THE GUT-HORMONE CONNECTION:

HOW BETA-GLUCURONIDASE SHAPES ESTROGEN METABOLISM AND PATIENT OUTCOMES

PRESENTED BY DAN KALISH, DC

Introduction - Dr. Dan Kalish

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Founded The Kalish Institute for Functional Medicine in 2006.

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Introduction

- Beta-glucuronidase is a hidden player in the gut that influences patient responses to hormone therapy.
- This enzyme is produced by specific gut bacteria and plays a pivotal role in estrogen metabolism and hormone-related conditions such as breast cancer, PCOS, and menopausal symptoms.
- Understanding the interplay between gut health and hormone metabolism is crucial for successful hormone treatments.
- Imbalances in gut bacteria (dysbiosis) and beta-glucuronidase activity can affect hormone levels and therapy efficacy.

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Symptoms of Estrogen Dominance

- PMS, cramping, sugar cravings, bloating, headaches, fatigue
- Weight gain, particularly around the stomach, hips, and thighs
- Endometriosis, fibroids, fibrocystic breasts - tissue growth
- Irregular menstrual cycle, missed cycles, long cycles
- Low sex drive
- Low mood or depression, mood swings
- Anxiety, depression, esp if certain times of the month
- Bloating, breast tenderness
- Sleep issues

Serious Ramifications of Estrogen Dominance Over Time

- Cancer: High levels of estrogen can put women at a higher risk of breast cancer, ovarian cancer, and endometrial cancer.
- Autoimmune conditions: Elevated estrogen can increase your body's inflammatory response, causing your immune system to produce antibodies that attack your own tissues.
- Thyroid issues: Excess estrogen can block thyroid hormones from reaching their receptor sites in order to do their job.
- Diabetes: Progesterone is a natural diuretic and helps to stabilize blood sugar. When estrogen is dominant, however, your risk of insulin resistance and diabetes may increase

