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# Cucurbitacins as Multifunctional Anticancer Agents: Chemistry, Molecular Mechanisms, Translational Challenges, and Emerging Therapeutic Opportunities

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**ABSTRACT:** Cancer continues to be a significant health challenge worldwide and one of the primary contributors to morbidity and mortality. Despite significant progress in the field of immunotherapy, targeted therapy and molecular oncology, the need for improved and safer anti-cancer drugs remains. For a long time, natural ingredients have been a significant source of novel medications. Among these bioactive substances, Cucurbitacins diverse pharmacological properties have made them very promising as madidates. Cucurbitacins represent a class of extremely oxygenated tetracyclic triterpenoids that are predominantly isolated from Cucurbitaceae plants but also isolated from many other plants and fungi. They have been shown to have potent anti tumour properties in various experiments using different types of cancers, including breast cancer, lung cancer, colon cancer, pancreatic cancer, hepatocellular carcinoma, ovarian cancer, prostate cancer, and skin cancer. The updated discussion builds on the idea of the Cucurbitacins as single cytotoxic agents, but incorporates a more comprehensive perspective on multitarget pharmacology, tumour signalling plasticity and translational oncology. When appropriate, the emphasis changes from descriptive reporting to mechanistic interpretation, comparison to other studies and identification of unanswered questions useful for clinical development.

In this review paper, the chemistry, biosynthesis, pharmacological properties and anticancer activity of cucurbitacins have been briefly discussed, with emphasis on the four main members of the group, namely cucurbitacin Q, I, E and D; and cucurbitacin B. These substances have anticancer effect thru a variety of methods, such as suppression of the JAK/STAT3, PI3K/Akt/mTOR, and NF-κB pathways; activation of autophagy and apoptosis; suppression of angiogenesis; disruption of the cytoskeleton; and control of EMT and cancer stem cells. Overall, cucurbitacins are potential and natural compounds to develop anticancer drugs. Furthermore, recent advances in NDDS, combination strategies with conventional chemotherapeutic agents, pharmacokinetic limitations, safety concerns, and future clinical prospects are discussed. Although substantial preclinical evidence supports the therapeutic value of Cucurbitacins, their clinical development remains constrained by challenges such as poor bioavailability, potential systemic toxicity, and limited clinical evaluation. Taken together, A diverse family of naturally occurring substances with great potential for cancer treatment is cucurbitacins. Continued research integrating medicinal chemistry, molecular pharmacology, nanotechnology, and clinical oncology may facilitate the development of cucurbitacin-based treatments for precision cancer medicine.

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## 1. INTRODUCTION

Cancer is a complex and diverse disease with the following characteristics: Abnormal cell proliferation, resistance to programed cell death, persistent angiogenesis, invasion of adjacent tissue, metastatic dissemination, and emergence of treatment resistance (1,2). Worldwide health surveys report cancer remains one of the leading causes of mortality and a significant burden on health care budgets worldwide (2–4). Many patients today have improved life expectancy due to advances in surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy, but there are still problems with treatment, such as side effects, resistance to the drugs, recurrence of the disease and poor tumour specificity (2,5). Natural products have been a significant source for developing anticancer drugs. These days, there are numerous approved anti-cancer drugs of natural origin. A large number of the currently approved anti-cancer agents are derived from nature or are natural products (6,7). Examples include paclitaxel, vincristine, drugs based on calprotectin, and anthracycline antibiotics. In the past few years, the plant-derived phytochemicals with multi-targeted anticancer activities have gained more attention, and the cucurbitacins have always been identified as showing a high therapeutic potential (7).

Cucumber, pumpkin, watermelon, bitter melon, squash and gourd species of the Cucurbitaceae family are the primary source of the highly oxygenated tetracyclic terpene class called cucurbitacins. (8,9,11). These secondary metabolites give many cucurbit plants a very bitter flavor and help to provide natural insect protection, herbivore protection, and microbiological disease protection (9,11). To date, over 200 cucurbitacin-related compounds and derivatives have been found and classified in a few structural groups (8,11).

Cucurbitacins have several pharmacological properties such as hepatoprotective, antidiabetic, antioxidant, antibacterial and antiviral properties in addition to their ecological properties. (9,12,13). Their anticancer activity is particularly remarkable as they may simultaneously regulate multiple cellular signalling pathways related to tumour genesis, tumour development, tumour metastasis and treatment resistance (8,10,14). Cucurbitacins are appealing candidates for overcoming tumour heterogeneity and lowering the risk of treatment resistance due to their capacity to target a variety of molecular processes (10,14,15).

The anticancer effects of cucurbitacins are believed to be mediated by their effects on various cellular and molecular pathways that play a role in tumour formation and progression (8,10,14). These chemicals are likely to induce programd cell death (apoptosis), halt the cell cycle, block angiogenesis, and prevent cancer invasion and metastasis, according to all data available (5,12,13). Moreover, it has been demonstrated that cucurbitacins are able to affect different processes, such as inducing autophagy, disturbing the cytoskeletal architecture and enhancing the production of reactive oxygen species (ROS), all of which cause Mayer cell death (13,14). They are also known to inhibit important cancer-promoting signalling pathways, such as JAK/STAT3, PI3K/Akt/mTOR and NF-$\varkappa$B (13,14,16).Furthermore, Cucurbitacins have been shown to inhibit epithelial–mesenchymal transition (EMT) and modulate the behaviour of Mayer stem cells, both of which are crucial in tumour progression, metastasis, and resistance to treatment (10,15).

Although promising in vitro and in vivo results have been obtained, the clinical development of the cucurbitacins is still hindered (8,9,14). Their medicinal use has been hampered by a number of factors, including as low water solubility, limited bioavailability, quick metabolic breakdown, and possible systemic toxicity (9,17). But recent advances in pharmacological and nanotechnological methods have opened up new avenues for improvement of their therapeutic potential. Methods such as prodrug, targeted drug delivery systems, nanoparticle formulation, and structural modification have consistently demonstrated their ability to enhance drug stability, bioavailability and therapeutic efficacy, and decrease undesirable effects (17).

## 2. CHEMISTRY AND STRUCTURAL CHARACTERISTICS OF CUCURBITACINS

### 2.1 General Chemical Structure

Cucurbitacins are tetracyclic triterpenoids that emerge from squalene cyclisation and are biosynthesized via the mevalonate route. They are produced from the cucuriate skeleton, which consists of thirty carbon atoms organized in a highly oxygenated framework (8,9,11).

**The basic cucurbitane skeleton contains:**

The cucurbitane skeleton represents the characteristic tetracyclic triterpenoid framework of Cucurbitacins and is composed of four fused rings (A–D) (8,11). Multiple hydroxyl groups, ketone moieties, double bonds, and an unsaturated side chain

functionalize this core structure, all of which are crucial in determining the physicochemical and biological characteristics of distinct analogues (11,12). The presence and specific arrangement of these structural elements are essential for the biological activity of Cucurbitacins, as they influence molecular interactions with biological targets (8,9,11). Consequently, these features contribute to the diverse pharmacological properties of Cucurbitacins, including their anticancer, anti-inflammatory, antioxidant, and other therapeutic activities (9,12)

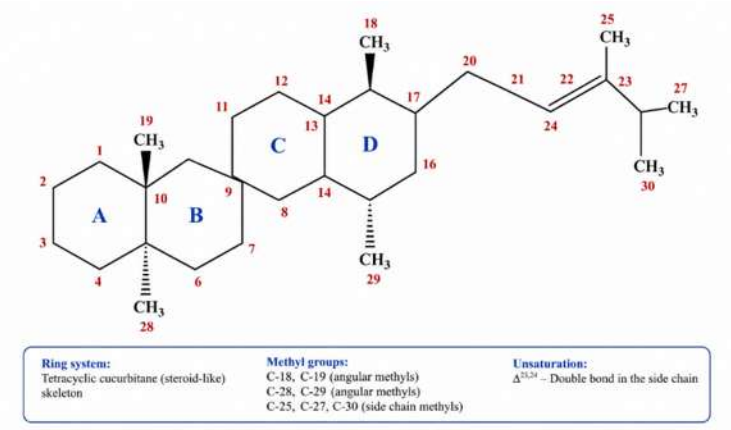


**Figure1**. Generalized Cucurbitacin Skeleton

**IUPAC NAME**

(8R,9S,10R, 13R, 145, 17R)-17-[(2E)-6,6,10-trimethylundeca-2,4-dien-1-yl]-1,2,3,4,4,5,6,7,8,8,9,10,11,12,13,14,15,16-tetradecahydrocyclopenta[a]phenanthrene)

**2.2 Major Types of Cucurbitacins**

| Sr. No. | Cucurbitacin Type | Major Biological Activities | Reference |
|---|---|---|---|
| 1 | Cucurbitacin B | STAT3 inhibition, apoptosis induction | (13,18,19) |
| 2 | Cucurbitacin D | Anti-metastatic activity | (20,21) |
| 3 | Cucurbitacin E | Cytoskeletal disruption | (22,23) |
| 4 | Cucurbitacin I | JAK/STAT inhibition | (18,22) |
| 5 | Cucurbitacin Q | Anti-proliferative effects | (8,24) |
| 6 | Cucurbitacin R | ROS generation | (8,24) |

**Table 1:** Major Cucurbitacin Analogues and Their Major Biological Activities

Cucurbitacins are classified into more than 12 main classes. The two that have been examined the most are cucurbitacin B and cucurbitacin I.

**2.3 Structure–Activity Relationship (SAR)**

The structural properties of cucurbitacins have a significant impact on their biological action., and even minor modifications within the cucurbitane framework can markedly alter their pharmacological properties (11,12,18). The α, β-unsaturated carbonyl group is considered the principal pharmacophore responsible for the biological activity of many cucurbitacin analogues (12,17,18). This electrophilic moiety can undergo Michael addition reactions with nucleophilic amino acid residues, particularly cysteine residues present in signalling proteins, leading to modulation of pathways such as STAT3, NF-ϰB, and PI3K/Akt (8,17,18,22). The number, position, and stereochemical orientation of hydroxyl groups substantially influence

cytotoxic activity, aqueous solubility, and target selectivity (11,12,18). Increased hydroxylation generally enhances hydrogen-bonding interactions with biological macromolecules and may improve affinity for molecular targets (12,25). Acetylation of hydroxyl groups increases lipophilicity and can facilitate membrane permeability and intracellular accumulation of cucurbitacin derivatives (17,25). The position and geometry of carbon–carbon double bonds also contribute to molecular conformation and biological activity, and the presence of a double bond between C-23 and C-24 has been associated with enhanced potency in several naturally occurring analogues (11,12,25). Furthermore, modifications of the side chain, including changes in chain length, oxidation state, and functional group substitution, can significantly affect cytotoxicity, selectivity, and pharmacokinetic behavior (20,25). Collectively, structure–activity relationship studies indicate that the combined effects of hydroxylation pattern, acetylation status, electrophilic carbonyl functionality, double-bond configuration, and side-chain modifications determine the potency and therapeutic potential of cucurbitacins (6,11,12,16,17,25).

**Important Structure–Activity Relationship (SAR)**

**Observations**

Studies on the structure–activity relationship of Cucurbitacins have demonstrated that specific structural modifications can markedly influence their biological and pharmacological properties (1–4). In general, an increased degree of hydroxylation is associated with enhanced cytotoxic activity, likely due to improved hydrogen-bonding interactions with biological macromolecules and greater affinity for molecular targets (12,22,25). Acetylation of hydroxyl groups has been reported to increase the lipophilicity of cucurbitacin derivatives, which may facilitate membrane permeability and improve cellular uptake (3,5,6). Furthermore, the presence of a double bond between C-23 and C-24 in the side chain is considered an important structural feature that contributes to the biological potency of several cucurbitacin analogues (2,7,8). Another critical determinant of activity is the carbonyl functionality, particularly when it forms part of an α, β-unsaturated carbonyl (neon) system. This electrophilic moiety readily undergoes Michael addition reactions with nucleophilic residues, especially cysteine thiol groups in cellular proteins, leading to the modulation of key signaling pathways involved in cell proliferation, apoptosis, and inflammation (3,6,9–11). Collectively, these structural characteristics play a pivotal role in defining the potency, selectivity, and therapeutic potential of Cucurbitacins (2,6,8,10,12,13).

## 3. NATURAL SOURCES AND BIOSYNTHESIS

### 3.1 Plant Sources

Cucurbitacins are naturally occurring, highly oxygenated tetracyclic triterpenoids that are mostly found in plants belonging to the Cucurbitaceae family.(14,15). Members of this family, including *Citrullus colocynthis, Cucumis sativus, Bryonia dioica, Momordica charantia,* and *Trichosanthes cucumerina,* represent the major natural reservoirs of different cucurbitacin analogues (8,14). Individual plant species differ considerably in both the type and concentration of cucurbitacins they produce owing to genetic, environmental, and developmental factors (8,15). Among the naturally occurring analogues, cucurbitacin B, C, D, E, and I are the most extensively investigated because of their remarkable pharmacological and anticancer activities (2,16).

**Important Sources**

| Sr. No | Plant Species | Major Cucurbitacins | References |
|---|---|---|---|
| 1. | Citrullus colocynthis | Cucurbitacin E | (2,14) |
| 2. | Cucumis sativus | Cucurbitacin C | (14,15) |
| 3. | Bryonia dioica | Cucurbitacin D | (2,8) |
| 4. | Momordica charantia | Cucurbitacin B | (8,17) |
| 5. | Trichosanthes cucumerina | Cucurbitacin I | (2,17) |

Table 2: Major Plant Sources of Cucurbitacins and Their Predominant Cucurbitacin Analogues

Although cucurbitacins are predominantly associated with higher plants, cucurbitacin-like triterpenoids and structurally related metabolites have also been reported in certain fungi and marine organisms, indicating a broader natural distribution of these bioactive compounds (16,18).

### 3.2 Biosynthetic Pathway

The biosynthesis of cucurbitacins originates from the mevalonate (MVA) pathway, which produces the universal isoprenoid precursor 2,3-oxidosqualene through a series of enzymatic reactions (14,18). Cyclization of 2,3-oxidosqualene by oxidosqualene cyclase's generates the characteristic cucurbitadienol skeleton, which serves as the primary precursor for the biosynthesis of all cucurbitacin analogues (18,19). Subsequent oxidation, hydroxylation, and rearrangement reactions catalyzed primarily by cytochrome P450 monooxygenases introduce multiple oxygen-containing functional groups, giving rise to structurally diverse cucurbitacins (14,19,20). The cucurbitane skeleton consists of four fused rings (A–D) and is subsequently modified by hydroxylation, ketone formation, acetylation, glycosylation, and side-chain oxidation to produce different cucurbitacin derivatives (14,19). Variations in the number, position, and stereochemistry of these functional groups are responsible for the remarkable structural diversity and biological activities of cucurbitacins (14,16,19). These structural modifications significantly influence their pharmacological properties, including anticancer, anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, antiviral, and antidiabetic activities (2,17,20). Cytochrome P450 enzymes play critical roles in catalyzing oxidation reactions that generate structurally diverse cucurbitacin analogues and regulate the accumulation of these metabolites in different plant species (14,20).

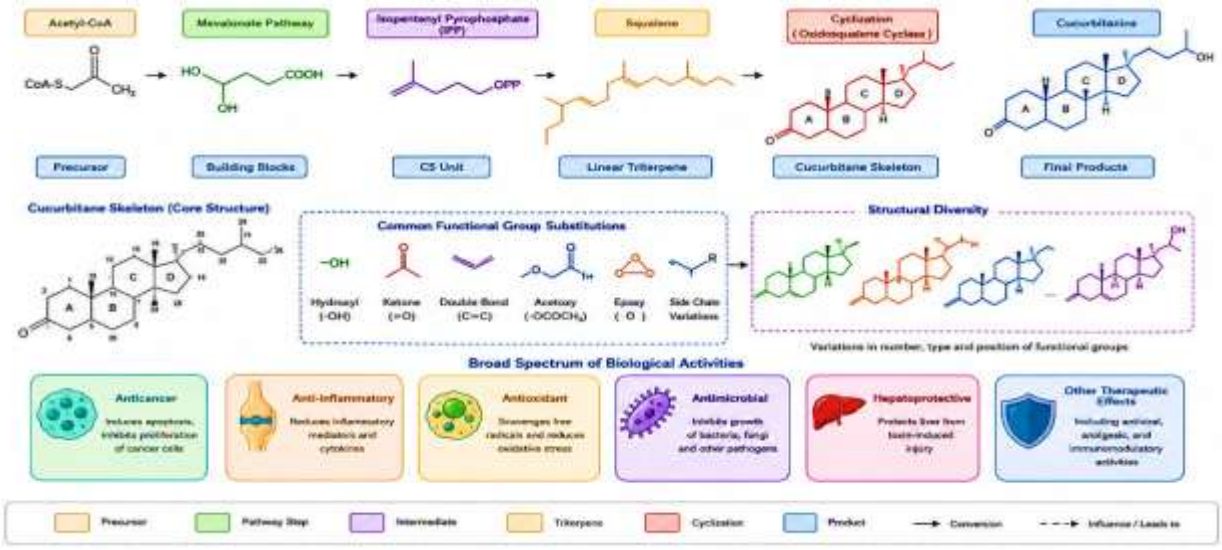


**Figure 2.** Simplified Biosynthetic Pathway

Cytochrome P450 enzymes play critical roles in catalysing oxidation reactions that generate structurally diverse cucurbitacin analogues and regulate the accumulation of these metabolites in different plant species (14,20).

## 4. PHARMACOLOGICAL PROPERTIES OF CUCURBITACINS

In addition to their well-documented anticancer potential, Cucurbitacins possess a broad spectrum of pharmacological activities that contribute to their therapeutic significance (3,8,9). These naturally occurring triterpenoids have hepatoprotective, immunomodulatory, antiviral, anti-inflammatory, antioxidant, and antibacterial properties (3,8,9,17). The capacity of cucurbitacins to influence many cellular signalling pathways involved in inflammation, oxidative stress, cell proliferation, and apoptosis is responsible for their wide range of biological actions (2,3,9).

