Abstract. The hydrolysis product of glucobrassicin, indole-3-carbinol (I3C), is metabolized to a variety of products, including the dimeric 3,3'-diindolylmethane (DIM). Both I3C and DIM exert a variety of biological and biochemical effects. Most of these effects appear to occur because I3C modulates several nuclear transcription factors. I3C induces phase I and phase II enzymes that metabolize carcinogens, including estrogens. Administration of either I3C or DIM results in increased 2-hydroxylation of estrogens. I3C also enhances DNA repair by affecting several of the proteins involved in this process. I3C induces both G1 cell cycle arrest and apoptosis. All of these activities lead to anticancer effects. Although I3C has been shown to protect against tumor induction by some carcinogens, it has also been observed to promote tumor development in animal models. In humans, I3C and DIM affect the metabolism of estrogens. Concerns have been raised that I3C might increase the formation of estrogen metabolites that induce or promote cancer, but this has not been demonstrated. I3C has been found to be effective in treating some cases of recurrent respiratory papillomatosis, and it may have other clinical uses.

Indole-3-carbinol (I3C, CAS No. 700-06-1, Figure 1) is a putative chemopreventive compound obtained from ingested cruciferous vegetables such as cabbage, broccoli and cauliflower (1). I3C has been shown to reduce tumorigenesis in animal models (2, 3), but it has also been found to have tumor-promoting activity in some carcinogen-treated animals (3). I3C also appears to enhance some therapeutic regimens (4, 5).

I3C is metabolized to several compounds, including the biologically-active dimer 3,3'-diindolylmethane (DIM, Figure 1) (6, 7). It is possible that DIM exerts some of the effects attributed to I3C, which has been shown to induce enzymes that metabolize carcinogens for excretion, modulate DNA repair, affect nuclear regulatory factors and induce apoptosis and cell cycle arrest. To evaluate the potential efficacy of I3C to reduce cancer risk and/or enhance therapy, it is important to understand the mechanisms by which I3C, and in some cases DIM, exert their effects.

Metabolism and Distribution of I3C in the Body

Under the acidic conditions of the gastric tract, I3C undergoes condensation to form several oligomeric products, particularly DIM (8). The tissue absorption and distribution of I3C and its condensation products has been studied in female CD-1 mice (9). I3C itself was rapidly absorbed and eliminated from the plasma and tissues within 1 h after an oral dose (200 mg/kg) had been administered. The I3C was concentrated particularly in the liver and kidney within 15 min; this was also the time of the highest concentration of I3C in the heart, lung and brain. At its maximum, the level in the liver was 6-fold greater than that in the plasma. DIM was detected in tissues and plasma within 15 min of I3C administration, and it persisted for at least 6 h. The level of DIM was highest in the liver, reaching 14-fold higher concentrations within 15 min and persisting at high levels for more than an hour. DIM was also concentrated in the kidney, as well as the lung and heart. In addition, other metabolites of I3C were observed in this study. While this study demonstrated the absorption, metabolism, distribution and elimination of I3C in mice, the fate of I3C in humans may be different due to a variety of factors. DIM has been detected in plasma, however, within 8 h following administration of 400 mg I3C to human volunteers (10).

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Key Words: Indole-3-carbinol (I3C), 3,3'-diindolylmethane (DIM), anticancer effects, estrogen metabolism, cell cycle arrest, apoptosis, review.

The Natural Chemopreventive Compound
Indole-3-carbinol: State of the Science

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Induction of Metabolizing Enzymes

I3C induces several enzymes that catalyze the metabolism of carcinogens. These include the phase I cytochrome P450 (CYP) 1 and CYP2B families and the phase II glutathione-S-transferases (GSTs).

When ovariectomized female Crj:Donryu rats received 2000 ppm I3C in the diet for 2 wk, expression of CYP1A1, CYP1A2 and CYP1B1 mRNA in the liver was determined by RT-PCR (11). CYP1A1 mRNA was not detected in the liver of control rats, although both CYP1A2 and CYP1B1 mRNAs were detected. In the livers of I3C-treated rats, the expression of all 3 CYP isoforms was approximately the same relative to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and all 3 were significantly induced. CYP1A1 appeared to be induced to the greatest extent. Another group of these rats were given a single dose of 20 mg/kg body weight N-ethyl-N’-nitro-N-nitrosoguanidine, followed by 500 ppm I3C in the diet for up to 12 months (11) and the levels of estradiol (E2) 2-, 4- and 16α-hydroxylase activities in the liver were determined after 3, 6, 9 and 12 months. The 2- and 4-hydroxylase activities in the livers of these I3C-treated rats were significantly elevated compared to the levels in the control rats after 12 months of treatment (p<0.01). This finding is consistent with the higher levels of expression of CYP1A1/2 and CYP1B1 observed after 2 wk of administration of dietary I3C, but continued induction of enzyme expression for the 12 months of treatment was not directly demonstrated.