The Microbiome–Estrogen Connection and Breast Cancer Risk

by Sheetal Parida and Dipali Sharma *

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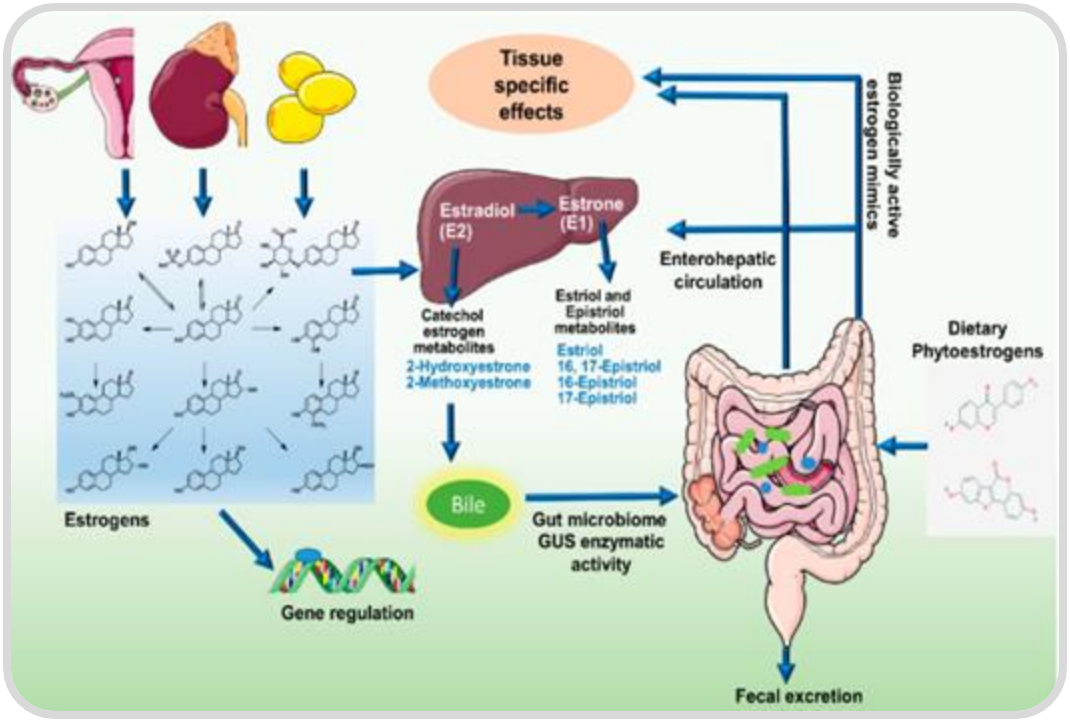
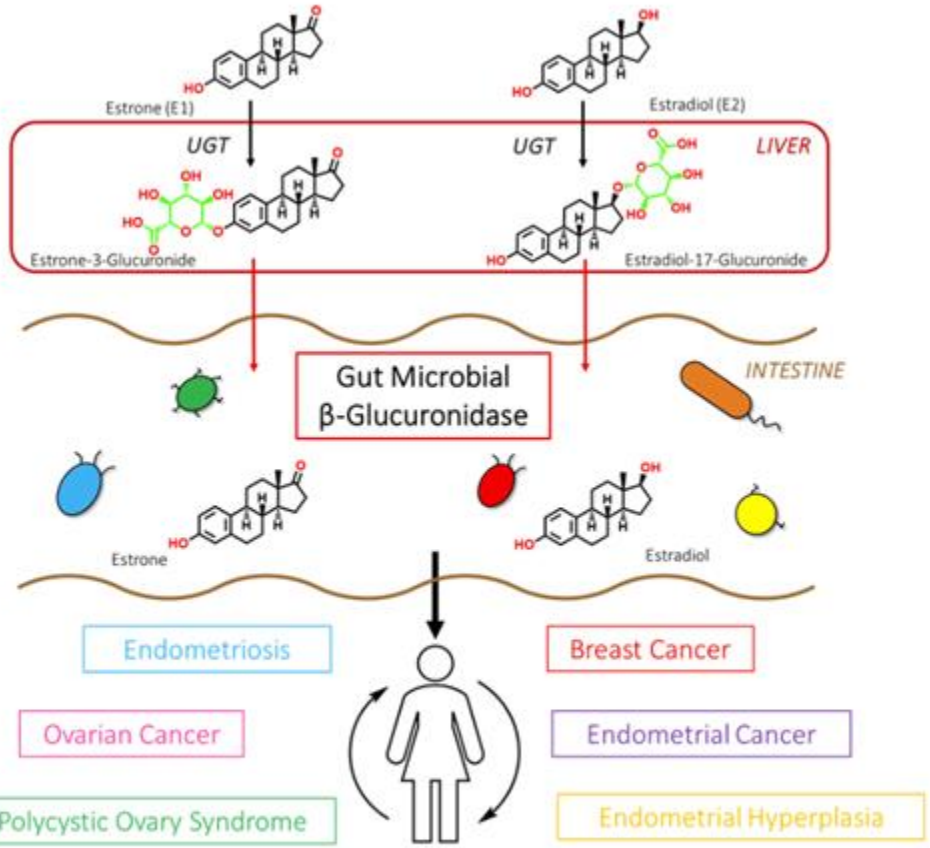


The Microbiome Estrogen Connection & Breast Cancer Risk



β-glucuronidase enzymes reactivate estrogens. Gut microbial β-glucuronidase enzymes within the GI deconjugate estrone-3-and estradiol-17-glucuronides to the aglycones estrone and estradiol, respectively. This reactivation allows unbound estrogens to be recirculated through the bloodstream, possibly contributing to a variety of hormonal disorders including breast cancer and endometriosis.

MICROBIOME ESTROGEN CONNECTION

Figure 1. Schematic representation of modulation of estrogens and its metabolites in circulation by the estrobolome. The C-18 steroid hormones, Estrogens (E1, E2, and E3) circulate in the blood stream either in free or protein bound form exerting diverse biological effects. Hepatic metabolism of parent estrogens E2 and E1 irreversibly hydroxylates the C2, C4, or C16 positions of the steroid ring producing estrogen metabolites with varying hormone potency, bioavailability, and half-life. Estrogens and their metabolites are then conjugated in the liver through glucuronidation and sulfonation to allow biliary excretion. While most of the conjugated estrogens are excreted in urine or feces, a significant proportion is reabsorbed into the circulation. Gut bacteria possessing β-glucuronidase activity can deconjugate the conjugated estrogens leading to reabsorption into the circulation. In addition, enteric microbes synthesize estrogen-like compounds or estrogen mimics from dietary sources.

