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Nutritional Approaches to Biotransformation

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Disclosures

- Lara Zakaria sits on the Scientific Advisory Board (SAB) at Gaia Herbs

Objectives

1. Review the interconnection between the gut, immune system, and detoxification pathways
2. Review strategies to upregulate detoxification capacity with nutrients and herbs
3. Identify dietary patterns and therapeutic foods that are part of detoxification protocol

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Paracelsus The Father of Toxicology

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

Bio-Transformation

AKA Detoxification

Detoxification Phases

Phase I

- Compound modification generally through hydroxylation, oxidation, and reduction reactions

Phase II

- Compound metabolism involving addition of side chains or functional groups (glucuronide, glutathione, methyl groups)

Phase III

- Antiporter (efflux) activity concentrated in the small intestines (tips of the villi)

Phase I

P450 modifications mainly include:

- **Oxidation, reduction**, and **hydrolysis**
- Mainly performed by the **Cytochrome "P450"** mixed-function oxidase **enzyme system**

Other important Phase I enzymes :

- **Peroxidases** (like glutathione peroxidase)
- Alcohol and aldehyde **dehydrogenases**
- **Monoamine oxidase**: metabolism of neurotransmitters serotonin, melatonin, dopamine, adrenalin, noradrenalin

Phase II

Products from phase I are joined with charged compounds

- Larger, **less active**, and more **water soluble**
- **More easily excreted** by the kidney into urine or by the liver into bile
- **Genetic variations** for these enzymes may **increase or decrease** phase II bio-transformation of specific toxins/substances

Phase II includes:

- Methylation, sulfation, acetylation, glucuronidation, glutathione conjugation, and glycine conjugation

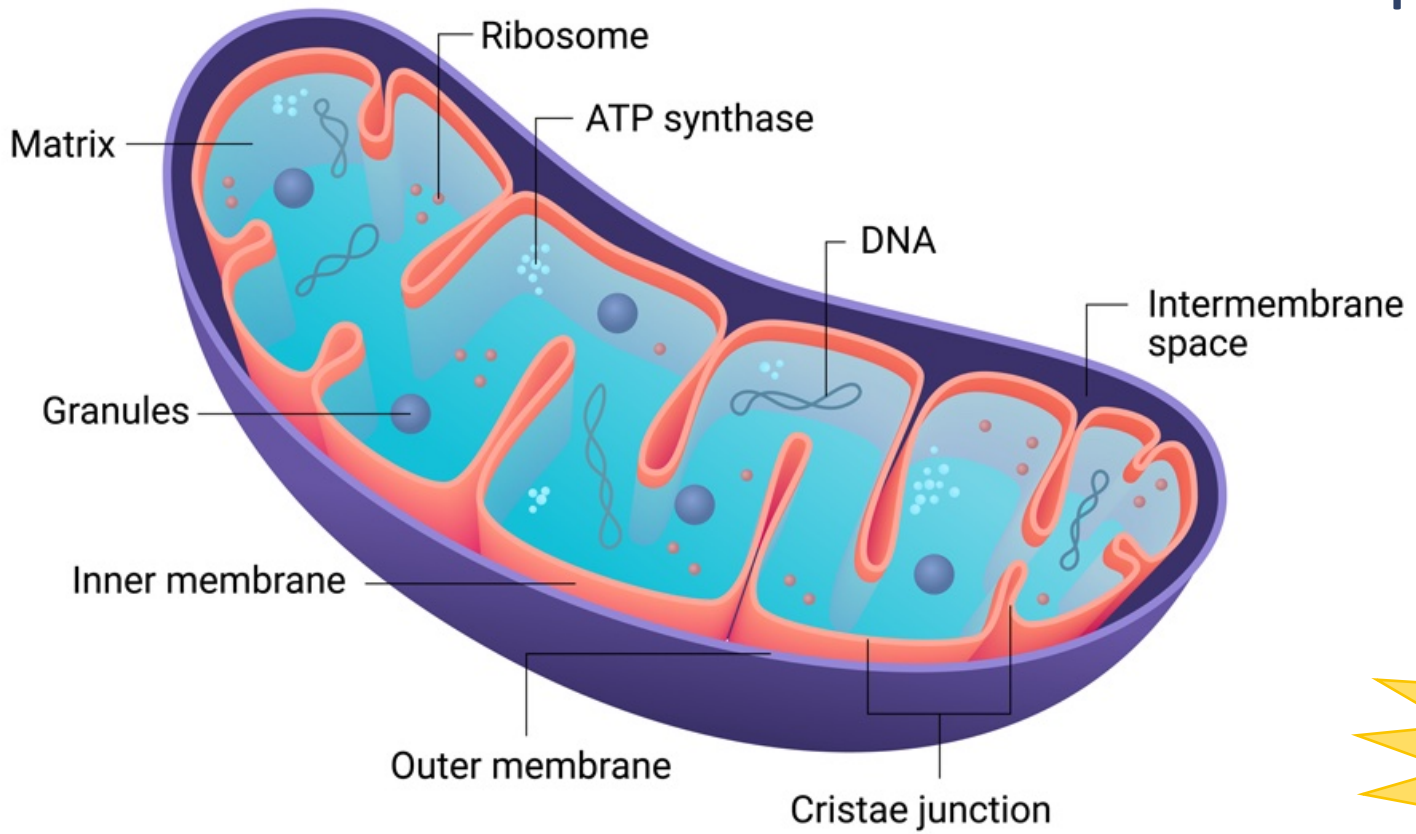
What if Phase II is out of sync with Phase I?

Bottleneck

- Build-up of **metabolites - more toxic than the original substance**
- Dangerous metabolites cannot be conjugated in Phase II and then **cannot be eliminated**
- This occurs typically when a person is “undernourished” prior to initiating or during a detoxification program


ROS = SOS

Mitochondria



Powerhouse of the cell

Connected to bio-transformation

https://researchoutreach.org/articles/identifying-mitochondrial-dna-mutations-cause-cancer/

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Mitochondria & the bacterial microbiome have a lot in common

We have ~10x the number of bacteria vs human cells in our body

But we have ~1,000x mitochondria per cell

~10 million billion total mitochondrion in the body, which equals ~10% of a person's body weight

On average each cell contains 200-2,000 mitochondrion with the concentrations varying based on energy demand (cardiac, liver, kidney, and neurons are the most *mito-rich*)

Mitochondria are thought to be evolutionary "leftovers" from bacteria

The most significant source of ROS is mitochondrial respiration

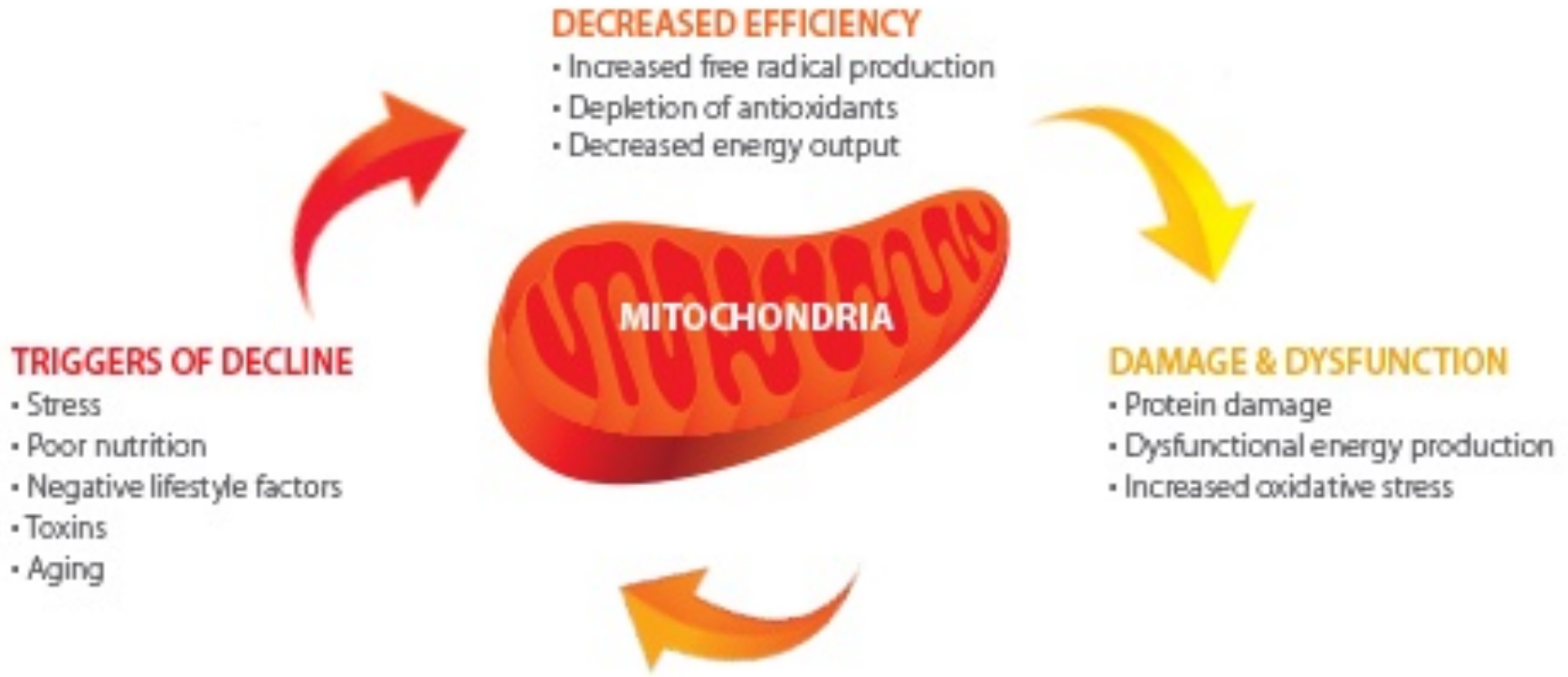
The reaction occurs in the mitochondrial respiratory chain, where 85% of O2 is metabolized

