Therapeutic Efficacy of Cucurbitacin

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Cucurbitacins are a class of secondary metabolites initially isolated from the Cucurbitaceae family. They are important for their analgesic, anti-inflammatory, antimicrobial, antiviral, and anticancer biological actions.

Keywords: cucurbitacins ; absorption ; Biological Activity

1. Introduction

There have been a large number of reports on the role of cucurbitacins in their medicinal and toxic properties. Among its most recognized effects is its anticancer potential through inhibition processes of the JAK/STAT3 signaling pathway, whose abnormal activation can direct cascade events involved in the development of cancer [1]. JAK (Janus kinase) is a family of tyrosine kinases: JAK1, JAK2, JAK3, and TYK2 [2], which, once activated by the interaction of cytosine and its receptor, undergoes phosphorylation in the accompanying sites of transcription factors, signal transducers and activators of transcription (STAT), to which it phosphorylates and, thus, becomes a transcription factor that translocates to the nucleus and regulates the expression of genes associated with proliferation mechanisms, such as cyclins and c-myc, and suppresses proapoptotic genes, such as survival, Bcl-xL, and Bcl-2 [3][4]. It has been described that the different members of the kinase family (JAK, JAK1, JAK2, JAK3, TYK2) can be constitutively activated in many hematopoietic malignancies, as well as in numerous types of cancer [5], such as bladder, colon, and cervical cancers and medulloblastoma [6], as well as leukemias [7] and lymphomas [8].

Evidence indicates that cucurbitacins are anticancer agents that prevent STAT3 DNA binding [9]. Since cucurbitacin treatments decrease the level of phosphorylated JAK or STAT3 and its downstream targets, such as Bcl-2, in cancer cells, the ability to stimulate apoptosis in cells has also been described [10]. However, cucurbitacins may target different therapeutic targets to inhibit the growth of cancer cells.

In this context, it has been found that CuB inhibits the epidermal growth factor receptor (EGFR), prevents the growth of pancreatic cancer cells, and produces apoptosis through the negative regulation of anti-apoptotic proteins such as Bcl-2 and the increase in the amount of the proapoptotic protein Bim [11]. CuE has been found to significantly affect apoptosis in bladder cancer through a decrease in the phospho-signal transducer and STAT3, which can trigger mitochondria-dependent pathways through sequential activation of caspase-8 and caspase-3 [12]. In addition, with CuB, arrest of the G2-M phase and induction of apoptosis in cancer cells was associated with the inhibition of JAK2, STAT3, and STAT5 by decreasing Bcl-xL [13].

The alteration of the actin cytoskeleton is another mechanism of cucurbitacins that promotes death in different types of carcinoma cell lines, possibly due to the direct alteration of the polymerization of the actin filaments [14]. In addition, CuE activates autophagy in human cancer cells by downregulating mTORC1 signaling, an essential pathway in the regulation of autophagy, which is a promoter of the autophagy mechanism through activation of ULK1, causing mTORC1 inhibition [15].

In addition to anticancer processes, cucurbitacins play an important role in preventing the migration and invasion of cancer cells. CuI has been reported to mitigate invasion in colon cancer cell lines associated with the downregulation of STAT3 phosphorylation and MMP-9 expression, an enzyme associated with cell invasion [16].

Another essential feature of cucurbitacins is their ability to disrupt the cell cycle of cancer cells [12]. One of the main mechanisms of action is the inhibition of genes encoding cyclins. CuB has been reported to reduce cyclins D1 and cdc-2, which are key to developing the G2/M phase in human hepatocellular carcinoma cells.

Cucurbitacins also inhibit the Raf/MEK/ERK signaling pathway in leukemic cells, which regulates cell proliferation, growth, differentiation, and senescence. Chan et al., 2010 [17], reported that CuB could interact with the Raf/MEK/ERK and JAK/STAT3 pathways in leukemia cells, thereby inhibiting their growth.

The role of cucurbitacins in inflammatory properties has been reported. CuE inhibits the COX and RNS enzymes, which are related to the severe inflammatory response in various chronic disorders [18].