Beta-Glucuronidase & Estrogen Metabolism

Role of Beta-Glucuronidase

Beta-glucuronidase is a gut bacterial enzyme within the estrobolome that deconjugates estrogen in the intestines, reactivating it and enabling its reabsorption into the bloodstream.

Estrobolome Function

The estrobolome, a bacterial gene network, metabolizes estrogens and regulates their excretion and reactivation, maintaining the balance of estrogen levels in the body.

Estrogen Metabolism Process

Estrogen is conjugated in the liver through glucuronidation, making it water-soluble for excretion via kidneys and bile into the intestines.

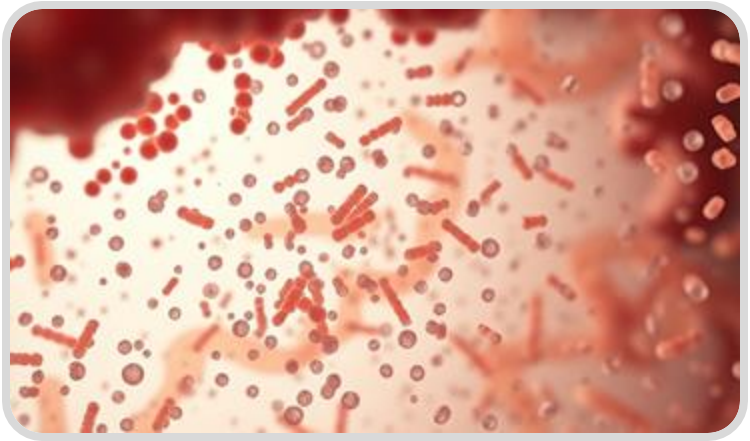
Enterohepatic Circulation

Beta-glucuronidase deconjugates estrogen in the intestines, allowing reactivated estrogen to re-enter the bloodstream through enterohepatic circulation, influencing overall hormone balance.

Overactive Estrobolome & Estrogen Dominance

Role of Beta-Glucuronidase in Estrogen Recycling

Beta-glucuronidase, produced by specific gut bacteria in the estrobolome, deconjugates estrogen in the intestines, reactivating it for reabsorption into the bloodstream through enterohepatic circulation.



Impact of Dysbiosis on Estrobolome Activity

Dysbiosis, an imbalance in gut microbiota, can cause an overgrowth of beta-glucuronidase-producing bacteria like Bacteroides and Clostridia, leading to excessive estrogen reabsorption and estrogen dominance.

Consequences of Estrogen Dominance

Elevated estrogen levels from overactive beta-glucuronidase contribute to hormone-driven disorders such as breast and endometrial cancers, endometriosis, and fibroids, increasing health risks for affected patients.

Beta-Glucuronidase and Estrogen-Related Disorders

Role in Gynecologic Cancers

Research by Sui et al. (2021) shows beta-glucuronidase reactivates estrogen, significantly contributing to gynecologic cancers and menopausal symptoms by increasing free estrogen circulation.

Dual Nature of Beta-Glucuronidase

Ervin et al. (2019) emphasize that while essential for hormone regulation, unchecked beta-glucuronidase activity leads to excess estrogen reabsorption, raising cancer risk.

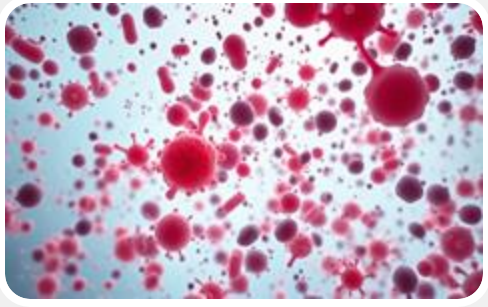
Estrobolome & Lifelong Estrogen Regulation

Shiwan Hu et al. (2023) highlight the estrobolome's role in estrogen regulation from menstruation through menopause; disruptions increase risks of estrogen-related disorders.

Impact of Dysbiosis

Elevated beta-glucuronidase levels in dysbiotic guts increase estrogen reabsorption and exacerbate menopausal symptoms and hormone-driven diseases in postmenopausal women.

