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REPORT

I3C vs DIM

Indole-3-carbinol is a phytochemical found in cruciferous vegetables such as cabbage. It shows great potential in preventing cancer, especially hormone-related cancers such as breast and prostate. Now available as a supplement, I3C is hugely popular both as an antioxidant and as a cancer fighter. Research on I3C dates to the 1960s when it was investigated for its actions against chemical carcinogens. Since that time, researchers have been able to show that I3C has powerful and diverse ways of stopping cancer.

Recently, it was brought to our attention that negative statements were being made about I3C. These were being generated by a man who owns a patent on a product he wants people to buy instead of I3C. The product is DIM (3,3'-Diindolylmethane). DIM is formed naturally when I3C is broken down in the gut. Unlike I3C, there are no published human studies on DIM. In fact, there are few published studies at all. This is one of the reasons we do not recommend substituting DIM for I3C.

Who is Michael Zeligs, and why is he saying negative things about I3C?

Michael Zeligs is a doctor who has a patent for a DIM product that combines DIM with d-alpha-tocopheryl polyethylene glycol-1000 succinate to make it absorbable by the gut.

What is d-alpha-tocopheryl polyethylene glycol-1000 succinate?

Polyethylene glycol is a detergent-like chemical that breaks down fat (not to be confused with propylene glycol which is used in anti-freeze). D-alpha-tocopheryl succinate is a synthetic, water-soluble form of vitamin E. According to Zeligs, this is the first time this combination has been used for a supplement.

What is DIM, anyway?

DIM is a break-down product of I3C. DIM forms naturally in the stomach when I3C is ingested. I3C is the parent molecule of not only DIM, but dozens of other phytochemicals that form in the gut. In addition to DIM, I3C also creates ICZ, NI3C and IAN. Although these others haven't been studied very well, there is some evidence that they may each have their own unique actions against cancer. For example, ICZ blocks the dioxin receptor better than DIM or I3C.^[1] This mechanism could potentially forestall some types of chemically-induced cancers. And while IAN doesn't seem to do much for breast cancer, it looks promising for stomach cancer.^[2] When a person takes I3C, they get all of these products, not just DIM. It has been suggested that the phytochemicals in cruciferous vegetables may work differently in combination than they do individually^[3]—a good reason to keep the spectrum as broad as possible.

Why has a chemical been added to DIM?

By itself, DIM is not absorbed adequately, so, an artificial system has to be created to make it bioavailable. This isn't necessary when DIM is converted naturally from I3C.

Zeligs claims that I3C “disappears” after it's ingested. What's the truth about this?

It “disappears” because it's converted to other products, including DIM. According to researchers, “At acid pH comparable to that found in the stomach, I3C forms to wide variety of condensation products ranging from linear and cyclic dimers, trimer and tetramers to extended heterocyclic compounds such as indolocarbazoles”.^[4] To put DIM's contribution into perspective, DIM represents about 6% of the total condensation products of I3C.^[5] I3C itself is one of hundreds of phytochemicals in cruciferous vegetables.

Zeligs claims that I3C creates “questionable reaction products” in the gut.

One of those “questionable” products is DIM. When DIM is administered by itself, it can actually provoke the growth of human breast cancer cells and upregulate the estrogen receptor under certain laboratory conditions.^[6] We want to stress that this does not occur when the full product, I3C, is taken under ordinary conditions.

While the break-down products of I3C may act unpredictably by themselves, when taken as I3C in their natural form, they are beneficial for preventing, and possibly treating, hormone-related cancers. The data is so compelling, it has provoked normally reserved researchers into such praise as, "I3C has tremendous potential in the treatment and prevention of cancer, particularly estrogen-enhanced cancer." [4] Although that comment was directed towards I3C's estrogen-blocking potential, I3C has equally important actions against all types of cancer. The list includes powerful DNA protection, carcinogen detoxification, modulation of the growth and invasion of cancer cells, induction of apoptosis selectively in cancer cells, bone marrow protection during chemotherapy, neutralization of cancer-causing heterocyclic amines (i.e., from cooked meat), modulation of the estrogen receptor (which is also a player in non-hormone related cancers), and possible upregulation of tumor suppressor genes.

Zeligs says that "no direct benefits can be attributed to absorbed I3C." The benefits of I3C have been proven in vitro, in rodents and in humans. Whether they are direct or indirect—I3C works.

According to Zeligs, DIM has been "extensively tested" in humans.

One of the biggest problems with DIM is that it hasn't been extensively tested in humans. In fact, there are no published human studies at all. This is a critical difference between DIM and I3C. One of the problems with DIM is that because human studies haven't been done, no one knows the proper dose. Is this important? You bet. In separate studies, using different amounts, researchers have gotten completely opposite results on DIM's effect on the estrogen receptor in vitro. [7,8]

Zeligs claims that DIM is more stable than I3C and therefore more desirable.

If I3C were stable, it would never form DIM or the myriad of other beneficial phytochemicals. I3C is inherently unstable in stomach acid which converts it to its multi-faceted products. As with all pro-active vitamins and supplements, I3C should be protected from heat and light. The product has been tested for 12 months at room temperature with no loss of potency.

According to Zeligs, the anti-cancer effects of I3C are due to DIM.

Far from it. DIM by itself has, in some cases, completely opposite effects of I3C on human breast cancer cells. Research indicates that there is a difference between the way I3C acts versus the way its individual products act. For example, regarding a study on androgen metabolism and I3C, researchers at Queen's University wrote that "the action of multiple inducers present in cruciferous and other vegetables might produce androgen metabolic profiles very different from those produced by individual components isolated from them." [9] There is a prevailing view that the effects of I3C are due to the combination of its condensation products together, not one single product. DIM may eventually prove to enhance the effects of I3C, but the research has not been done.