The antiviral potential of CuB, CuE, and CuD against hepatitis C virus (HCV), bovine viral diarrhea (BVDV), and hepatitis C virus (HCV) has been reported. However, as a consequence of the contingency problems caused during the last two years due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the working group of Kapoor et al., 2020 [19], analyzed 16 cucurbitacin analogs and their interaction with the main protease protein (Mpro) of the coronavirus, demonstrating that all proteins bind efficiently and specifically with cucurbitacin G 2-glucoside, which suggests the possibility of inhibiting the activity of helicase enzymes involved in the virus replication cycle.

2. Biological Action of Cucurbitacin B

CuB, (2β,9β,10α,16α,23*E*)-25-(acetyloxy)-2,16,20-trihydroxy-9-methyl-19-norlanosta-5,23-diene-3,11,22-trione, is one of the most abundant classes of cucurbitacins and is one of the most explored cucurbitacins due to its role in biological systems [20]. There have been numerous reports on the anticancer properties of cucurbitacin B, which include the inhibition of tumor cell lines [21], as well as its anti-inflammatory properties [22]; antimicrobial and antiviral properties [23]; antiaging properties [24]; antidiabetic properties [25]; antihypertrophic and antifibrosis properties [26]; and its actions as a memory protector of mice in APP/PS1 and neurogenesis inducer [27].

One of the most interesting attributes of CuB is its potential as an anticancer agent, both in vivo and in vitro, which includes growth inhibition, cell cycle arrest in the G2/M phase, and the induction of apoptosis in numerous cancer cell lines. It has been implied that these effects could derive from the disruption of STAT3 phosphorylation, Bcl-2, and cyclin B1 expression [28]. In addition, modifications in the composition of the cytoskeleton have been demonstrated in myeloid leukemia cells [29].

Regarding breast cancer, Liang et al., 2018 [30], showed that CuB inhibits the adhesion and viscoelasticity of various cell lines, reduces cell abnormalities, and prevents the invasion and migration of malignant cells associated with the expression of F actin/vimentin/FAK/vinculin (directs the distribution and arrangement of the cytoskeleton). Similarly, CuB inhibited the RAC1/CDC42/RhoA signaling pathway (key elements in cell viability and migration) and prevented the generation of metastasis in cancer cells.

CuB-related methylation studies could represent a new pathway through which to counteract breast cancer. Aberrant methylation is a trigger in the development of tumors, and for this reason, special attention has recently been paid to the role it plays in the development of cancer cells caused by the abnormal expression of genes due to the presence of epigenetic factors. In a study by Dittharot et al., 2019 [21], CuB extracted from *Trichosanthes cucumerina* acted as a hypermethylation agent and suppressed the expression of the oncogenic promoters of c-Myc and cyclin D1; therefore, it is considered a potential therapeutic agent against breast cancer.

It has been reported that CuB induces apoptosis and prevents proliferation in lung cancer cell lines through the disruption of the specific inactive transcript of lncRNA X (XIST) [31], which at irregular levels is associated with the presence of tumors (colon and breast cancer) , also confirming that CuB induces apoptosis through upregulation of miR-let-7c [31].

Additionally, CuB may benefit osteosarcoma, and one of the most diagnosed tumors in children and young adults [32] revealed that osteosarcoma cells (U-2 OS) treated with CuB downregulated the phosphorylated ERK1/2, p38, and JNK. Substantial decreases were also observed in the levels of p38 and ERK1/2 and levels of JNK and p-JNK, thus demonstrating that the decrease in the expression of the MAPK signaling pathway is an important mechanism in the stimulation of apoptosis of U-2 OS cells.

Another regulatory mechanism in which CuB may have relevant effects in oncogenesis has been described by Qin et al., 2018 [33]. CuB prevents proliferation and invasion in human glioblastoma multiforme (GBM) cell lines, in addition to downregulating the expression of the oncoprotein CIP2A and its downstream signaling molecule phospho-Akt, suggesting that CuB could be a potential inhibitor of CIP2A.

Regarding its anti-inflammatory effects, CuB reduced inflammatory responses in conditions such as periodontitis. As reported by Zhong et al., 2020 [34], based on an experimental periodontitis induction in rats through the ligation method,

CuB treatments (12.5 mg, 25 mg, and 50 mg kg^{-1} body weight) for 12 days showed a significant decrease in alveolar bone loss through the regulation of RANK/OPG levels, as well as the reduction of inflammatory responses in periodontitis in a preclinical trial.