### 4.1 Anti-Inflammatory Activity

Through the modulation of various important mediators and signal transduction pathways implicated in the inflammation process, cucurbitacins exhibit potent anti-inflammatory properties (3,9). This results in inhibition of inflammatory enzymes such as COX-2 and iNOS as well as reduction in the release of various pro-inflammatory cytokines such as IL-6 and TNF-α

(2,3,9). Cucurbitacins also inhibit the NF-ϰB signalling pathway that acts as an important regulatory pathway for inflammatory genes (3,21,22). In light of the fact that inflammation has been shown to have an important role in the initiation and progression of cancers, anti-inflammatory properties of cucurbitacins have been considered one of the major mechanisms underlying their chemoprotective effects (22,27).

### 4.2 Antioxidant Activity

Cucurbitacins have an essential function in regulating cellular oxidative stress by lowering the production of ROS, enhancing the inherent antioxidant defenses of the body and maintaining mitochondrial health (2,17,23). The above actions assist in maintaining cellular redox balance and protecting healthy cells from oxidative stress (17, 23). It is important to observe that the activity of cucurbitacins results in a controlled increase in the level of intracellular ROS in cancer cells, resulting in oxidative stress that is beyond the antioxidant capacity of the cell and thus causes apoptosis (2,17,24). Excess ROS activity leads to the loss of the mitochondrial membrane potential, activates the intrinsic apoptotic pathway and causes caspase-mediated cell death (17,24,25). Cucurbitacins not only induce ROS activity but also regulate antioxidant signalling pathways such as Nrf2/Keap1 pathway, affecting the synthesis of antioxidant enzymes such as GPx, CAT and SOD (2,25). Cucurbitacins not only induce ROS activity but also regulate antioxidant signalling pathways such as Nrf2/Keap1 pathway, affecting the synthesis of antioxidant enzymes such as GPx, CAT and SOD (2,25).

### 4.3 Antimicrobial and Antiviral Activity

The interest in the pharmacological properties of cucurbitacins has grown significantly owing to their wide-spectrum antibacterial and antiviral activity as well as anticancer activity (2,8,17). The inhibitory effects of cucurbitacins on the development of various kinds of pathogenic fungi, Gram-positive and Gram-negative bacteria have been proven in scientific experiments (2,8). Such antimicrobial effects are believed to be related to the interference with the key intracellular signalling pathways, metabolic suppression in cells and destruction of membranes in microbes (2,17). Moreover, a number of studies prove that cucurbitacins possess antiviral activity against various DNA and RNA viruses due to the suppression of virus replication, the suppression of interactions between virus and host and the modulation of host immunity (8,9). In addition, the suppression of JAK/STAT and NF-ϰB signalling pathways has been identified in various studies as the factor promoting the antiviral activity of cucurbitacins by limiting the virus proliferation and inflammation induced by the virus (9,17). Despite the promising results in this field, additional studies in vivo and clinical trials are required to identify the effectiveness and safety of using cucurbitacins as the antiviral and antibacterial agents (2,8,9,17).

### 4.4 Immunomodulatory Activity

It has been demonstrated that cucurbitacins possess immunomodulatory properties by affecting the activation, differentiation and cytokine production of immune cells (9,10,17). Cucurbitacins affect the secretion of proinflammatory cytokines and chemokines; therefore, they help to maintain the balance of immune responses and regulation of inflammatory responses (9,17). In addition, cucurbitacins can regulate the signalling pathways including JAK/STAT3 and NF-ϰB involved in immune cell function, inflammatory signalling and tumour immune escape mechanisms (9,10,17). By inhibiting these pathways, cucurbitacins could increase antitumour immunity, reduce chronic inflammation, and change the tumour microenvironment for immune-mediated destruction of cancer cells (10,17). Thus, cucurbitacins become promising compounds for the development of combination treatments using immunotherapy and targeted anticancer therapy (10,17,26). However, further investigation is needed to understand the immunomodulatory activities of cucurbitacins and apply these compounds in clinical practice (9,10,17,26).

## 5. MOLECULAR MECHANISMS OF ANTICANCER ACTIVITY

### 5.1 Induction of Apoptosis

By eliminating dysfunctional cells, either through damage, malfunctions, or unnecessary cells, apoptosis – which is a highly regulated and energy-requiring type of programmed cell death – acts as a significant factor in maintaining tissue homeostasis (27, 28). Contrary to necrosis, apoptosis allows for maintenance of tissue integrity, since the process occurs systematically and without causing inflammation (12, 28). Malignant cell resistance to apoptosis forms part of the cancer hallmarks which causes uncontrolled growth, formation of tumours, and resistance to conventional cancer therapies (5, 12, 28). Therefore, reinstating apoptotic signalling has formed a key therapeutic approach in cancer treatment (5, 12). Various in vitro studies have

demonstrated that cucurbitacins induce apoptosis in several human cancer cell lines by triggering the intrinsic and extrinsic apoptotic pathways (24, 29-31).

**Intrinsic (Mitochondrial) Pathway**

Intracellular stress signals, including DNA damage, oxidative stress, hypoxia, endoplasmic reticulum stress, and chemotherapeutic drug exposure, are examples of some stimuli that activate the intrinsic apoptotic pathway (24, 27). Mitochondrial outer membrane permeabilization followed by the release of cytochrome c into the cytosol is a direct consequence of injury caused by the above stimuli on the integrity of the mitochondrial membrane (28, 29). Once cytochrome c connects with the apoptotic protease-activating factor-1 (Apaf-1) to form the apoptosome, it activates caspase-9. Executioner caspases, which include caspase-3 and caspase-7, follow (27, 28, 30). Proteins of the Bcl-2 family strictly regulate the mitochondrial pathway, where anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, prevent the permeabilization of the mitochondrial membrane while the pro-apoptotic proteins, including Bax and Bak, promote it (5,12). Cucurbitacins induce mitochondrial apoptosis through the activation of the mitochondrial pathway. Proteins of the Bcl-2 family strictly regulate the mitochondrial pathway, where anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, prevent the permeabilization of the mitochondrial membrane while the pro-apoptotic proteins, including Bax and Bak, promote it (5,12) Cucurbitacins induce mitochondrial apoptosis by activating the caspase cascade, upregulating Bax expression, downregulating Bcl-2, and promoting cytochrome c release, all of which result in apoptotic cell death, according to several studies (24, 29–32).

**Extrinsic (Death Receptor) Pathway**

Death ligands present outside the cell, such as FasL and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), bind to death receptors in the cell surface to initiate the extrinsic apoptotic pathway (12,27). The activation of initiator caspase-8 occurs via death-inducing signalling complex (DISC) formation, which happens after the interaction of ligand and death receptors (5,28). Programmed cell death results from the cleavage and activation of executioner caspases by activated caspase-8, primarily caspase-3 (5,27). Moreover, through mitochondrial membrane permeabilization, activated caspase-8 cleaves Bid to truncated Bid (tBid), thus linking both intrinsic and extrinsic apoptotic pathways (12,28). It has been proven experimentally that cucurbitacins have increased apoptotic signalling in cancer cells, which enhances death receptor-mediated apoptosis via caspase-8 activation, DISC formation, and Bid cleavage (29–32).

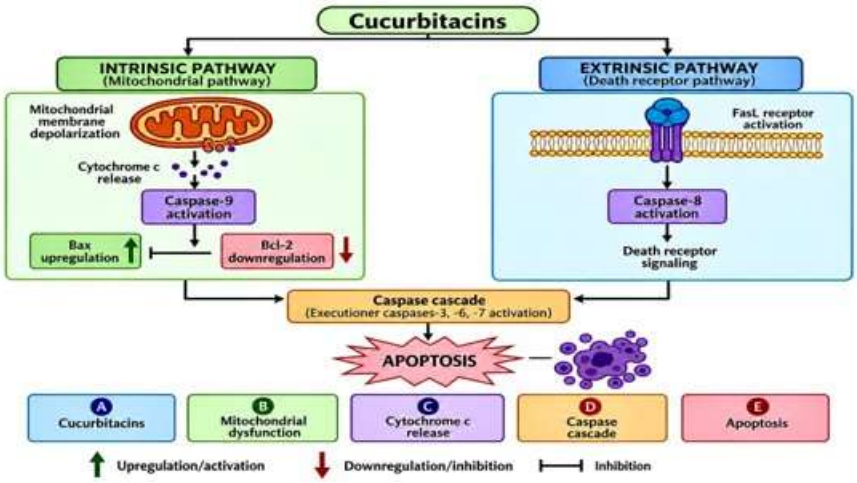


**Figure 3:** Molecular Mechanisms of Cucurbitacin-Induced Apoptosis in Cancer Cells

**5.2 Cell Cycle Arrest**

The tightly regulated process of cell cycle development ensures precise DNA replication and cell division (30, 33). Cancer cells often evade these regulatory checkpoints, resulting in unregulated proliferation (34, 35). One of cucurbitacins' primary anticancer actions is their ability to induce cell cycle arrest, which prevents malignant cells from multiplying and dividing (30, 36). Depending on the kind of cancer and the specific cucurbitacin analogue, cell cycle arrest can happen during the G1, S, or G2/M phase (33, 37). This impact is produced via modulating cyclins, cyclin-dependent kinases (CDKs), and cell cycle

regulatory proteins such as p21, p27, and p53 (37, 38).Cucurbitacins inhibit the growth of cancer cells and encourage apoptosis by interfering with the advancement of the cell cycle (30, 38).

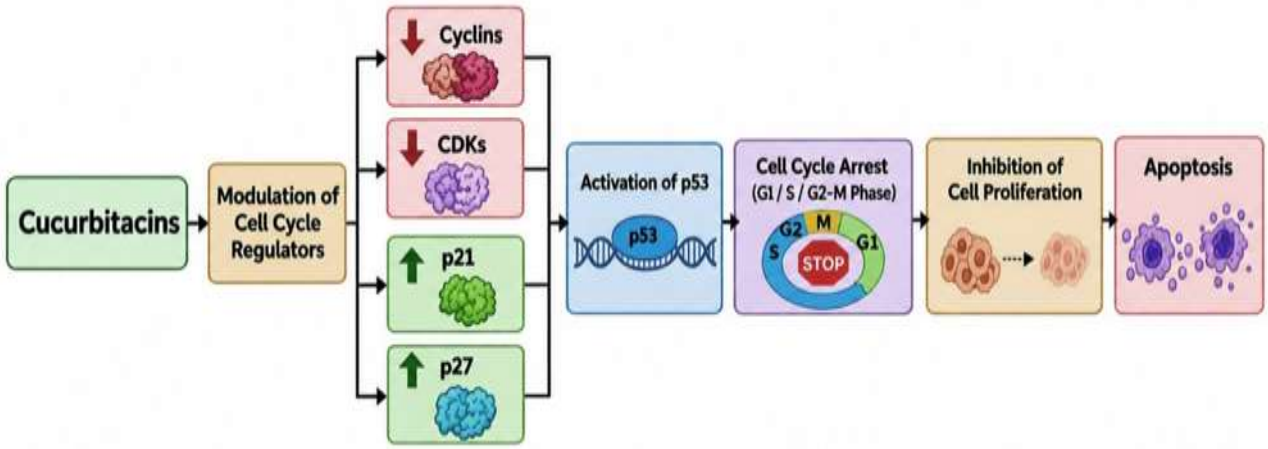


**Figure 4:** Mechanism of Cucurbitacin-Induced Cell Cycle Arrest in Cancer Cells

### 5.3 Inhibition of JAK/STAT3 Signalling

Angiogenesis, immunological evasion, cell proliferation, survival, and metastasis are all regulated by the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signalling pathway (40,41). In a number of human malignancies, persistent STAT3 activation is linked to treatment resistance and a poor prognosis (42, 43). Thus, blocking the JAK/STAT3 pathway has become an essential therapeutic approach for cancer therapy (40,44). By preventing STAT3 phosphorylation and nuclear translocation, cucurbitacins, especially Cucurbitacin I, have shown significant inhibitory efficacy against STAT3 signalling (45,46). This inhibition increases the anticancer effects of cucurbitacins by lowering the expression of genes involved in tumour growth, survival, and metastasis (45, 47).

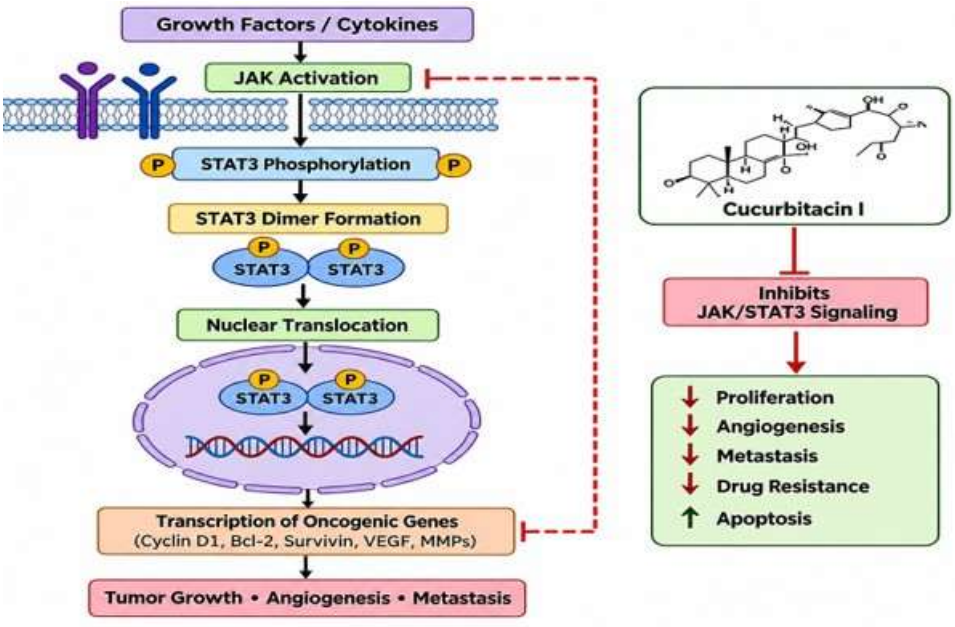


**Figure 5**: Inhibition of the JAK/STAT3 Signalling Pathway by Cucurbitacin I

### 5.4 PI3K/Akt/mTOR Pathway Suppression

One of the main intracellular systems that controls cell growth, proliferation, survival, metabolism, and protein synthesis is the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signalling pathway (48, 49). Many human malignancies have this system improperly active, which promotes tumour growth, metastasis, and treatment resistance

(50,51). Consequently, blocking the PI3K/Akt/mTOR pathway has become a crucial treatment approach for cancer (48,52). According to research, cucurbitacins block downstream signalling by blocking the phosphorylation and activation of PI3K, Akt, and mTOR (53,54). This results in an inhibition of tumour growth, an increase in apoptosis, and a decrease in the proliferation of cancer cells (53,55).

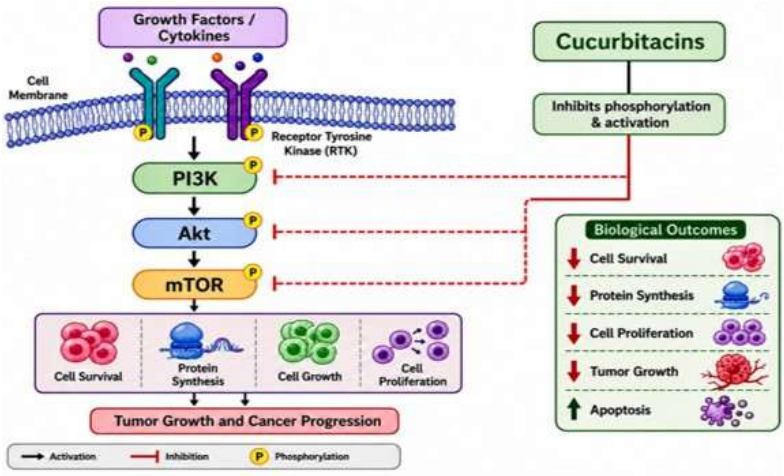


**Figure 6:** Suppression of the PI3K/Akt/mTOR signalling pathway by Cucurbitacins

### 5.5 NF-κB Signalling Inhibition

Nuclear factor-kappa B (NF-κB) is a pivotal transcription factor that regulates inflammation, cell proliferation, apoptosis, angiogenesis, immune responses, and tumour progression (56,57). Constitutive activation of NF-κB has been reported in numerous human malignancies and is closely associated with chronic inflammation, enhanced tumour cell survival, metastatic progression, and resistance to chemotherapy (57–59). Under resting conditions, NF-κB remains sequestered in the cytoplasm through its interaction with inhibitor of κB (IκB) proteins (56,59). Following stimulation by inflammatory cytokines, growth factors, or oxidative stress, IκB undergoes phosphorylation by the IκB kinase (IKK) complex, leading to its ubiquitination and proteasomal degradation, thereby permitting NF-κB nuclear translocation (57,58). Activated NF-κB subsequently induces the transcription of genes involved in inflammation, cell survival, angiogenesis, invasion, metastasis, and anti-apoptotic signalling (59,60). Experimental evidence indicates that cucurbitacins suppress NF-κB signalling by inhibiting IKK activation, preventing IκB degradation, blocking nuclear translocation of the p65 subunit, and reducing the expression of NF-κB-regulated genes (61–63). Consequently, cucurbitacins decrease the production of pro-inflammatory cytokines and anti-apoptotic proteins while enhancing apoptosis and suppressing tumour progression, highlighting NF-κB inhibition as an important mechanism underlying their anticancer activity (60–63).