Tissue damage occurs unless free radicals are neutralized via electron transfer requiring enzymatic conversion ***(i.e. Glutathione peroxidase, Glutathione reductase, SOD***) or vitamin transfer

Imbalances of key vitamins including **vitamins A, C, or E** or minerals like **zinc, copper, selenium** or ETC cofactor insufficiencies of **CoQ10, iron, heme or cytochromes** can cause disruptions in the massive flow of electrons through these systems

Lord R, Bralley JA. Laboratory Evaluations for Functional and Integrative Medicine. 2012

“Inflammaging”



Building metabolic reserve to power detoxification

Adequate macronutrient balance

- Amino acids
- Antiinflammatory fats
- Fiber

Adequate micro-nutrient reserve

- Cofactors for energetic/metabolic and enzymatic pathways

Strong antioxidant reserve

- Neutralizing ROS
- Modulating transcription factors

Mitochondrial

- Intermediate and cofactors for ATP production
- Antioxidants to quench oxidative stress as mitochondrial demand increases

Barrier integrity & Microbiome balance

- Support intestinal permeability
- Microbiome and metabolome contributions

Antioxidants

Antioxidants function in concert → single supplementation increases potential for imbalance

When antioxidants are consumed out of proportion, can become part of the problem

Radicals removed as water and reduced antioxidant

Important Antioxidant Compounds

Major antioxidants

- Ascorbate (vitamin C)
- Vitamin E
- Vitamin A/B-carotene
- Riboflavin
- Selenium
- Zinc
- Copper
- Manganese
- Glutathione
- Isoflavones

Building blocks or cofactors

- Cysteine, Glycine, Mg (glutathione building blocks)
- Selenium, copper, zinc (glutathione peroxidase)
- Riboflavin (glutathione reductase)
- Copper, Zinc, Manganese (SOD)

How strong is your defensive line?

frontiers in Cellular and Infection Microbiology

REVIEW
published: 08 September 2017
doi: 10.3389/fcimb.2017.00396

Gut Dysbiosis in Animals Due to Environmental Chemical Exposures

Cheryl S. Rosenfeld[1,2,3,4]*

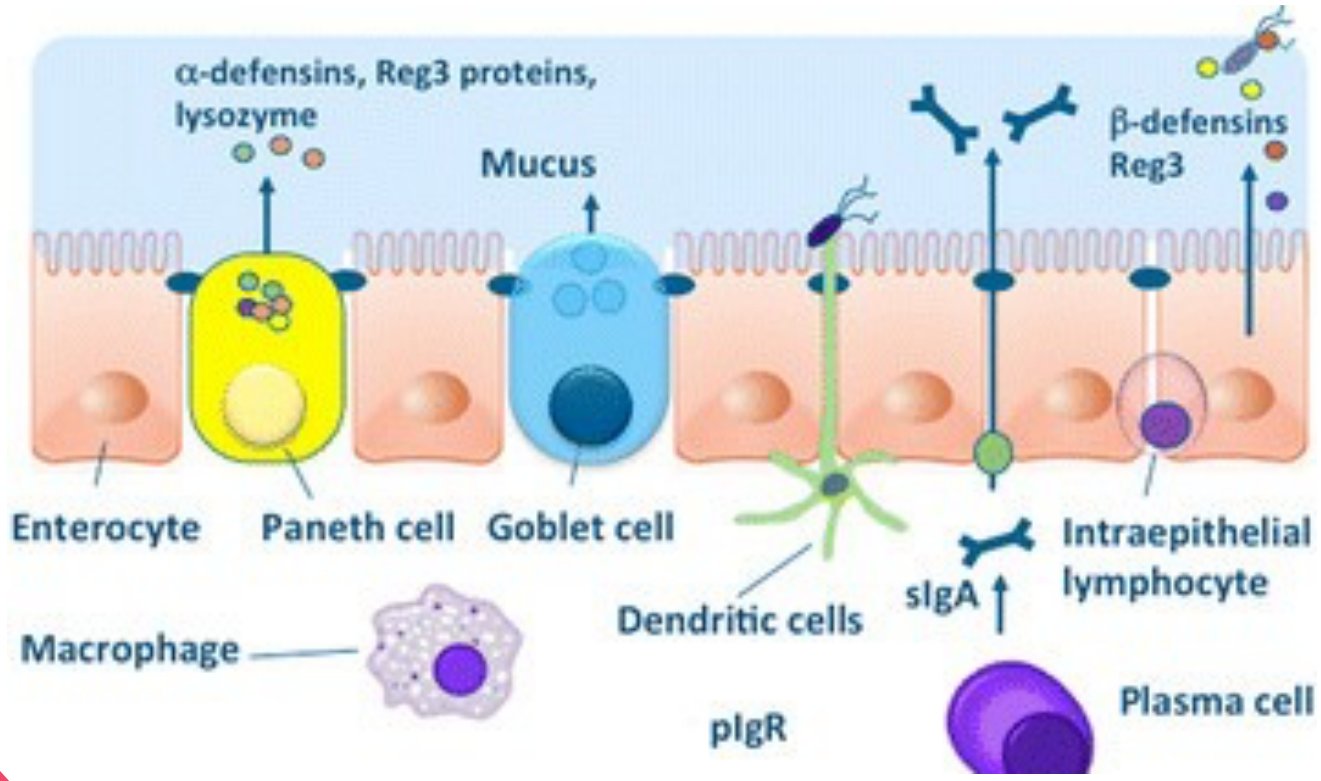
[1] *Bond Life Sciences Center, University of Missouri, Columbia, MO, United States,* [2] *Biomedical Sciences, University of Missouri, Columbia, MO, United States,* [3] *Thompson Center for Autism and Neurobehavioral Disorders, University of Missouri, Columbia, MO, United States,* [4] *Genetics Area Program, University of Missouri, Columbia, MO, United*

The gut microbiome consists of over 10^3–10^4 microorganism inhabitants possess 150 times more genes that the human genome and thus should l an "organ" in of itself. Such communities of bacteria are in dynamic flux and changes in host environment and body condition. In turn, gut microbiome can affect health status of the host. Gut dysbiosis might result in obe gastrointestinal, immunological, and neurobehavioral disorders. Such host originate due to shifts in microbiota favoring more pathogenic species various virulence factors, such as lipopolysaccharide. Bacterial virulenc metabolites may be transmitted to distal target sites, including the brain. (mechanisms by which gut dysbiosis can affect the host include bacte metabolites, production of hormones and factors that mimic those pro host, and epimutations. All animals, including humans, are exposed da environmental chemicals that can influence the gut microbiome. Expo chemicals might lead to downstream systemic effects that occur secon microbiome disturbances. Increasing reports have shown that environmental exposures can target both host and the resident gut microbiome. In this review, we will first consider the current knowledge of how endocrine disrupting chemicals (EDCs), heavy metals, air pollution, and nanoparticles can influence the gut microbiome. The second part of the review will consider how potential environmental chemical-induced gut microbiome changes might subsequently induce pathophysiological responses in the host, although definitive evidence for such effects is still lacking. By understanding

Gut dysbiosis might result in obesity, diabetes, gastrointestinal, immunological, and neurobehavioral disorders.