Impact of Dysbiosis on Hormonal Health



Beta-Glucuronidase Overproduction

Dysbiosis causes an overgrowth of bacteria like Bacteroides and Clostridia that produce excessive beta-glucuronidase, leading to elevated enzyme levels and increased estrogen reabsorption.

Hormone Metabolism Disruption

Dysbiosis affects not only estrogen but also androgen metabolism (testosterone, DHT), exacerbating symptoms of androgen excess seen in conditions like PCOS.

Chronic Inflammation

Harmful bacteria release lipopolysaccharides (LPS), endotoxins that cross a leaky gut barrier, triggering systemic inflammation that disrupts hormone regulation.

HPG Axis Interference

LPS-induced inflammation impairs GnRH production in the hypothalamus, disrupting LH and FSH release from the pituitary, leading to imbalanced sex hormone production.

Vicious Cycle of Hormonal Imbalance

Inflammation reduces liver detoxification efficiency, allowing more estrogen reabsorption via beta-glucuronidase, creating a cycle of estrogen dominance and persistent hormonal disruption.

Diagnostic Tools for Beta-Glucuronidase & Hormonal Imbalances

GI-360 FOR MICROBIOME & BETA-GLUCURONIDASE

- The Doctor's Data GI-360 test has sophisticated analysis for dysiosis.
- Measures gut microbiota diversity, dysbiosis markers, and beta-glucuronidase enzyme activity.
- Provides insights on digestive function, inflammation, and gut barrier integrity.
- Helps identify gut imbalances affecting estrogen metabolism and hormone health.

HUMAP URINARY HORMONE METABOLISM TESTING

- HuMAP from Doctor's Data evaluates estrogen metabolism through urinary steroid hormones.
- Measures metabolites like 4-OH Estrone and 16A-OH Estrone linked to proliferative estrogen activity.
- Assesses critical metabolite such as 2-OH.

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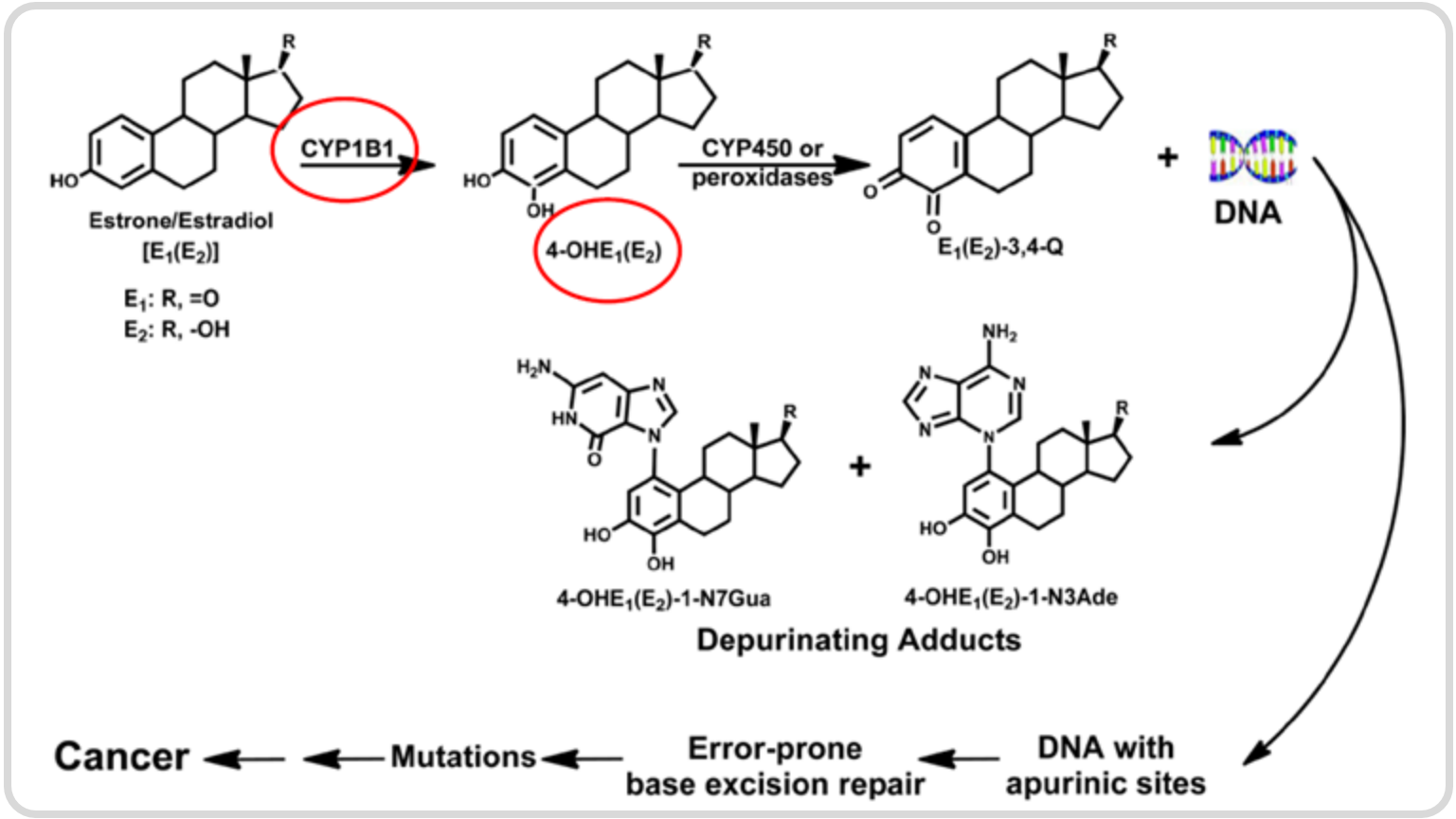

