I3C SAP

Targeted nutraceutical therapy for the prevention and treatment of estrogen-dependent cancers

Indole-3-carbinol (I3C) is a phytochemical derived in high concentrations from the *Brassica* family of vegetables, including broccoli, cauliflower, Brussels sprouts, and cabbage. I3C and its derivative compounds have been shown to exert anticancer mechanisms in the human body. I3C has been shown to exhibit direct antiestrogenic activity via competitive inhibition of estrogen receptors; upregulate the cytochrome P450 isoenzymes *CYP1A1*, *CYP1A2*, and *CYP1B1*, thereby increasing estrogen metabolism; shift estrogen metabolism away from the more proliferative (16-OHE_1) towards the more protective (2-OHE_1) estrogen species; induce cancer-cell apoptosis via NF-κB pathways; inhibit cancer cell growth at the G_1 stage; and increase the expression of p21, p27, and p53 tumour suppressors. The use of I3C for the prevention and treatment of breast, endometrial, colon, and prostate cancers, as well as for the treatment of herpes simplex virus (HSV) and human papillomavirus (HPV), including cervical dysplasia and cervical cancer, has been studied in depth in both animals and humans with favorable results.

ACTIVE INGREDIENTS

Each non-GMO vegetable capsule contains:

Indole-3-carbinol . . . . . 150 mg

This product is non-GMO.

Contains no: Gluten, soy, wheat, corn, dairy, yeast, preservatives, artificial flavour or colour, sugar, or starch.

I3C SAP contains 60 capsules per bottle.

DIRECTIONS FOR USE

Adults: Take 2 capsules once daily with food or as directed by your healthcare practitioner. Do not exceed recommended dosage.

INDICATIONS

I3C SAP may be used:

- In the prevention and treatment of estrogen-dependent breast, colon, endometrial, cervical, and prostate cancers.
- In the prevention and treatment of HSV and HPV infections.
- To support healthy estrogen and androgen metabolism.

TOXICITY

No side effects or adverse events have been reported at regular therapeutic dosages. In doses exceeding 800 mg/d, oral administration of I3C may cause reversible symptoms of tremor, nausea, and imbalance or unsteadiness.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for all **I3C SAP** lot numbers have been tested by a third-party laboratory for identity, potency, and purity.

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

NFH®

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BACKGROUND AND PHARMACOKINETICS

Indole-3-carbinol (I3C) is a naturally occurring phytonutrient present in high quantities in cruciferous vegetables from the *Brassica* genus, including broccoli, cauliflower, Brussels sprouts, and cabbage. I3C is a highly researched phytonutrient, particularly in terms of its ability to modulate the effects of estrogen and its implications in estrogen-sensitive cancers via various mechanisms of action.[1, 2, 3]

After human ingestion in the presence of an acidic environment, I3C is hydrolyzed mainly into the dimer, 3,3′-diindolylmethane (DIM), amongst other metabolites. Both I3C and DIM, in addition to the more minor metabolites of I3C, are biologically active and exert a number of health-promoting effects that may have primarily antiestrogenic and antiandrogenic effects, which may be harnessed for the prevention and treatment of various cancers.[1, 2, 3]

Both I3C and DIM are rapidly absorbed into human plasma and tissues within one hour of dosage and eliminated primarily via the urine initially, and also via fecal route after 40 h of continuous therapy. I3C metabolites demonstrate a serum half-life greater than 48 h following one-week continuous oral administration.[1, 2]

BREAST CANCER AND ANTIESTROGEN

Increased estrogen levels and exposure to estrogens are well-known to be risk factors in the development of breast cancer and other estrogen-sensitive cancers. I3C and its metabolites exhibit antiestrogenic activity via competitive inhibition of estrogen receptors. DIM has been specifically demonstrated to selectively bind estrogen receptors and act as an estrogen antagonist.[1, 2] Through direct inhibition of estrogen receptors and other antiestrogenic effects, I3C has been rigorously implicated in the literature as a preventative and treatment for breast cancer, both in conjunction with and independent of tamoxifen and other conventional, pharmaceutical treatments.[1, 2, 3, 4, 5, 6]