[…] we will first consider the current knowledge of how endocrine disrupting chemicals (EDCs), heavy metals, air pollution, and nanoparticles can influence the gut microbiome. The second part of the review will consider how potential environmental chemical-induced gut microbiome changes might subsequently induce pathophysiological responses in the host […]

The gut-immune interface



- Significance of the connection between GI and immune
- Major site of host defense (mechanical, chemical, immunological)
- Comprises 70-80% of host immune cells reside in the GI

BMC Gastroenterol 2014

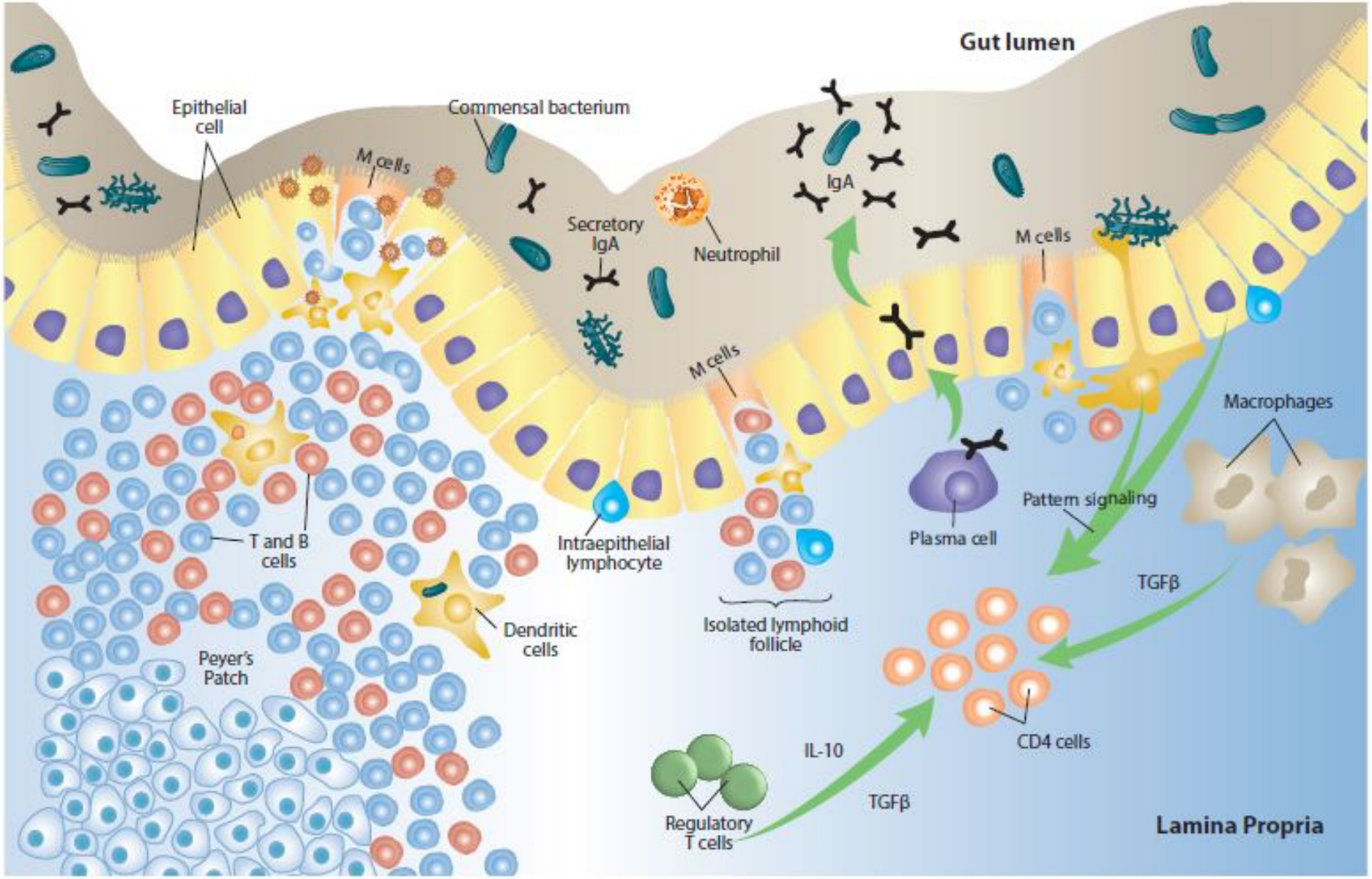


Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT). See the text for detailed explanation.

Supporting Immune Function: A Lifestyle and Nutrient Approach. Thomas G. Guilliams, Point Institute.

A breach in the defensive line

- “Leaky gut” allows unprocessed antigens and organisms to pass between the epithelium
- Permeability has been associated with endotoxemia and passage of pathogens into circulation

The GI is a major site of immunity

- Gastric pH and digestive enzymes
- Barrier integrity (“the fence”)
- Microbiome
- Metabolome
- Glycome
- “Building the immune system” 70-80%
- sIgA regulation of the mucosal barrier and antigen response

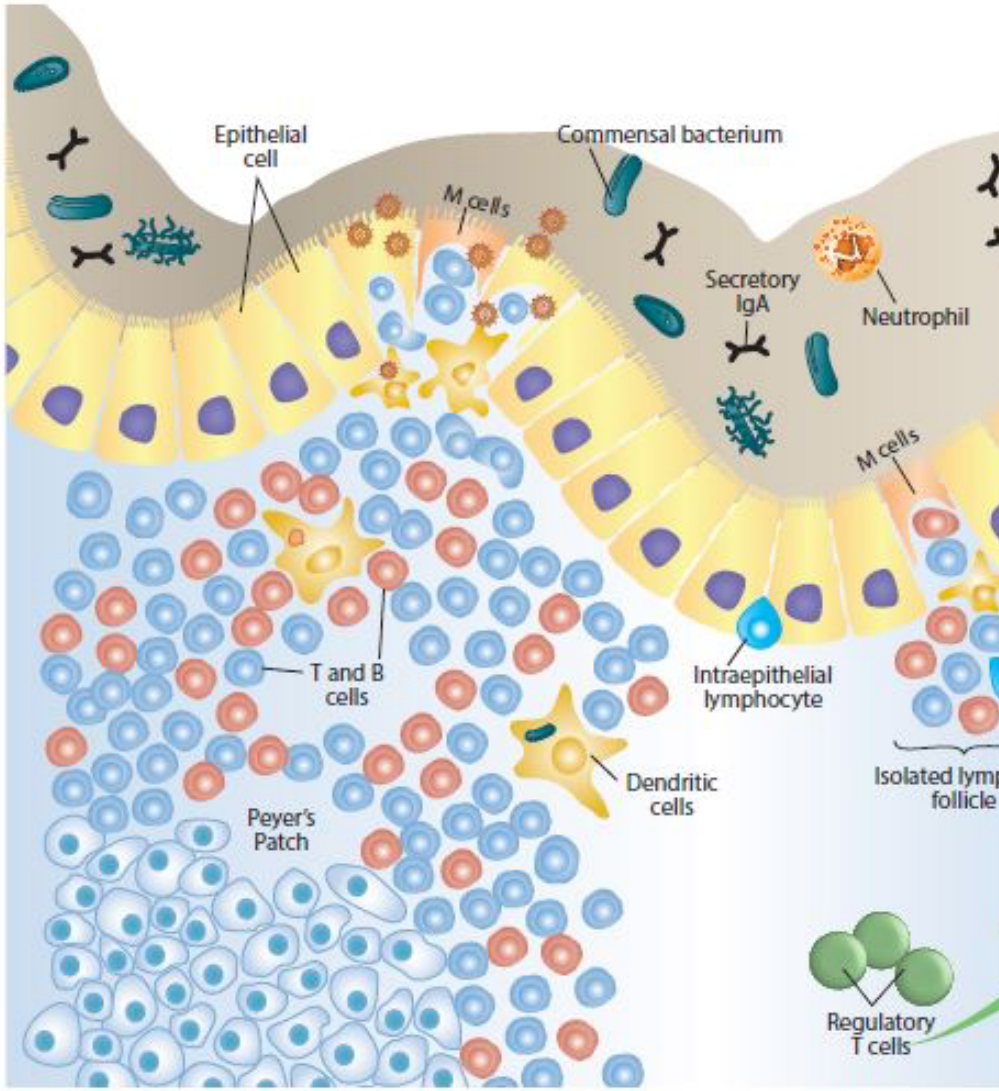


Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT).

Impact of Xenoestrogens

Gut-Biotransformation axis

Heavy Metals

ALUMINUM

LEAD

ARSENIC

CADMIUM

MERCURY

Metallothionein

Metal ion binding protein

- Small cysteine-rich proteins → play important roles in metal homeostasis and protection against heavy metal toxicity, DNA damage, and oxidative stress.