Cavalieri and Rogan. Molecular Etiology and Prevention of Estrogen-Iniated Cancers. Mol Aspects Med. 2014

Oregon State University

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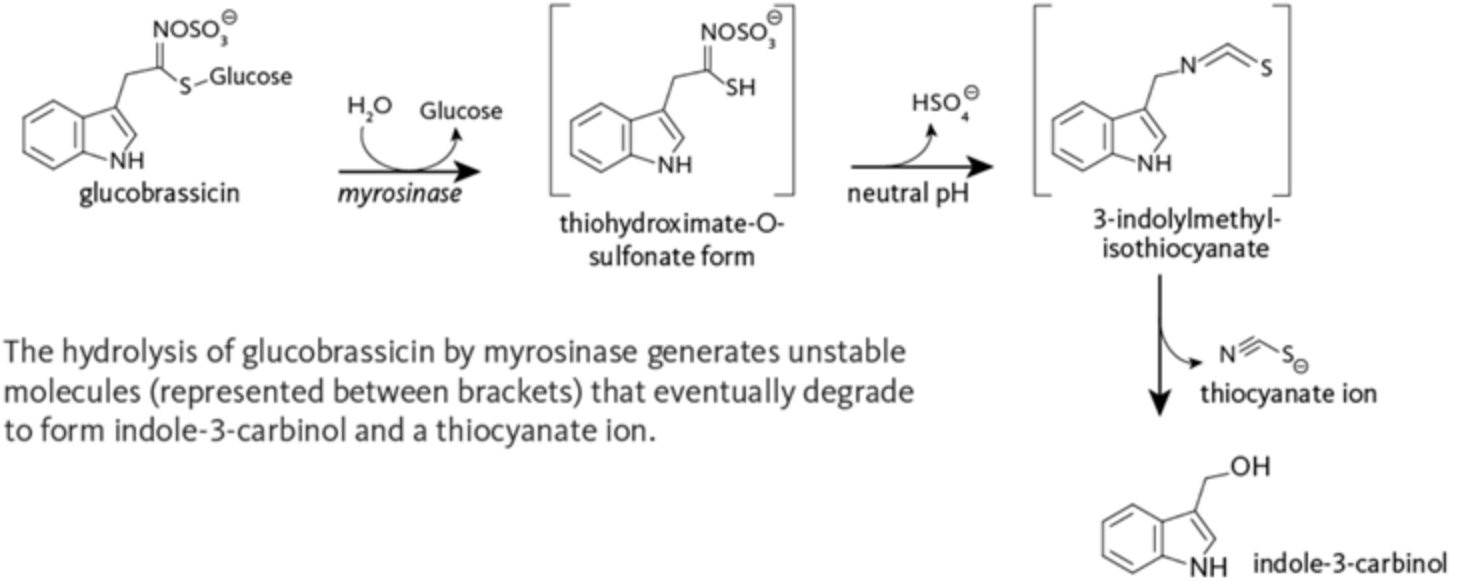
Why You Should Eat Broccoli, Cabbage & Brussels Sprouts