Administration of I3C to female Sprague-Dawley rats by oral gavage at a high level (250 mg/kg body weight) for 4 or 10 days induced the expressions of CYP1A1, CYP1B1 and CYP2B1/2 at the mRNA level in the liver and CYP1A1 in the mammary gland by approximately 2-fold, as determined by RT-PCR (12). Liver microsomes from these rats demonstrated enzymatic activities indicative of induction of CYP1A1, CYP1A2 and CYP2B1/2. The metabolism of E2 to hydroxylated products, especially 2-hydroxyestradiol (2-OHE2), was also induced. The effects on these carcinogen-metabolizing enzymes all required administration of I3C at a high dose, suggesting that the biological activities of I3C observed at lower doses may not be related to effects on carcinogen metabolism.

I3C has, however, been shown to affect metabolism in humans. In one study, men received 500 mg (6-7 mg/kg) of I3C daily and their urinary excretion of estrogen metabolites was determined before and after ingestion of I3C for 7 days (15). Analyses were conducted using ion-exchange chromatography coupled with gas chromatography-mass spectrometry. The level of 2-hydroxyestrone (2-OHE1) in the urine almost doubled, a statistically significant change (p<0.01). Changes in the levels of 2-OHE2 and 4-OHE1 were not significant (2-fold increase, p<0.30 and 35% increase, p<0.44, respectively). The levels of most of the other estrogen metabolites decreased, with 16α-OHE1 falling 45%. In this same study, women received 400 mg (6-7 mg/kg) I3C daily and their urinary excretion of estrogens was determined before and after ingestion of I3C for 2 months. The urinary excretion of 2-OHE1 and 2-OHE2 was significantly increased after ingestion of I3C (doubled, p<0.046 and 50% increase, p<0.033, respectively). The level of urinary 4-OHE1 increased by approximately 27%, but the change was not significant (p<0.16). The levels of most other metabolites decreased. The levels of E1 and E2 were decreased in both men and women by ingestion of I3C. In this small study (7 men and 10 premenopausal women), there was great variability between individuals in the effects of I3C on the levels of the 13 estrogen compounds analyzed.

In a more recent study, 17 women from a high-risk breast cancer cohort (16 premenopausal; 1 post-menopausal) ingested a placebo for 4 wk, 400 mg/day I3C for 4 wk and 800 mg I3C/day for 4 wk (16). A number of serum and urinary biomarkers, as well as several enzyme activities, were measured at the end of each 4-wk period. After the 800 mg I3C/day regimen, serum E2, progesterone, luteinizing hormone, follicle-stimulating hormone and sex hormone...
binding globulin levels showed no significant change compared to the placebo. CYP1A2 increased in almost all of the subjects by an average of 4.1-fold. Subjects with naturally high N-acetyltransferase-2 (NAT-2) activity showed small decreases in activity, but I3C did not alter the NAT-2 activity in subjects with normally low activity. GST activity in lymphocytes was increased 69%. The higher level of CYP1A2 activity was consistent with a 66% increase in the ratio of 2-OHE$_1$/16α-OHE$_1$ in the urine. These biomarkers were also analyzed after ingestion of the 400 mg/day dose of I3C. The maximum ratio of 2-OHE$_1$/16α-OHE$_1$ in the urine was achieved after the 400 mg/day regimen and the ingestion of 800 mg I3C/day did not increase the ratio. These results suggest that 400 mg/day may be an effective dose of I3C to achieve chemoprevention against estrogen-induced cancers.

Some effects of administering the I3C dimer, DIM, to women have also been investigated (17). Healthy women with a high risk of breast cancer were administered oral DIM. A group of 10 postmenopausal women received 108 mg DIM/day and 9 postmenopausal women received a placebo for 1 month. First-morning urine samples were obtained on days 0 and 31; they were analyzed for E$_1$, E$_2$, estriol, 2-OHE$_1$ and 16α-OHE$_1$. Consumption of DIM led to a significant increase in the level of urinary 2-OHE$_1$ ($p<0.02$) and a non-significant increase in the 2-OHE$_1$/16α-OHE$_1$ ratio, suggesting that DIM induces CYP1A1.