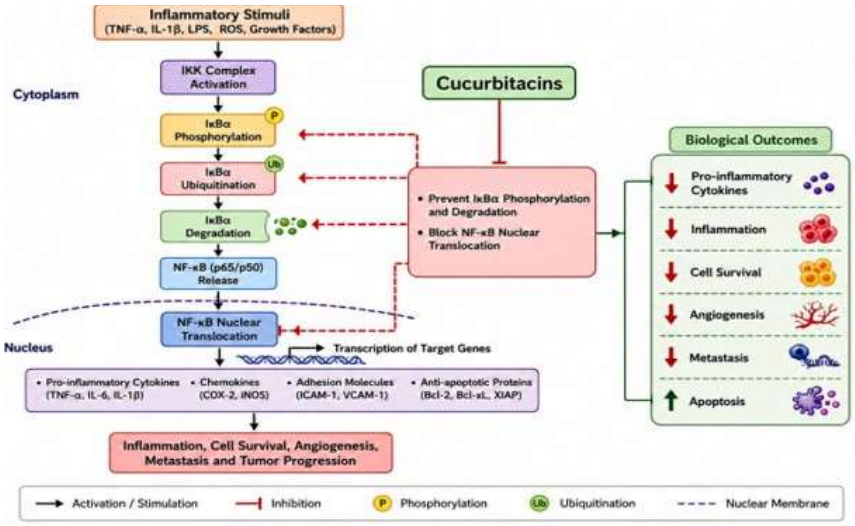

**Figure 7.** Inhibition of the NF-κB Signalling Pathway by Cucurbitacins

### 5.6 Reactive Oxygen Species (ROS) Generation

Reactive oxygen species (ROS) are highly reactive oxygen-containing molecules that function as important mediators of cellular signalling, proliferation, differentiation, and survival under physiological conditions. However, excessive ROS production disturbs intracellular redox homeostasis, resulting in oxidative stress that damages DNA, proteins, lipids, and other cellular components (64,65). Cancer cells generally maintain higher basal ROS levels than normal cells because of their increased metabolic activity and mitochondrial dysfunction, making them more susceptible to further oxidative stress induced by anticancer agents (65,66). Several studies

have demonstrated that cucurbitacins markedly increase intracellular ROS accumulation, leading to mitochondrial membrane depolarization, oxidative DNA damage, endoplasmic reticulum (ER) stress, and activation of apoptotic signalling pathways (24,67,68). ROS generated by cucurbitacins also promotes cytochrome *c* release, caspase activation, and mitochondrial dysfunction, thereby enhancing intrinsic apoptosis in cancer cells (67,68). Furthermore, excessive ROS production contributes to inhibition of tumour cell proliferation and sensitizes cancer cells to chemotherapy by disrupting cellular antioxidant defence mechanisms (24,69). Collectively, ROS-mediated oxidative stress represents one of the major mechanisms through which cucurbitacins exert their anticancer effects (24,67–69).

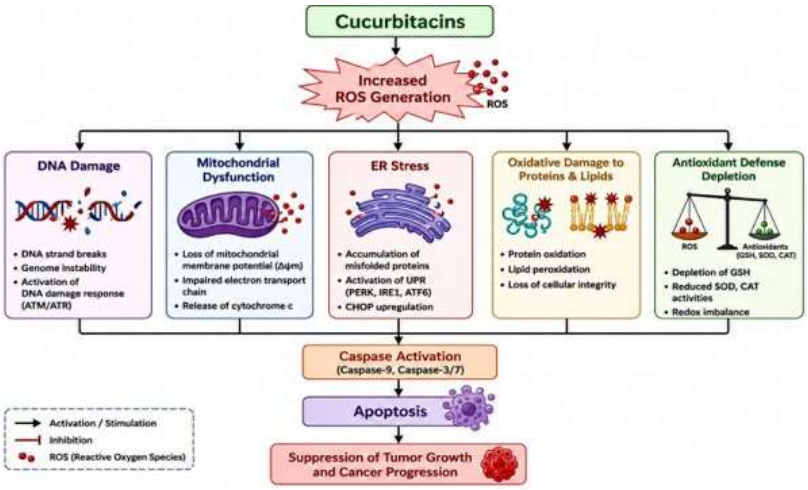


**Figure 8:** ROS-Mediated Anticancer Mechanism of Cucurbitacins

### 5.7 Autophagy Modulation

Autophagy is a highly conserved lysosome-dependent intracellular degradation process that maintains cellular homeostasis by eliminating damaged organelles, protein aggregates, and dysfunctional macromolecules (70,71). Under physiological conditions, autophagy serves as a cytoprotective mechanism that enables cells to survive nutrient deprivation, oxidative stress, and other adverse conditions (70,71). In cancer, however, autophagy exhibits a dual role by either promoting tumour cell survival or facilitating programmed cell death depending on the tumour type, genetic background, and stage of disease (72,73). Increasing evidence indicates that cucurbitacins regulate autophagy in a dose-, time-, and cell type-dependent manner through modulation of multiple signalling pathways, including PI3K/Akt/mTOR and AMPK signalling (69,74,75). Experimental studies have demonstrated that cucurbitacins alter the expression of autophagy-related proteins such as microtubule-associated protein light chain 3 (LC3-II), Beclin-1, p62/SQSTM1, and ATG proteins, thereby influencing autophagic flux and cellular fate (69,74–77). Furthermore, autophagy induced by cucurbitacins frequently interacts with apoptotic signalling, and the balance between these two processes determines the overall therapeutic response of cancer cells (75–77). Therefore, modulation of autophagy represents an important mechanism contributing to the anticancer activity of cucurbitacins and may provide opportunities for combination therapies targeting both apoptosis and autophagy (69,74–77).

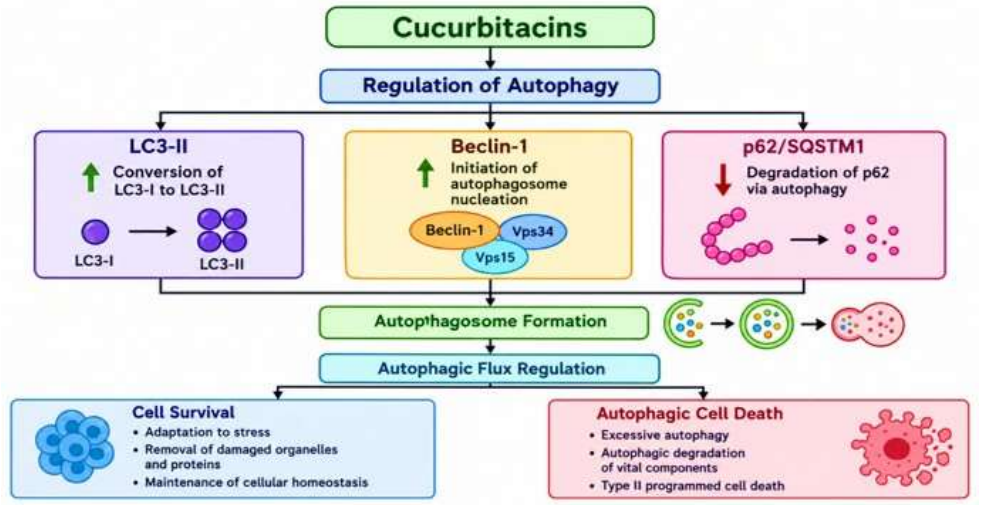


**Figure 9:** Modulation of Autophagy by Cucurbitacin

### 5.8 Cytoskeletal Disruption

Maintaining cell shape, intracellular transport, cell division, migration, and invasion all depend on the cytoskeleton, a highly dynamic intracellular network made up of actin filaments, microtubules, and intermediate filaments (78,79). Remodelling of the cytoskeleton is a hallmark of malignant transformation and plays a critical role in tumour progression and metastasis (78,80). Among naturally occurring triterpenoids, cucurbitacins are unique because they exert profound effects on the actin cytoskeleton, resulting in rapid morphological alterations and inhibition of cancer cell motility (8,81). Experimental studies have demonstrated that cucurbitacins induce depolymerization, aggregation, and abnormal reorganization of filamentous actin (F-actin), leading to loss of cell polarity, disruption of focal adhesions, and impairment of migratory capacity (8,81,82). In addition to actin remodelling, certain cucurbitacin analogues have been shown to interfere with microtubule dynamics and mitotic spindle organization, thereby contributing to G2/M cell-cycle arrest and inhibition of tumour cell proliferation (82,83). Recent mechanistic studies further suggest that cucurbitacins alter actin dynamics indirectly through interactions with actin-regulatory proteins, including cofilin, rather than by directly binding polymerized actin filaments (81,84). Collectively, disruption of cytoskeletal organization suppresses cancer cell migration, invasion, and metastatic dissemination while promoting apoptotic cell death, representing an important component of the multifaceted anticancer activity of cucurbitacins (8,81–84).

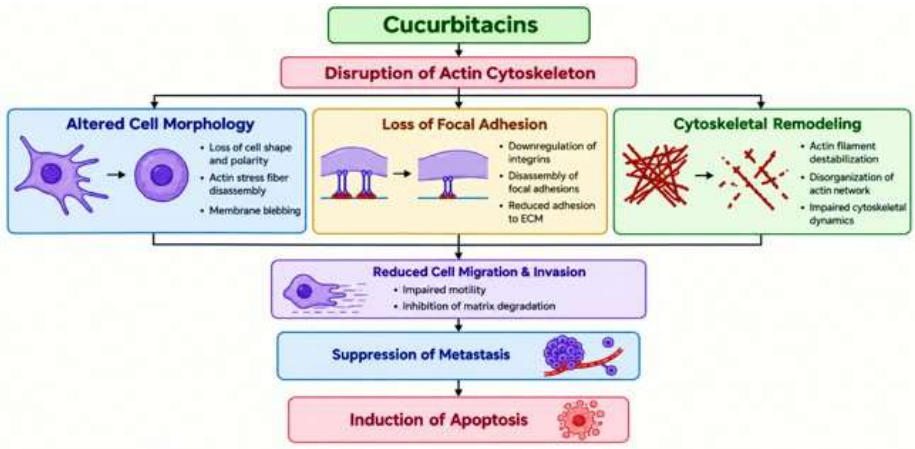


**Figure 10**: Cucurbitacin-Induced Cytoskeletal Disruption and Inhibition of Cancer Cell Migration

### 6. Hallmarks of Cancer Targeted by Cucurbitacins

Tumour start, development, metastasis, and treatment resistance are all made possible by a set of biological abilities known as the hallmarks of cancer (12,85). Sustained proliferative signalling, growth suppressor evasion, resistance to apoptosis, replicative immortality, angiogenesis stimulation, invasion and metastasis activation, metabolic reprogramming, immunological evasion, and genomic instability are some of these characteristics (85,86). Unlike conventional chemotherapeutic agents that often target a single molecular pathway, cucurbitacins exert broad-spectrum anticancer activity by simultaneously modulating multiple hallmarks of cancer through regulation of interconnected signalling networks (17,87). Experimental evidence has demonstrated that cucurbitacins suppress tumour cell proliferation, induce apoptosis, inhibit angiogenesis, interfere with epithelial–mesenchymal transition (EMT), reduce metastatic potential, modulate oxidative stress, and alter the tumour microenvironment (39,87–89). Moreover, inhibition of key oncogenic pathways, including JAK/STAT3, PI3K/Akt/mTOR, and NF-ϰB, enables cucurbitacins to overcome several mechanisms responsible for tumour progression and therapeutic resistance (39,88–90). Owing to their multitarget mode of action, cucurbitacins have emerged as promising natural compounds for the development of novel anticancer therapies capable of targeting multiple cancer hallmarks simultaneously (17,39,87–89,91).

#### 6.1 Inhibition of Angiogenesis

Because it provides oxygen and nutrients to rapidly reproducing cancer cells, angiogenesis—the physiological process by which new blood vessels are formed from pre-existing vasculature—is crucial for tumour progression beyond 1-2 $mm^3$ (92,93). Vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and other pro-inflammatory cytokines are the main drivers of tumour angiogenesis (93,94). Aggressive tumour development, metastatic spread, and a poor clinical prognosis are often linked to overexpression of these angiogenic mediators (94,95). Numerous experimental studies have demonstrated that cucurbitacins inhibit angiogenesis by suppressing VEGF expression, reducing HIF-1α accumulation, inhibiting endothelial cell proliferation and migration, and interfering with STAT3-mediated angiogenic signalling (30,91,96,97). In addition, cucurbitacins decrease micro vessel density within tumours and impair the formation of capillary-like structures, thereby limiting tumour vascularization and nutrient supply (30,91,97). Through simultaneous inhibition of angiogenic signalling pathways and endothelial cell function, cucurbitacins effectively suppress tumour progression and metastatic potential, highlighting their promise as antiangiogenic agents in cancer therapy (30,91,96,97).

| Sr. No. | Target | Effect of Cucurbitacins | Biological Outcome | References |
|---|---|---|---|---|
| 1. | VEGF | Down Regulation | Reduced angiogenesis | (30,96) |
| 2. | HIF- 1α | Inhibition | Reduced VEGF expression | (30,96) |
| 3. | STAT 3 | Suppression | Decreased angiogenic signalling | (30,97) |
| 4. | Endothelial cell proliferation | Inhibited | Reduced vessel formation | (91,97) |
| 5. | Tube formation | Suppressed | Impaired neovascularization | (30,91) |
| 6. | Tumour micro vessel density | Decreased | Reduced tumour growth | (96,97) |

**Table 3:** Anti-angiogenic Mechanisms of Cucurbitacins

#### 6.2 Anti-Angiogenic Effects

Angiogenesis, the physiological process by which new blood vessels are formed from pre-existing vasculature, is crucial for tumour development beyond 1-2 $mm^3$ because it provides oxygen and nutrients to rapidly proliferating cancer cells (92,93). Vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), fibroblast growth factors (FGFs), platelet-

derived growth factor (PDGF), and other pro-inflammatory cytokines are the main drivers of tumour angiogenesis (93,94). Furthermore, by preventing endothelial cell migration, proliferation, and capillary tube development, cucurbitacins obstruct the production of new blood vessels required for the progression of cancer (99,101). produced from pre-existing vasculature—is essential for the growth of tumours larger than 1-2 mm³ (92,93). Tumour angiogenesis is primarily driven by vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and other pro-inflammatory cytokines (93,94). Furthermore, cucurbitacins impede the establishment of new blood vessels necessary for cancer growth by inhibiting endothelial cell migration, proliferation, and capillary tube formation (99,101). Cucurbitacins have also been shown in several studies to interfere with angiogenesis-associated signalling molecules, such as matrix metalloproteinases (MMPs) and focal adhesion kinase (FAK), which results in decreased neovascularization and poor tumour vascularization (100,102). Through inhibition of tumour angiogenesis, Cucurbitacins restrict tumour growth, reduce metastatic potential, and enhance their overall anticancer efficacy (99–102).

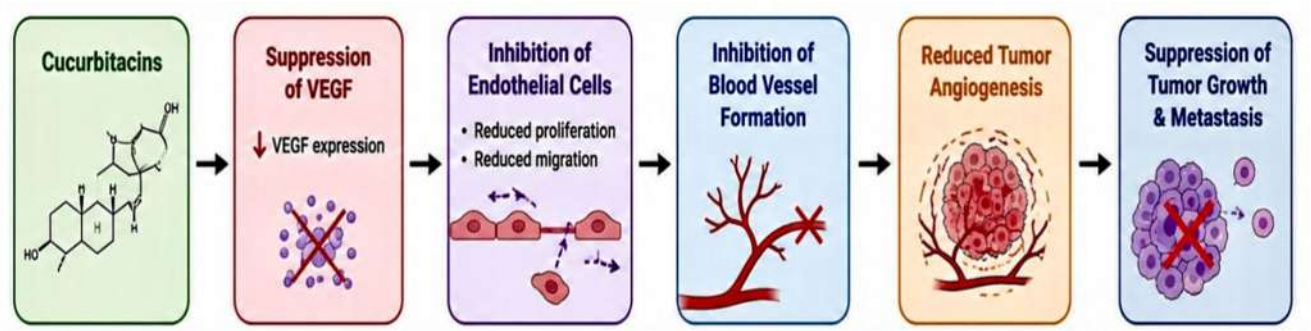


**Figure 11:** Anti-Angiogenic Mechanism of Cucurbitacins

### 6.3 Anti-Metastatic Effects

Cancer cells separate from the original tumour, infiltrate adjacent tissues, intravasate into the circulation, survive in the bloodstream, extravasate into distant organs, and form additional tumours during the intricate, multi-step process of metastasis (103,104). One of the main obstacles to cancer treatment is metastatic spread, which accounts for around 90% of cancer-related fatalities (103,105). By focusing on many signalling pathways involved in tumour invasion and migration, experimental research has shown that cucurbitacins have strong anti-metastatic effect (100,106). By controlling EMT-associated transcription factors and re-establishing epithelial traits in cancer cells, cucurbitacins inhibit the epithelium–mesenchymal transition (EMT Additionally, these substances reduce extracellular matrix breakdown and tumour invasion by inhibiting the production and activity of matrix metalloproteinases (MMP-2 and MMP-9) (100,107). Additionally, cucurbitacins interfere with focal adhesion dynamics and actin cytoskeletal architecture, which impairs cell migration and lowers the potential for metastasis (106,107).Collectively, these mechanisms suppress cancer cell invasion, migration, and distant metastasis, highlighting Cucurbitacins as promising anti-metastatic agents for cancer therapy (100,105–107).

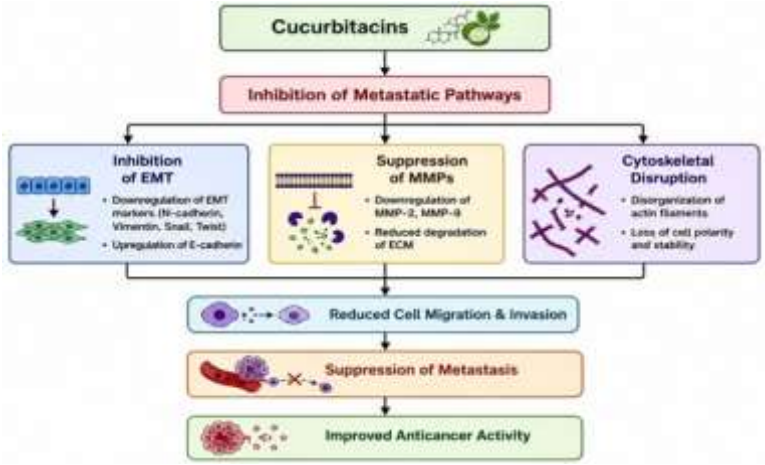

**Figure 12:** Molecular Mechanisms Underlying the Anti-Metastatic Effects of Cucurbitacins

### 6.4 Targeting of Cancer Stem Cells

Tumour recurrence, metastasis, and treatment resistance are all significantly influenced by cancer stem cells (CSCs), a tiny subset of tumour cells distinguished by their ability to self-renew, differentiate, and initiate tumours (108,109). A growing body of research indicates that CSCs are inherently resistant to traditional chemotherapy and radiation, which may contribute to disease recurrence after treatment (109,110). According to recent research, Cucurbitacins efficiently target CSCs by inhibiting stemness-associated signalling pathways such as Notch, JAK/STAT3, and Wnt/β-catenin (106,111). Additionally, stem cell markers such CD44, ALDH1, Nanog, Oct4, and Sox2 have been shown to be downregulated by cucurbitacins, which reduces their ability to self-renew and initiate tumours (106,110). Moreover, Cucurbitacins' suppression of CSC-associated signalling increases chemosensitivity and lowers the risk of cancer recurrence and metastatic spread (99,106). Cucurbitacins are attractive therapeutic possibilities for overcoming drug resistance and enhancing long-term clinical outcomes in cancer treatment because they target CSC maintenance and survival (99,106,110,111).

