

# hormone detox support

- Supports Estrogen Balance
- Supports Proper Estrogen Metabolism for Women and Men
- Improves Estrogen Detoxification Pathways
- Provides Cellular Antioxidant Support for DNA Stability

This product is a targeted supplement that combines the synergistic benefits of the cruciferous vegetable metabolites indole-3-carbinol (I3C) and 3-3'-diindolylmethane (DIM) to support balanced estrogen metabolism. Formulating I3C and DIM together creates the ideal combination of beneficial metabolites that work together to support estrogen balance and breast and prostate health.

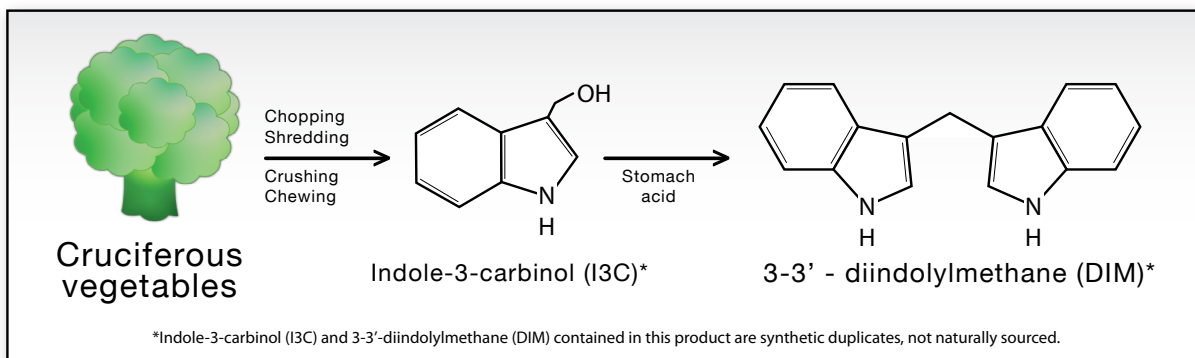
## The Health Benefits of Cruciferous Vegetable Metabolites†

Many of the health benefits derived from eating cruciferous vegetables (e.g., cabbage, Brussels sprouts, broccoli, etc.), especially those shown to be beneficial for breast and prostate health, are thought to be derived from the group of secondary metabolites known as glucosinolates. When these vegetables are cut, crushed or chewed, the actions of the enzyme myrosinase (released from the plant cells) hydrolyses these glucosinolates into other compounds. For instance, glucosinolates from broccoli and Brussels sprouts readily convert into I3C when consumed. I3C can then be further converted via stomach acid into other health promoting compounds, including DIM. These compounds have generally been thought to be responsible for the various cellular activities that lead to hormone health.

## Overview

Estrogen collectively refers to the female hormones estrone (E1), estradiol (E2) and estriol (E3). Estrogen is an important hormone messenger that interacts with cells throughout the body, including tissues that are more sensitive to estrogen, such as breast and prostate tissues. The most important message hormones deliver is to grow, divide and multiply. For this reason, hormones (especially estrogen) are critically important in human development and tissue repair. However, estrogen's proliferative effects must be balanced and controlled for optimal health. Therefore, to ensure proper hormonal balance, estrogen synthesis and detoxification should be supported. Estrogen has several downstream metabolites, some of which are beneficial while others possess potentially harmful biological activity. By keeping hormones in balance and ensuring the body can process estrogen properly, cruciferous vegetable metabolites (i.e., I3C and DIM) work together to maintain cellular health.

Preclinical data on I3C and DIM suggest that these phytonutrient metabolites have a strong potential for supporting breast, cervical, endometrium and prostate health.<sup>1-4</sup> Together, I3C and DIM promote the metabolism of the more favorable and protective estrogen metabolite, 2-hydroxyestrogen (2-OHE), versus production of the less favorable 4-hydroxyestrogen (4-OHE) and 16- $\alpha$ -hydroxyestrogen (16- $\alpha$ OHE).<sup>5,6</sup> In contrast



to 2-OHE, both 4-OHE and 16- $\alpha$ OHE have been shown to overstimulate cells and create free radicals that contribute to DNA damage.<sup>7,8</sup> Several human supplementation studies with both male and female subjects consistently show that urinary levels of 2-OHE and the ratio of 2-OHE to 16- $\alpha$ OHE increase following supplementation with I3C.<sup>5,6,9-11</sup> The increases seen in the ratio of 2-OHE to 16- $\alpha$ OHE in subjects supplementing with I3C are advantageous as this ratio of estrogen metabolites is a marker of a more favorable estrogen metabolite profile.<sup>9</sup> With this in mind, this product is formulated with targeted doses of both I3C and DIM in two capsules per day to make the daily balancing of hormones easy and convenient.