Particularly abundant in the kidney

- Sequester essential elements, prevents spilling into urine
- Site of a lot of *ROS* (think HIGH energy demand)*

Heavy metals compete for binding site

- Competative binding with nutritional minerals, nutrient deficiency → increased toxin damage

Urinary challenge

- Can help determine level of metallothionein loading with toxic elements
- Renal metallothionein – use EDTA, DMSA, DMPS prior to urinary collection
- Chelating agents compete for binding release toxic elements to allow them to spill into the urine

Mineral Depletion: Iron

Divalent metal transporter (DMT1)

- Mediates absorption of non-heme iron
- Upregulated in iron deficiency
- Cadmium and lead share the same transporter
- **Iron deficiency predisposes an individual to a <u>cadmium or lead toxicity</u>**
- Adequate iron is protective from element toxicities

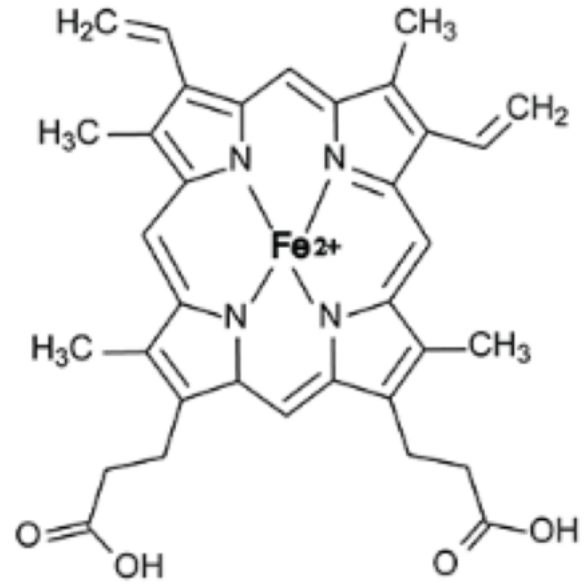


Figure 1. Structure of Heme b

https://lpi.oregonstate.edu/mic/minerals/iron

Published in final edited form as:
Curr Opin Toxicol. 2020 February ; 19: 21–27. doi:10.1016/j.cotox.2019.09.009.

Intestinal Microbiome and Metal Toxicity

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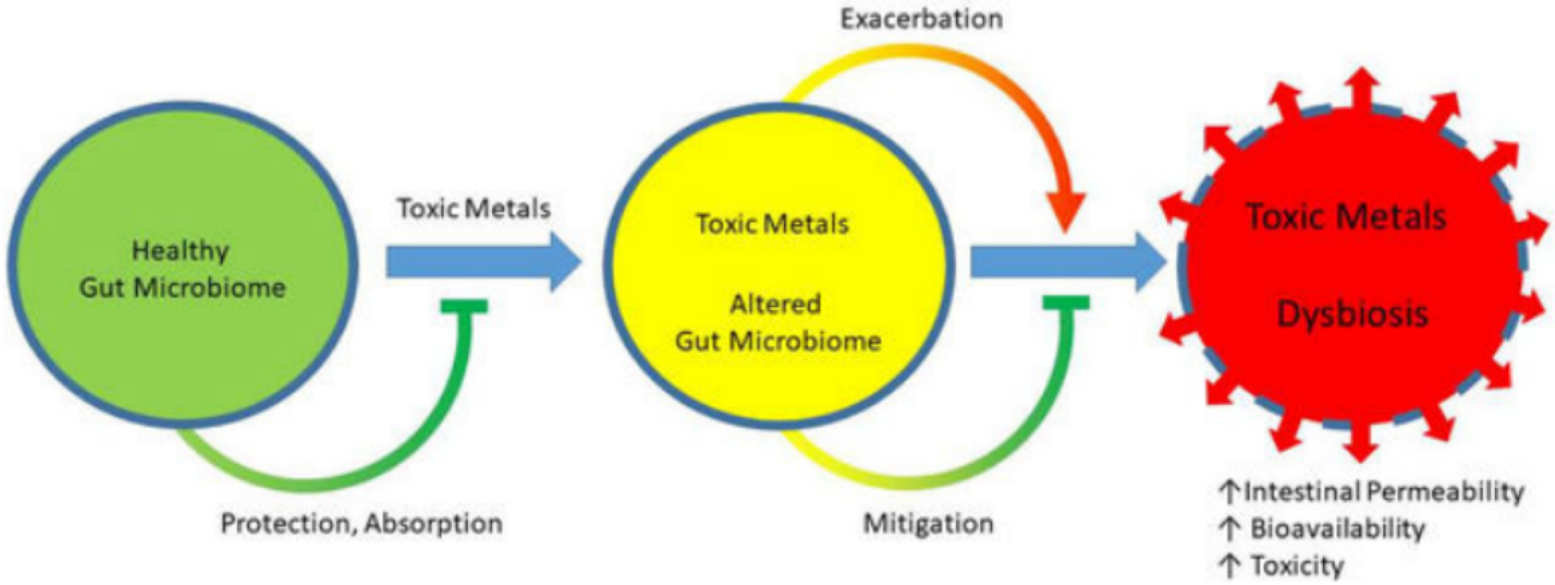
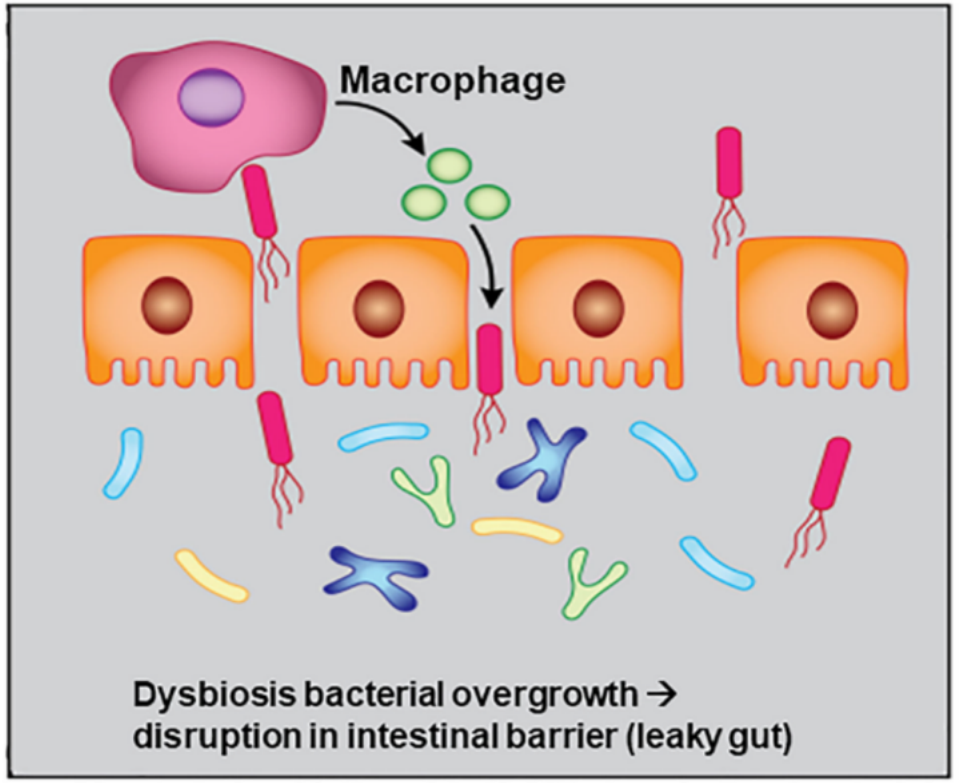
[1]Department of Biochemistry & Microbiology, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma, U.S.A.

Graphical Abstract



Xenoestrogen Effects on the Gut Microbiome

- Endocrine disrupting chemicals (EDCs) - including bisphenol A (BPA), phthalates, and phytoestrogens - act as xenoestrogens
- Bacteria in the gut and elsewhere in the body can dramatically influence host responses



Curr Opin Endocr Metab Res. 2021;19:41-45.

Beta-glucuronidase & the Estrobolome

Modulation of estrogens and its metabolites by the estrobolome

Estrogens (E1, E2, and E3) circulate → Hepatic metabolism E2 and E1 via hydroxylation producing estrogen metabolites

Estrogens and their metabolites are then **conjugated in the liver** through glucuronidation and sulfonation to prepare for biliary excretion