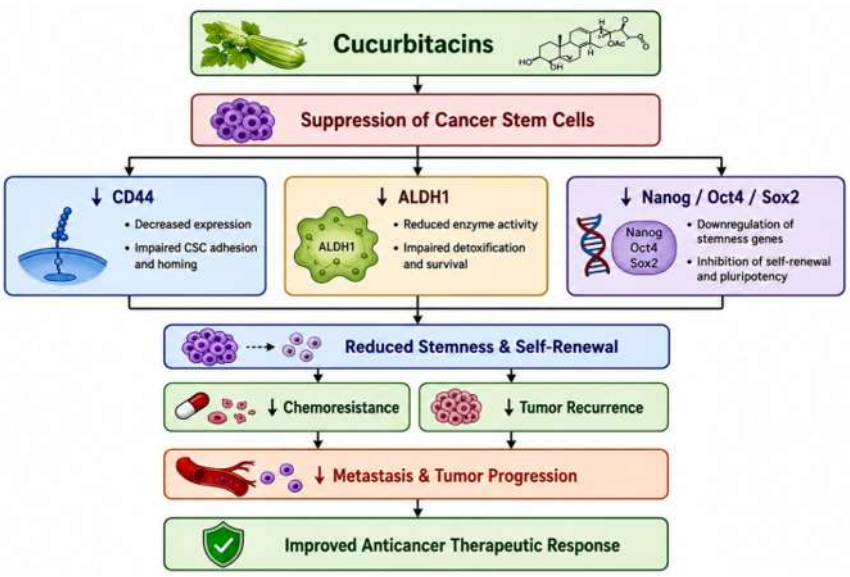


**Figure 13**: Modulation of Cancer Stem Cell Signalling by Cucurbitacins

### 7. Cucurbitacins in Specific Cancer Types

Cucurbitacins' primary molecular targets and treatment efficiency fluctuate depending on the biological traits and genetic landscape of various cancer types, despite the fact that the basic molecular pathways underlying their anticancer action are mostly consistent (11,112). Numerous preclinical studies have shown that different cucurbitacin analogues have strong antitumour activity against a wide range of solid and haematological malignancies by regulating several signalling pathways related to cell proliferation, apoptosis, angiogenesis, metastasis, oxidative stress, autophagy, and therapeutic resistance (1,11,112). Among the different analogues, Cucurbitacins B, D, E, I, and Q have shown particularly promising anticancer activity against breast cancer, lung cancer, colorectal cancer, pancreatic cancer, leukaemia, glioblastoma, and several other malignancies through inhibition of oncogenic pathways such as JAK/STAT3, PI3K/Akt/mTOR, NF-κB, MAPK, VEGFR, and Wnt/β-catenin signalling (1,88,112). In addition to their direct cytotoxic effects, increasing evidence indicates that cucurbitacins can enhance the efficacy of conventional chemotherapeutic agents, suppress cancer stem cell populations, inhibit tumour invasion and metastasis, and partially overcome multidrug resistance, highlighting their potential as

multifunctional adjuncts in cancer therapy (1,11,88). Consequently, substantial research efforts have focused on evaluating the therapeutic potential of cucurbitacins across different cancer types, providing a strong rationale for the development of novel targeted treatment strategies and future clinical translation (1,11,88,112).

| Sr. No. | Cancer Type | Predominant Cucurbitacin Analogue(s) | Major Molecular Targets | References |
|---|---|---|---|---|
| 1 | Breast Cancer | B, D, I | STAT3, Akt, NF-κB | ###### |
| 2 | Lung Cancer | E, I | EGFR, JAK/STAT3, PI3K/Akt | ###### |
| 3 | Colorectal cancer | D, E | Wnt/β-catenin, PI3K/Akt | (7,117–119) |
| 4 | Pancreatic cancer | B | KRAS, JAK/STAT3 | (113,120–122) |
| 5 | Leukaemia | I | JAK/STAT3, Caspases | (10,123–127) |

**Table 4:** Major Cucurbitacin Analogues Investigated in Different Cancer Types and Their Primary Molecular Targets

**7.1 Breast Cancer**

Despite significant advancements in early diagnosis and focused therapy, breast cancer remains one of the top causes of cancer-related death and is the most often diagnosed disease among women globally (17,113). Treatment resistance, tumour recurrence, and metastatic progression remain significant therapeutic problems, especially for patients with advanced-stage illness and triple-negative breast cancer (TNBC) (11,113). By inhibiting several oncogenic signalling pathways involved in cell survival, proliferation, invasion, and metastasis, Cucurbitacin B, Cucurbitacin D, and Cucurbitacin I have shown notable antiproliferative activity against breast cancer cells among the different cucurbitacin analogues (11,17,114,115). According to experimental research, cucurbitacins suppress constitutive STAT3, Akt, and NF-κB signalling, which lowers the production of anti-apoptotic proteins, inhibits the growth of cancer cells, and triggers caspase-dependent apoptosis (11,114,115). Additionally, cucurbitacins reduce the potential for metastasis by increasing intracellular reactive oxygen species (ROS), inducing mitochondrial dysfunction, suppressing the epithelial–mesenchymal transition (EMT), and impairing the invasive and migratory capabilities of breast cancer cells (17,114,115). Crucially, preclinical studies have shown that Cucurbitacin D reverses STAT3- and NF-κB-mediated chemoresistance in drug-resistant breast cancer cells, increasing the cytotoxic efficiency of doxorubicin, indicating its possible use as an adjuvant treatment agent (115). Due to their capacity to concurrently control apoptosis, oxidative stress, oncogenic signalling pathways, and treatment resistance, these results collectively suggest that cucurbitacins constitute prospective multifunctional agents for breast cancer therapy (11,17,113–115).

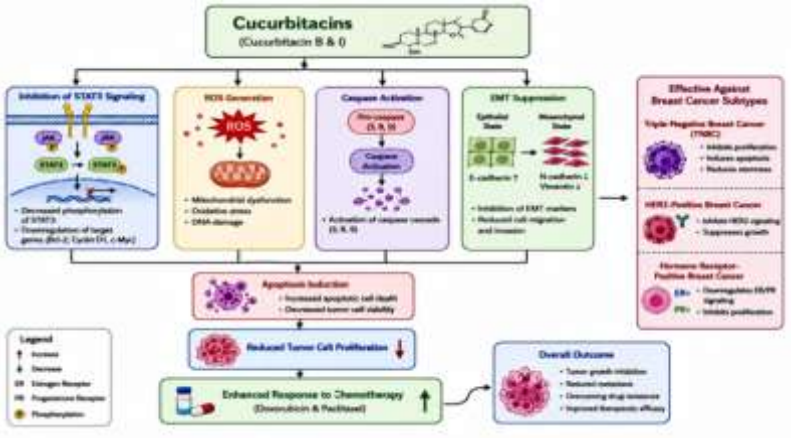


**Figure 14:** Molecular mechanisms underlying the anticancer effects of Cucurbitacins in breast cancer

### 7.2 Lung Cancer

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and remains one of the leading causes of cancer-related mortality worldwide despite remarkable advances in targeted therapy and immunotherapy (113,116). The development of therapeutic resistance, persistent activation of oncogenic signalling pathways, and metastatic progression continue to limit long-term clinical outcomes in patients with advanced NSCLC ((113,117). Among the various cucurbitacin analogues, Cucurbitacin B, Cucurbitacin E, and Cucurbitacin I have demonstrated potent antiproliferative activity against NSCLC through modulation of multiple signalling pathways involved in cell growth, apoptosis, and metastasis (7,117–119). Experimental studies have shown that Cucurbitacin E suppresses EGFR/MAPK signalling, inhibits cell-cycle progression, and activates caspase-dependent apoptosis in A549 lung cancer cells (118). Similarly, Cucurbitacin B inhibits STAT3 and PI3K/mTOR signalling while activating AMPK-dependent pathways, resulting in reduced proliferation and enhanced apoptotic cell death in both EGFR-wild-type and EGFR-mutant NSCLC cells (7,117). Furthermore, Cucurbitacin I effectively suppresses STAT3 activation in CD133-positive lung cancer stem cells, thereby reducing tumorigenicity, inhibiting self-renewal, and enhancing the sensitivity of NSCLC cells to chemotherapy and radiotherapy (119). Collectively, these findings indicate that cucurbitacins exert multifaceted anticancer effects against lung cancer by targeting EGFR, STAT3, PI3K/Akt/mTOR, and cancer stem cell-associated signalling pathways, highlighting their potential as promising adjunctive therapeutic agents for NSCLC (7,117–119).

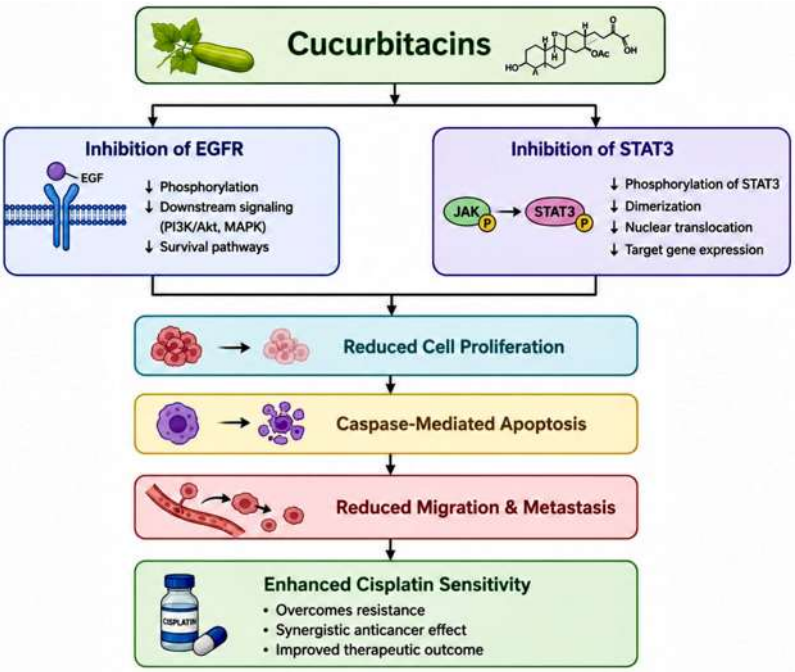

**Figure 15:** Molecular Mechanisms of Cucurbitacins in Lung Cancer (NSCLC)

### 7.3 Colorectal Cancer

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies and remains a leading cause of cancer-related mortality worldwide despite considerable advances in screening, surgical management, and systemic therapies (113,120). Aberrant activation of the Wnt/β-catenin, PI3K/Akt, and EGFR signalling pathways plays a pivotal role in colorectal tumour initiation, progression, and resistance to chemotherapy (120,121). Recent experimental studies have demonstrated that several cucurbitacin analogues, particularly Cucurbitacin D and Cucurbitacin E, exert potent antiproliferative activity against colorectal cancer cells by simultaneously targeting multiple oncogenic signalling pathways (121,122,128). Cucurbitacins suppress Wnt/β-catenin signalling, thereby reducing the nuclear accumulation of β-catenin and inhibiting the transcription of genes associated with cell proliferation, invasion, and tumour progression (121,122). In addition, these compounds induce cell-cycle arrest, activate mitochondrial-mediated apoptosis through regulation of Bax, Bcl-2, and caspase-3, and suppress the proliferative capacity of colorectal cancer cells (122,128). Furthermore, inhibition of PI3K/Akt signalling and modulation of oxidative stress contribute to the antitumor activity of cucurbitacins, ultimately reducing tumour growth and enhancing apoptotic cell death (128,129). Collectively, these findings suggest that cucurbitacins represent promising multitarget therapeutic agents for colorectal cancer owing to their ability to inhibit oncogenic signalling, induce apoptosis, and suppress tumour progression (121,122,128,129).

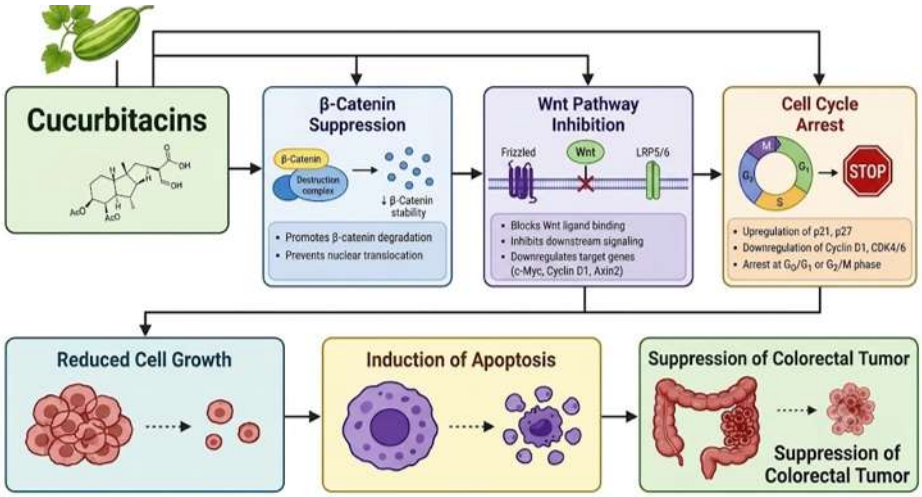


**Figure 16:** Molecular Mechanisms of Cucurbitacins in Colorectal Cancer

### 7.4 Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies, with a five-year survival rate of less than 10% owing to its late diagnosis, rapid metastatic progression, and poor response to conventional chemotherapy (123,130). Constitutive activation of oncogenic pathways, particularly KRAS, JAK/STAT3, PI3K/Akt, and NF-κB, plays a central role in pancreatic tumour initiation, progression, chemoresistance, and maintenance of cancer stem cell populations (130,131). Among the different cucurbitacin analogues, Cucurbitacin B has demonstrated significant antitumor activity against pancreatic cancer by suppressing multiple signalling pathways associated with tumour growth, invasion, and therapeutic resistance (131–134). Experimental studies have shown that Cucurbitacin B inhibits JAK/STAT3 signalling, resulting in reduced STAT3 phosphorylation, downregulation of anti-apoptotic proteins, suppression of tumour cell proliferation, and induction of caspase-dependent apoptosis (131,132). In addition, Cucurbitacin B interferes with KRAS-associated downstream signalling and inhibits PI3K/Akt activation, thereby reducing cell survival, impairing metastatic potential, and enhancing mitochondrial-mediated apoptotic cell death (132,133). Recent evidence further suggests that cucurbitacins suppress the expression of cancer stem cell-associated markers, including CD44, CD133, and ALDH1, thereby reducing self-renewal capacity and increasing the sensitivity of pancreatic cancer cells to conventional chemotherapeutic agents such as gemcitabine (133,134). Collectively, these findings indicate that cucurbitacins represent promising multitarget therapeutic

agents for pancreatic cancer by simultaneously inhibiting oncogenic signalling pathways, inducing apoptosis, suppressing cancer stem cell characteristics, and overcoming chemoresistance (131–134).

