximal Inhibitory Concentration; PK, Pharmacokinetics; GRP78, Glucose-Regulated Protein 78; FOXM1, Forkhead Box M1; KIF20A, Kinesin Family Member 20A; MTCH2, Mitochondrial Carrier Homolog 2; ATM, Ataxia Telangiectasia Mutated; PI3K, Phosphoinositide 3-Kinase; AKT, Protein Kinase B; ZFP91, Zinc Finger Protein 91; HCC, Hepatocellular Carcinoma; NSCLC, Non-Small Cell Lung Cancer; CRC, Colorectal Cancer; GBM, Glioblastoma; GSDMD, Gasdermin D; NLRP3, NOD-like Receptor Protein 3; TLR4, Toll-like Receptor 4;

LXRα, Liver X Receptor alpha; SREBP1, Sterol Regulatory Element-Binding Protein 1; mTORC1, Mechanistic Target of Rapamycin Complex 1; NPC, Nasopharyngeal Carcinoma

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Author contributions

Qiancheng Mao: Conceptualization, Investigation, Writing – original draft preparation, Writing – review & editing, Methodology, Software, Visualization. Suyun Li: Project administration. Tianhe Fang: Resources, Supervision.

Data availability

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researchers.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Ethics approval

Not applicable. This article is a review and does not involve any human or animal subjects.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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