### I3C and DIM

Indole-3-carbinol (I3C) and 3-3'-diindolylmethane (DIM) are natural metabolites of compounds found in numerous vegetables from the Brassicaceae family. Following I3C ingestion either through the diet or supplementation, I3C molecules combine to form a complex group of compounds in the acidic environment of the stomach, one of which is DIM.<sup>12,13</sup> In fact, a human pharmacokinetic study evaluated the plasma response to oral supplementation with I3C in 24 healthy women and found that I3C itself was not present in the plasma of subjects, but the only detectible metabolite in plasma samples was DIM.<sup>13</sup> The levels of plasma DIM following I3C supplementation increased in a dose-dependent fashion.

Both I3C and DIM, as well as many other I3C metabolites, have been shown to impact metabolic shifts and cellular activities for improved health outcomes. I3C and DIM have been shown to induce some phase I and phase II biotransformation genes in preclinical models through pathways such as Nrf2, suggesting I3C and DIM may have a role in detoxification.<sup>14-17</sup> Additionally, both I3C and DIM have been shown in vitro to decrease aromatase expression, which is the enzyme that converts androgens to estrogen.<sup>19</sup> Further, I3C has been shown to temper estrogen signals by competing for binding sites and inhibiting the activity of estrogen receptors.<sup>3,18,19</sup>

### Calcium D-Glucarate †

Calcium D-glucarate is the supplemental calcium salt form of D-glucaric acid, a substance produced naturally in the body and obtained through consumption of certain fruits and vegetables. Calcium D-glucarate has been extensively studied and has been shown to inhibit beta-glucuronidase, an enzyme found in certain bacteria that reside in the gut. This activity supports the body's ability to detoxify estrogens, foreign molecules and fat-soluble toxins.<sup>20-23</sup>

### Dosage

2 capsules per day or as recommended by your health care professional.

### Does Not Contain

Gluten, corn, yeast, artificial colors or flavors.

### Cautions

Do not consume this product if you are pregnant or nursing. Consult your physician for further information.

<b>Supplement Facts</b> <sup>v3</sup>		
Serving Size 2 Capsules		
Servings Per Container 30		
	Amount Per Serving	% Daily Value
Vitamin E (from 50 IU as d-Alpha Tocopherol Succinate USP)	33.5 mg	223%
Calcium (as Calcium D-Glucarate USP)	120 mg	9%
Calcium D-Glucarate USP	1 g	*
Dietary Indoles (Total Indole Blend containing Indole-3-Carbinol (I3C, 200 mg input) and Diindolylmethane (DIM, 100 mg input))	300 mg	*
* Daily Value not established.		

Other Ingredients: Hypromellose (Natural Vegetable Capsules), Magnesium Stearate, Silicon Dioxide and Stearic Acid.