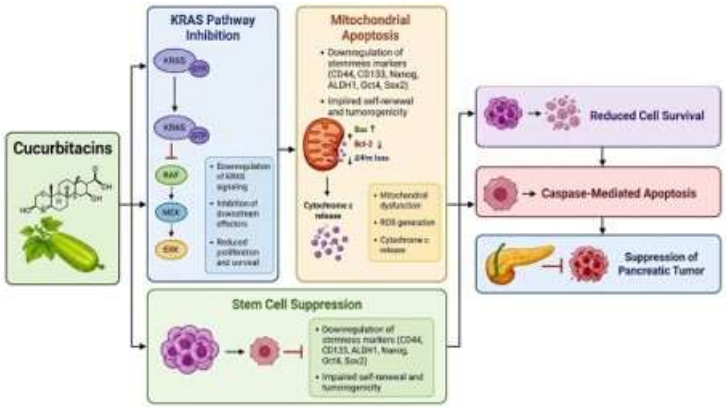


**Figure 17**: Molecular Mechanisms of Cucurbitacins in Pancreatic Cancer

### 7.5 Leukemia

Leukaemia comprises a heterogeneous group of haematological malignancies characterized by the uncontrolled proliferation and accumulation of abnormal hematopoietic cells in the bone marrow and peripheral blood. Despite substantial advances in chemotherapy, targeted therapy, and hematopoietic stem cell transplantation, treatment failure and disease relapse remain major clinical challenges, particularly in acute and drug-resistant Leukaemia (124,135). Persistent activation of oncogenic signalling pathways, especially the JAK/STAT3, PI3K/Akt, and NF-κB pathways, contributes to leukemic cell survival, uncontrolled proliferation, resistance to apoptosis, and therapeutic failure (10,124). Among the various cucurbitacin analogues, Cucurbitacin I has demonstrated remarkable antileukemic activity by targeting multiple signalling pathways involved in leukemic cell growth and survival (10,125–127). Experimental studies have shown that Cucurbitacin I potently inhibits STAT3 phosphorylation and its nuclear translocation, resulting in suppression of STAT3-dependent transcription, downregulation of anti-apoptotic proteins, and induction of caspase-mediated apoptosis in Leukaemia cells (10,125). Furthermore, Cucurbitacin I induces cell-cycle arrest, disrupts mitochondrial membrane potential, and activates intrinsic apoptotic pathways through modulation of Bax, Bcl-2, and caspase-3, thereby significantly reducing leukemic cell viability (125,126). Recent investigations also indicate that cucurbitacins may enhance the sensitivity of leukemia cells to conventional chemotherapeutic agents and represent promising candidates for combination therapy to overcome drug resistance (126,127). Collectively, these findings suggest that cucurbitacins, particularly Cucurbitacin I, possess considerable therapeutic potential for Leukaemia through simultaneous inhibition of oncogenic signalling pathways, induction of apoptosis, and suppression of leukemic cell proliferation (10,125–127)

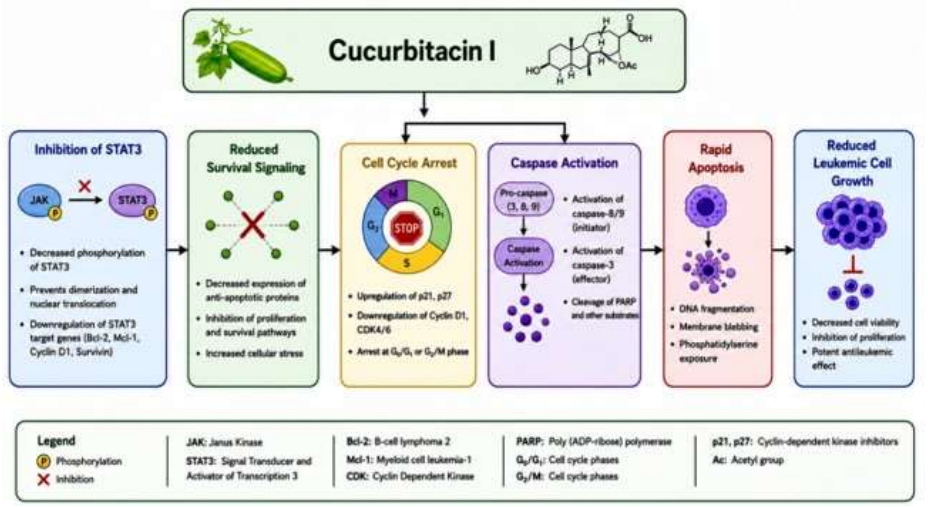


**Figure 18:** Molecular Mechanisms of Cucurbitacin I in Leukemia

**8. Synergistic Combination Therapy**

Combination therapy has emerged as an effective therapeutic strategy for cancer treatment by combining agents with complementary mechanisms of action to enhance antitumour efficacy, reduce systemic toxicity, and overcome drug resistance (136,137). Growing evidence indicates that cucurbitacins can sensitize cancer cells to conventional chemotherapeutic agents and targeted therapies through simultaneous modulation of multiple oncogenic signalling pathways involved in cell proliferation, apoptosis, metastasis, and therapeutic resistance (17,138). Experimental studies have demonstrated that cucurbitacins exhibit synergistic interactions with several anticancer drugs, including doxorubicin, cisplatin, paclitaxel, and gemcitabine, resulting in enhanced apoptosis, inhibition of survival signalling, increased oxidative stress, and improved therapeutic response in various malignancies (11,138,139). Furthermore, the ability of cucurbitacins to inhibit key signalling pathways such as JAK/STAT3, PI3K/Akt/mTOR, NF-κB, and EGFR highlights their potential as adjuvant agents capable of improving treatment efficacy and overcoming acquired drug resistance (17,138,139). Collectively, these findings suggest that combination therapy involving cucurbitacins represents a promising approach for improving clinical outcomes and may facilitate the development of more effective multimodal anticancer treatment strategies (11,17,136–139).

**8.1 Combination with Chemotherapy**

Combination chemotherapy remains a cornerstone of cancer treatment; however, the development of multidrug resistance, dose-limiting toxicity, and nonspecific systemic effects often compromise therapeutic efficacy (140,141). Consequently, considerable efforts have been directed toward identifying naturally occurring compounds that can enhance the activity of conventional chemotherapeutic agents while minimizing adverse effects (131,141). Accumulating preclinical evidence indicates that cucurbitacins exhibit significant synergistic interactions with several clinically used chemotherapeutic drugs, including doxorubicin, cisplatin, paclitaxel, and gemcitabine (24,141,142). These synergistic effects are primarily mediated through suppression of JAK/STAT3, PI3K/Akt, and NF-κB signalling pathways, increased intracellular reactive oxygen species (ROS) generation, activation of mitochondrial-dependent apoptosis, and reversal of drug resistance mechanisms (24,131,142,143). Among the various analogues, Cucurbitacin B has been reported to enhance the cytotoxic activity of doxorubicin and gemcitabine, whereas Cucurbitacin E and Cucurbitacin I have demonstrated synergistic effects with cisplatin and paclitaxel, respectively, resulting in greater inhibition of tumour cell proliferation and induction of apoptosis than either agent alone (24,142,143). Overall, these findings suggest that cucurbitacin-based combination therapy represents a promising strategy to improve chemotherapy responsiveness, reduce therapeutic resistance, and achieve enhanced anticancer efficacy while potentially lowering the required doses of conventional chemotherapeutic agents (24,131,142,143).

**Examples**

| Sr. No | Chemotherapeutic Agent | Combined Cucurbitacin | Therapeutic Outcome | References |
|---|---|---|---|---|
| 1. | Doxorubicin | Cucurbitacin B | Enhanced apoptosis | (24) |
| 2. | Cisplatin | Cucurbitacin E | Reduced resistance | (142) |
| 3. | Paclitaxel | Cucurbitacin I | Synergistic cytotoxicity | (143) |
| 4. | Gemcitabine | Cucurbitacin B | Improved pancreatic cancer response | (131) |

**Table 4:** Representative Combinations of Cucurbitacins with Conventional Chemotherapeutic Agents and Their Therapeutic Outcomes

**8.2 Combination with Targeted Therapy**

Targeted therapies have significantly improved cancer treatment by selectively inhibiting molecular pathways involved in tumour growth and progression. However, the emergence of acquired resistance and activation of compensatory signalling pathways frequently limit their long-term clinical efficacy (140,144). Recent preclinical studies suggest that cucurbitacins can enhance the therapeutic efficacy of targeted anticancer agents through simultaneous inhibition of multiple oncogenic signalling pathways, including JAK/STAT3, EGFR, PI3K/Akt/mTOR, and VEGF signalling (1,11,17). By targeting these

interconnected pathways, cucurbitacins suppress tumour cell proliferation, promote apoptosis, inhibit angiogenesis, and reduce metastatic potential, thereby improving the overall antitumour response (11,17). In addition, cucurbitacins have been reported to overcome resistance to targeted therapies by blocking compensatory survival pathways and downregulating the expression of proteins associated with drug resistance and tumour progression (1,11). Although most evidence has been obtained from in vitro and animal studies, these findings indicate that cucurbitacins may serve as promising adjuvant agents in combination with molecularly targeted therapies. Nevertheless, further preclinical investigations and well-designed clinical trials are required to validate their efficacy and safety before clinical application (1,145).

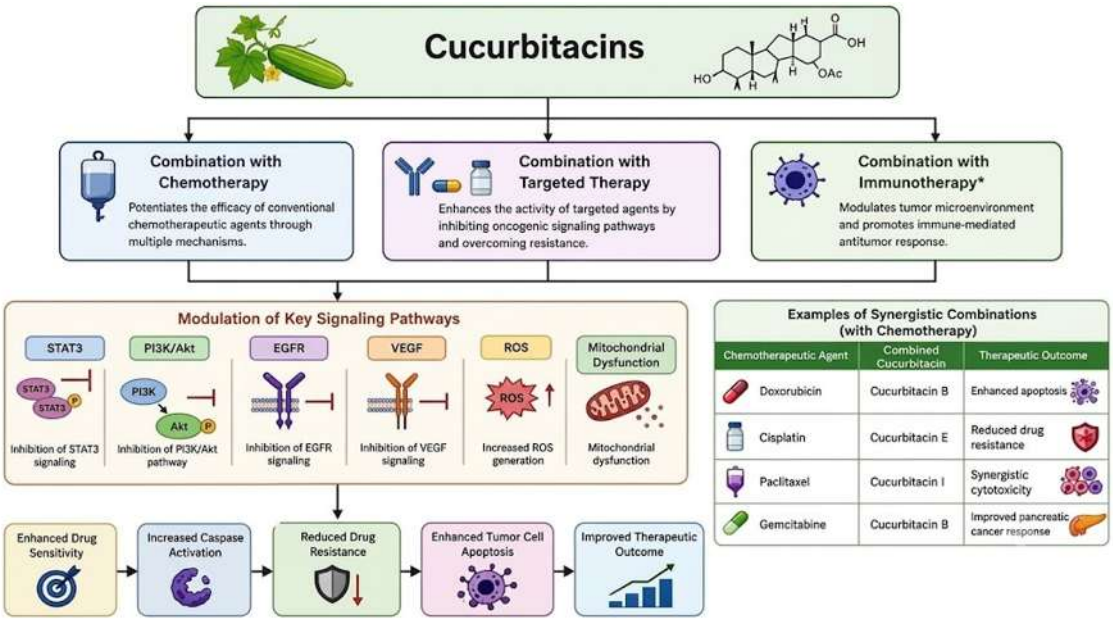


**Figure 19 :** Proposed mechanisms underlying the synergistic anticancer effects of cucurbitacins in combination with chemotherapy and targeted therapy

### 8.3 Combination with Immunotherapy

Cancer immunotherapy has revolutionized oncology by harnessing the host immune system to recognize and eliminate malignant cells. Immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have demonstrated remarkable clinical success in several malignancies. (146). However, only a subset of patients achieves durable responses because tumour-associated immunosuppression, immune evasion, and the immunosuppressive tumour microenvironment often limit therapeutic efficacy (146,147). Recent preclinical studies suggest that cucurbitacins possess immunomodulatory properties that may complement current immunotherapeutic strategies by regulating inflammatory signalling pathways and modifying the tumour immune microenvironment (26,148). Inhibition of JAK/STAT3 and NF-κB signalling by cucurbitacins reduces the production of immunosuppressive cytokines while promoting antitumour immune responses (26,47,148). Experimental evidence further indicates that cucurbitacins can enhance the activation and cytotoxic function of $CD8^+$ T lymphocytes, reduce the accumulation of immunosuppressive cells within the tumour microenvironment, and improve immune-mediated tumour cell killing (26,47). These immunomodulatory effects may increase the responsiveness of tumours to immune checkpoint blockade and other immunotherapeutic approaches. Although the available findings are encouraging, current evidence is derived predominantly from preclinical investigations, and direct clinical evidence remains limited. Therefore, further mechanistic studies and well-designed clinical trials are required to establish the safety and therapeutic efficacy of cucurbitacins in combination with cancer immunotherapy (47,149).

### 9. Translational Challenges and Emerging Therapeutic Strategies

Despite the remarkable anticancer potential demonstrated by cucurbitacins in numerous preclinical studies, their successful clinical translation remains limited because of several pharmacokinetic, pharmaceutical, and toxicological challenges (150,151). The clinical development of cucurbitacin-based therapeutics is hindered by poor aqueous solubility, low oral bioavailability,

rapid metabolic degradation, short systemic half-life, nonspecific tissue distribution, and dose-dependent toxicity, all of which reduce their therapeutic efficacy and limit clinical applicability (151–153). To overcome these limitations, considerable research efforts have focused on the development of advanced drug delivery systems, structural modification of cucurbitacin molecules, targeted delivery approaches, and rational combination therapies (152–154). Nanotechnology-based formulations, including liposomes, polymeric nanoparticles, micelles,

and solid lipid nanoparticles, have demonstrated the ability to improve drug solubility, prolong circulation time, enhance tumour-specific accumulation through the enhanced permeability and retention (EPR) effect, and reduce systemic toxicity (153–155). Furthermore, structural optimization of cucurbitacins and the synthesis of novel derivatives have been investigated to improve pharmacokinetic properties while preserving or enhancing their biological activity (154,156). Combination strategies involving conventional chemotherapeutic agents, molecularly targeted therapies, and immunotherapeutic approaches have also shown promising synergistic effects in preclinical studies by enhancing apoptosis, overcoming drug resistance, and suppressing multiple oncogenic signalling pathways simultaneously (155–157). Although these emerging therapeutic strategies have significantly improved the translational potential of cucurbitacins, most investigations remain at the in vitro or animal-study stage. Therefore, comprehensive pharmacokinetic evaluation, toxicity assessment, standardized formulation development, and well-designed clinical trials are essential to establish the safety and efficacy of cucurbitacin-based therapies for cancer treatment (156–158).

### 9.1 Translational Challenges

Despite the remarkable anticancer efficacy of cucurbitacins demonstrated in numerous in vitro and in vivo studies, their successful translation into clinical oncology remains limited owing to several pharmaceutical, pharmacokinetic, and toxicological challenges (17,139). One of the major limitations is their poor aqueous solubility, which restricts dissolution in biological fluids and significantly reduces oral absorption and systemic bioavailability (139,151). Furthermore, cucurbitacins undergo rapid metabolic degradation and extensive first-pass metabolism, resulting in a short plasma half-life and limited drug exposure at tumour sites (151,152). Another important challenge is the dose-dependent toxicity associated with cucurbitacins. Although these compounds exhibit selective cytotoxicity toward cancer cells at appropriate concentrations, higher doses have been associated with hepatotoxicity, gastrointestinal toxicity, nephrotoxicity, and other systemic adverse effects in experimental models (152,153). The narrow therapeutic window and limited safety data remain significant barriers to their clinical application. In addition, the absence of standardized pharmaceutical formulations, poor tumour-specific accumulation, and variability in pharmacokinetic behavior further hinder the clinical development of cucurbitacin-based therapeutics (153,155). These limitations highlight the need for innovative drug delivery strategies, structural optimization, and rational combination therapies to improve therapeutic efficacy while minimizing systemic toxicity (150,155). Overall, overcoming these translational barriers is essential for advancing cucurbitacins from promising preclinical anticancer compounds to clinically viable therapeutic agents (17,139,150–153,155).

### 9.2 Clinical Studies and Translational Potential

Despite extensive evidence demonstrating the anticancer activity of cucurbitacins in cellular and animal models, their clinical translation remains at an early stage (11,17). To date, most investigations have focused on elucidating the molecular mechanisms underlying their antitumour activity, including inhibition of JAK/STAT3, PI3K/Akt/mTOR, NF-κB, and Wnt/β-catenin signalling pathways, induction of apoptosis, suppression of angiogenesis, and inhibition of metastasis (2,11). However, these encouraging preclinical findings have not yet been translated into substantial clinical evidence. The limited clinical advancement of cucurbitacins is primarily attributed to their unfavorable pharmacokinetic properties, dose-dependent toxicity, poor aqueous solubility, 4ewaand the absence of standardized pharmaceutical formulations suitable for human administration (2,87,151). Furthermore, the lack of comprehensive pharmacokinetic studies, long-term safety evaluations, and well-designed randomized clinical trials has hindered regulatory approval and routine clinical application (87,151). Recent advances in formulation science, nanotechnology-based drug delivery systems, and rational combination therapies have substantially improved the translational potential of cucurbitacins by enhancing bioavailability, reducing systemic toxicity, and increasing tumour-selective drug accumulation (151,152). These developments provide a promising foundation for future clinical investigations and support the continued evaluation of cucurbitacins as potential adjuvant or targeted anticancer agents (152). Future clinical studies should focus on establishing optimal dosage regimens, evaluating long-term safety, identifying predictive biomarkers of therapeutic response, and assessing the efficacy of cucurbitacin-based formulations in

combination with existing chemotherapeutic, targeted, and immunotherapeutic agents (150,152). Such investigations will be essential for bridging the gap between preclinical discoveries and clinical implementation (153).

### 9.3 Emerging Therapeutic Strategies

Emerging therapeutic strategies are being actively investigated to enhance the clinical applicability of cucurbitacins and overcome the pharmacokinetic and toxicological limitations associated with these natural compounds (150,151). Recent advances have focused on improving drug delivery, increasing tumour specificity, enhancing bioavailability, and minimizing systemic toxicity through innovative pharmaceutical and molecular approaches (151,155). Nanotechnology-based drug delivery systems, including liposomes, polymeric nanoparticles, micelles, and solid lipid nanoparticles, have shown considerable promise in improving the physicochemical properties of cucurbitacins. These delivery platforms enhance aqueous solubility, prolong systemic circulation, facilitate controlled drug release, and promote preferential accumulation within tumour tissues via the enhanced permeability and retention (EPR) effect. Consequently, nanocarrier-based formulations have demonstrated improved therapeutic efficacy and reduced off-target toxicity in preclinical studies (151,154,155). Another promising strategy involves the structural modification of cucurbitacin molecules to generate semisynthetic derivatives with improved pharmacokinetic properties and enhanced anticancer activity (2,154). Rational chemical modifications may improve metabolic stability, reduce toxicity, and optimize interactions with molecular targets while preserving the characteristic biological activity of the parent compounds (154). In addition, advances in targeted drug delivery have enabled the development of ligand-conjugated nanoparticles capable of selectively delivering cucurbitacins to tumour tissues by recognizing cancer-specific receptors, thereby improving therapeutic selectivity and minimizing damage to normal tissues (156,157). Combination with conventional chemotherapy, molecularly targeted agents, and immunotherapeutic approaches also represents a promising strategy for enhancing antitumour efficacy while overcoming therapeutic resistance (152,157). Collectively, these emerging therapeutic strategies have substantially improved the translational potential of cucurbitacins and provide a strong foundation for future clinical development. Nevertheless, additional pharmacokinetic investigations, toxicity studies, and randomized clinical trials are required before these approaches can be successfully translated into routine oncology practice (152,158).

