

# A REVIEW ARTICLE: INDOLE 3 CARBINOL A NOVEL APPROACH TO ANTICANCEROUS DRUG

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## Abstract

A diet rich in cruciferous vegetables such as cauliflower, broccoli, and cabbage has long been considered healthy, and various epidemiological studies suggest that the consumption of cruciferous vegetables contributes to a cancer-protecting diet. While these vegetables contain a vast array of phytochemicals, the mechanism by which these vegetables counteract cancer is still largely unresolved. Numerous *in situ* studies have implicated indole-3-carbinol, a breakdown product of the glucosinolate indole-3-ylmethylglucosinolate, as one of the phytochemicals with anti-cancer properties. Indole-3-carbinol influences a range of cellular processes, but the mechanisms by which it acts on cancer cells are slowly being revealed. Recent studies on the role of indole-3-carbinol in *Arabidopsis* opens the door for cross-kingdom comparisons that can help in understanding the roles of this important phytohormone in both plant biology and combatting cancer.

**Keywords:** Glucosinolates, Indole-3-carbinol, Cancer Prevention, Cruciferous Vegetables

## Introduction

Some observational studies have reported significant associations between high intakes of cruciferous vegetables and lower risk of several types of cancer. Cruciferous vegetables differ from other classes of vegetables in that they are rich sources of sulfur-containing compounds known as glucosinolates (for detailed information, see the article on Cruciferous Vegetables). The potential health benefits of consuming cruciferous vegetables are attributed to compounds derived from the enzymatic hydrolysis (breakdown) of glucosinolates. Among these compounds is indole-3-carbinol (I3C), a compound derived from the degradation of an indole glucosinolate commonly known as glucobrassicin. A diet rich in cruciferous vegetables such as cauliflower, broccoli, and cabbage has long been considered healthy. Even in ancient times, extracts from these vegetables were thought to have medicinal and curative properties, and both Pythagoras and Hippocrates understood the medicinal properties of mustard extracts. In the 20<sup>th</sup> century, epidemiological studies pointing to the protective properties of cruciferous vegetables in a cancer-protecting diet started to accumulate. A meta-analysis of studies carried out over 18 years in Europe revealed an inverse association between weekly consumption of cruciferous vegetables and several common cancers, including colorectal, breast, kidney, and upper digestive tract cancers. While these vegetables contain a vast array of phytochemicals, the mechanism by which these vegetables counteract cancer is still largely unresolved.

## How does it work?

Researchers are interested in indole-3-carbinol for cancer prevention, particularly breast, cervical and endometrial, and colorectal cancer. Their reason is that diets with higher

amounts of fruit and vegetable consumption are associated with a decreased risk of developing cancer. Researchers suspect indole-3-carbinol is one of several vegetable components that might protect against cancer

### **Indole-3-carbinol and cancer**

The glucosinolates breakdown products, rather than intact glucosinolates, primarily contribute to the ant carcinogenic effects of eating cabbage, broccoli, and related vegetables . I3C has long been studied regarding potential roles in cancer management , and many studies showed that I3C suppresses the proliferation of various cancer cell lines, including breast, colon, prostate, and endometrial cancer cells .One example of its anti-proliferative properties comes from a study conducted on non-tumorigenic and tumorigenic breast epithelial cells (MCF10A and MCF10CA1a, respectively), which showed that I3C induced apoptosis in the breast cancer cells but not in the non-tumorigenic breast epithelial cells . I3C and one of its reaction products, diindolylmethane (DIM), were implicated in the induction of phase 1 detoxification enzymes, which can result in the breakdown of other dietary carcinogens. Both *in situ* and *in vivo* studies point to a role for I3C as a chemoprotective agent in breast and prostate cancerThe exact mechanisms by which I3C influences human cells are unclear, though direct interaction with a variety of signaling pathways has been proposed. The treatment of various cancer cells with I3C induces G1 cell cycle arrest.Other studies pointed to a connection between treatment of I3C and stimulation of apoptosis in several tumor cells . I3C also induced autophagy in different cell lines. For example, the treatment of human colon cancer HT-29 cells with I3C and genistin induced autophagy and suppressed the cells' viability . The treatment of human breast cancer cell lines with a cyclic tetrameric derivative of I3C resulted in upregulation of key signaling molecules involved in endoplasmic reticulum stress response and autophagy . I3C also has the potential to modulate the metabolism of estrogen, and, through this, it may lower the risk of hormone-dependent cancers . In addition, I3C inhibited tumor invasion and metastasis and modulated the activity of several transcription factors and various protein kinases Interestingly, I3C may also be involved in the inhibition of amyloid fibril formation I3C was proposed to act as an angiogenesis agent, as it was shown to inhibit the development of new blood vessels . A number of studies have shown that I3C treatment leads to various changes in gene expression, including changes in key microRNAs .The complex mixture of indole metabolites found in cruciferous vegetables likely has synergistic anticarcinogenic effects that are not seen in experiments with individual compounds