Figure 1. Breakdown of Glucobrassicin



The hydrolysis of glucobrassicin by myrosinase generates unstable molecules (represented between brackets) that eventually degrade to form indole-3-carbinol and a thiocyanate ion.

All Six Phase 2 Pathways and Their Respective Things They Attach to Clear Toxins

Molecules Used to Attach to Toxins In Phase II Detox Pathways

Conjugation Reaction	Attached Group
Glucuronidation	Glucuronic acid molecule
Glutathione Conjugation	Glutathione
Sulfation	Sulfate group
Methylation	Methyl group (CH3)
Acetylation	Acetyl group (CH3CO)
Amino Acid Conjugation	Amino acids (e.g., glycine, taurine, glutamine)

Glucuronic Acid (Glucuronidation)

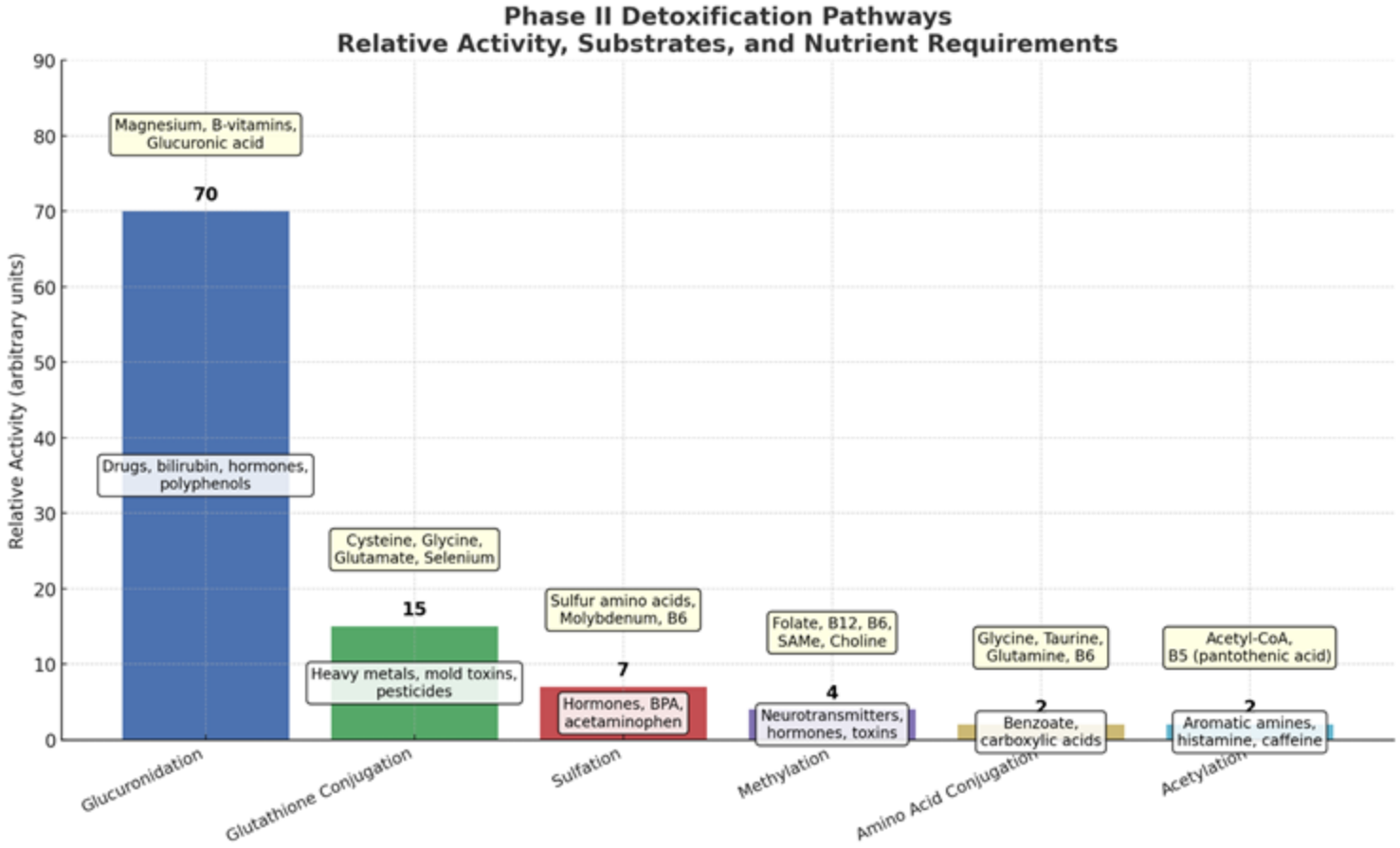
Core Function: Facilitates elimination of toxins and endogenous metabolites by conjugating them to glucuronic acid, making them water-soluble.