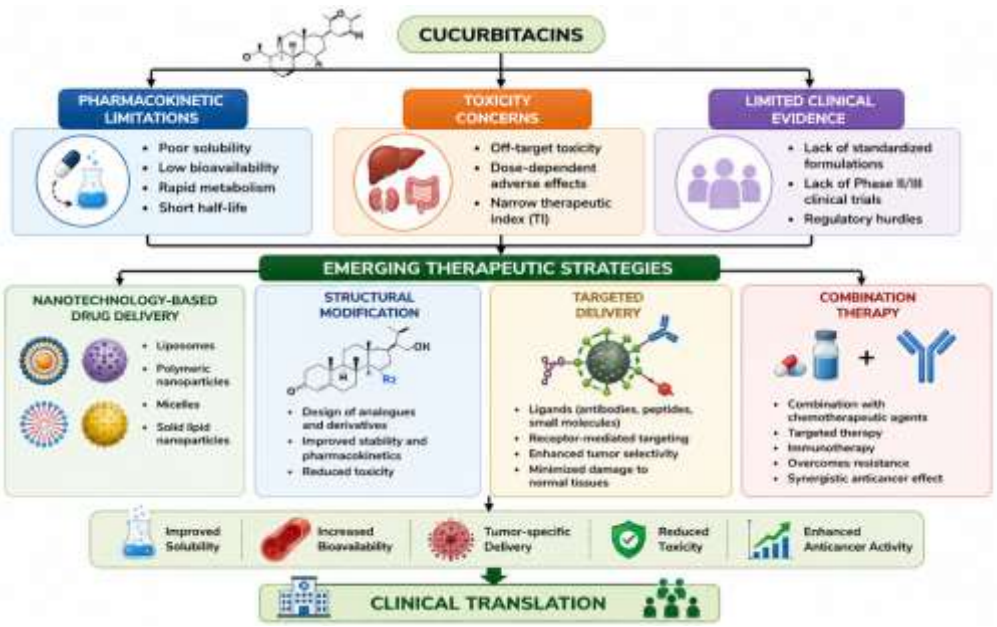


**Figure 20 :** Translational Challenges and Emerging Therapeutic Strategies for Clinical Development of Cucurbitacins

Summary of the molecular mechanisms, translational challenges, and emerging therapeutic strategies of cucurbitacins in cancer therapy. The figure illustrates the principal anticancer mechanisms of cucurbitacins, major barriers limiting clinical translation, and current strategies aimed at improving their therapeutic efficacy and clinical applicability (159,160).

### 10. Future Perspectives

The future of cucurbitacin research is highly promising because of the growing understanding of its molecular mechanisms and broad-spectrum anticancer activity. Numerous preclinical studies have demonstrated that cucurbitacins effectively inhibit tumour cell proliferation, induce apoptosis, suppress angiogenesis, and interfere with multiple oncogenic signalling pathways, including JAK/STAT3, PI3K/Akt/mTOR, NF-ϰB, Wnt/β-catenin, and MAPK. However, despite these encouraging findings, several challenges such as poor aqueous solubility, limited oral bioavailability, rapid metabolism, and systemic toxicity continue to hinder their successful clinical application. Future investigations should therefore focus on improving the pharmacokinetic profile, therapeutic selectivity, and safety of cucurbitacin-based therapies to facilitate their transition from laboratory research to clinical oncology.

One of the most important future directions is the development of advanced nanotechnology-based drug delivery systems. Nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and micelles, have demonstrated considerable potential to enhance drug solubility, prolong systemic circulation, improve tumour accumulation through the enhanced permeability and retention (EPR) effect, and minimize off-target toxicity. Surface modification with tumour-specific ligands such as antibodies, peptides, folic acid, and aptamers may further improve active targeting and increase therapeutic efficacy while reducing adverse effects.

Structural modification of naturally occurring cucurbitacins also represents an important strategy for future drug development. Medicinal chemistry approaches can generate semisynthetic derivatives with improved physicochemical properties, enhanced pharmacological potency, reduced toxicity, and greater selectivity toward malignant cells. The development of prodrug formulations and chemically modified analogs may further overcome limitations associated with poor stability and extensive first-pass metabolism, thereby improving bioavailability and therapeutic performance.

Future clinical research is expected to emphasize combination therapy, where cucurbitacins are administered alongside conventional chemotherapeutic agents, molecularly targeted drugs, immunotherapeutic agents, or radiotherapy. Such combination strategies may produce synergistic anticancer effects, overcome multidrug resistance, reduce the required therapeutic dose of individual agents, and decrease treatment-related toxicity. Additionally, the immunomodulatory properties of cucurbitacins may enhance antitumour immune responses and improve the effectiveness of immune checkpoint inhibitors.

The integration of biomarker-guided precision medicine is another promising direction. Identification of predictive biomarkers, including STAT3 activation status, PI3K/Akt pathway alterations, epithelial-to-mesenchymal transition (EMT) markers, inflammatory mediators, and reactive oxygen species (ROS)-associated signatures, may facilitate personalized patient selection and optimize therapeutic outcomes. Such biomarker-based approaches could enable clinicians to identify patients who are most likely to benefit from cucurbitacin-based treatment while minimizing unnecessary toxicity.

Artificial intelligence (AI), machine learning, and computational drug discovery are expected to play an increasingly significant role in accelerating cucurbitacin research. AI-assisted molecular docking, virtual screening, quantitative structure–activity relationship (QSAR) analysis, pharmacokinetic prediction, toxicity modeling, and de novo drug design can substantially reduce drug development time and

improve candidate selection. These computational approaches may facilitate the identification of novel cucurbitacin derivatives with enhanced efficacy and improved safety profiles. Future translational research should also focus on conducting large-scale, randomized, multicenter clinical trials to establish the long-term safety, pharmacokinetics, optimal dosing regimens, and clinical efficacy of cucurbitacin formulations across different cancer types. Standardization of extraction procedures, purification methods, formulation techniques, and quality-control protocols will be essential to ensure reproducibility and regulatory acceptance for clinical use.

Finally, successful clinical translation of cucurbitacins will require close collaboration among medicinal chemists, pharmacologists, oncologists, nanotechnology researchers, molecular biologists, bioinformaticians, and regulatory scientists. Such multidisciplinary efforts will accelerate the development of safe, targeted, and personalized cucurbitacin-based therapeutics. With continued advances in nanomedicine, biomarker-guided therapy, artificial intelligence, and precision oncology, cucurbitacins have significant potential to emerge as an important class of next-generation anticancer agents for improving patient outcomes.

**11. Research Gaps**

Although substantial progress has been made in elucidating the anticancer mechanisms of cucurbitacins, several critical research gaps continue to impede their successful clinical translation. Most available evidence is derived from in vitro experiments and animal models, whereas robust clinical investigations evaluating the safety, pharmacokinetics, and therapeutic efficacy of cucurbitacins in human patients remain extremely limited. Consequently, the clinical relevance of many promising preclinical findings has yet to be established.

Another major limitation is the lack of comprehensive pharmacokinetic and toxicological studies. Poor aqueous solubility, low oral bioavailability, rapid metabolism, and dose-dependent toxicity remain significant barriers to clinical application. Furthermore, standardized pharmaceutical formulations, optimized dosing regimens, and long-term safety evaluations have not been sufficiently investigated, limiting reproducibility and regulatory advancement.

The molecular mechanisms underlying cucurbitacin activity also require further investigation. Although multiple signalling pathways, including JAK/STAT3, PI3K/Akt/mTOR, NF-κB, Wnt/β-catenin, and MAPK, have been identified as therapeutic targets, the precise interactions between these pathways, tumour heterogeneity, and resistance mechanisms remain incompletely understood. In addition, limited information is available regarding predictive biomarkers that could identify patients most likely to benefit from cucurbitacin-based therapies.

Another important research gap is the limited exploration of structure–activity relationships (SAR) and rational structural modification of cucurbitacins. A better understanding of how specific structural features influence biological activity, selectivity, and toxicity would facilitate the development of safer and more effective derivatives with improved pharmacological properties.

Finally, although nanotechnology-based delivery systems and combination therapies have demonstrated encouraging preclinical outcomes, their scalability, manufacturing reproducibility, regulatory feasibility, and clinical applicability require further systematic evaluation. Addressing these research gaps through multidisciplinary collaboration will be essential for advancing cucurbitacins from promising experimental compounds to clinically effective anticancer therapeutics.

## 12. Conclusion

Cucurbitacins represent a unique class of naturally occurring tetracyclic triterpenoids that have attracted considerable attention because of their broad-spectrum anticancer activities and ability to modulate multiple oncogenic signalling pathways simultaneously. Extensive preclinical investigations have demonstrated that cucurbitacins inhibit tumour growth through diverse molecular mechanisms, including induction of apoptosis, cell cycle arrest, suppression of JAK/STAT3, PI3K/Akt/mTOR, and NF-κB signalling, inhibition of angiogenesis and metastasis, modulation of autophagy, generation of reactive oxygen species, and disruption of cytoskeletal organization. These multifaceted biological activities highlight the potential of cucurbitacins as promising candidates for the treatment of a wide range of human malignancies.

In addition to their direct anticancer effects, cucurbitacins have demonstrated encouraging therapeutic potential when combined with conventional chemotherapy, molecularly targeted agents, and emerging immunotherapeutic strategies. Such combination approaches may enhance therapeutic efficacy, overcome drug resistance, and reduce the doses of standard anticancer drugs, thereby minimizing treatment-associated toxicity. Furthermore, advances in nanotechnology-based drug delivery systems and structural optimization have provided effective strategies for improving the pharmacokinetic properties, bioavailability, and tumour selectivity of cucurbitacins, thereby addressing several limitations that have hindered their clinical development.

Despite these promising findings, the translation of cucurbitacins from experimental models to routine clinical oncology remains challenging because of poor aqueous solubility, limited oral bioavailability, rapid metabolism, dose-dependent toxicity, and the scarcity of well-designed clinical studies. Addressing these limitations through optimized formulations, targeted delivery systems, comprehensive pharmacokinetic evaluation, and rigorous safety assessment will be essential for successful clinical translation.

Future research should focus on the development of standardized pharmaceutical formulations, identification of predictive biomarkers, elucidation of molecular targets using advanced omics technologies, and validation of therapeutic efficacy through large-scale clinical trials. The integration of artificial intelligence-assisted drug discovery, precision oncology, and multifunctional nanocarriers may further accelerate the development of cucurbitacin-based therapeutics and facilitate personalized cancer treatment strategies.

Overall, the available evidence indicates that cucurbitacins possess significant potential as multifunctional anticancer agents capable of targeting numerous hallmarks of cancer through diverse molecular mechanisms. Continued multidisciplinary research integrating medicinal chemistry, pharmaceutical sciences, molecular oncology, and clinical medicine will be crucial for translating these promising natural compounds into safe, effective, and clinically applicable anticancer therapy.

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- **Dr. Rao V. Javvaji :** Conceptualization, Investigation and review
- **Yash N. Nandan :** Review of Literature and Preparation of skeleton.
- **Suraj S. Ingale :** Data Curation and Preparation of Diagrams
- **Pratik K. Patil :** Study of Literature and Supervision
- **Pratiksha V. Sangale :** Writing and Review.
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**References**

[1] Delgado-Tiburcio EE, Cadena-Iñiguez J, Santiago-Osorio E, Ruiz-Posadas L del M, Castillo-Juárez I, Aguiñiga-Sánchez I, et al. Pharmacokinetics and Biological Activity of Cucurbitacins. Pharmaceuticals. 2022 Nov;15(11):1325. doi:10.3390/ph15111325

[2] Chen JC, Chiu MH, Nie RL, Cordell GA, Qiu SX. Cucurbitacins and cucurbitane glycosides: structures and biological activities. Nat Prod Rep. 2005 Jun;22(3):386–99. doi:10.1039/b418841c PubMed PMID: 16010347.

[3] Jayaprakasam B, Seeram NP, Nair MG. Anticancer and antiinflammatory activities of cucurbitacins from *Cucurbita andreana*. Cancer Lett. 2003 Jan 10;189(1):11–6. doi:10.1016/S0304-3835(02)00497-4

[4] Liu M, Chen X, Chen H, Wu X, Fan W, Chen J. Nanotechnology-Based Drug Delivery System for Anticancer Active Ingredients from Traditional Chinese Medicines: A Review. Am J Chin Med. 2022 Jan;50(08):2011–32. doi:10.1142/S0192415X22500860

[5] Fulda S, Debatin KM. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. Oncogene. 2006 Aug 7;25(34):4798–811. doi:10.1038/sj.onc.1209608 PubMed PMID: 16892092.

[6] Sun J, Blaskovich MA, Jove R, Livingston SK, Coppola D, Sebti SM. Erratum: Cucurbitacin Q: a selective STAT3 activation inhibitor with potent antitumour activity. Oncogene. 2008 Feb;27(9):1344–1344. doi:10.1038/sj.onc.1211028

[7] Hsu HL, Lin BJ, Lin YC, Tu CC, Nguyen NL, Wang CC, et al. Cucurbitacin E Exerts Anti-Proliferative Activity via Promoting p62-Dependent Apoptosis in Human Non-Small-Cell Lung Cancer A549 Cells. Curr Issues Mol Biol. 2023 Oct;45(10):8138–51. doi:10.3390/cimb45100514

[8] Duncan KLK, Duncan MD, Alley MC, Sausville EA. Cucurbitacin E-induced disruption of the actin and vimentin cytoskeleton in prostate carcinoma cells. Biochem Pharmacol. 1996 Nov 22;52(10):1553–60. doi:10.1016/S0006-2952(96)00557-6

[9] Rios JL, Andujar I, Escandell JM, Giner RM, Recio MC. Cucurbitacins as Inducers of Cell Death and a Rich Source of Potential Anticancer Compounds. Curr Pharm Des. 18(12):1663–76. doi:10.2174/138161212799958549

[10] Blaskovich MA, Sun J, Cantor A, Turkson J, Jove R, Sebti SM. Discovery of JSI-124 (cucurbitacin I), a selective Janus kinase/signal transducer and activator of transcription 3 signalling pathway inhibitor with potent antitumour activity against human and murine cancer cells in mice. Cancer Res. 2003 Mar 15;63(6):1270–9. PubMed PMID: 12649187.

[11] Li Y, Li Y, Yao Y, Li H, Gao C, Sun C, et al. Potential of cucurbitacin as an anticancer drug. Biomed Pharmacother. 2023 Dec 1;168:115707. doi:10.1016/j.biopha.2023.115707

[12] Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell. 2011 Mar 4;144(5):646–74. doi:10.1016/j.cell.2011.02.013 PubMed PMID: 21376230.

[13] Tarrado-Castellarnau M, Cortés R, Zanuy M, Tarragó-Celada J, Polat IH, Hill R, et al. Methylseleninic acid promotes antitumour effects via nuclear FOXO3a translocation through Akt inhibition. Pharmacol Res. 2015 Dec 1;102:218–34. doi:10.1016/j.phrs.2015.09.009

[14] Shang Y, Ma Y, Yuan Z, Zhang H, Lixin D, Chen H, et al. Biosynthesis, regulation, and domestication of bitterness in cucumber. Science. 2014 Nov 28;346:1084–8. doi:10.1126/science.1259215

[15] Zhou Y, Ma Y, Zeng J, Duan L, Xue X, Wang H, et al. Convergence and divergence of cucurbitacin biosynthesis and regulation in Cucurbitaceae. Nat Plants. 2016 Nov 28;2:16183. doi:10.1038/nplants.2016.183 PubMed PMID: 27892922; PubMed Central PMCID: PMC5449191.

[16] Nie W, Wang Y, Tian X, Liu J, Jin Z, Xu J, et al. Cucurbitacin B and Its Derivatives: A Review of Progress in Biological Activities. Molecules. 2024 Sep 4;29:4193. doi:10.3390/molecules29174193

[17] Zieniuk B, Pawelkowicz M. Recent Advances in the Application of Cucurbitacins as Anticancer Agents. Metabolites. 2023 Oct 14;13(10):1081. doi:10.3390/metabo13101081 PubMed PMID: 37887406; PubMed Central PMCID: PMC10608718.

[18] Thimmappa R, Geisler K, Louveau T, O'Maille P, Osbourn A. Triterpene Biosynthesis in Plants. Annu Rev Plant Biol. 2014 Apr 29;65(Volume 65, 2014):225–57. doi:10.1146/annurev-arplant-050312-120229

[19] Osbourn A. Secondary metabolic gene clusters: evolutionary toolkits for chemical innovation. Trends Genet. 2010 Oct 1;26(10):449–57. doi:10.1016/j.tig.2010.07.001

[20] Chen G, Guo Z, Shu Y, Zhao Y, Qiu L, Duan S, et al. Biosynthetic pathway of prescription cucurbitacin IIa and high-level production of key triterpenoid intermediates in engineered yeast and tobacco. Plant Commun. 2024 Jun 10;5(6). doi:10.1016/j.xplc.2024.100835 PubMed PMID: 38425040.

[21] Aggarwal BB, Sung B. NF-κB in cancer: A Matter of Life and Death. Cancer Discov. 2011 Nov;1(6):469–71. doi:10.1158/2159-8290.CD-11-0260 PubMed PMID: 22586649; PubMed Central PMCID: PMC3392037.

[22] Escandell JM, Recio MC, Máñez S, Giner RM, Cerdá-Nicolás M, Gil-Benso R, et al. Dihydrocucurbitacin B Inhibits Delayed Type Hypersensitivity Reactions by Suppressing Lymphocyte Proliferation. J Pharmacol Exp Ther. 2007 Sep 1;322(3):1261–8. doi:10.1124/jpet.107.122671 PubMed PMID: 17562851.

[23] Ruan Z, Yang X, Cheng W. OCT4 Accelerates Tumourigenesis Through Activating JAK/STAT Signalling in Ovarian Cancer Side Population Cells [Retraction]. Cancer Manag Res. 2024 Apr 1;Volume 16:281–2. doi:10.2147/CMAR.S472069

[24] Ku JM, Hong S, Kim H, Lim Y, Lee S, Kim M, et al. Cucurbitacin D exhibits its anti-cancer effect in human breast cancer cells by inhibiting Stat3 and Akt signalling. Eur J Inflamm. 2018 Jan 30;16:1721727X1775180. doi:10.1177/1721727X17751809

[25] Sies H. Oxidative stress: A concept in redox biology and medicine. Redox Biol. 2015 Jan 2;25. doi:10.1016/j.redox.2015.01.002

[26] Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009 Nov;9(11):798–809. doi:10.1038/nrc2734 PubMed PMID: 19851315; PubMed Central PMCID: PMC4856025.

[27] Elmore S. Apoptosis: A Review of Programmed Cell Death. Toxicol Pathol. 2007;35(4):495–516. doi:10.1080/01926230701320337 PubMed PMID: 17562483; PubMed Central PMCID: PMC2117903.

[28] Kerr JFR, Wyllie AH, Currie AR. Apoptosis: A Basic Biological Phenomenon with Wide-ranging Implications in Tissue Kinetics. Br J Cancer. 1972 Aug;26(4):239–57. doi:10.1038/bjc.1972.33 PubMed PMID: 4561027; PubMed Central PMCID: PMC2008650.