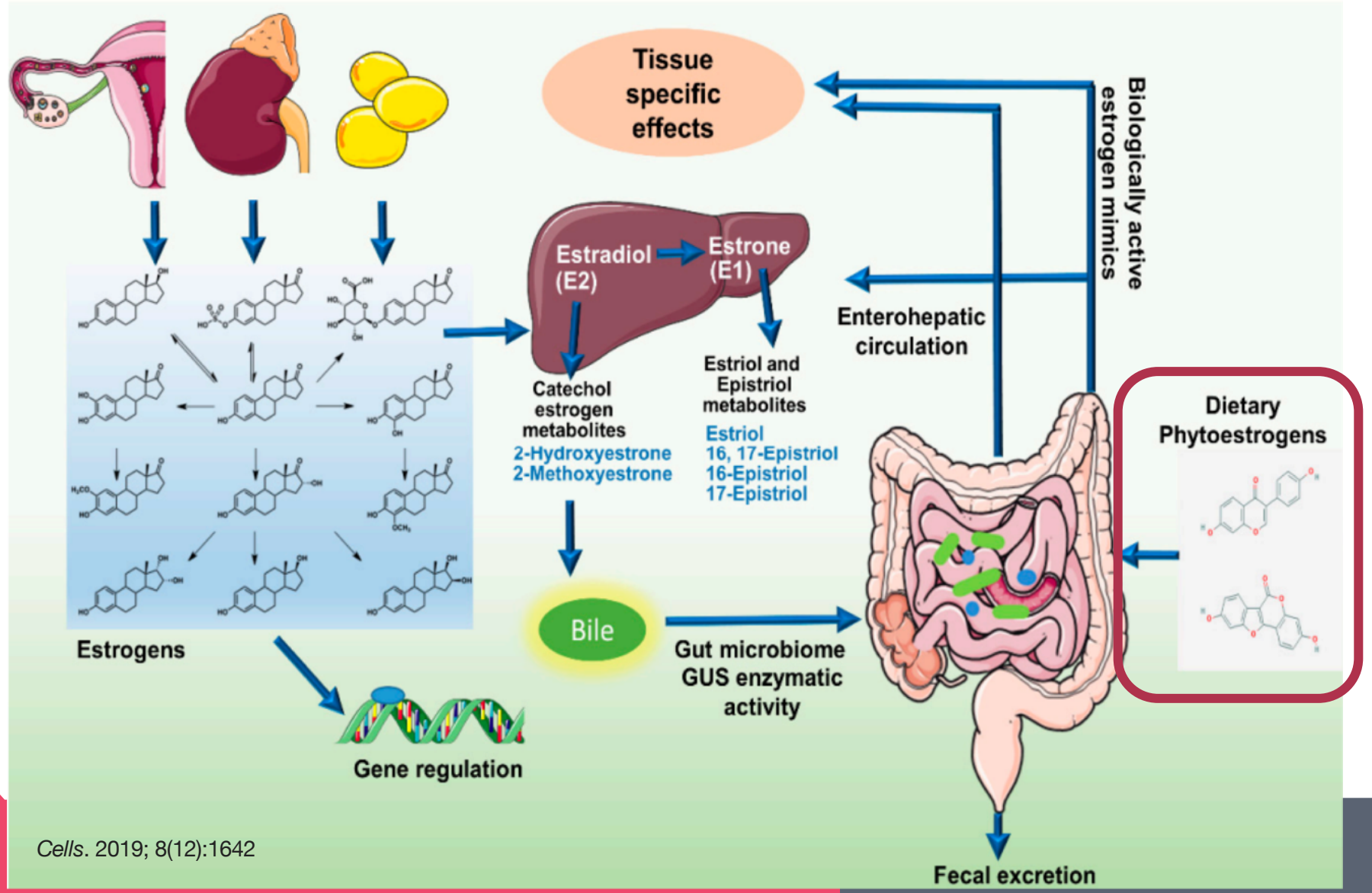
Most conjugated estrogens are removed via stool (and urine), but a significant proportion is reabsorbed into the circulation

Gut bacteria possessing β-glucuronidase activity can deconjugate the conjugated estrogens → leading to reabsorption into the circulation.

Enteric microbes synthesize estrogen-like compounds or estrogen mimics from dietary sources

Cells. 2019; 8(12):1642
Front Cell Dev Biol. 2021;9:631552.

Regulation of estrogen is largely dependent on the microbiome



Cells. 2019; 8(12):1642

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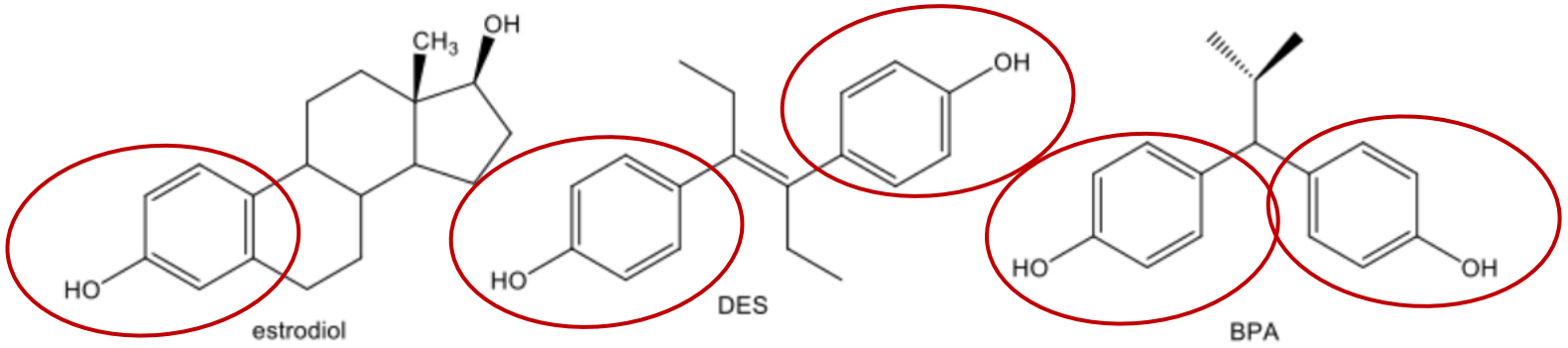
Xenoestrogens



What functional group is responsible for endocrine mimicking effect?

Shanle EK, Xu W. Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. *Chem Res Toxicol*. 2011;24(1):6–19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119362/

Phytoestrogens

Plant-produced compounds found in a wide variety of herbs and foods, most notably, soy-containing foods

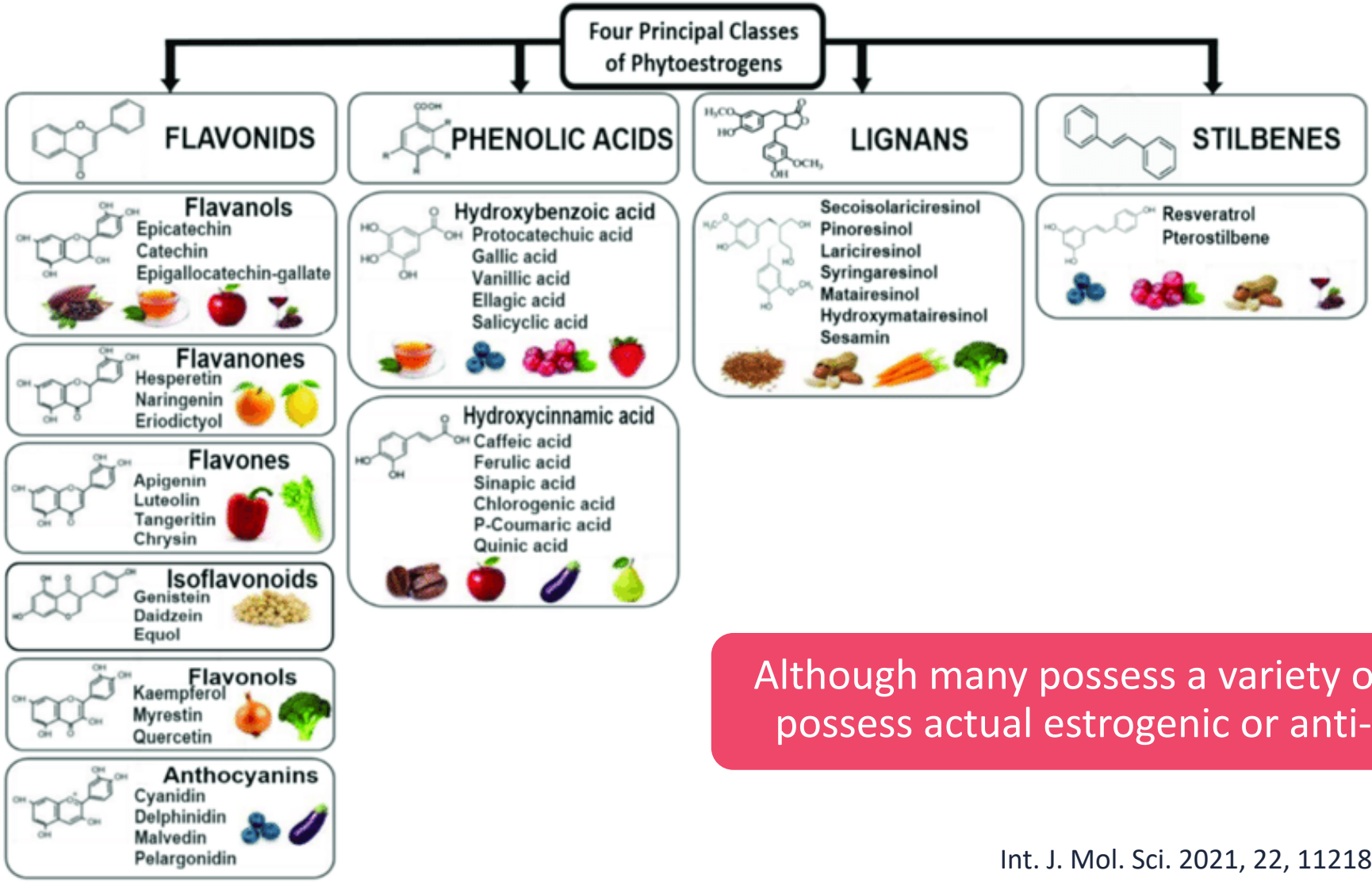
Made naturally and often share structural features with endogenous E2, allowing phytoestrogens to cause estrogenic and/or anti-estrogenic effects

Suggested to have a large spectrum of beneficial effects, including the reduction of cancer risk and postmenopausal symptoms

Include **isoflavanoids, flavonoids, lignans, coumestans, ellagitannins, stilbenes, genistein, daidzein** and its metabolite **S-equol, and coumestrol**.