HEPATOPROTECTION AND DETOXIFICATION

In addition to the direct competitive inhibition of estrogen receptors, I3C and its metabolites — specifically DIM and indolylcarbazole (ICZ) — induce the human cytochrome P450 isoenzymes *CYP1A1*, *CYP1A2* and in Sprague-Dawley rats, *CYP1B1/2*. Through induction of these isoenzymes, I3C promotes Phase I and Phase II detoxification and exhibits hepatoprotective activity.[1, 2, 3, 4, 7, 8]

2:16-HYDROXYESTRONE RATIO

The metabolism of estradiol (E_2) by hepatocytes results in the primary production of either 2-hydroxyestrone (2-OHE_1) or 16-α-hydroxyestrone (16-OHE_1). It is generally accepted that 16-OHE_1 causes the proliferation of some breast cancer cell lines, while 2-OHE_1 has a protective effect for breast cancers. A 2:1 urinary ratio appears to be optimal, while a 1:1 ratio has been associated with increased risk of breast cancers. The 2:16-hydroxyestrone ratio may therefore be considered a risk factor for breast cancer; supplementation of I3C has been demonstrated to increase this ratio.[1, 2, 3, 4, 8] In a study, upon I3C oral administration, urinary excretion levels of 2-OHE_1 doubled, while 16-OHE_1 levels decreased by 45%, demonstrating the ability of I3C to increase the 2:16-hydroxyestrone ratio.[9] These findings are echoed by results of a study that showed a 66% increase in urinary 2:16-hydroxyestrone ratio in response to oral I3C administration.[10]

ANTIPROLIFERATIVE AND APOPTOSIS-INDUCING

In vitro studies have shown I3C's ability to inhibit breast-cancer cells' ability to invade surrounding tissues via upregulation of tumour-suppressing genes PTEN and E-cadherin. p53, p21 and p27 are cyclin-dependent kinase inhibitors which control cell cycle progression; I3C is known to increase p21, p27 and p53 expression, thereby arresting tumour cell growth cycles in the G_1 state. Additionally, incubation of human breast cancer cells with DIM has been found to stimulate apoptosis independent of p53 and downregulates NF-κB, inducing apoptosis in various cell lines, including myeloid, leukemia and breast cancer cells.[1, 3, 7, 8]

DNA-PROTECTIVE

BRCA1 and *BRCA2* are human caretaker genes that repair breaks in DNA due to transcription error or mutation. Upregulation of both *BRCA1* and *BRCA2* by I3C oral supplementation is suggested to play a role in breast cancer prevention.[2, 6, 8]

PROSTATE CANCER AND ANTIANDROGEN

DIM inhibits dihydrotestosterone (DHT) stimulation of DNA synthesis and competitively inhibits androgen-receptor binding of DHT. I3C and DIM have both been independently shown to suppress proliferation of prostate cancer cells. As in studies focused on breast cancer, increased p21, 27 and p53 expression and downregulation of NF-κB have also been demonstrated in prostate cancer, leading to healthy cancer cell apoptosis.[2, 3, 7, 11, 12, 13, 14, 15] Furthermore, I3C and DIM have also been shown to decrease PSA levels 5-fold within 48 h via inhibition of PSA gene transcription.[14]

OTHER CLINICAL INDICATIONS

I3C and DIM have also been studied in the treatment and prevention of HSV, HPV, and cervical cancer, colon cancer, and endometrial cancer.[1, 3, 5]

DOSAGE, TOXICITY, AND CONTRAINDICATIONS

Optimal therapeutic dosage for I3C has been cited as 400 mg/d — equivalent to about that found in one-third of a head of cabbage.[1, 8, 10]

No therapeutic advantage has been shown for the direct oral administration of DIM over I3C.[16] In fact, DIM administration alone has been shown to inhibit *CYP1A1*, *CYP1A2* and *CYP2B1/2*; processes that would contradict the estrogen detoxification benefits shown by upstream I3C oral administration.[8]

No adverse events or side effects are expected at a dose of 400 mg/d in humans, and I3C administration is generally well tolerated. Over 800 mg/d, symptoms including tremor, unsteadiness, nausea, and imbalance have been recorded. Observed side effects are reversible upon dose reduction or withdrawal and are not life threatening.[1, 16]

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