[29] Chan KT, Meng FY, Li Q, Ho CY, Lam TS, To Y, et al. Cucurbitacin B induces apoptosis and S phase cell cycle arrest in BEL-7402 human hepatocellular carcinoma cells and is effective via oral administration. Cancer Lett. 2010 Aug 1;294(1):118–24. doi:10.1016/j.canlet.2010.01.029

[30] Duangmano S, Dakeng S, Jiratchariyakul W, Suksamrarn A, Smith DR, Patmasiriwat P. Antiproliferative Effects of Cucurbitacin B in Breast Cancer Cells: Down-Regulation of the c-Myc/hTERT/Telomerase Pathway and Obstruction of the Cell Cycle. Int J Mol Sci. 2010 Dec 22;11(12):5323–38. doi:10.3390/ijms11125323 PubMed PMID: 21614210; PubMed Central PMCID: PMC3100835.

[31] ZHANG M, BIAN ZG, ZHANG Y, WANG JH, KAN L, WANG X, et al. Cucurbitacin B inhibits proliferation and induces apoptosis via STAT3 pathway inhibition in A549 lung cancer cells. Mol Med Rep. 2014 Dec;10(6):2905–11. doi:10.3892/mmr.2014.2581 PubMed PMID: 25242136; PubMed Central PMCID: PMC4227420.

[32] Wakimoto N, Yin D, O'Kelly J, Haritunians T, Karlan B, Said J, et al. Cucurbitacin B has a potent antiproliferative effect on breast cancer cells in vitro and in vivo. Cancer Sci. 2008 Sep;99(9):1793–7. doi:10.1111/j.1349-7006.2008.00899.x PubMed PMID: 18627377; PubMed Central PMCID: PMC11159161.

[33] Kong Y, Chen J, Zhou Z, Xia H, Qiu MH, Chen C. Cucurbitacin E Induces Cell Cycle G2/M Phase Arrest and Apoptosis in Triple Negative Breast Cancer. PLoS ONE. 2014 Jul 29;9(7):e103760. doi:10.1371/journal.pone.0103760 PubMed PMID: 25072848; PubMed Central PMCID: PMC4114842.

[34] Tuli HS, Rath P, Chauhan A, Ranjan A, Ramniwas S, Sak K, et al. Cucurbitacins as Potent Chemo-Preventive Agents: Mechanistic Insight and Recent Trends. Biomolecules. 2023 Jan;13(1):57. doi:10.3390/biom13010057

[35] Tannin-Spitz T, Grossman S, Dovrat S, Gottlieb HE, Bergman M. Growth inhibitory activity of cucurbitacin glucosides isolated from *Citrullus colocynthis* on human breast cancer cells. Biochem Pharmacol. 2007 Jan 1;73(1):56–67. doi:10.1016/j.bcp.2006.09.012

[36] Jing S, Zou H, Wu Z, Ren L, Zhang T, Zhang J, et al. Cucurbitacins: Bioactivities and synergistic effect with small-molecule drugs. J Funct Foods. 2020 Sep 1;72:104042. doi:10.1016/j.jff.2020.104042

[37] Lahouar L, El-Bok S, Achour L. Therapeutic Potential of Young Green Barley Leaves in Prevention and Treatment of Chronic Diseases: An Overview. Am J Chin Med. 2015 Jan;43(07):1311–29. doi:10.1142/S0192415X15500743

[38] Ishii T, Kira N, Yoshida T, Narahara H. Cucurbitacin D induces growth inhibition, cell cycle arrest, and apoptosis in human endometrial and ovarian cancer cells. Tumour Biol. 2013 Feb 1;34(1):285–91. doi:10.1007/s13277-012-0549-2

[39] Lee DH, Iwanski GB, Thoennissen NH. Cucurbitacin: ancient compound shedding new light on cancer treatment. ScientificWorldJournal. 2010 Mar 5;10:413–8. doi:10.1100/tsw.2010.44 PubMed PMID: 20209387; PubMed Central PMCID: PMC5763727.

[40] Turkson J, Jove R. STAT proteins: novel molecular targets for cancer drug discovery. Oncogene. 2000 Dec;19(56):6613–26. doi:10.1038/sj.onc.1204086

[41] Bromberg J. Stat proteins and oncogenesis. J Clin Invest. 2002 May 1;109(9):1139–42. doi:10.1172/JCI15617 PubMed PMID: 11994401; PubMed Central PMCID: PMC150969.

[42] Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol. 2007 Jan;7(1):41–51. doi:10.1038/nri1995 PubMed PMID: 17186030.

[43] Aggarwal BB, Kunnumakkara AB, Harikumar KB, Gupta SR, Tharakan ST, Koca C, et al. Signal transducer and activator of transcription-3, inflammation, and cancer: how intimate is the relationship? Ann N Y Acad Sci. 2009 Aug;1171:59–76. doi:10.1111/j.1749-6632.2009.04911.x PubMed PMID: 19723038; PubMed Central PMCID: PMC3141289.

[44] Yue P, Turkson J. Targeting STAT3 in cancer: how successful are we? Expert Opin Investig Drugs. 2009 Jan;18(1):45–56. doi:10.1517/13543780802565791 PubMed PMID: 19053881; PubMed Central PMCID: PMC2610472.

[45] Arpin CC, Mac S, Jiang Y, Cheng H, Grimard M, Page BDG, et al. Applying Small Molecule Signal Transducer and Activator of Transcription-3 (STAT3) Protein Inhibitors as Pancreatic Cancer Therapeutics. Mol Cancer Ther. 2016 May 5;15(5):794–805. doi:10.1158/1535-7163.MCT-15-0003

[46] Sen M, Joyce S, Panahandeh M, Li C, Thomas SM, Maxwell J, et al. TARGETING STAT3 ABROGATES EGFR INHIBITOR RESISTANCE IN CANCER. Clin Cancer Res Off J Am Assoc Cancer Res. 2012 Sep 15;18(18):4986–96. doi:10.1158/1078-0432.CCR-12-0792 PubMed PMID: 22825581; PubMed Central PMCID: PMC3445706.

[47] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol. 2018 Apr;15(4):234–48. doi:10.1038/nrclinonc.2018.8 PubMed PMID: 29405201; PubMed Central PMCID: PMC5858971.

[48] Manning BD, Cantley LC. AKT/PKB Signalling: Navigating Downstream. Cell. 2007 Jun 29;129(7):1261–74. doi:10.1016/j.cell.2007.06.009 PubMed PMID: 17604717; PubMed Central PMCID: PMC2756685.

[49] Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009 Aug;9(8):550–62. doi:10.1038/nrc2664 PubMed PMID: 19629070.

[50] Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signalling in Cancer. Front Oncol. 2014 Apr 14;4:64. doi:10.3389/fonc.2014.00064 PubMed PMID: 24782981; PubMed Central PMCID: PMC3995050.

[51] Fresno Vara JÁF, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev. 2004 Apr 1;30(2):193–204. doi:10.1016/j.ctrv.2003.07.007

[52] Courtney KD, Corcoran RB, Engelman JA. The PI3K Pathway As Drug Target in Human Cancer. J Clin Oncol. 2010 Feb 20;28(6):1075–83. doi:10.1200/JCO.2009.25.3641 PubMed PMID: 20085938; PubMed Central PMCID: PMC2834432.

[53] Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov. 2005 Dec;4(12):988–1004. doi:10.1038/nrd1902 PubMed PMID: 16341064.

[54] LoRusso PM. Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumours. J Clin Oncol. 2016 Nov 1;34(31):3803–15. doi:10.1200/JCO.2014.59.0018 PubMed PMID: 27621407; PubMed Central PMCID: PMC6366304.

[55] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. Cell. 2017 Aug 10;170(4):605–35. doi:10.1016/j.cell.2017.07.029 PubMed PMID: 28802037; PubMed Central PMCID: PMC5726441.

[56] Karin Michael. NF-κB as a Critical Link Between Inflammation and Cancer. Cold Spring Harb Perspect Biol. 2009 Nov;1(5):a000141. doi:10.1101/cshperspect.a000141 PubMed PMID: 20066113.

[57] Perkins ND. The diverse and complex roles of NF-κB subunits in cancer. Nat Rev Cancer. 2012 Jan 19;12(2):121–32. doi:10.1038/nrc3204 PubMed PMID: 22257950.

[58] DiDonato JA, Mercurio F, Karin M. NF-κB and the link between inflammation and cancer. Immunol Rev. 2012;246(1):379–400. doi:10.1111/j.1600-065X.2012.01099.x

[59] Hayden MS, Ghosh S. Shared Principles in NF-κB Signalling: Cell [Internet]. [cited 2026 Jul 20]. Available from: https://www.cell.com/cell/fulltext/S0092-8674(08)00120-

7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867408001207%3Fshowall%3Dtrue

[60] Xia Y, Shen S, Verma IM. NF-κB, an active player in human cancers. Cancer Immunol Res. 2014 Sep;2(9):823–30. doi:10.1158/2326-6066.CIR-14-0112 PubMed PMID: 25187272; PubMed Central PMCID: PMC4155602.

[61] Jin HR, Song MG. Cucurbitacin B Promotes Tumour Necrosis Factor Receptor 1 Ectodomain Shedding by Selectively Activating the Extracellular Signal-Regulated Kinase Signalling Pathway [Internet]. [cited 2026 Jul 20]. Available from: https://www.mdpi.com/1422-0067/27/11/5011

[62] Zhang ZR, Gao MX, Yang K. Cucurbitacin B inhibits cell proliferation and induces apoptosis in human osteosarcoma cells via modulation of the JAK2/STAT3 and MAPK pathways. Exp Ther Med. 2017 Jun 6;14(1):805. doi:10.3892/etm.2017.4547 PubMed PMID: 28673003.

[63] Si W, Lyu J, Liu Z, Wang C, Huang J, Jiang L, et al. Cucurbitacin E inhibits cellular proliferation and enhances the chemo-response in gastric cancer by suppressing AKt activation. J Cancer. 2019 Oct 6;10(23):5843–51. doi:10.7150/jca.31303 PubMed PMID: 31737120; PubMed Central PMCID: PMC6843881.

[64] Schieber M, Chandel NS. ROS Function in Redox Signalling and Oxidative Stress. Curr Biol CB. 2014 May 19;24(10):R453–62. doi:10.1016/j.cub.2014.03.034 PubMed PMID: 24845678; PubMed Central PMCID: PMC4055301.

[65] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 May;44(5):10.3109/10715761003667554. doi:10.3109/10715761003667554 PubMed PMID: 20370557; PubMed Central PMCID: PMC3880197.

[66] Reczek CR, Chandel NS. The Two Faces of Reactive Oxygen Species in Cancer. Annu Rev Cancer Biol. 2017 Mar;1:79–98. doi:10.1146/annurev-cancerbio-041916-065808 PubMed PMID: 40034143; PubMed Central PMCID: PMC11875389.

[67] Klungsaeng S, Kukongviriyapan V, Prawan A, Kongpetch S, Senggunprai L. Cucurbitacin B induces mitochondrial-mediated apoptosis pathway in cholangiocarcinoma cells via suppressing focal adhesion kinase signalling. Naunyn Schmiedebergs Arch Pharmacol. 2019 Mar;392(3):271–8. doi:10.1007/s00210-018-1584-3 PubMed PMID: 30470919.

[68] Ren G, Sha T, Guo J, Li W, Lu J, Chen X. Cucurbitacin B induces DNA damage and autophagy mediated by reactive oxygen species (ROS) in MCF-7 breast cancer cells. J Nat Med. 2015 Oct;69(4):522–30. doi:10.1007/s11418-015-0918-4 PubMed PMID: 26018422.

[69] Abdelwahab SI, Hassan LEA, Abdul Majid AMS, Yagi SMA, Mohan S, Elhassan Taha MM, et al. Cucurbitacin L 2-O-β-Glucoside Demonstrates Apoptogenesis in Colon Adenocarcinoma Cells (HT-29): Involvement of Reactive Oxygen and Nitrogen Species Regulation. Evid-Based Complement Altern Med ECAM. 2012;2012:490136. doi:10.1155/2012/490136 PubMed PMID: 22685485; PubMed Central PMCID: PMC3350939.

[70] Galluzzi L, Pietrocola F, Levine B, Kroemer G. Metabolic Control of Autophagy. Cell. 2014 Dec 4;159(6):1263–76. doi:10.1016/j.cell.2014.11.006 PubMed PMID: 25480292; PubMed Central PMCID: PMC4500936.

[71] Levine B, Kroemer G. Autophagy in the Pathogenesis of Disease. Cell. 2008 Jan 11;132(1):27–42. doi:10.1016/j.cell.2007.12.018 PubMed PMID: 18191218; PubMed Central PMCID: PMC2696814.

[72] Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature. 2008 Feb 28;451(7182):1069–75. doi:10.1038/nature06639 PubMed PMID: 18305538; PubMed Central PMCID: PMC2670399.

[73] White E. The role for autophagy in cancer. J Clin Invest. 2015 Jan 2;125(1):42–6. doi:10.1172/JCI73941 PubMed PMID: 25654549; PubMed Central PMCID: PMC4382247.

[74] Tao Zhou, Ye L, Bai Y, Sun A, Cox B, Liu D, et al. Autophagy and Apoptosis in Hepatocellular Carcinoma Induced by EF25-(GSH)2: A Novel Curcumin Analog. PLoS ONE. 2014 Sep 30;9(9):e107876. doi:10.1371/journal.pone.0107876 PubMed PMID: 25268357; PubMed Central PMCID: PMC4182433.

[75] Tiejun Zhang, Li Y, Park KA, Byun HS, Won M, Jeon J, et al. Cucurbitacin induces autophagy through mitochondrial ROS production which counteracts to limit caspase-dependent apoptosis. Autophagy. 2012 Apr 1;8(4):559–76. doi:10.4161/auto.18867 PubMed PMID: 22441021.

[76] Ni Y, Wu S, Wang X, Zhu G, Chen X, Ding Y, et al. Cucurbitacin I induces pro-death autophagy in A549 cells via the ERK-mTOR-STAT3 signalling pathway [Internet]. doi:https://doi.org/10.1002/jcb.26808

[77] Minfei Su, Mei Y, Sinha S. Role of the Crosstalk between Autophagy and Apoptosis in Cancer. J Oncol. 2013 Jun 5;2013:102735. doi:10.1155/2013/102735 PubMed PMID: 23840208.

[78] Fletcher DA, Mullins RD. Cell mechanics and the cytoskeleton. Nature. 2010 Jan 28;463(7280):485–92. doi:10.1038/nature08908 PubMed PMID: 20110992; PubMed Central PMCID: PMC2851742.

[79] Pollard TD, Cooper JA. Actin, a Central Player in Cell Shape and Movement. Science. 2009 Nov 27;326(5957):1208–12. doi:10.1126/science.1175862 PubMed PMID: 19965462; PubMed Central PMCID: PMC3677050.

[80] Yilmaz M, Christofori G. Mechanisms of Motility in Metastasizing Cells. Mol Cancer Res. 2010 May 17;8(5):629–42. doi:10.1158/1541-7786.MCR-10-0139

[81] Knecht DA, LaFleur RA, Kahsai AW, Argueta CE, Beshir AB, Fenteany G. Cucurbitacin I Inhibits Cell Motility by Indirectly Interfering with Actin Dynamics. PLoS ONE. 2010 Nov 24;5(11):e14039. doi:10.1371/journal.pone.0014039 PubMed PMID: 21124831; PubMed Central PMCID: PMC2991314.

[82] Wang X, Tanaka M, Peixoto HS, Wink M. Cucurbitacins: elucidation of their interactions with the cytoskeleton. PeerJ. 2017 May 30;5:e3357. doi:10.7717/peerj.3357 PubMed PMID: 28584704; PubMed Central PMCID: PMC5452965.

[83] Boykin C, Zhang G, Chen YH, Zhang RW, Fan XE, Yang WM, et al. Cucurbitacin IIa: a novel class of anti-cancer drug inducing non-reversible actin aggregation and inhibiting survivin independent of JAK2/STAT3 phosphorylation. Br J Cancer. 2011 Mar 1;104(5):781–9. doi:10.1038/bjc.2011.10 PubMed PMID: 21304528; PubMed Central PMCID: PMC3048206.

[84] Gabrielsen M, Schuldt M, Munro J, Borucka D, Cameron J, Baugh M, et al. Cucurbitacin covalent bonding to cysteine thiols: the filamentous-actin severing protein Cofilin1 as an exemplary target. Cell Commun Signal CCS. 2013 Aug 14;11:58. doi:10.1186/1478-811X-11-58 PubMed PMID: 23945128; PubMed Central PMCID: PMC3751690.

[85] Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan 12;12(1):31–46. doi:10.1158/2159-8290.CD-21-1059

[86] Pavlova NN, Thompson CB. THE EMERGING HALLMARKS OF CANCER METABOLISM. Cell Metab. 2016 Jan 12;23(1):27–47. doi:10.1016/j.cmet.2015.12.006 PubMed PMID: 26771115; PubMed Central PMCID: PMC4715268.

[87] Mir SR, Kaushik U. Cucurbitacins - An insight into medicinal leads from nature. Pharmacogn Rev. 2015;9(17):12. doi:10.4103/0973-7847.156314

[88] Varela C, Melim C, Neves BG, Sharifi-Rad J, Calina D, Mamurova A, et al. Cucurbitacins as potential anticancer agents: new insights on molecular mechanisms. J Transl Med. 2022 Dec 31;20:630. doi:10.1186/s12967-022-03828-3 PubMed PMID: 36585670; PubMed Central PMCID: PMC9805216.

[89] Qiang Fu, Lu Z, Chang Y, Jin T, Zhang M. Bibliometric and visualized analysis of resveratrol in anticancer investigations. Food Sci Nutr. 2024 Jan 6;12(4):2223–39. doi:10.1002/fsn3.3932 PubMed PMID: 38628201; PubMed Central PMCID: PMC11016421.

[90] Zheng Liu, Zhang T, Xue C miao, Zhang W tong, Zhu B chen, Hua G dong. Research Hotspots of Traditional Chinese Medicine for Liver Cancer in the Future Directions: A Bibliometric Analysis. J Hepatocell Carcinoma. 2025 Dec 31;12:3105–61. doi:10.2147/JHC.S555310 PubMed PMID: 41496746; PubMed Central PMCID: PMC12766475.