### **Indole-3-carbinol and plants**

The model plant *Arabidopsisthaliana* provides an excellent system for elucidating the molecular mechanisms involved in I3C action, as 1) it produces I3C endogenously following herbivory, 2) small amounts of I3C are produced constitutively in the roots, hinting at an endogenous role in maintaining homeostasis, and 3) its short life cycle and small stature coupled with advanced available genetic and genomic resources make *Arabidopsis* an excellent model system not only for plant biology but also for eukaryotic research in general .While the role of I3C in deterring herbivores is well studied , as is the biochemical pathway leading to the production of I3C , the secondary responses in plants induced by I3C are only now starting to be revealed. Our recent studies highlight that I3C is not only a defensive chemical targeting herbivores but also a signaling molecule modulating different

cellular and developmental pathways. Using Arabidopsis as a model system, we showed that exogenously applied I3C rapidly and reversibly inhibited root elongation in a dose-dependent manner. This inhibition was accompanied by three I3C-induced responses that are relevant for our understanding of I3C activity in inhibiting cancer.

### What Are the Signs and Symptoms?

It can cause side effects such as **skin rashes and diarrhea**. In higher doses, indole-3-carbinol can cause balance problems, tremor, and nausea.

### Special Precautions & Warnings

- **Pregnancy and breast-feeding:** If you are pregnant or breast-feeding, stick with indole-3-carbinol in amounts typically found in the diet. Not enough is known about the safety of using indole-3-carbinol in larger medicinal amounts.
- **Children-:** Indole-3-carbinol is **POSSIBLY SAFE** for children when taken by mouth as a medicine under proper medical supervision. Doses of 6-17 mg/kg body weight have been safely used in children and teenagers for 12-76 months.
- **Bleeding conditions:** Indole-3-carbinol might slow blood clotting. In theory, taking indole-3-carbinol might increase the risk of bleeding in people with bleeding disorders. **Surgery:** Indole-3-carbinol might slow blood clotting. In theory, taking indole-3-carbinol might cause bleeding complications during surgery. Stop taking indole-3-carbinol at least 2 weeks before surgery.

### Interactions

**Medications changed by the liver (Cytochrome P450 1A2 (CYP1A2) substrates)** Interaction Rating: **Moderate** Be cautious with this combination. Talk with your health provider. Some medications are changed and broken down by the liver. Indole-3-carbinol might increase how quickly the liver breaks down some medications. Taking indole-3-carbinol along with some medications that are changed by the liver can decrease the effectiveness of some medications. Before taking indole-3-carbinol, talk to your healthcare provider if you take any medications that are changed by the liver.

### Uses & Effectiveness

#### Possibly Effective for...

- Abnormal development and growth of cells of the cervix (cervical dysplasia).

#### Insufficient Evidence to Rate Effectiveness for...

- **Respiratory papillomatosis.** There is some evidence that long-term use of indole-3-carbinol might reduce tumor (papilloma) growth in patients with recurrent respiratory papillomatosis.
- **Laryngeal papillomatosis.**
- **Prevention of breast cancer.**
- **Colon cancer.**
- **Fibromyalgia.**
- **Systemic lupus erythematosus (SLE).**
- **Hormone imbalances.**
- **Other conditions.**

More evidence is needed to rate the effectiveness of indole-3-carbinol for these uses.

Some of these medications that are changed by the liver include clozapine (Clozaril), cyclobenzaprine (Flexeril), fluvoxamine (Luvox), haloperidol (Haldol), imipramine (Tofranil), mexiletine (Mexitil), olanzapine (Zyprexa), pentazocine (Talwin), propranolol (Inderal), tacrine (Cognex), theophylline, zileuton (Zyflo), zolmitriptan (Zomig), and others

### **Side Effects**

Indole-3-carbinol is likely safe for most people when used in amounts typically found in the diet. It seems to be safe for most people when used in medicinal amounts under proper medical supervision. It can cause side effects such as skin rashes and small increases in liver enzymes. In very high doses, indole-3-carbinol can cause balance problems, tremor, and nausea.

### **Discussion**

Several experimental studies have shown that I3C possesses preventive anti-cancer and disrupting estrogen signalling properties. Indole-3-carbinol is considered a potential agent in the prevention and treatment of hormone-dependent breast tumors. Thus, it is freely available in the stores and supermarkets as a dietary phytochemical (non as an approved pharmaceutical drug) for preventing cancer, diminishing premenstrual syndrome and perimenopause-related disturbances. Nevertheless, the effect of I3C on patients with neoplasms, especially breast cancer is poorly documented. To the best of our knowledge, this is the first study regarding the effects of I3C treatment on experimental or spontaneous IMC. Both IBC and canine IMC are considered a special and very aggressive type of breast cancer due to its particular/unique biological, molecular, pathological, genetic and clinical signature features. In the present study, I3C treatment on a xenograft model of canine IMC reduced tumor growth and increased apoptosis, although metastasis and alterations in the peripheral levels of steroid hormones were also observed in some animals.

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### **Conclusion**

Our data reveal for the first time that the ingestion of indole-3-carbinol, as administered, diminishes proliferation and increases apoptosis of tumor cells in an experimental model of inflammatory breast cancer, although this effect could not be enough to avoid the appearance of tumor embolization and metastasis. Future clinical trials will be needed to clarify the usefulness of indole-3-carbinol in this cancer and to understand the molecular mechanisms involved.

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