CuB activity may also have antiaging effects. Lin et al., 2019 [24], found that treatments with CuB yielded a significant increase in the replicative rate and the chronological life in survival years of the yeast mutant strain *Saccharomyces cerevisiae* K6001 via modulation of autophagy and antioxidant activity to increase the longevity of yeast.

Finally, the anticancer CuB mechanism is not limited to JAK/STAT pathway disruption but also induces disruption of many other types of signaling that increase tumor cell growth, such as NFκB [35], PI3K/Akt/mTOR [11], MAPK/ERK [32], or Wnt/β-catenin progression [36]. It also induces the expression of those tumor suppressor genes, such as p53, and, thus, induces apoptosis, regulates cell survival, or inactivates the overexpression of oncogenic agents [37]. Some other important pathways involved in the anticancer effect in different cell lines have recently been described, such as the induction of apoptosis through the inhibition of matrix metalloproteinases (MMPs) and interleukin-6 (IL-6) [32]; pyroptosis death by inhibition of non-small cell lung cancer (NSCLC) by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis [38]; anti-angiogenesis effects by triggering angiogenesis through the mitochondrial signaling pathway, which causes the inhibition of vascular endothelial growth factor (VEGF) and subsequent inactivation of vascular endothelial growth factor receptor 2 (VEGFR2) in endothelial cells [39]; and inhibition of metastasis through the inactivation of TGF-β1-induced epithelial–mesenchymal transition (EMT) in NSCLC through regulation of the ROS and PI3K/Akt/mTOR pathways [40]. However, although there are an increasing number of new conditions in which CuB can be a potential treatment, particularly in cancer, more clinical studies are still needed to define its effectiveness.

3. Biological Action of Cucurbitacin D

CuD has been described as a potential antitumor agent in several cancer models due to its ability to induce apoptosis through the inactivation of NF-κB and STAT3 or to produce autophagy in some tumor cell lines [41]. CuD is also known to control cancer cell proliferation, migration, and spread[42]. It has been observed to promote immunomodulatory activity in macrophages since it increases the production of IL-1β induced by lipopolysaccharides, which stimulates inflammasome activation [43].

Authors such as Sikander et al., 2019 [42], studied the efficiency of CuD against prostate cancer by reprogramming the metabolic switch and molecular interaction with the GLUT1 receptor. Among the main results, they observed that CuD has significant cytotoxic effects on prostate cancer cell lines (PrCa) since it stops the progression of the cell cycle in the G2/M phase. Another important finding is that a lack of glucose is a sufficient mechanism to generate growth arrest and cell death in PrCa. Similarly, CuD reduced the expression of GLUT1 since its overexpression is correlated with glucose uptake. This showed that CuD could reprogram glucose metabolism, leading to growth inhibition of metastatic PrCa cells.

Studies conducted by Ku et al., 2018 [44], revealed that CuD increased p-p53 levels but directed the downregulation of p-Akt, p-NF-κB, and p-Stat3 in breast cancer cell lines MCF7, SKBR3, and MDA-MB. The results of this assay were comparable to those of the assay for drug doxorubicin, which individually failed to lower p-Akt and p-Stat3 levels. The combination of doxorubicin and CuD increases the potential effect by increasing the levels of p-p53 and disrupting the expression of Akt, NF-κB, Stat3, and Bcl-2.

Zhang et al., 2018 [45], focused on the growth and death of three cell lines related to gastric cancer (AGS, SNU1, and Hs746T) under CuD treatment. When the antiproliferative potential was highlighted, it induced the production of ROS and, therefore, the induction of apoptosis. The presence of CuD increased the intracellular levels of Ca^{2+} and ATP. CuD activated the mitochondrial apoptosis pathway, and with its positive expression of Bax, CuD modulated the activation of the iNOS pathway, which produced ROS and nitric oxide molecules, to activate the apoptosis of cancer cell lines.

Recently, the role of CuD as an adjuvant therapy has been investigated. Kodidela et al., 2021 [46], studied the anti-HIV effect of CuD in HIV-infected macrophages using the blood–brain barrier (BBB) as an in vitro model. The results showed that CuD decreased viral load significantly, and there was also a decrease in the proinflammatory cytokine IL-1β and HIV replication; thus, CuD can be considered a potential compound to be used as adjuvant therapy with two purposes: to decrease brain toxicity from antiretroviral failure and to prevent HIV in the brain.