† These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

## References

1. Jin L, Qi M, Chen DZ, et al. Indole-3-carbinol prevents cervical cancer in human papilloma virus type 16 (HPV16) transgenic mice. *Cancer Res.* 1999;59(16):3991-3997.
2. Kojima T, Tanaka T, Mori H. Chemoprevention of spontaneous endometrial cancer in female Donryu rats by dietary indole-3-carbinol. *Cancer Res.* 1994;54(6):1446-1449.
3. Auburn KJ, Fan S, Rosen EM, et al. Indole-3-carbinol is a negative regulator of estrogen. *J Nutr.* 2003;133(7 Suppl):2470s-2475s.
4. Chinni SR, Li Y, Upadhyay S, Koppolu PK, Sarkar FH. Indole-3-carbinol (I3C) induced cell growth inhibition, G1 cell cycle arrest and apoptosis in prostate cancer cells. *Oncogene.* 2001;20(23):2927-2936.
5. Michnovicz JJ, Adlercreutz H, Bradlow HL. Changes in Levels of Urinary Estrogen Metabolites After Oral Indole-3-Carbinol Treatment in Humans. *J Natl Cancer Inst.* 1997;89(10):718-723.
6. McAlindon TE, Gulin J, Chen T, Klug T, Lahita R, Nuite M. Indole-3-carbinol in women with SLE: effect on estrogen metabolism and disease activity. *Lupus.* 2001;10(11):779-783.
7. Cavalieri EL, Stack DE, Devanesan PD, et al. Molecular origin of cancer: catechol estrogen-3,4-quinones as endogenous tumor initiators. *Proc Natl Acad Sci U S A.* 1997;94(20):10937-10942.
8. Telang NT, Suto A, Wong GY, Osborne MP, Bradlow HL. Induction by estrogen metabolite 16 alpha-hydroxyestrone of genotoxic damage and aberrant proliferation in mouse mammary epithelial cells. *J Natl Cancer Inst.* 1992;84(8):634-638.
9. Reed GA, Peterson KS, Smith HJ, et al. A phase I study of indole-3-carbinol in women: tolerability and effects. *Cancer Epidemiol Biomarkers Prev.* 2005;14(8):1953-1960.
10. Wong GY, Bradlow L, Sepkovic D, Mehl S, Mailman J, Osborne MP. Dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biochem Suppl.* 1997;28-29:111-116.
11. Bradlow HL, Michnovicz JJ, Halper M, Miller DG, Wong GY, Osborne MP. Long-term responses of women to indole-3-carbinol or a high fiber diet. *Cancer Epidemiol Biomarkers Prev.* 1994;3(7):591-595.
12. Linus Pauling Institute. Indole-3-Carbinol. 2017; <https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/indole-3-carbinol#reference5>. Accessed January 21, 2021.
13. Reed GA, Arneson DW, Putnam WC, et al. Single-dose and multiple-dose administration of indole-3-carbinol to women: pharmacokinetics based on 3,3'-diindolylmethane. *Cancer Epidemiol Biomarkers Prev.* 2006;15(12):2477-2481.
14. Li Y, Li X, Sarkar FH. Gene expression profiles of I3C- and DIM-treated PC3 human prostate cancer cells determined by cDNA microarray analysis. *J Nutr.* 2003;133(4):1011-1019.
15. Wu TY, Saw CL, Khor TO, Pung D, Boyanapalli SS, Kong AN. In vivo pharmacodynamics of indole-3-carbinol in the inhibition of prostate cancer in transgenic adenocarcinoma of mouse prostate (TRAMP) mice: involvement of Nrf2 and cell cycle/apoptosis signaling pathways. *Mol Carcinog.* 2012;51(10):761-770.
16. Saw CL, Cintrón M, Wu TY, et al. Pharmacodynamics of dietary phytochemical indoles I3C and DIM: Induction of Nrf2-mediated phase II drug metabolizing and antioxidant genes and synergism with isothiocyanates. *Biopharm Drug Dispos.* 2011;32(5):289-300.
17. Leibelt DA, Hedstrom OR, Fischer KA, Pereira CB, Williams DE. Evaluation of chronic dietary exposure to indole-3-carbinol and absorption-enhanced 3,3'-diindolylmethane in sprague-dawley rats. *Toxicol Sci.* 2003;74(1):10-21.
18. Meng Q, Yuan F, Goldberg ID, Rosen EM, Auburn K, Fan S. Indole-3-carbinol is a negative regulator of estrogen receptor-alpha signaling in human tumor cells. *J Nutr.* 2000;130(12):2927-2931.
19. Ashok BT, Chen Y, Liu X, Bradlow HL, Mittelman A, Tiwari RK. Abrogation of estrogen-mediated cellular and biochemical effects by indole-3-carbinol. *Nutr Cancer.* 2001;41(1-2):180-187.
20. Hanausek M, Walaszek Z, Slaga TJ. Detoxifying cancer causing agents to prevent cancer. *Integr Cancer Ther.* 2003 Jun;2(2):139-44.
21. Singh J, Gupta KP. Calcium glucarate prevents tumor formation in mouse skin. *Biomed Environ Sci.* 2003 Mar;16(1):9-16.
22. Review. Calcium-D-glucarate. *Altern Med Rev.* 2002 Aug;7(4):336-9.
23. Walaszek Z, Szemraj J et al. Metabolism, uptake, and excretion of a D-glucaric acid salt and its potential use in cancer prevention. *Cancer Detect Prev.* 1997;21(2):178-90.