

Indole-3-Carbinol and DIM (the best protection against Breast cancer) "I3C Plus"

DESCRIPTION

Indole-3-carbinol or I3C is a breakdown product of the glucosinolate glucobrassicin, also known as indole-3-glucosinolate. Glucosinolates are beta-thioglucoside N-hydroxysulfates, which are primarily found in cruciferous vegetables (cabbage, broccoli sprouts, brussels sprouts, cauliflower, bok choy and kale).

Indole-3-carbinol has cancer chemopreventive activity. Glucosinolates themselves have minimal anticancer activity. Indole-3-carbinol is produced from indole-3-glucosinolate via the action of the enzyme myrosinase (thioglucoside glucohydrolase), an enzyme which is present in cruciferous vegetables and activated upon maceration of the vegetables.

The anticancer activity of substances such as I3C was recognized by the Roman statesman, Cato the Elder (234-149 BC), who in his treatise on medicine wrote: "If a cancerous ulcer appears upon the breasts, apply a crushed cabbage leaf and it will make it well." Crushing a cabbage leaf would convert indole-3-glucosinolate to I3C, among other reactions.

ACTIONS AND PHARMACOLOGY

ACTIONS

Indole-3-carbinol modulates estrogen metabolism. It also has anticarcinogenic, antioxidant and anti-atherogenic activities and has been shown to prevent development of estrogen-enhanced cancers of breast, endometrium/uterus and cervical. .

MECHANISM OF ACTION

The estrogen metabolites 16 alpha-hydroxyestrone and 4-hydroxyestrone have been demonstrated to be carcinogens and are thought to be responsible for the possible carcinogenic effects of estrogen. On the other hand, the estrogen metabolite 2-hydroxyestrone has been found to be protective against several types of cancer, including breast cancer. Indole-3-carbinol has been shown **to increase the ratio of 2-hydroxyestrone to 16 alpha-hydroxyestrone** (2/16 ratio-see Estronex test by Metamatrix) and also to inhibit the 4-hydroxylation of estradiol. Indole-3-carbinol increases 2-hydroxylation of estrogens via induction of cytochrome P4501A1 (CYP1A1). Indole-3-carbinol is converted by stomach acid to diindolymethane (DIM) and indole (3,2,b) carbazole (ICZ). DIM and ICZ have similar activities regarding estrogen metabolism.

Regarding its anticarcinogenic effects, indole-3-carbinol has been shown to modulate the activities of both Phase I enzymes, such as cytochrome P4501A1, -1A2, -2B1, -2B2, -3A1 and -3A2, and Phase II enzymes, such as glutathione S-transferase (GST), quinone reductase and uridine glucuronide transferase. Indole-3-carbinol modulates the metabolism of

carcinogens, such as benzo(a)pyrene, aflatoxin B1 and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK). Indole-3-carbinol has also been shown to upregulate apoptosis in some cancer cell lines.

As mentioned above, indole-3-carbinol induces the synthesis of 2-hydroxyestrone. 2-hydroxyestrone has been found to inhibit the oxidation of low-density lipoprotein. This indicates that indole-3-carbinol has indirect antioxidant activity. 2-hydroxyestrone also appears to inhibit smooth muscle proliferation. Inhibition of smooth muscle proliferation and inhibition of the oxidation of LDL could account for the anti-atherogenic (clogged arteries) activity of indole-3-carbinol.

PHARMACOKINETICS

There is much unknown about the pharmacokinetics of indole-3-carbinol in humans. It is converted to DIM and ICZ by stomach acid, and DIM and ICZ are absorbed from the gastrointestinal tract. The extent of absorption of I3C, DIM and ICZ, as well as their distribution, metabolism and excretion, are currently being studied.

INDICATIONS AND USAGE

I3C has anticarcinogenic effects and some anti-atherogenic activity. It may be useful in inhibiting the formation of papillomatosis cysts caused by the human papilloma virus (HPV). Claims that it helps build muscle are unsubstantiated.

RESEARCH SUMMARY

I3C has the following anti-cancer effects: anti-invasion and anti-migration activities; activates function of invasion suppressor molecules associated with breast cancer; may suppress breast cancer invasion and metastasis. It modulates estrogen receptor transcription activity; competitively inhibits receptor binding of stronger estrogens; detoxifies xenoestrogens (chemicals with estrogenic effect); modulates cell-cycle regulation; prevents adhesion, migration and invasion of cancer cell lines; increases apoptosis (normal cell death-cancer cells don't die when they should); anti-estrogenic and anti-tumorigenic activity through interaction with the aryl hydrocarbon receptor (AhR); antioxidant scavenging of free radicals.

I3C has significantly reduced the number of tumor-bearing animals and the number of tumors per animal, compared with controls, in an animal model of spontaneous mammary tumorigenesis. I3C, administered after carcinogen initiation, also significantly inhibited chemically induced mammary tumors.

Aflatoxin-induced tumors in fish were inhibited by I3C when given before exposure to aflatoxin. On the other hand, I3C appeared to promote aflatoxin-induced tumor activity when given after initiation with aflatoxin in these animals. In a rat study, however, I3C had inhibitory effects on aflatoxin-induced tumor formation when given both before and after aflatoxin exposure. More research on this issue is needed. Still other animal studies have demonstrated that I3C exerted protective effects of various types against cancers of the endometrium, lung, tongue, colon and liver.

Cell culture work has shown that HPV proliferation was inhibited by the action of I3C. Subsequently, it was shown that feeding I3C to nude mice significantly inhibited the formation of papillomatous cysts. This, in turn, led to a human study in which I3C again significantly inhibited the formation of these lesions—this time in children.

There is preliminary evidence from in vitro studies that I3C-induced metabolites can inhibit oxidation of LDL-cholesterol and that they can also inhibit smooth muscle cell proliferation.

It has been shown to be effective against HPV-mediated tumors in human patients.

CONTRAINDICATIONS

Indole-3-carbinol is contraindicated in those hypersensitive to this substance or to any component of an indole-3-carbinol-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid indole-3-carbinol supplements pending long-term safety studies. Those with cancer should confer with their physician before deciding to use indole-3-carbinol.

INTERACTIONS

DRUGS:

Antacids, H2 blockers, proton-pump inhibitors: The conversion of indole-3-carbinol to DIM and ICZ requires stomach acid. It is unclear if indole-3-carbinol itself would have all the possible activities mentioned above if it were not converted to DIM and ICZ.

Tamoxifen: Indole-3-carbinol may be synergistic with tamoxifen in protecting against breast cancer.

DOSAGE AND ADMINISTRATION: I3C Plus (contains DIM and HCl as well)

Indole-3-carbinol is available as a stand-alone supplement and in combination products. Dosage ranges from 200 mg to 800 mg daily. It is best to take both I3C and DIM due to their synergistic actions. HCl helps convert I3C to DIM for those with low stomach acid.