4. Biological Action of Cucurbitacin E

CuE is another of the most abundant forms of cucurbitacin, the biological activity of which is mainly associated with anticancer properties [47], but it has also been described as having anti-inflammatory [18], antiviral [48], and hepatoprotective attributes [49].

The anticancer mechanism of CuE is described by suppressing the activation of the transducer and transcriptional activator 3 (STAT3). It was also observed that p53 and p21 could be increased in cancer cells treated with CuE and produce alterations in the levels of a protein associated with the G2/M phase in cancer cells and, therefore, arrest in the cell cycle. Similar studies are highlighting the effect of this cucurbitacin on other signaling pathways. For example, He et al., 2017 [47], evaluated the effect of CuE targeting human colon cancer cells (LNCaP), demonstrating cytotoxic action, suppression of cell viability, and activation of apoptosis via an increase in cofilin-1, AMP-activated protein kinase, p53, and expression of the caspase-9 protein; therefore, it is proposed that the mechanism of action of CuE is exerted through the signaling of cofilin-1, mTOR, AMPK, p53, and caspase-9.

Other authors, such as Saeed et al., 2019 [50] developed multiple studies of CuE isolated from *Citrullus colocynthis* against drug-resistant tumor cell lines. Three members of the ABC transporter superfamily related to multidrug resistance, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and ABCB5, were investigated. It was found that lines positive for overexpression of P-gp and BCRP show cross-resistance to CuE, while those that overexpress ABCB5 show chemosensitivity to this cucurbitacin, demonstrating that CuE is not beneficial for patients with tumors overexpressing P-gp and BCRP.

CuE has played an important role in chronic diseases such as asthma. Recently, Shang et al., 2019 [51], investigated the role of CuE in the inflammatory process of asthma due to its potential to inactivate the NF-κB pathway and, thus, counteract the production of proinflammatory cytokines such as TNF-α and INF-γ, for which the protective effect of CuE on the human bronchial epithelial cell line BEAS-2B was measured by means of an in vitro assay, in which the inflammatory response in epithelial cells exposed to lipopolysaccharides (LPS) simulated asthmatic conditions. The results showed that the administration of CuE inhibited the production of inflammatory cytokines induced by LPS, such as TNF-α, IL-6, and IL-8, by inhibiting the activation of HMGB1, TLR4, and p-p65 NF-κB, as well as reducing the release of mucin 5AC (MUC5AC); therefore, CuE could be considered a promising agent in asthma therapy.

5. Biological Action of Cucurbitacin I

It has been reported that in human breast carcinoma and lung adenocarcinoma cell lines, CuI inhibits STAT3 activation [52]. In a study conducted by van Kester et al., 2008 [53], it was shown that CuI downregulates the dose-dependent STAT3 phosphorylation and induction of apoptosis by CuI in Seax cells derived from the aggressive cutaneous lymphoma line of CD4+ T cells with tumor cells (Sz).

Dandawate et al., 2020[21], described the effect that CuI promotes against different colorectal cancer (CRC) cell lines, thus demonstrating that CuI suppresses cell proliferation in CRC. This revealed G2/M cell cycle arrest within 24 h, coupled with a significant decrease in cyclin B1 and cyclin-dependent kinase 1 (CDK1). Among other affected compounds were the proteins involved in the transition of cells from the S phase (cyclin A2, CDK2, Wee1, and CDC25C to G2/M), which provided greater support for the interruption of the cell cycle in the lines, also highlighting important effects for triggering apoptosis. Another interesting finding was that CuI produced an increase in cleaved caspase 3 and PARP proteins, registering a higher expression of the proapoptotic marker Bax and, at the same time, a decrease in the antiapoptotic markers Bcl-xL, Mcl-1, and Bcl-2; therefore, this could suggest that the activation of apoptosis occurs through caspase in CRC cells. In addition, CuI showed binding to the ankyrin domain of the Notch receptor, so it is inferred that the suppressive effect of CuI in colon cancer is mediated by inhibiting the Notch signaling pathway.