Cells. 2019; 8(12):1642
Int. J. Mol. Sci. 2021, 22, 11218
Front Cell Dev Biol. 2021;9:631552.

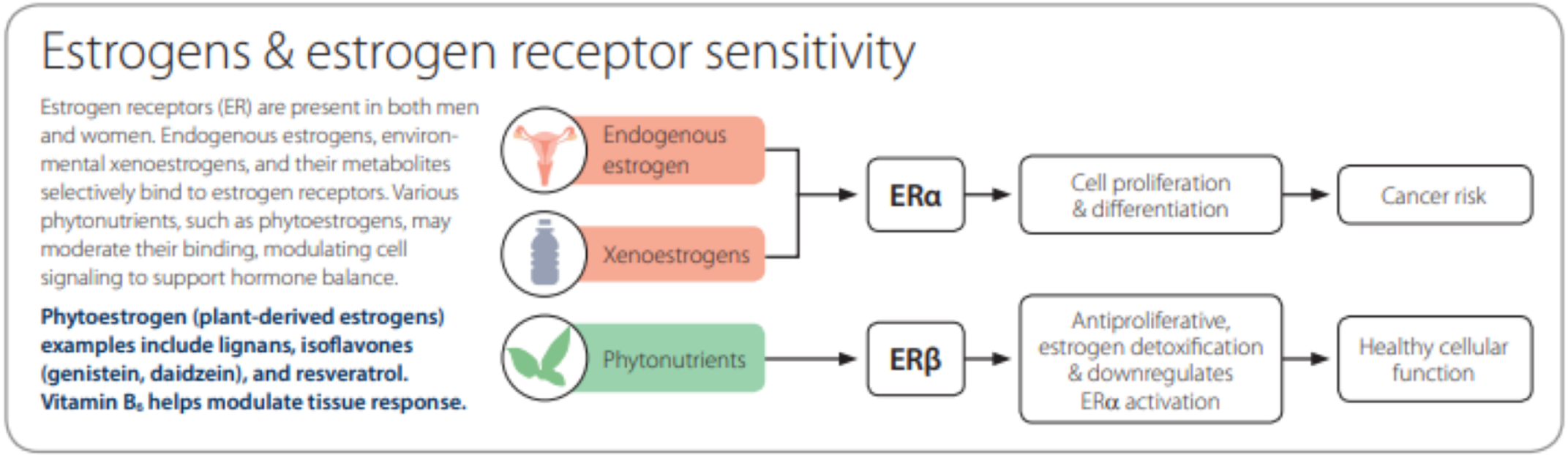
Principle Classes of Phytoestrogens



Although many possess a variety of benefits, only a few possess actual estrogenic or anti-estrogenic activities

Int. J. Mol. Sci. 2021, 22, 11218

Phytoestrogen vs Xenoestrogens



https://www.metagenicsinstitute.com/wp-content/uploads/2019/02/MET2695V2-Estrogen-Metabolism-Science-Review-IPAD-050119.pdf

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Bioactive mechanism in estrogen detoxification

Nutrients affecting mechanism of action

There are several pathways in the estrogen metabolism cascade where certain nutrients and bioactives have been studied for their influence on the mechanism of action, either in humans or in preclinical studies. These mechanisms of action and the nutrients that have been studied are referenced in the table below:

Nutrients and Bioactives	Mechanism of Action
Cruciferous vegetables, indole-3-carbinol, 3,3′-diindolylmethane (DIM), xanthohumol, rosemary, isoflavones (soy, kudzu, clover)[20-25]	Promote C-2 hydroxylation over C-4 and/or C-16α hydroxylation of estrogens
Vitamins A, E, & C, N-acetylcysteine, superoxide dismutase (SOD), turmeric, green tea, lycopene, α-lipoic acid, flavonoids[26-30]	Reduce the oxidation of catechol estrogens (2-OH and 4-OH)
Folate; vitamins B_2, B_6, & B_{12}; trimethylglycine; magnesium[31-32]	Promote the methylation of catechol estrogens (2-OH and 4-OH)
Fiber, lignans (flaxseed), isoflavones (soy, kudzu, clover)[33-37]	Increase circulating concentrations of SHBG, thus reducing levels of unbound, active estrogens
Lignans (flaxseed), flavonoids (chrysin)[38-40]	Inhibit the activity of aromatase, which converts into estrogens
Turmeric or curcumin; milk thistle; D-limonene; magnesium; vitamins B_2, B_6, & B_{12}; flavonoids[19, 30, 41]	Promote the detoxification of estrogens by upregulating Phase I and Phase II enzymes
Fiber, probiotics (*L. acidophilus* NCFM®, Bifidobacteria), calcium D-glucarate[42-45]	Inhibit the activity of β-glucuronidase, which deconjugates estrogens in the large intestine, allowing them to be reabsorbed and remetabolized
Isoflavones (soy, kudzu), lignans (flaxseed), indole-3-carbinol, DIM, xanthohumol, resveratrol[46-52]	Modify estrogen receptor activity

https://www.metagenicsinstitute.com/wp-content/uploads/2019/02/MET2695V2-Estrogen-Metabolism-Science-Review-IPAD-050119.pdf

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Resilience

Phytochemicals (AKA phytonutrients, bioactive compounds)

Naturally occurring compounds in plants

- Contribute to their color, but they're part of their defense mechanism
- Potentially tens of thousands (30k+) different compounds

Compounds help plants survive via various mechanisms

- Natural pesticides: help the plant resist fungi, bacteria, plant viruses, as well as repel insects and other animals

Environmental struggles → plant resilience

- "Rough" environment leads to more complex phytonutrient composition

Consider the impact of conventional/modern agriculture on nutrient content

Organic & regenerative farming practices vs conventional farming methods

Are organic & regenerative farming practices better?

Significant positive outcomes were seen in longitudinal studies where increased organic intake was associated with reduced incidence of infertility, birth defects, allergic sensitisation, otitis media, pre-eclampsia, metabolic syndrome, high BMI, and non-Hodgkin lymphoma. The current evidence base does not allow a definitive statement on the health benefits of organic dietary intake. However, ***a growing number of important findings are being reported from observational research linking demonstrable health benefits with organic food consumption****. Future clinical research should focus on using long-term whole-diet substitution with certified organic interventions as this approach is more likely to determine whether or not true measurable health benefits exist.*

~ Vigar V et all 2020

Nutrients. 2019;12(1):7.

Why are phytochemicals important?

