EXCLI Journal 2015;14:562-566 – ISSN 1611-2156
Received: April 20, 2015, accepted: April 27, 2015, published: May 05, 2015

Letter to the editor:

AN UPDATED REVIEW OF CUCURBITACINS AND THEIR BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

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http://dx.doi.org/10.17179/excli2015-283

Dear Editor,

Cucurbitacins (Cus) are a class of highly oxidized tetracyclic triterpenoids that confer a bitter taste to cucurbits such as cucumber, melon, watermelon, squash, and pumpkin. To date, a large number of Cus and Cu-derived compounds have been isolated from the Cucurbitaceae family and from other species of the plant (Alghasham, 2013; Shang et al., 2014).

Cus have a range of biological and pharmacological activities that first attracted attention in the 1960s (Chen et al., 2012). Cucurbitacin B (CuB) and Cucurbitacin E (CuE) have been particularly widely studied (Lan et al., 2013). Recent reports have demonstrated that CuE has growth-inhibitory effects in the proliferation of many cancer cells such as bladder cancer, hepatocellular carcinoma, pancreatic cancer, breast cancer, and leukemia (Dong et al., 2010; Sörensen et al., 2012). CuB has been shown to have antimicrobial and anti-inflammatory activity. However, most reports on CuB focus on its anticancer activity. CuB inhibits the growth of human malignant cells, both in vitro and in vivo, and has been shown to be effective against breast cancer, head and neck squamous cell carcinoma, pancreatic cancer, hepatocellular carcinoma, osteosarcoma, and myeloid leukemia (Duangmano et al., 2010; Kausar et al., 2013; Guo et al., 2014a).

Consequently, natural and semisynthetic Cus are proposed as a promising source for the development of new drugs for the prevention and treatment of various cancers. Here, we summarize key recent studies that have evaluated the biological and pharmacological activities of Cu and its derivatives (Table 1).

Acknowledgements

This research was supported by Agriculture, Food and Rural Affairs Research Center Support Program, Ministry of Agriculture, Food and Rural Affairs.

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Table 1: Recent studies on Cus and their biological and pharmacological activities

Key message	Reference
CuB dose dependently inhibited lung cancer cell proliferation by cell cycle inhibition and cyclin B1 downregulation. CuB was suggested to be a useful agent in the chemotherapy of lung cancer.	Zhang et al., 2014
CuD was shown to have a blocking effect in the G1 phase of the cell cycle in nonsmall lung cancer-N6 cells prior to apoptotic cell death. This study provided new insight into the mechanisms of proliferation arrest in tumor cells and potentially opens new ways of treatment to target tumor growth.	Jacquot et al., 2014
CuE significantly inhibited triple negative breast cancer (TNBC) cell growth by inducing cell cycle G2/M phase arrest and apoptosis. Thus, CuE was shown to be a viable compound for developing novel TNBC therapeutics.	Kong et al., 2014
Reactive oxygen species (ROS) were shown to mediate CuB-induced DNA damage, G2/M arrest, and apoptosis in K562 leukemia cells. This study provided novel mechanisms to better understand the underlying anticancer mechanisms of CuB.	Guo et al., 2014b
CuE inhibited cell proliferation and modulated the expression of cell cycle regulators in cancer cells using A549, Hep3B, and SW480 cells. This study provided a novel mechanism that may contribute to the antineoplastic effects of CuE in cancer cells.	Feng et al., 2014
This study explored the antiproliferation and cell cycle G2/M arrest induced by CuE in colorectal cancer (CRC) cells, and suggested that CuE may have antitumor activities in established CRC.	Hsu et al., 2014
CuB mediated breast tumor growth suppression associated with the inhibition of HER2, an oncogenic receptor implicated in HER2/integrin signaling. The results suggest novel targets of CuB in breast cancer, both *in vitro* and *in vivo*.	Gupta and Srivastava, 2014
CuB was shown to have potent chemopreventive activity for prostate cancer, and a novel antitumor mechanism of CuB via inhibition of ATP citrate lyase phosphorylation signaling in human cancer was reported.	Gao et al., 2014
This study provided new insights into the molecular mechanisms underlying CuI-mediated glioblastoma multiforme (GBM) cell death, and suggested CuI as an efficacious therapy for patients harboring GBM.	Yuan et al., 2014
Cucurbitacin IIb (CuIIb) was shown to exhibit anti-inflammatory activity through modulating multiple cellular behaviors and signaling pathways, leading to the suppression of the adaptive immune response.	Wang et al., 2014
CuB showed potent inhibitory activity against hypoxia-inducible factor-1 (HIF-1) activation induced by hypoxia in various human cancer cell lines. The paper provided new insight into the anticancer mechanism of CuB's activity.	Ma et al., 2014
Cus were suggested as a new strategy to treat metabolic diseases and implicate STAT3 as a new target for the development of functional foods and drugs.	Seo et al., 2014
CuD extracted from *Trichosanthes kirilowii* was shown to be a potent therapeutic agent for breast cancer, blocking tumor cell proliferation and inducing apoptosis through the suppression of STAT3 activity.	Kim et al., 2013
CuI was suggested to have value as an adjunct chemotherapy agent.	Johnson et al., 2013
CuD was shown to initiate immunomodulating activity in macrophages, leading to inflammasome activation as well as enhancement of lipopolysaccharide signaling.	Song et al., 2013
CuE inhibited the growth of human breast cancer cells in a dose- and time-dependent manner, further indicating the potential clinical value of CuE for the prevention or treatment of human breast cancer.	Lan et al., 2013

Key message	Reference
CuE was shown to induce cell death by a mechanism that is not dependent on apoptosis induction, representing a promising anticancer agent for the prevention and treatment of human oral squamous cell carcinoma.	Hung et al., 2013
Both CuD and goyazensolide were shown to effectively inhibit the proliferation of neurofibromatosis type 2 (NF2)-deficient schwannoma and meningioma cells, suggesting that these natural compounds should be further evaluated as potential treatments for NF2-related tumors.	Spear et al., 2013
The induction of apoptosis and enhancement of autophagy was shown to contribute to the anti-inflammatory activity of CuIIa against inflammation-related diseases.	He et al., 2013
CuE was shown to display anti-inflammatory effects through the suppression of nuclear factor (NF)-κB nuclear translocation, leading to a decreased expression of tumor necrosis factor (TNF)-α and interleukin (IL)-1β in lipopolysaccharide-stimulated RAW 264.7 cells.	Qiao et al., 2013
The physical interaction of CuB with N-acetylcysteine and GSH in a cell-free system was demonstrated, suggesting that CuB interacts with and modulates cellular thiols to mediate its anticancer effects.	Kausar et al., 2013
Cucurbitacins I, D, and E were shown to present a potent cytotoxic activity toward the chondrosarcoma SW 1353 cell line, and are metabolized as sulfate and glucuronide conjugates.	Abbas et al., 2013
The combination of CuB at a relatively low concentration with either of the chemotherapeutic agents docetaxel or gemcitabine was shown to have a prominent antiproliferative activity against breast cancer cells without increased toxicity. This promising combination was suggested for therapeutic trials against breast cancer.	Aribi et al., 2013
CuB exhibited strong antiproliferative effects against breast cancer cells in a dose-dependent manner, and was shown to prominently alter the cytoskeletal network of breast cancer cells, inducing rapid morphologic changes and improper polymerization of the microtubule network.	Duangmano et al., 2012
CuE was shown to block breast cancer metastasis by suppressing tumor cell migration and invasion, and was suggested as a potential candidate for treating breast cancer metastasis.	Zhang et al., 2012

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