- Bilirubin Clearance: Prevents toxic accumulation of bilirubin.
- Drug Detoxification: Handles opioids, NSAIDs, and hormones.
- Steroid Hormone Regulation: Eliminates excess estrogens, cortisol, and androgens.
- Carcinogen Removal: Neutralizes hydrocarbons from smoke and pollutants.
- Neuroprotection: Conjugates neurotoxic metabolites in the brain.

Methyl Groups (Methylation)

Core Function: Addition of CH_3 groups, a cornerstone of epigenetics, neurotransmitter metabolism, and detoxification.

- DNA Methylation: Essential for gene regulation and survival.
- Detox of Homocysteine: Converts homocysteine to methionine.
- Neurotransmitter Balance: Inactivates histamine, dopamine, serotonin.
- Viral Defense: Silences retroviruses and transposons.
- Liver & Brain Function: Supports phosphatidylcholine production.



Glucuronidation Pathway Support - Clinical Reference

Glucuronidation is the most active Phase II detoxification pathway, responsible for conjugating bilirubin, steroid hormones, bile acids, many drugs, and polyphenols. It accounts for 40-70% of Phase II detox activity in humans.

Category	Details
Primary Substrates	Bilirubin; steroid hormones (estrogens, androgens); thyroid hormones; bile acids; polyphenols; many drugs (NSAIDs, statins, morphine).
Key Nutrients (Cofactors)	Magnesium; B-vitamins (B1, B3, B5, B6); manganese.
Direct Support	Calcium D-glucarate - provides D-glucaro-1,4-lactone and inhibits beta-glucuronidase to reduce deconjugation.
Botanical/Phytonutrient Inducers	Resveratrol; quercetin; curcumin; green tea catechins (EGCG); citrus flavonoids (hesperidin, naringenin); sulforaphane.
Supportive Measures	Soluble fiber (psyllium, pectin, flax) to bind conjugates; probiotics to reduce beta-glucuronidase-producing bacteria.
Clinical Applications	Estrogen dominance; environmental chemical and drug clearance; hormone metabolism; support in chronic disease and longevity protocols.

Methylation Pathway Support - Clinical Reference

Methylation transfers a methyl group to toxins, neurotransmitters, and hormones; critical for detoxification, DNA regulation, and neurotransmitter metabolism.

Category	Details
Primary Substrates	Estrogens; catecholamines (dopamine, norepinephrine); histamine; homocysteine.
Key Nutrients (Cofactors)	Folate (5-MTHF); vitamin B12 (methylcobalamin); B6; SAMe; choline; magnesium; zinc.
Direct Support	Methylated B-complex; SAMe; trimethylglycine (betaine).
Botanical/Phytonutrient Inducers	Leafy greens (folate); beets (betaine).
Supportive Measures	Balanced protein intake; manage homocysteine; maintain gut health for folate production.
Clinical Applications	Hormone clearance; mood regulation; epigenetic stability; cardiovascular health.