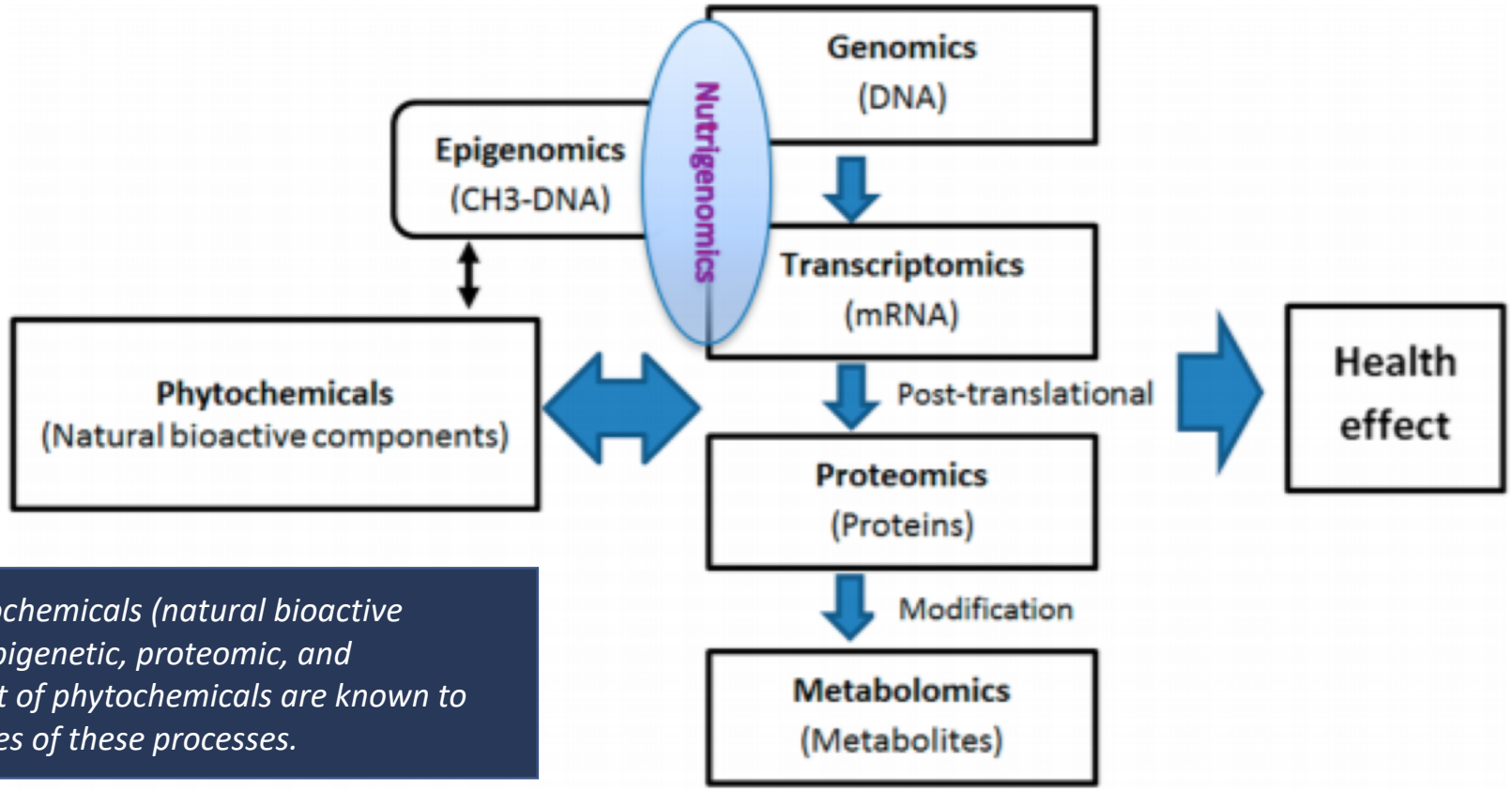


Figure 1. *Influence of phytochemicals (natural bioactive components) on genetic, epigenetic, proteomic, and metabolomic events. A host of phytochemicals are known to influence one or more stages of these processes.*

J Proteome Res. 2013

Phytochemicals sit at the interface of the microbiome, genetics, environment, lifestyle and health outcomes

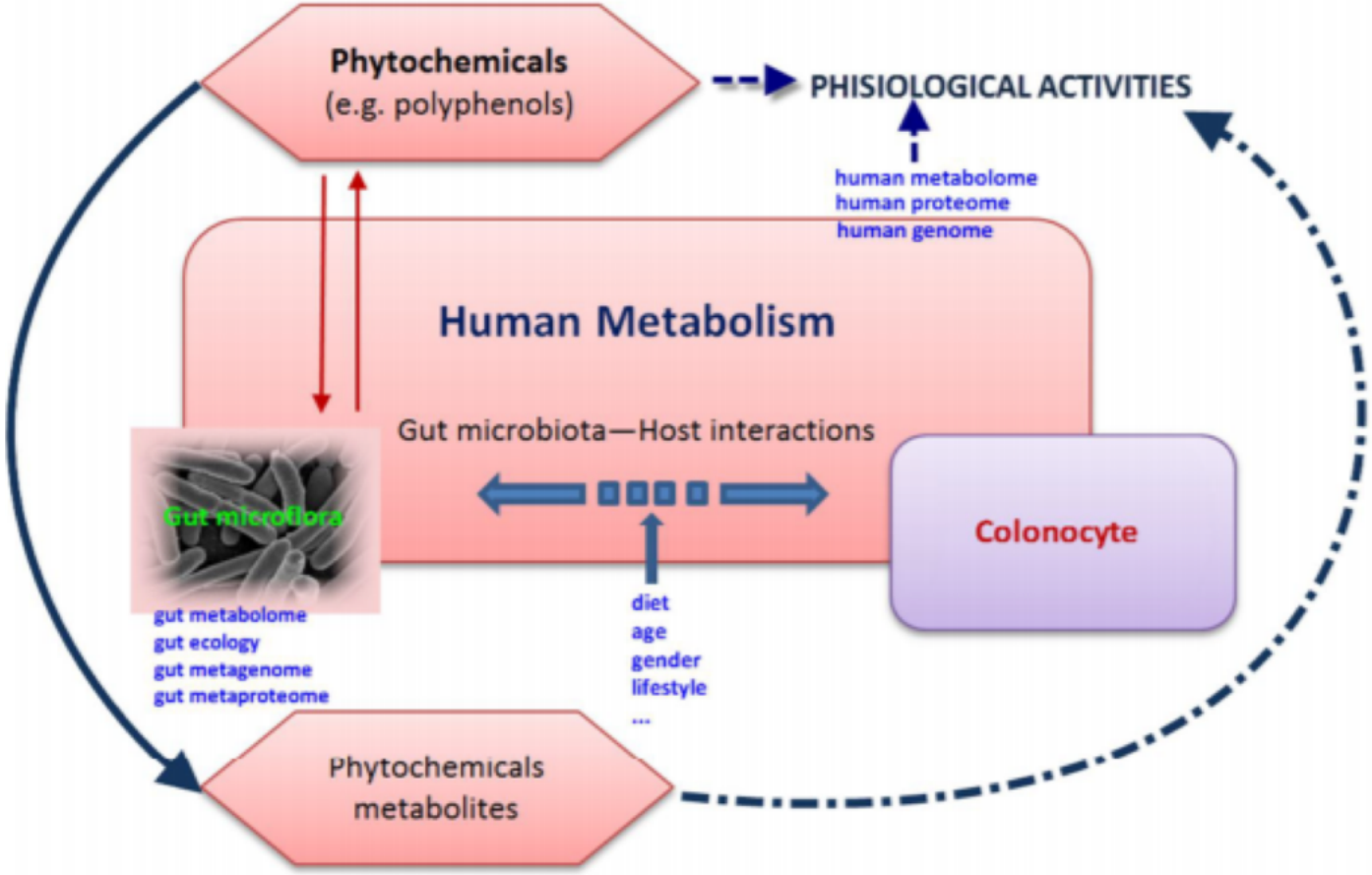
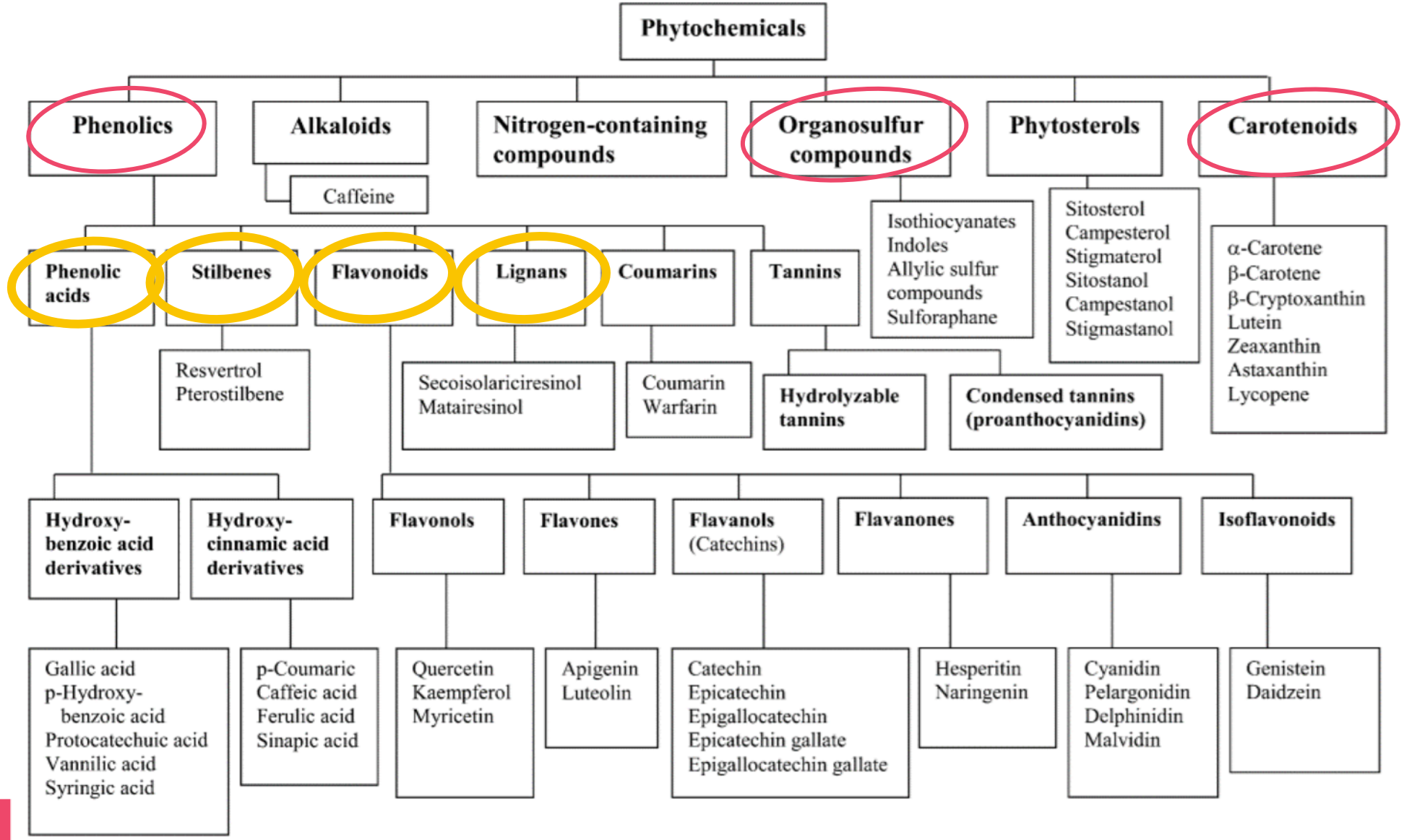