[91] Suwit Duangmano, Sae-lim P, Suksamrarn A, Domann FE, Patmasiriwat P. Cucurbitacin B inhibits human breast cancer cell proliferation through disruption of microtubule polymerization and nucleophosmin/B23 translocation.

BMC Complement Altern Med. 2012 Oct 12;12:185. doi:10.1186/1472-6882-12-185 PubMed PMID: 23062075; PubMed Central PMCID: PMC3527297.

[92] Carmeliet P. Angiogenesis in life, disease and medicine. Nature. 2005 Dec 15;438(7070):932–6. doi:10.1038/nature04478 PubMed PMID: 16355210.

[93] Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer. 2002 Oct;2(10):795–803. doi:10.1038/nrc909 PubMed PMID: 12360282.

[94] Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011 May 19;473(7347):298–307. doi:10.1038/nature10144 PubMed PMID: 21593862; PubMed Central PMCID: PMC4049445.

[95] Folkman J. Role of angiogenesis in tumour growth and metastasis. Semin Oncol. 2002 Dec 16;29(6, Supplement 16):15–8. doi:10.1016/S0093-7754(02)70065-1

[96] Piao XM, Gao F, Zhu JX, Wang LJ, Zhao X, Li X, et al. Cucurbitacin B inhibits tumour angiogenesis by triggering the mitochondrial signalling pathway in endothelial cells. Int J Mol Med. 2018 Aug 1;42(2):1018–25. doi:10.3892/ijmm.2018.3647

[97] Yanmin Dong. Cucurbitacin E, a tetracyclic triterpenes compound from Chinese medicine, inhibits tumour angiogenesis through VEGFR2-mediated Jak2–STAT3 signalling pathway | Carcinogenesis | Oxford Academic [Internet]. [cited 2026 Jul 24]. Available from: https://academic.oup.com/carcin/article-abstract/31/12/2097/2476860?login=false

[98] Napoleone Ferrara. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004 Aug;25(4):581–611. doi:10.1210/er.2003-0027 PubMed PMID: 15294883.

[99] Phi LTH, Sari IN, Yang YG, Lee SH, Jun N, Kim KS, et al. Cancer Stem Cells (CSCs) in Drug Resistance and their Therapeutic Implications in Cancer Treatment. Stem Cells Int. 2018 Feb 28;2018:5416923. doi:10.1155/2018/5416923 PubMed PMID: 29681949; PubMed Central PMCID: PMC5850899.

[100] Sonam Sinha, Khan S, Shukla S, Lakra AD, Kumar S, Das G, et al. Cucurbitacin B inhibits breast cancer metastasis and angiogenesis through VEGF-mediated suppression of FAK/MMP-9 signalling axis. Int J Biochem Cell Biol. 2016 Aug;77(Pt A):41–56. doi:10.1016/j.biocel.2016.05.014 PubMed PMID: 27210504.

[101] William W. Li. Tumour angiogenesis: Molecular pathology, therapeutic targeting, and imaging. Acad Radiol. 2000 Oct 1;7(10):800–11. doi:10.1016/S1076-6332(00)80629-7

[102] Rafii S. (PDF) Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? ResearchGate. 2026 Jul 13. doi:10.1038/nrc925

[103] Fidler IJ. The pathogenesis of cancer metastasis: the "seed and soil" hypothesis revisited. Nat Rev Cancer. 2003 Jun;3(6):453–8. doi:10.1038/nrc1098 PubMed PMID: 12778135.

[104] Gupta GP, Massagué J. Cancer Metastasis: Building a Framework. Cell. 2006 Nov 17;127(4):679–95. doi:10.1016/j.cell.2006.11.001 PubMed PMID: 17110329.

[105] Valastyan S, Weinberg RA. Tumour Metastasis: Molecular Insights and Evolving Paradigms. Cell. 2011 Oct 14;147(2):275–92. doi:10.1016/j.cell.2011.09.024 PubMed PMID: 22000009; PubMed Central PMCID: PMC3261217.

[106] Shukla S, Sinha S, Khan S, Kumar S, Singh K, Mitra K, et al. Cucurbitacin B inhibits the stemness and metastatic abilities of NSCLC via downregulation of canonical Wnt/β-catenin signalling axis. Sci Rep. 2016 Feb 24;6:21860. doi:10.1038/srep21860 PubMed PMID: 26905250; PubMed Central PMCID: PMC4764833.

[107] Friedl P, Alexander S. Cancer Invasion and the Microenvironment: Plasticity and Reciprocity. Cell. 2011 Nov 23;147(5):992–1009. doi:10.1016/j.cell.2011.11.016 PubMed PMID: 22118458.

[108] Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001 Nov 1;414(6859):105–11. doi:10.1038/35102167 PubMed PMID: 11689955.

[109] Clarke MF, Dick JE, Dirks PB, Eaves CJ, Jamieson CHM, Jones DL, et al. Cancer Stem Cells—Perspectives on Current Status and Future Directions: AACR Workshop on Cancer Stem Cells. Cancer Res. 2006 Oct 3;66(19):9339–44. doi:10.1158/0008-5472.CAN-06-3126

[110] Saygin C, Matei D, Majeti R, Reizes O, Lathia JD. Targeting Cancer Stemness in the Clinic: From Hype to Hope. Cell Stem Cell. 2019 Jan 3;24(1):25–40. doi:10.1016/j.stem.2018.11.017 PubMed PMID: 30595497.

[111] Batlle E, Clevers H. Cancer stem cells revisited [Internet]. 2017 Oct 1 [cited 2026 Jul 25]. Available from: https://hdl.handle.net/2445/201023

[112] Bartłomiej Zieniuk. Recent Advances in the Application of Cucurbitacins as Anticancer Agents [Internet]. [cited 2026 Jul 28]. Available from: https://www.mdpi.com/2218-1989/13/10/1081?utm_source=chatgpt.com

[113] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49. doi:10.3322/caac.21660 PubMed PMID: 33538338.

[114] Dai S, Wang C, Zhao X, Ma C, Fu K, Liu Y, et al. Cucurbitacin B: A review of its pharmacology, toxicity, and pharmacokinetics. Pharmacol Res. 2023 Jan;187:106587. doi:10.1016/j.phrs.2022.106587 PubMed PMID: 36460279.

[115] Ku JM, Kim SR, Hong SH, Choi HS, Seo HS, Shin YC, et al. Cucurbitacin D induces cell cycle arrest and apoptosis by inhibiting STAT3 and NF-κB signalling in doxorubicin-resistant human breast carcinoma (MCF7/ADR) cells. Mol Cell Biochem. 2015;409(1–2):33–43. doi:10.1007/s11010-015-2509-9 PubMed PMID: 26169986; PubMed Central PMCID: PMC4589559.

[116] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018 Jan 24;553(7689):446–54. doi:10.1038/nature25183 PubMed PMID: 29364287.

[117] Khan N, Jajeh F, Khan MI, Mukhtar E, Shabana SM, Mukhtar H. Sestrin-3 modulation is essential for therapeutic efficacy of cucurbitacin B in lung cancer cells. Carcinogenesis. 2017 Feb;38(2):184–95. doi:10.1093/carcin/bgw124 PubMed PMID: 27881463; PubMed Central PMCID: PMC6075515.

[118] Jing SY, Wu ZD, Zhang TH, Zhang J, Wei ZY. In vitro antitumour effect of cucurbitacin E on human lung cancer cell line and its molecular mechanism. Chin J Nat Med. 2020 Jul;18(7):483–90. doi:10.1016/S1875-5364(20)30058-3 PubMed PMID: 32616188.

[119] Hsu HS, Huang PI, Chang YL, Tzao C, Chen YW, Shih HC, et al. Cucurbitacin I inhibits tumourigenic ability and enhances radiochemosensitivity in nonsmall cell lung cancer-derived CD133-positive cells. Cancer. 2011 Jul 1;117(13):2970–85. doi:10.1002/cncr.25869 PubMed PMID: 21225866.

[120] Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019 Oct 19;394(10207):1467–80. doi:10.1016/S0140-6736(19)32319-0 PubMed PMID: 31631858.

[121] Feng H, Zang L, Zhao ZX, Kan QC. Cucurbitacin-E Inhibits Multiple Cancer Cells Proliferation Through Attenuation of Wnt/β-Catenin Signalling. Cancer Biother Radiopharm. 2014 Jun 1;29(5):210–4. doi:10.1089/cbr.2014.1614

[122] Wei J, Chen X, Li Y, Li R, Bao K, Liao L, et al. Cucurbitacin B-induced G2/M cell cycle arrest of conjunctival melanoma cells mediated by GRP78–FOXM1–KIF20A pathway. Acta Pharm Sin B. 2022 Oct 1;12(10):3861–76. doi:10.1016/j.apsb.2022.05.021

[123] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49. doi:10.3322/caac.21820 PubMed PMID: 38230766.

[124] Döhner H. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345–77. doi:10.1182/blood.2022016867

[125] Guo H, Kuang S, Song Q ling, Liu M, Sun X xiao, Yu Q. Cucurbitacin I inhibits STAT3, but enhances STAT1 signalling in human cancer cells in vitro through disrupting actin filaments. Acta Pharmacol Sin. 2018 Mar;39(3):425–37. doi:10.1038/aps.2017.99 PubMed PMID: 29119966; PubMed Central PMCID: PMC5843842.

[126] Huang WW, Yang JS, Lin MW, Chen PY, Chiou SM, Chueh FS, et al. Cucurbitacin E Induces G2/M Phase Arrest through STAT3/p53/p21 Signalling and Provokes Apoptosis via Fas/CD95 and Mitochondria-Dependent Pathways in Human Bladder Cancer T24 Cells. Evid-Based Complement Altern Med ECAM. 2012;2012:952762. doi:10.1155/2012/952762 PubMed PMID: 22272214; PubMed Central PMCID: PMC3261502.

[127] Liang Y, Zhang T, Ren L, Jing S, Li Z, Zuo P, et al. Cucurbitacin IIb induces apoptosis and cell cycle arrest through regulating EGFR/MAPK pathway. Environ Toxicol Pharmacol. 2021 Jan 1;81:103542. doi:10.1016/j.etap.2020.103542

[128] Liu J, Zhang X, Yang H, Zhu C, Fan D, Deng J. Preliminary investigation of the anti-colon cancer activity of cucurbitacin C from cucumber: A network pharmacological study and experimental validation. Food Front. 2024;5(1):142–59. doi:10.1002/fft2.317

[129] Huang H, Fu J, Peng H, He Y, Chang A, Zhang H, et al. Co-delivery of polyphyllin II and IR780 PLGA nanoparticles induced pyroptosis combined with photothermal to enhance hepatocellular carcinoma immunotherapy. J Nanobiotechnology. 2024 Oct 21;22:647. doi:10.1186/s12951-024-02887-6 PubMed PMID: 39434141; PubMed Central PMCID: PMC11495104.

[130] Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020 Jun 27;395(10242):2008–20. doi:10.1016/S0140-6736(20)30974-0 PubMed PMID: 32593337.

[131] Thoennissen NH, Iwanski GB, Doan NB, Okamoto R, Lin P, Abbassi S, et al. Cucurbitacin B Induces Apoptosis by Inhibition of the JAK/STAT Pathway and Potentiates Antiproliferative Effects of Gemcitabine on Pancreatic Cancer Cells. Cancer Res. 2009 Jul 15;69(14):5876–84. doi:10.1158/0008-5472.CAN-09-0536

[132] Xu D, Shen H, Tian M, Chen W, Zhang X. Cucurbitacin I inhibits the proliferation of pancreatic cancer through the JAK2/STAT3 signalling pathway in vivo and in vitro. J Cancer. 2022 Mar 28;13(7):2050–60. doi:10.7150/jca.65875 PubMed PMID: 35517401; PubMed Central PMCID: PMC9066209.

[133] Casarcia N, Rogers P, Guld E, Iyer S, Li Y, Burcher JT, et al. Phytochemicals for the prevention and treatment of pancreatic cancer: Current progress and future prospects. Br J Pharmacol. 2025;182(10):2181–234. doi:10.1111/bph.16249

[134] Dehelean CA, Marcovici I, Soica C, Mioc M, Coricovac D, Iurciuc S, et al. Plant-Derived Anticancer Compounds as New Perspectives in Drug Discovery and Alternative Therapy. Molecules. 2021 Feb 19;26(4):1109. doi:10.3390/molecules26041109 PubMed PMID: 33669817; PubMed Central PMCID: PMC7922180.

[135] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33. doi:10.3322/caac.21708

[136] Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, et al. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022–43. doi:10.18632/oncotarget.16723 PubMed PMID: 28410237; PubMed Central PMCID: PMC5514969.

[137] Chou TC. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol Rev. 2006 Sep;58(3):621–81. doi:10.1124/pr.58.3.10 PubMed PMID: 16968952.

[138] Cai Y, Fang X, He C, Li P, Xiao F, Wang Y, et al. Cucurbitacins: A Systematic Review of the Phytochemistry and Anticancer Activity. Am J Chin Med. 2015;43(7):1331–50. doi:10.1142/S0192415X15500755 PubMed PMID: 26503558.

[139] Sánchez-Hernández IM. Pharmacokinetics and Biological Activity of Cucurbitacins [Internet]. [cited 2026 Jul 28]. Available from: https://www.mdpi.com/1424-8247/15/11/1325?utm_source=chatgpt.com

[140] Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013 Oct;13(10):714–26. doi:10.1038/nrc3599 PubMed PMID: 24060863.

[141] Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med. 2002;53:615–27. doi:10.1146/annurev.med.53.082901.103929 PubMed PMID: 11818492.

[142] Liu T, Peng H, Zhang M, Deng Y, Wu Z. Cucurbitacin B, a small molecule inhibitor of the Stat3 signalling pathway, enhances the chemosensitivity of laryngeal squamous cell carcinoma cells to cisplatin. Eur J Pharmacol. 2010 Sep 1;641(1):15–22. doi:10.1016/j.ejphar.2010.04.062

[143] Escandell, J. M., Andujar, I. Inhibition of Transcription Factors by Plant-Derived Compounds an...: Ingenta Connect [Internet]. Bentham Science Publishers; [cited 2026 Aug 1]. Available from: https://www.ingentaconnect.com/content/ben/cpd/2009/00000015/00000011/art00007 doi:https://doi.org/10.2174/138161209787846874

[144] Roskoski R. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res. 2019 Jun 1;144:19–50. doi:10.1016/j.phrs.2019.03.006

[145] Song L, Han J, Wang R, Cao S, Tai Y, Wang X, et al. Cucurbitacin B inhibits HIF-1α and attenuates non-small cell lung cancer via ZFP91. Front Oncol. 2025 Aug 11;15:1607264. doi:10.3389/fonc.2025.1607264 PubMed PMID: 40860815; PubMed Central PMCID: PMC12375561.

[146] Ribas A, Wolchok JD. Cancer Immunotherapy Using Checkpoint Blockade. Science. 2018 Mar 23;359(6382):1350–5. doi:10.1126/science.aar4060 PubMed PMID: 29567705; PubMed Central PMCID: PMC7391259.

[147] Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive and Acquired Resistance to Cancer Immunotherapy. Cell. 2017 Feb 9;168(4):707–23. doi:10.1016/j.cell.2017.01.017 PubMed PMID: 28187290; PubMed Central PMCID: PMC5391692.

[148] Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S, Pilon-Thomas S, et al. Inhibiting Stat3 signalling in the hematopoietic system elicits multicomponent antitumour immunity. Nat Med. 2005 Dec;11(12):1314–21. doi:10.1038/nm1325 PubMed PMID: 16288283.

[149] Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumour immune microenvironment (TIME) for effective therapy. Nat Med. 2018 May;24(5):541–50. doi:10.1038/s41591-018-0014-x PubMed PMID: 29686425; PubMed Central PMCID: PMC5998822.

[150] Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017 Jan;17(1):20–37. doi:10.1038/nrc.2016.108 PubMed PMID: 27834398; PubMed Central PMCID: PMC5575742.

[151] Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101–24. doi:10.1038/s41573-020-0090-8 PubMed PMID: 33277608; PubMed Central PMCID: PMC7717100.

[152] Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Adv Drug Deliv Rev. 2017 Jan 1;Editor's Collection 2016108:25–38. doi:10.1016/j.addr.2016.04.025

[153] Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. Pharm Res. 2016 Oct 1;33(10):2373–87. doi:10.1007/s11095-016-1958-5

[154] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007 Dec;2(12):751–60. doi:10.1038/nnano.2007.387 PubMed PMID: 18654426.

[155] Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015 Sep;33(9):941–51. doi:10.1038/nbt.3330 PubMed PMID: 26348965; PubMed Central PMCID: PMC4978509.

[156] Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2012 Dec 1;MOST CITED PAPERS IN THE HISTORY OF ADVANCED DRUG DELIVERY REVIEWS: A TRIBUTE TO THE 25TH ANNIVERSARY OF THE JOURNAL64:302–15. doi:10.1016/j.addr.2012.09.031

[157] Ting-Chao Chou. Drug combination studies and their synergy quantification using the Chou-Talalay method. Cancer Res. 2010 Jan 15;70(2):440–6. doi:10.1158/0008-5472.CAN-09-1947 PubMed PMID: 20068163.

[158] Barenholz Y. Doxil®--the first FDA-approved nano-drug: lessons learned. J Control Release Off J Control Release Soc. 2012 Jun 10;160(2):117–34. doi:10.1016/j.jconrel.2012.03.020 PubMed PMID: 22484195.

[159] Lin X, Farooqi AA. Cucurbitacin mediated regulation of deregulated oncogenic signalling cascades and non-coding RNAs in different cancers: Spotlight on JAK/STAT, Wnt/β-catenin, mTOR, TRAIL-mediated pathways. Semin Cancer Biol. 2021 Aug;73:302–9. doi:10.1016/j.semcancer.2020.10.012 PubMed PMID: 33152487.

[160] Wang J, Hu T, Wang Q, Chen R, Xie Y, Chang H, et al. Repression of the AURKA-CXCL5 axis induces autophagic cell death and promotes radiosensitivity in non-small-cell lung cancer. Cancer Lett. 2021 Jul 1;509:89–104. doi:10.1016/j.canlet.2021.03.028