**Effects on DNA Repair**

I3C and its dimer, DIM, have been shown to affect the repair of DNA damage in a variety of ways (Figure 2). Several of these effects are related to estrogen receptor-α (ER-α). In addition, I3C affects the expressions of the tumor suppressor gene BRCA1 and other proteins involved in DNA repair processes, for example, RAD51, as well as growth arrest and DNA damage (GADD) proteins.

BRCA1 is co-localized with RAD51 in vivo and can be co-immunoprecipitated with it (18). In response to DNA damage, BRCA1 becomes phosphorylated and relocates to the nucleus along with RAD51 (16), apparently participating in repair of the DNA damage. BRCA1 has been associated with repair of double-strand breaks in mouse embryos (19). BRCA1 also regulates the transcription of other DNA damage response proteins, such as GADD45a (20, 21).

Addition of I3C to the culture medium (10-125 μM) up-regulated the amount of BRCA1 protein made in 3 breast cancer cell lines, MCF-7, T-47D and MDA-MB-231 (22). Furthermore, I3C and BRCA1 together inhibited the transcriptional activity of ER-α, inhibiting proliferative activity in these cells. This effect appeared to be mediated through c-Myc (23). BRCA1 also inhibited the transcriptional activation function AF-2 in ER-α in both breast (MCF-7, T-47D and MDA-MB-231) and prostate (LNCaP, TsuPr-1 and Du-145) cancer cells (24). This anti-proliferative effect of I3C provides one of its anticancer activities.

I3C (50 or 100 μM in medium) also inhibited the capacity for cell adhesion, migration and invasion in the estrogen receptor-negative breast cell line MDA-MB-468 and the estrogen receptor-positive breast cell line MCF-7 (25). This appeared to be due in part, to I3C-induced up-regulation of BRCA1.

The effects of I3C (50-300 μM in medium) and DIM (100 μM in medium) on a number of tumor-derived and non-tumor-derived cell lines was studied by microarray, semi-quantitative RT-PCR and/or Western blot analysis (14). The transcriptional regulatory protein GADD153 was induced in the cervical cancer cell line C33A by both I3C and DIM within 4 h. This effect is consistent with a response to DNA damage in these cells. By using microarray analyses, altered transcription of many other genes within 6 h of DIM treatment was detected in normal, immortalized and tumor-derived cell lines.

In summary, I3C and DIM affect the proliferation of cells containing DNA damage and induce DNA repair proteins. These activities would produce anticancer effects.

**Effects on Nuclear Regulatory Factors**

I3C (10-125 μM in medium) and/or DIM (10-50 μM in medium) have been observed to affect several nuclear transcription factors, including the ER, aryl hydrocarbon receptor (AhR), Sp1 and NF-κB, in a variety of complex ways, some direct and some indirect (26). These effects then modulate the expression of genes that affect carcinogen metabolism, DNA repair, cell cycle progression and apoptosis. For example, both I3C and DIM can bind to the AhR, resulting in induction of CYP1A1 and/or CYP1B1, which metabolize estrogens and other carcinogens.

In concert with BRCA1, I3C (10-125 μM in medium) inhibited the transcriptional activity of ER-α in breast and cervical cancer cell lines (22). This can result in the diminished proliferation of cells, an antitumor effect. I3C (15-100 μM in medium) appeared to induce apoptosis in MCF-10A-derived cell lines by inhibiting activation of NF-κB (27). This inhibition may be a direct effect or may be modulated by a NF-κB kinase (26).

There is substantial cross-talk between the nuclear transcription factors mentioned above, as well as others. The effects of I3C and DIM on the expression of genes may well arise from interactions between several of these factors. Some of these interactions have been reviewed already (26). In general, the net result of these effects, however, is to reduce the proliferation of tumor cells.

