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Letter to the editor:

CURRENT RESULTS ON THE BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES OF INDOLE-3-CARBINOL

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Dear Editor,

Indole-3-carbinol (I3C; C_9H_9NO) is a phytochemical that is derived from the breakdown of the glucosinolate, glucobrassicin. I3C is present at relatively high levels in most cruciferous vegetables such as broccoli, cabbage, cauliflower, brussels sprouts, collard greens, and kale (Fujioka et al., 2016; Licznerska and Baer-Dubowska, 2016). The enzyme, myrosinase (β-thioglucosidase), catalyzes the hydrolysis of glucosinolates in intact plant cells (Zhao et al., 2015). After chopping or chewing of raw cruciferous vegetables, the plant cells are damaged and glucobrassicin is exposed to myrosinase. This catalyzes the conversion of glucobrassicin to a glucose molecule and an unstable aglycone, which is hydrolyzed to thiohydroximate-O-sulfonate (de Vos et al., 2008). If the sulfate ion is released spontaneously, this may form another unstable intermediate, 3-indolylmethylisothiocyanate. This released compound readily converts to a thiocyanate ion and I3C (Kim et al., 2008).

I3C has recently become available as a nutritional supplement and it provides an attractive natural product for drug development in the pharmaceutical industry. It has been reported to show diverse promising biological properties, with anti-atherogenic, antioxidant, anti-carcinogenic, and anti-inflammatory activities (Fuentes et al., 2015; Maruthanila et al., 2014). I3C has attracted considerable attention in recent years within the pharmaceutical and functional food industries. Here, we summarize recent studies performed to evaluate the biological and pharmacological activities of I3C (Table 1).

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Table 1: Recent studies on the biological and pharmacological activities of Indole-3-carbinol

Key findings	Reference
I3C produced anti-leukemic effects through aryl hydrocarbon receptor activation, which is associated with programmed cell death and G1 cell cycle arrest. This could provide a novel treatment possibility in acute myeloid leukemia.	Mohammadi et al., 2017
I3C reduced the expression of endothelial and leukocytic adhesion proteins, resulting in attenuated leukocyte-endothelial cell interactions during ischemia-reperfusion. Accordingly, dietary supplements containing I3C may be beneficial for the treatment of ischemia-reperfusion-induced inflammation.	Ampofo et al., 2017
I3C feeding attenuated the symptoms of peanut allergy. This dietary compound could therefore positively influence vital immune functions within the gut.	Hammerschmidt-Kamper et al., 2017
The oncogenic signal transducer and activator of transcription 5/Akt pathway was a cellular target for I3C in chronic myeloid leukemia cells.	Safa et al., 2017
Combined application of linagliptin and I3C significantly improved ovarian morphology in a polycystic ovarian syndrome group. Combined use of these compounds was more effective than either drug alone. Combined application of linagliptin/I3C could contribute to the amelioration of this condition.	Kabel et al., 2017
This preliminary structure-activity relationship study of a series including I3C and closely related compounds identified a potent lead compound with low micromolar activity against a particularly resistant glioblastoma cell line, suggesting a new platform for future development of a novel therapy in this area.	Sherer et al., 2017
Nano-capsules formulated with rose hip oil increased the antitumor effects of I3C on breast cancer (MCF-7) and glioma (C6) cells by about two-fold, without a significant reduction in astrocyte cell viability. This formulation might represent a promising innovation for cancer treatment.	Gehrcke et al., 2017
A novel set of anti-cancer compounds were derived from I3C analogues. These could be used to treat human melanomas and other cancers expressing indolecarbinol-sensitive target enzymes.	Quirit et al., 2017
Hazardous effects of I3C supplementation on the gastrointestinal tract in an immuno-compromised model were reported, indicating that caution is warranted when using I3C as a dietary supplement.	Fletcher et al., 2017
I3C reduced the impact of *Clostridium difficile* infection in mice via both aryl hydrocarbon receptor-dependent and -independent mechanisms. Dietary supplementation of I3C could provide a potential therapy for the prevention and amelioration of *C. difficile* infection.	Julliard et al., 2017
The oncogenic BRAF V600E mutation is considered to represent a cellular target of I3C, indicating that this compound is a potential candidate for novel mono- or combination therapies for melanoma.	Kundu et al., 2017
Lipid droplet accumulation in adipocytes was reduced by I3C and adipocyte-stimulated angiogenesis was suppressed in endothelial cells. This suggested that I3C could provide a potential therapeutic agent for obesity and obesity-associated disorders.	Wang et al., 2016
The molecular mechanism underlying the effects of I3C in colorectal cancer may be novel. Continued preclinical studies of both I3C and the aryl hydrocarbon receptor pathway are required, and may lead to novel diet-derived treatments for colon cancer.	Megna et al., 2016
I3C reduced cisplatin-induced nephrotoxicity. This compound reduced the expression of calcitonin gene-related peptide; this may play a positive role in the pathogenesis of cisplatin-induced renal injury.	El-Naga and Mahran, 2016
I3C inhibited estradiol-mediated stimulation of rat osteoblast proliferation and differentiation and increased the 2-hydroxylation of estrone, thus promoting the formation of inactive and anti-estrogenic metabolites. These findings suggested that the anti-estrogenic effect of I3C is mediated by 2-hydroxy estradiol via the estrogen receptor α in neonatal rat osteoblasts.	Enríquez et al., 2016