Treatments for Estrogen Dominance

Calcium-D-Glucarate

- This form of calcium promotes phase 2 glucuronidation; a phase II biotransformation reaction that helps to make molecules more water-soluble. It's also believed to be a beta-glucuronidase inhibitor, which helps prevent the reabsorption of detoxified estrogens through second-pass metabolism.
- Simply put, calcium-d-glucarate binds to circulating estrogen that would otherwise be reabsorbed by your body, then allows it to be flushed out.

Diindolylmethane (DIM)

- Diindolylmethane is a compound formed in the body from plant substances of cruciferous vegetables such as cabbage, Brussels sprouts, cauliflower, and broccoli.
- DIM supplementation helps to metabolize estrogen into more good metabolites than the potentially harmful metabolites. It also appears to help destroy cancer cells and reduce inflammation.

Treatments for Estrogen Dominance

- Fix liver detox pathways, clear estrogens, clear environmental toxins
- Fix gut/dysbiosis
- Balance progesterone
- Consider genetic issues, COMT, MTHFR
- Glutathione essential to remove harmful free radicals inside cells that damage DNA
- NAC and resveratrol reduce formation of estrogen-DNA adducts

How to Increase 2-OH Estrogen

- Sulforaphane
- Indole 3 Carbinol/DIM
- Omega 3's
- Curcumin
- Methylation support nutrients

COMT Pathways Treatments

- B6, B12, Folate
- Magnesium
- TMG/Betaine/Trimethylglycine
- SAMe
- Methionine

Clinical Strategies for Balancing Beta-Glucuronidase

Liver Detoxification Regulates Hormones

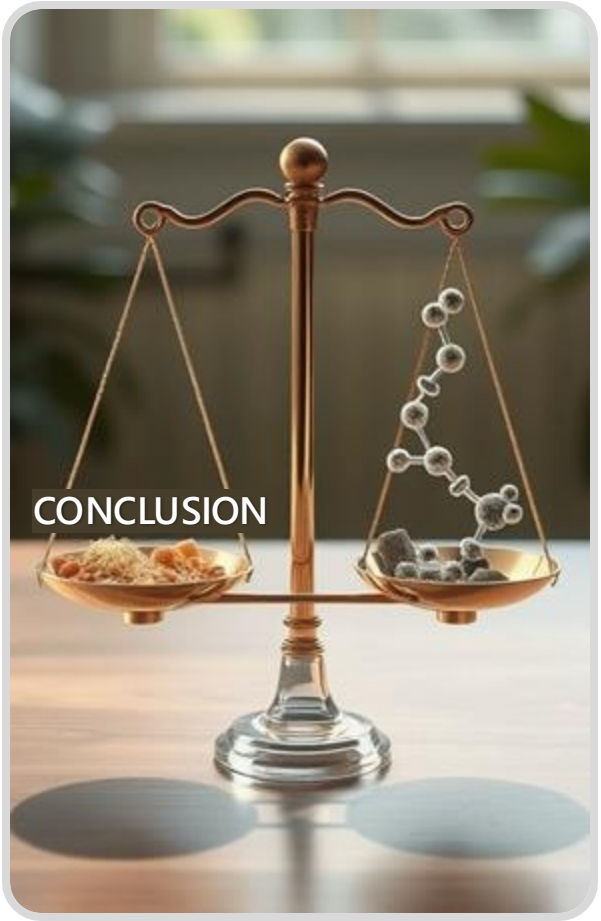
Milk thistle & curcumin support liver detoxification of estrogen and reduce inflammation..

GI Testing & Dysbiosis Treatments

Gut health required for healthy estrogen levels to be maintained.

Calcium-D-Glucarate

Calcium-D-glucarate inhibits beta-glucuronidase and promotes estrogen excretion, especially helpful in dysbiosis to reduce estrogen dominance and improve hormone balance.



The Bottom Line

- Balancing beta-glucuronidase activity is essential for managing estrogen metabolism and improving hormonal health.
- Addressing gut health through diet, probiotics, and supplements like calcium-D-glucarate supports better outcomes in estrogen dominance, PCOS, and hormone-sensitive cancers.
- Regular monitoring with stool and hormone testing ensures treatment protocols can be adjusted effectively.
- Elevated beta-glucuronidase can lead to excessive estrogen reabsorption, contributing to hormone-related diseases.
- Managing gut dysbiosis and reducing systemic inflammation improves hormone regulation and patient well-being.

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