In another study carried out by Li et al., 2019[54], the effect of CuI on endoplasmic reticulum stress (ERS) was studied, where ERS is a fundamental response to confer protection against any alteration in the endoplasmic reticulum and, therefore, is an important factor in the development of tumors. Thus, CuI showed potent anticancer action by inducing apoptosis due to excessive induction of ERS and C/EBP homologous protein (CHOP) and caspase-12-dependent ERS-generated apoptosis. In addition, the ERS, IRE1α, and PERK pathways, as well as CHOP, were activated after CuI treatment in SKOV3 and PANC-1 cancer cell lines. Therefore, CuI could have potential for the development of new anticancer therapeutic approaches.

Ni et al., 2018[55], reported that CuI decreased cell viability and colony formation through the activation of apoptosis in lung cancer lines (A549) and the production of autophagic vacuoles with increased apoptosis by inhibiting ERK activation

as well as the downstream phosphorylation of mTOR and STAT3. Although much remains to be elucidated regarding the profile of CuI and several of its biological effects, to date, a possible therapeutic window for the development of anticancer phytopharmaceuticals is provided.

6. Biological Action of Cucurbitacin IIa

CuIIa, also named hemslecin A or 25-*O*-acetyl-23,24 dihydrocucurbitacin F, is the most important bioactive component in *Hemsleya* species and has in its structure five active sites: C-2 hydroxy, C-3 hydroxyl, C-16 hydroxyl, B-ring double bond, and C-22 aldehyde groups. All five of these are widely used for derivative synthesis [56][57]. CuIIa has multiple biological effects in pharmacological studies as an anticancer [58], anti-inflammatory [59], antiviral [60], or antidepressant agent [61].

Zhang et al. (2019) [62] evaluated the effect of CuIIa on the lung cancer cell line A549. They reported that CuIIa is a repressor of mitogen-activated protein kinase MAPK signaling through competitive inhibition of the EGF-binding site on the EGFR protein. As a result, transcription, agglomeration, and phosphorylation of signaling constituents (such as STAT3) are altered, inducing apoptosis and cell cycle arrest in the G2/M phase of cancer cells.

An assay conducted by Boykin et al. (2011) [58] described that CuIIa eliminates the distribution of cancer cells in vitro through the suppression of the actin cytoskeleton and the pathways involved in survivin and PARP, mediators of the apoptosis process in prostate cancer cells (CWR22Rv-1). In addition, the cell cycle was interrupted with the reduction of phospho-histone H3 and survivin, suggesting an important correlation between mitosis and survivin together with the p53 and p21 pathways to enhance the anticancer action of CuIIa. In addition, since the function of PARP is limited, there is less capacity to repair damaged DNA, resulting in a much faster process of apoptosis through the p53 and p21 pathways. This demonstrated that the CuIIa biological effect is not conferred in a conventional manner to other cucurbitacins by not suppressing JAK2/STAT3 phosphorylation; instead, the trigger is mediated by suppression of actin cytoskeleton arrest and related signaling pathways.

Studies conducted by Zhou et al., 2017 [61], showed that CuIIa could pass through the blood–brain barrier and had antidepressant-like effects in trials with mouse models, in which they were subjected to chronic unpredictable mild stress (CUMS) through elevated plus maze, open field, forced swimming, and tail suspension (induction of behavioral changes) tests for antidepressant treatments. In the tests described, CuIIa treatment restored the irregular behavior of the mice through more significant locomotor activity and less immobility time. Decreased levels of brain-derived neurotrophic factor (BDNF) are known to cause erratic synaptic plasticity, which can subsequently lead to depression, suggesting that CuIIa has a potential use in antidepressant diseases and as a neuroprotectant by downregulating the CaMKII-CREB-BDNF pathway.

The above evidence demonstrates that the diversity of biological effects of CuIIa may be implicit through the JAK2/STAT3, ERBB MAPK [62], and CaMKII α/CREB/BDNF pathways [61], among others; however, there are still mechanisms to elucidate and explore its effects on other chronic diseases [56], which would contribute to its relevance as a phytopharmaceutical.

7. Biological Action of Cucurbitacin IIb

CuIIb, named 23,24-dihydrocucurbitacin F or hemslecin B, is isolated from the plant *Hemsleya amabilis* [63]. It has been described for its effects on the induction of apoptosis and cell cycle suppression through regulation of the EGFR/MAPK pathway or by inhibition of STAT3 [64] and apoptotic activity in cancer cell lines of the cervix or lung [65] and anti-inflammatory activity [63].