**Induction of Cell Cycle Arrest**

One of the major antitumor effects of I3C is to induce G1 cell cycle arrest of cancer cells (26, 28-31). This has been
I3C modulated cyclin-dependent kinases, but the specific factors were different. I3C-induced changes in the nuclear transcription factor Sp1 appeared to play a critical role in G1 cell cycle arrest (32). I3C interfered with the interaction of Sp1 with the DNA-binding site of the cyclin-dependent kinase (CDK6) promoter (33), as well as inducing Sp1 binding to the CDK2 inhibitor p21 (6).

I3C (100 μM in medium) has been shown to inhibit CDK2-specific kinase activity, inducing G1 cell cycle arrest in MCF-7 human breast cancer cells (28). The inhibition appears to arise from a change in the CDK2 protein complex from the enzymatically-active 90 kDa complex to a larger complex with reduced kinase activity. This effect was specific to I3C and was not induced by 30 μM DIM in the medium (28), although DIM did induce G1 cell cycle arrest (28, 29). Inhibition of the expression of CDK6 and induction of G1 cell cycle arrest in human breast cancer cells by I3C was independent of estrogen receptor signaling (32). I3C (25-100 μM) has also been shown to down-regulate the expression of CDK6 and CDK6 kinase activities in PC3 prostate cancer cells and up-regulate the expression of CDK6 inhibitors (30). These effects induced G1 cell cycle arrest in PC3 cells.

G1 cell cycle arrest was also induced by I3C (300 μM in medium) in the immortalized, but not transformed, MCF-10A human breast epithelial cells (29). In these cells, the cell cycle arrest by I3C appeared to be mediated through phosphorylation of p53 and several other signaling molecules to induce the CDK inhibitor p21. In the immortalized HaCaT human keratinocyte cancer cell line, I3C (200-500 μM in medium) induced G1 cell cycle arrest through another CDK inhibitor, p15INK4b (31).
Induction of Apoptosis

In addition to inducing G1 cell cycle arrest, I3C can arrest cell growth by pushing a variety of cancer cells into apoptosis. I3C has been shown to induce apoptosis by affecting specific cell signaling processes. In premalignant and malignant derivatives of the human breast epithelial cell line MCF-10A, treatment with I3C (15-100 μM in medium) inhibited Akt kinase activity and activation of Akt (27). This, in turn, abrogated the NF-κB pathway, reducing the DNA binding activity of NF-κB. Significantly, I3C did not induce this effect in the immortalized, but not transformed, MCF-10A cells themselves. DIM (15-60 μM in medium) also induced these effects in a malignant derivative of MCF-10A cells, but not in the non-tumorigenic parent MCF-10A cells (34). Thus, it appears that I3C and DIM may induce apoptosis in breast cancer cells by inhibiting the Akt family of protein kinases, leading to inactivation of the NF-κB signaling pathway. I3C and DIM inhibited the Akt and NF-κB pathways in PC3 prostate cancer cells (30, 35, 36). The induction of apoptosis by this pathway was independent of the p53 gene (37).

Another apoptotic effect of I3C and DIM has been demonstrated in human colorectal carcinoma (HCT-116) cells. Both I3C (25-100 μM in medium) and DIM (12.5 or 25 μM in medium) up-regulated the expression of a TGF-β superfamily gene, nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1), which is pro-apoptotic and represses proliferation of these cancer cells (38). I3C-induced up-regulation of NAG-1 expression appears to proceed through a p53-independent pathway.

E2 stimulates the growth of many tissues, exerting anti-apoptotic effects on cells. The ability of I3C (200 μM in medium) to counterbalance the effects of E2 was investigated in 3 different cervical cancer cell lines (39). I3C, indeed, induced apoptosis in the cervical cancer cell lines and counteracted the anti-apoptotic effects of E2 in a dose-responsive manner. These effects may occur through the Bcl-2 signaling pathway. The expression of Bcl-2 was reduced by I3C in the culture medium, but the presence of E2 in the medium partially restored the level of Bcl-2 in the cells and reduced apoptosis.

I3C appears to exert anti-proliferative effects in human non-small cell lung adenocarcinoma cells (A549) through a very different mechanism. I3C inhibited the proliferation of A549 cells in a dose-responsive manner at relatively high concentrations of I3C (50-250 μM) in the medium (40). I3C, however, did not increase the number of cells with subdiploid DNA contents, which is an indication of apoptosis, after 24 or 48 h of treatment. Although I3C did not induce apoptosis in A549 cells at concentrations as high as 250 μM in the medium, 50-250 μM I3C did induce apoptosis in human breast and prostate cancer cells (37,41). The authors speculate that the difference in how I3C exerts its anti-proliferative effects in lung cancer cells as compared to human breast and prostate cancer cells lies in the hormone-responsiveness of the breast and prostate cells.

