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This information is provided as a medical and scientific educational resource for the use of physicians and other licensed health-care practitioners ("Practitioners"). This information is intended for Practitioners to use as a basis for determining whether to recommend these products to their patients. All recommendations regarding protocols, dosing, prescribing, and/or usage instructions should be tailored to the individual needs of the patient considering their medical history and concomitant therapies. This information is not intended for use by consumers.

DIM-Evail™ provides 100 mg of diindolylmethane (DIM), a compound classified as a "plant indole." Plant indoles are also called glucosinolates, which are found in cruciferous vegetables such as broccoli, cabbage, and cauliflower, and they are among the nutrients responsible for the widely recognized healthful properties of these foods, including the support of a healthy estrogen balance.*

DIM-Evail™ is manufactured using Designs for Health's proprietary Evail® emulsification technology, which is designed to enhance the bioavailability and absorption of bioactive ingredients. This Evail® process uses quillaja extract along with delta- and gamma-tocotrienols and medium-chain triglycerides to support absorption.

Ingredient Highlights

- 100 mg of diindolylmethane per serving
- Formulated with Evail® technology to optimize bioavailability and absorption

Diindolylmethane (DIM) is derived from the primary plant indole found in cruciferous vegetables, known as indole-3-carbinol (I3C). Mastication, cooking, and other actions activate the enzyme myrosinase to convert I3C to DIM. Stomach acid additionally contributes to the formation of DIM, which is a more stable compound than I3C.^{1,2} Research identifies beneficial actions of DIM on estrogen metabolism and associated conditions.

Estrogen Metabolism

Estrogen balance plays an important role in health, and disturbances of this hormone are associated with polycystic ovary syndrome, endometriosis, osteoporosis, Alzheimer's disease, autoimmune disorders, male hypogonadism, schizophrenia, and breast, ovarian, and other estrogen-related cancers. Estrogen is involved in glucose homeostasis, lipid homeostasis, bone metabolism, brain function, follicular growth, skeletal growth, and ovulation. Estrogen biosynthesis involves the aromatization of androgen into estrogen.^{3,4}

The main circulating estrogen is 17 beta-estradiol (E2), which is produced in the ovaries as a circulating hormone. In postmenopausal females and those without ovaries, E2 is synthesized in extragonadal sites to act locally as a paracrine, with the aromatization of androgens to estrogens playing a more significant role. Estrogen metabolism involves hydroxylation at the A-ring or D-ring by cytochrome P450 isoforms. This may occur on the C2 or C4 position in the A-ring or in the 16-alpha position in the D-ring, producing the metabolites 2-hydroxy estrone/estradiol, 4-hydroxy estrone/estradiol, and 2-hydroxy estrone/estradiol.⁵⁻¹¹

The specific cytochrome P450 enzyme promotes which metabolite is produced. For example, CYP1B1 converts E2 to 16 alpha-hydroxy estradiol, whereas CYP1A1 converts it to 2-hydroxyestradiol. Both enzymes can also convert E1 and E2 into 4-hydroxy metabolites. The different metabolites have different functions in the body, and a balance is required for optimal health. The 16-alpha hydroxy estrone has a high capacity to bind to estrogen receptors and produce estrogenic effects, and 2-hydroxyestrone has little to no affinity for the estrogen receptor. The 4-hydroxy estrogens have the potential to cause DNA damage, generate mutations, and create oxidative damage. The lower affinity and subsequent decrease of bioavailable estrogens may be why the two-pathway metabolites relate to a lower risk of breast cancer. However, the ratio of metabolites and the clearance of estrogens may matter more than the level of the individual metabolites.⁶⁻¹¹

Higher levels of 4-hydroxy estrogens and 16-alpha-hydroxy estrogens are associated with a higher risk of breast cancer.⁷ High levels of 4-hydroxy estrogens are also associated with endometriosis.¹² A high 2:16 ratio (with 2 hydroxy to 16 hydroxy estrogens) is associated with reduced inflammation and a lower risk of breast cancer.^{8,13} Upon activation, estrogen receptors trigger pathways for cell growth, proliferation, and inflammation in addition to pre-malignant pathology. These estrogen metabolites may stimulate the synthesis of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). They may also impact other conditions, including autoimmune diseases. Studies have found that higher levels of estrogen, including the hydroxylated metabolites, were significantly increased in the synovial fluid of patients with rheumatoid arthritis (RA).¹³⁻¹⁵ One study found that the 2:16 ratio in patients with RA and systemic lupus erythematosus (SLE) was more than 20 times lower than healthy subjects due to significantly lower levels of 2-hydroxy estrogens. These results were independent of steroid use and sex.¹⁶

Benefits*

- Supports healthy estrogen balance
- Promotes healthy inflammatory response

Supplement Facts

Serving Size 1 softgel

Amount Per Serving	% Daily Value
Diindolylmethane (DIM)	100 mg *

* Daily Value not established.

Other Ingredients: Medium chain triglycerides, softgel ingredients (bovine gelatin, glycerine, purified water, annatto [color]), DeltaGold® tocotrienols, quillaja extract.

DIM and Estrogen Metabolism

Certain compounds, such as DIM, can influence estrogen metabolism to determine which metabolite is synthesized, pushing the pathways toward the more harmful or beneficial metabolites.^{6,17} DIM supports the synthesis of 2-hydroxyestrone, which in turn supports an increase of the 2:16 ratio without elevating the 4-hydroxy estrogens. This is likely due to its impact on cytochromes P450 (CYP) enzymes, supporting the expression of CYP1A1 over the other enzymes.¹⁸ This positive impact on estrogen metabolism may also support conditions associated with higher levels of the more harmful estrogen metabolites.

In one prospective clinical trial, supplementing with 100 mg of DIM per day for a year in breast cancer gene (BRCA) carriers (with a high risk of breast cancer) was associated with a significant decline in fibroglandular tissue, whereas a control group did not experience any significant changes. Breast density is a surrogate marker for breast cancer risk.¹⁷ DIM has also been shown to promote more favorable estrogen metabolism by increasing the 2-hydroxy:16-alpha-hydroxy ratio due to increasing the 2-hydroxy pathway when used as adjunct therapy for breast cancer.¹⁹ Another trial found that DIM supplementation improved bleeding patterns in patients with endometriosis, especially when used as adjunct therapy. This was likely due to its reduction of estradiol secretion.²⁰

In addition to acting on estrogen, DIM may also impart anti-inflammatory effects by inhibiting TNF- α . DIM inhibits TNF- α and transforming growth factor-beta 1)-associated signaling pathways, including the activation of epithelial-mesenchymal transition, the initial step of cancer metastasis. It may also inhibit the NF-kB pathway and suppress T22/type 1 T helper 17 (Th17)-type immune reactions while promoting Treg differentiation.^{2,21-23}

Recommended Use: Take 1 softgel per day with a meal or as directed by your health-care practitioner.

For a list of references cited in this document, please visit:

<https://www.designsforhealth.com/api/library-assets/literature-reference---dim-evail-tech-sheet-references>

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Healthcare practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

DeltaGold® is a registered trademark of American River Nutrition, LLC and protected by US Patent No. 8,586,109.

***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.**

To contact Designs for Health, please call us at (860) 623-6314, or visit us on the web at www.designsforhealth.com.