CuIIb has a relevant effect on systemic lupus erythematosus (SLE) since it breaks the imbalance between Th17 and Treg cells and is involved in the pathogenesis of SLE. Wu et al., 2020 [66], evaluated CuIIb regulation in Th17/Treg cells using in vivo mouse models of SLE. After treatment with CuIIb, the production of Treg cells was increased in mice, but the opposite effect was produced in Th17 cells. In addition, CuIIb induced the expression of foxp3 but repressed RORγt in SLE mice and repressed IL-6 and IL17, which were highly expressed, and induced IL-10 TGF-β in lymphocytes, which was expressed at low levels in lymphocytes from SLE mice. Thus, CuIIb mitigated the kidney damage caused by SLE.

Liang et al., 2021 [64], described the antiproliferative activity of CuIIb in A549 lung cancer cell lines through the STAT3 pathway that is modulated by the mitochondria and is caspase-dependent, in conjunction with an alteration of cellular activity in the G2/M phase, which is also attributed to the ability to intervene in the signaling of the mitogen-activated

protein kinase/EGFR (MAPK) pathway. Finally, it was demonstrated by molecular docking that CuIIb-EGFR binding is due to hydrophobic and hydrogen bonding interactions, strongly supporting CuIIb as a potential EGFR TKI.

8. Cucurbitacin Derivatives and Their Biological Activity

The chemical structure of cucurbitacins can be modified to obtain various derivatives; therefore, 200 derivatives of these compounds have been described [67]. These derivatives include substitutions at C2 or C3, isomerization, deoxidization, or dihydro derivatives [67]. Remarkably, derivatives of cucurbitacins B, D, E, and I have mainly been studied for their potential anticancer effect [68].

Some important studies of derivatives, such as 23,24-dihydrocucurbitacin B, have been highlighted for their antiarthritic effects in mice that were treated with this compound, which produced an anti-inflammatory effect by downregulation of proinflammatory enzymes, such as elastase, cyclooxygenase-2, and nitric oxide synthase-2, and mediators, such as tumor necrosis factor-α and interleukin-1β, without modifying macrophages. In addition, dihydrocucurbitacin B was able to decrease cell inflammation, infiltration, joint damage, and osteoclast activity [69].

In another study conducted by Ren et al., 2012 [70], the antiproliferative effect of 23,24-dihydrocucurbitacin F, another derivative, on human prostate cancer cells was studied, with the results demonstrating that this compound had the ability to stop cell growth and inhibit the cell cycle in the G2/M phase, which could be directed through the induction of actin aggregation and cofilin-actin rod formation by disruption of cytokinesis with minimal effect on microtubules.

In addition, it has been possible to determine an important antihyperglycemic effect of 23,24-dihydrocucurbitacin D and 2-*O*-*β*-glucopyranosyl-23,24-dihydrocucurbitacin D isolated from *Ibervillea lindheimeri* in diabetic mice, where both compounds reduced blood glucose in diabetic mice compared with healthy controls, due to translocation of glucose transporter type 4 (Glut4) to the plasma membrane (PM) on epididymal adipose tissue (EAT) as its main target; however, these cucurbitacins also produce activation of AMP-induced protein kinase (AMPK) in soleus muscle (SM) or dual activation of AMPK and protein kinase B (AKT) in EAT independent of insulin. In addition, both cucurbitacins had the ability to bind to different sites of activation of cystathionine β-synthetase (CBS) and showed a high affinity to the binding site of the competitive inhibitor AKT G98, which possibly contributed to the activation in adipose tissue [71].

In a recent study by Qing et al., 2022 [72], it was found that postmodified derivatives of cucurbitacin C (CuC) from *Cucumis sativus,* which were named Cu6 and Cu7, showed growth inhibition capabilities against the tumor cell lines HepG2, A549, DU145, and HCT116 by apoptosis induction.

However, it has been found that derivatives of cucurbitacins can have a different effect from their predecessors; for example, it has been described that cucurbitacin D has a significant effect against different cancer lines of lung cancer or human colon cancer, unlike its derivative 2-*O*-glucoside of cucurbitacin D, which does not show any relevant anticancer activity in this way. It is inferred that the different types of derivatives of cucurbitacins will not necessarily have the same effect as that of the class to which they belong [73].

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