Effects in Animal Models

In laboratory animals, I3C has been found to inhibit the development of chemically-induced tumors (42), as well as the spontaneous development of tumors in estrogen-susceptible tissues, such as the mammary glands (70-200 mg/kg in mice) and endometrium (200-1000 ppm in the diet of rats) (43, 44). In addition, low doses of DIM (5 mg/kg every other day) inhibited the growth of mammary tumors in Sprague-Dawley rats (7).

More recently, the ability of I3C (injected twice weekly at 20 μg/rat i.v. or 80 μg/rat i.p.) to inhibit prostate cancer was investigated in Copenhagen rats injected with the transplantable prostate cancer cell line, MAT-LyLu (45). When injected either i.v. or i.p., I3C reduced the incidence, proliferation and metastasis of tumors arising from the MAT-LyLu cells. Treatment with I3C almost completely eliminated lung metastases and lengthened the lifespan of the tumor-bearing animals dramatically.

I3C was also found to reduce the development of altered hepatic foci in carcinogen-treated Wistar rats (46). I3C was administered by oral intubation (0.5 mg/kg for 5 days) following initiation of hepatocarcinogenesis with diethyl-nitrosamine and promotion with 2-acetylaminofluorene and partial hepatectomy.

Some evidence suggests that DIM has anti-angiogenic properties that could be useful in chemoprevention. DIM (5 μM in medium) inhibited the proliferation, migration, invasion and capillary tube formation of cultured human umbilical cord vein endothelial cells (47). DIM inhibited G1 cell cycle arrest in these cells, down-regulated the expressions of CDK2 and CDK6, and up-regulated the CDK inhibitor p27Kip1. DIM (5 mg/kg injected s.c.) inhibited angiogenesis in an in vivo assay of neovascularization in female C57Bl/6 mice. In addition, injection of DIM (5 mg/kg) into female nude mice inhibited growth of the MCF-7 human breast cancer cells in the mice (47). These results point to a number of the chemopreventive properties that I3C and DIM possess.

I3C has also been shown to protect female rats against the hepatotoxicity of an antitumor drug, without reducing the efficacy of the drug against mammary carcinomas. Prior ingestion of 0.5% I3C in the diet almost eliminated hepatotoxicity in female Fisher rats transplanted with the 13762 mammary carcinoma (48). In this study ET-743 (Trabectidin) reduced the size of the carcinomas to the same extent in the presence or absence of I3C. DIM did not have the protective effects that I3C had.

Nonetheless, dietary I3C has also been shown to promote carcinogen-induced carcinomas. When rat uterine adenocarcinomas were induced with N-ethyl-N’-nitro-N-
other metabolites, including 16α-OHE1, decreased 2-OHE1 to 16α-OHE1, were investigated in a double-blind study, specifically their 2-hydroxylation and the ratio of urinary estrogen metabolites was analyzed by gas chromatography-mass spectrometry (15). The excretion of 2-OHE1 and 2-OHE2 increased significantly, while the excretion of 7 other metabolites, including 16α-OHE1, decreased significantly, but the marginal increases in urinary excretion of 4-OHE2 in both men and women were not significant (35%, \( p < 0.25 \) and 27%, \( p < 0.16 \), respectively).

In another study, 17 women at high risk of breast cancer ingested 400 mg I3C daily for 4 weeks, followed by 800 mg daily for 4 wk (16). The ratio of urinary 2-OHE1 to 16α-OHE1 was increased by about 65% after the 400 mg dose or the 800 mg dose, but the actual values were not reported. This increase in the ratio was mirrored by an increase in the expression of CYP1B1 nor the level of urinary 4-OHE1 was included among the parameters used in this study.

The effects of DIM on the metabolism of estrogens, specifically their 2-hydroxylation and the ratio of urinary 2-OHE1 to 16α-OHE1, were investigated in a double-blind study of 10 women ingesting 108 mg of absorbable DIM daily for 30 days and 9 women ingesting a placebo daily for 30 days (17). DIM significantly increased the level of urinary 2-OHE2 (\( p = 0.045 \)) and the ratio of 2-OHE1/16α-OHE1, but the 47% increase in the ratio was not statistically significant (\( p = 0.059 \)). These results suggest that ingestion of absorbable DIM increased the 2-hydroxylation of estrogens.