What are some of DIM's "opposite effects" on breast cancer cells?

I3C studies show that I3C stops the growth of estrogen receptor-positive and negative breast cancer cells in culture. [10] DIM reportedly either makes estrogen receptor positive breast cancer cells grow [11] or inhibits them [9] in culture. According to researchers at the University of California, DIM promotes the growth of human breast cancer cells about as half as well as estrogen when no estrogen is present in the culture. In addition, DIM's inhibition of cancer cell growth was "weak" in the presence of estrogen. Remember, these are laboratory conditions only and probably don't occur in real life. How DIM behaves, however, may depend on dose. Researchers at Texas A&M report that DIM significantly counteracts estrogen-induced growth of MCF-7 cells in culture at higher doses. However, unlike I3C which retards the growth of estrogen receptor negative breast cancer cells, DIM has no effect on estrogen receptor negative cells. [10] Another question about DIM is whether it can increase aromatase in breast and other tissue. Aromatase is an enzyme that helps create estrogen. DIM reportedly enhances the enzyme in adrenocortical cancer cells. [11]

Not only is DIM not responsible for the anti-cancer effects of I3C, it has fewer anti-cancer effects (due to fewer molecular mechanisms), when it's isolated from the other phytochemicals that naturally occur with it.

ANTI-CANCER EFFECTS OF I3C

	I3C	DIM
Induces Apoptosis (Cell Suicide)	•	•
Inhibits Breast Cancer in Rodents	•	•
Inhibits Growth of Estrogen Receptor Positive Breast Cancer Cells	•	•
Inhibits Growth of Estrogen Receptor Negative Breast Cancer Cells	•	
Prevents DNA Damage	•	
Enhances 2-Hydroxylation of Estrogen (beneficial) at the Expense of 16 a-Hydroxylation	•	•
Antioxidant	•	
Blocks Dioxin	•	•
Blocks Estrogen	•	•
Enhances Effects of Tamoxifen	•	
Blocks Chemically Induced 16 a-Hydroxylation of Estrogen (including that induced by pesticides and estrogen mimickers)	•	
Blocks Enzyme (CYP1B1) that Promotes 4-Hydroxylation of	•	

Why does Zeligs say that DIM is the “active form” of I3C responsible for improved estrogen metabolism?

Good question, because the study Zeligs uses to back that up doesn't say that. It points to another product, ICZ, as potentially having greater estrogen metabolizing potential than either DIM or I3C.[12] Not only is DIM not the active form of I3C, it may not even be a desirable form of I3C. In the cited study, DIM had to be injected to reach the level of estrogen modulation obtained with oral I3C.

Zeligs claims that DIM promotes cervical health.

The women in the study he refers to took I3C, not DIM.

According to Zeligs, DIM makes estrogen replacement therapy safer in women and DHEA therapy safer in men.

Estrogen (cancer-promoting)	
Inhibits DNA Damage in Bone Marrow of Rodents Treated with Cyclophosphamide	•
Effective Against Cervical Cancer in Rodents	•
Stops the Growth of Prostate Cancer Cells	•
Upregulates BRCA1 Tumor Suppressor Gene	•

It's a plausible theory, but DIM's ability to modulate hormone replacement therapy is unknown. The studies cited by Zeligs were done with I3C, not DIM. Studies on I3C show that it modulates hormones in addition to estrogen, including androsterone, androstenedione and testosterone.[13, 14] This, along with the fact that I3C prevents uterine-related cancers, suggests that I3C will be beneficial for people taking hormone replacement therapy. These kinds of studies have not been done with DIM.

According to Zeligs, “Supplemental use of DIM promotes higher levels of 2-hydroxy estrogens. This use in animals has been shown to be associated with the prevention of spontaneous, estrogen related cancer of the breast and uterus.”

It sounds good, but the problem is that, again, the research was done with I3C, not DIM.

Zeligs claims that DIM is unique in its ability to shift estrogen metabolism, and that DIM decreases the “activity” of the estrogen receptor “system”.

The study Zeligs says backs this up tested both I3C and DIM. DIM was less effective when taken orally. Only when it was injected, did DIM reach I3C's level of estrogen modulation. Far from being “unique” in its ability, DIM was less effective than I3C when taken orally. As for the claim that DIM decreases estrogen receptor “system activity”, estrogen receptors were not evaluated in the study at all.

However, another study has evaluated the effect of DIM on the estrogen receptor. According to the results, DIM activates, not deactivates, the estrogen receptor.[15] Activating the estrogen receptor enhances, rather than prevents, the growth of estrogen-dependent cancer cells. Again, this points up the problem of isolating DIM from its natural milieu. When DIM is taken in its natural form, I3C, the estrogen receptor is downregulated.[4]

Zeligs claims that people should buy DIM instead of I3C.

Only if they want to take something that's untested versus something that's proven. Part of I3C is naturally converted to DIM when I3C is taken as a supplement or eaten in vegetables. I3C forms dozens of other phytochemicals in addition to DIM which have proven anti-cancer effects. Anyone who metabolizes I3C will get DIM along with other naturally-occurring products.

The importance of co-factors in determining how these phytochemicals behave is illustrated by what vitamin C does to I3C. If vitamin C is not present when cruciferous vegetables are eaten, more I3C will naturally form. If vitamin C is added, less I3C will form, but more of a different product will result from digestion. It's called ascorbigen, and it can produce 20 times more ICZ than I3C.[16] No one knows the significance of this yet, although it's been suggested that ICZ may be able to change estrogen metabolism better than I3C or DIM.

The cancer fighting compounds in cruciferous vegetables clearly work synergistically. That's why a person wanting to gain an extra edge over cancer should stick with I3C, which has valid scientific studies behind it.

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