Key findings	Reference
Acetylsalicylic acid (aspirin)-mediated regulation of Wnt signaling and I3C-targeted signaling pathways converged at distinct DNA elements within the microphthalmia-associated transcription factor isoform M promoter, disrupting the expression of this gene and thus modulating melanoma cell proliferation.	Poindexter et al., 2016
I3C plus silibinin acted as a potential lung cancer chemopreventive agent in smokers/former smokers with chronic pulmonary inflammatory conditions.	Song et al., 2015
I3C reduced the cytotoxicity of dexamethasone by blocking the over-accumulation of reactive oxygen species and enhancing the expression of Nrf2. The findings of this study could provide a sustainable strategy for molecular intervention in glucocorticoid-induced osteoporosis, using natural products.	Lin et al., 2015
I3C was reported to suppress the acute hepatic inflammation caused by staphylococcal enterotoxin B; this was mediated by decreasing the expression of miR-31, and subsequent caspase-2-dependent apoptosis in T cells.	Busbee et al., 2015
I3C was used in combination with anthracyclines in acute lymphoblastic leukemia, providing a new insight into the development of a novel combination therapy for this condition.	Safa et al., 2015
I3C was used as a miR-21 regulator, leading to repression of the phosphatase and tensin homolog/Akt pathway, which might provide a new approach to the eradication of drug-resistant cells. This could improve therapeutic outcomes in patients diagnosed with hepatocellular carcinoma.	Wang et al., 2015
Estrogen receptor α signaling enhanced the pro-apoptotic effect of I3C-mediated induction of the aryl hydrocarbon receptor in luminal breast cancer cell lines; this involved oxidative stress-induced upregulation of ATF-3 (activating transcription factor 3) and the downstream protein, BH3 (Bcl-2 homology3).	Caruso et al., 2014
I3C and its condensation dimer (3,3'-diindolylmethane) extended survival and reduced tumor burdens in mice with Epstein-Barr virus-positive Burkitt's lymphoma (DAUDI) cells.	Perez-Chacon et al., 2014
The E3 ubiquitin-protein ligase, NEDD4-1, was identified as a new I3C target protein. I3C disrupted this enzyme activity, triggering stabilization of a tumor suppressor (wild-type phosphatase and tensin homologue detected on chromosome 10) and thus inducing an antiproliferative response in melanoma.	Aronchik et al., 2014
Exposure to low levels of I3C increased adenovirus-mediated oncolysis and cytotoxicity in human carcinoma cells via synergistic upregulation of apoptosis. A dietary supplement containing I3C may help to prevent cancer and improve oncolytic therapies.	Chen et al., 2014
I3C produced an anti-adipogenic effect in zebrafish. This study suggested that I3C could reduce lipid accumulation within cells via several molecular mechanisms.	Choi et al., 2014
The growth of nasopharyngeal carcinoma cells was reduced by I3C, which induced apoptosis both *in vivo* and *in vitro*. This study suggested that I3C suppressed the phosphatidylinositol 3-kinase/Akt pathway.	Mao et al., 2014
Antioxidant scavenging was enhanced in mice treated with 3,3'-diindolylmethane; this effect was greater than that of I3C, which was comparable to the standard drug, metformin.	Jayakumar et al., 2014
Maternal I3C feeding during pregnancy protected male offspring exposed to bisphenol A, indicating a reduction of harmful effects on the prostate.	Brandt et al., 2014
Plant-derived indoles were potent suppressors of staphylococcal enterotoxin B-induced T cell activation and cytokine production; they may mediate these effects by acting as histone deacetylase inhibitors.	Busbee et al., 2014

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Conflict of interest

The authors declare no conflict of interest.

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