In summary, ingestion of I3C or absorbable DIM increased the 2-hydroxylation of estrogens in humans, as seen in the higher levels of urinary 2-hydroxylated estrogens. No statistically significant data have been published on the possible effects of I3C or DIM on 4-hydroxylation of estrogens in humans.

**Clinical Use of I3C**

I3C has been used to treat patients with recurrent respiratory papillomatosis (4, 5, 49). In a prospective study, 24 adult patients and 9 pediatric patients were treated with 200 mg of I3C twice daily, or a dose proportional to weight for the pediatric patients (4). Ten adult patients and 1 pediatric patient had a complete response to I3C and did not require further surgery during a follow-up period of 31 to 75 months (mean=56.7 months). Seven adult patients and 3 pediatric patients had a partial response to I3C and required surgery less often during a follow-up period of 41 to 76 months (mean=56.2 months). Seven adult and 5 pediatric patients had no response to I3C therapy during a mean follow-up period of 59.2 months. No immediate or long-term side-effects from the I3C therapy were detected. The varying effectiveness of I3C against recurrent respiratory papillomatosis cannot be explained, but the authors speculate that it might be related to differences in estrogen metabolism. I3C was more effective in adult patients, while its use in pediatric patients appears to be less warranted.

In a related study with an 8-year-old girl with recurrent respiratory papillomatosis, I3C was used as adjuvant therapy with Cidofovir, an effective drug against human papilloma virus (50). The combination, administered by intralesional and i.v. injection, achieved a complete remission of lung lesions, which was sustained for at least 24 months (5).

The chemopreventive properties of I3C are also being investigated by the National Cancer Institute in a phase I clinical prevention trial against breast cancer (51).

**Summary and Conclusion**

The hydrolysis product of glucobrassicin, I3C, is metabolized in humans in a variety of ways; both I3C and its dimeric product DIM have been shown to affect a number of cellular functions (Figure 2). These include induction of enzymes that metabolize carcinogens, such as the cytochrome P450s. Some of these CYP isoforms also metabolize estrogens. I3C induces DNA repair proteins, cell cycle arrest and apoptosis, as well as affecting nuclear transcription factors and other cell signaling molecules. Most of these effects of I3C and DIM are anticancer effects. I3C has been shown to have antitumor effects in animal models, but has also been found to promote tumor development following treatment of the animals with specific carcinogens.

Through the induction of CYP isoforms, I3C and DIM affect the metabolism of estrogens in humans (Figure 2). Ingestion of I3C has been suggested to raise the levels not only of urinary 2-catechol estrogens (2-OHE1 and 2-OHE2), but also of urinary 4-catechol estrogens (4-OHE1 and 4-OHE2) (15). Concerns have been raised about the safety of I3C (52), in particular that increased levels of the 4-catechol estrogens could lead to the enhancement or promotion of cancer (52). This could be a valid concern about the safety of I3C, since elevated levels of 4-catechol estrogens have been associated with breast cancer (53-55).
No data are available, however, showing significant elevation of 4-catechol estrogens in humans following ingestion of I3C. The data acquired to date (15) show only marginal, non-significant increases in 4-catechol estrogens. Furthermore, the catechol estrogens can be methylated to form methoxyestrogens, which do not pose a risk for cancer. I3C appears to induce the formation of the 2- and 4-catechol estrogens more effectively than DIM. The formation of higher levels of catechol estrogens is generally accompanied by lower levels of 16α-hydroxyestrogens. This could be beneficial in reducing the risk of cancer because the catechol estrogens, especially 4-catechol estrogens, can be methylated, removing them as risk factors, whereas 16α-hydroxyestrogens cannot be methylated to reduce their potential to induce mitogenesis. These considerations indicate that I3C may provide more benefits and fewer risks than DIM.

Few side-effects of I3C or DIM ingestion by humans have been reported. Further studies of both I3C and DIM in humans should resolve questions about safety issues and demonstrate their efficacy as chemopreventive and/or therapeutic compounds.

Acknowledgements

This research was supported by Grant P01 CA49210 from the National Cancer Institute and Grant DAMD17-03-10229 from the Department of Defense Breast Cancer Research Program. Core support at the Eppley Institute was provided by grant P30 CA36727 from the National Cancer Institute, U.S.A.

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