Figure 3. *Interactions between phytochemicals, gut microbiota and host as a combined contribution to human metabolism. The interplay between gut microbiota and host, and its modulation by nutrition, will benefit from the integration of information on a systems biology-wide approach.*

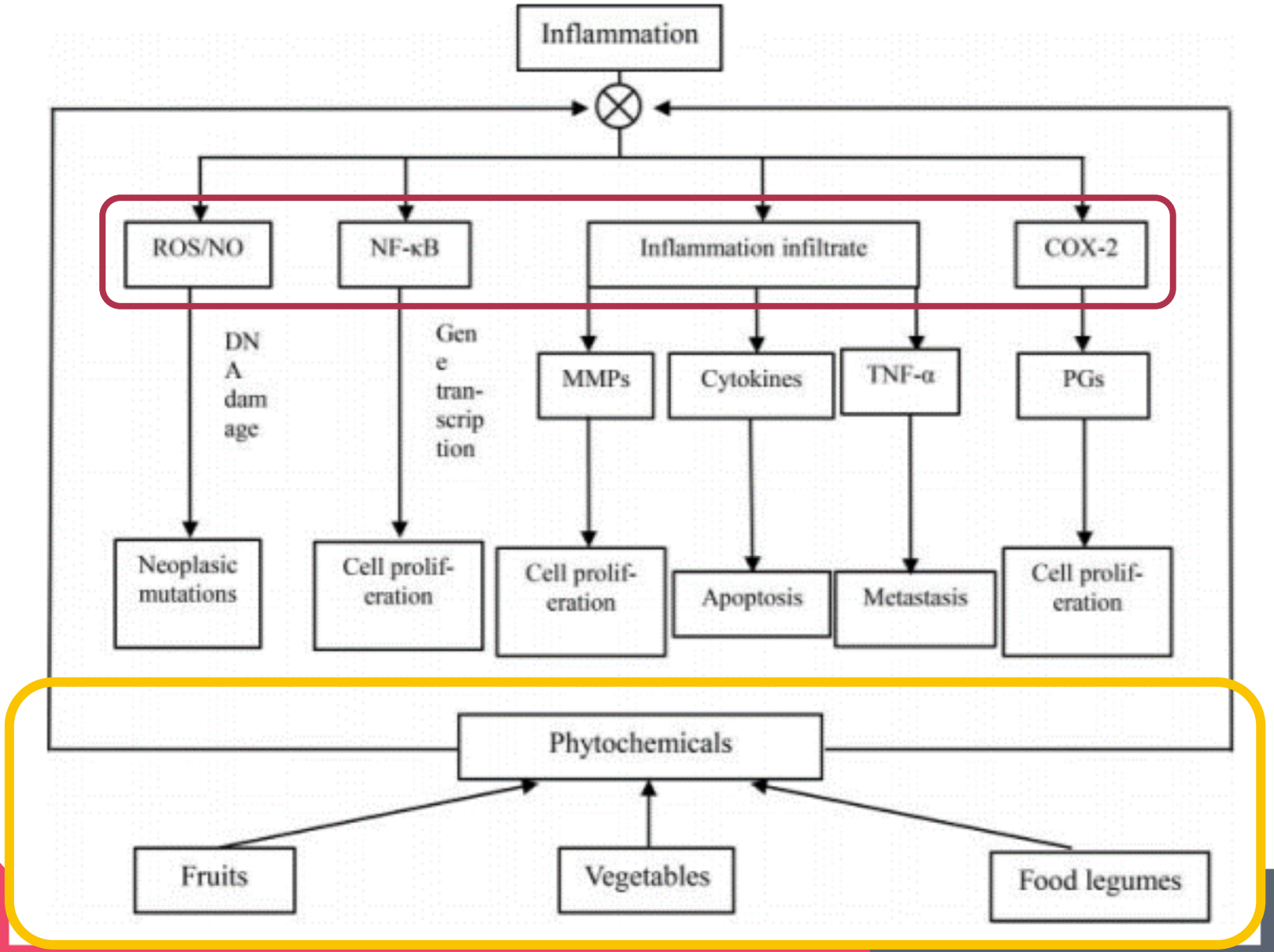
J Proteome Res. 2013

Dietary Phytochemicals



Adv Nutr. 2013 May; 4(3): 384S–392S

Phytochemicals & Inflammatory Modulation



ROS/Nitric Oxide

Cytokines

TNF-α

NF-κβ

COX-2/ Prostaglandin

Crit Rev Food Sci Nutr. 2018

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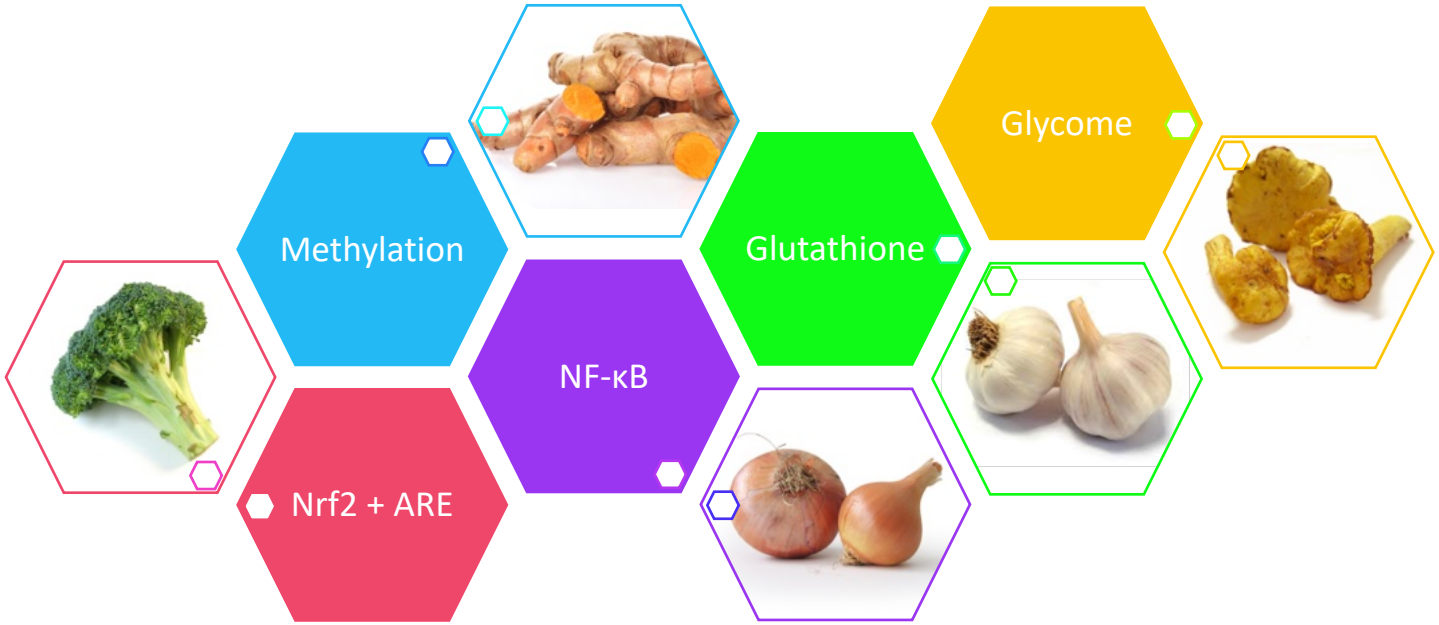
Direct & Indirect Targets



- Direct modulation on phase I & II biotransformation
- Enhance antioxidant reserve
- Upregulate capacity to neutralize ROS
- Support mitochondrial capacity
- Modulate inflammation/immune response
- Modify epigenetic expression via microbiome modulation/"omics"

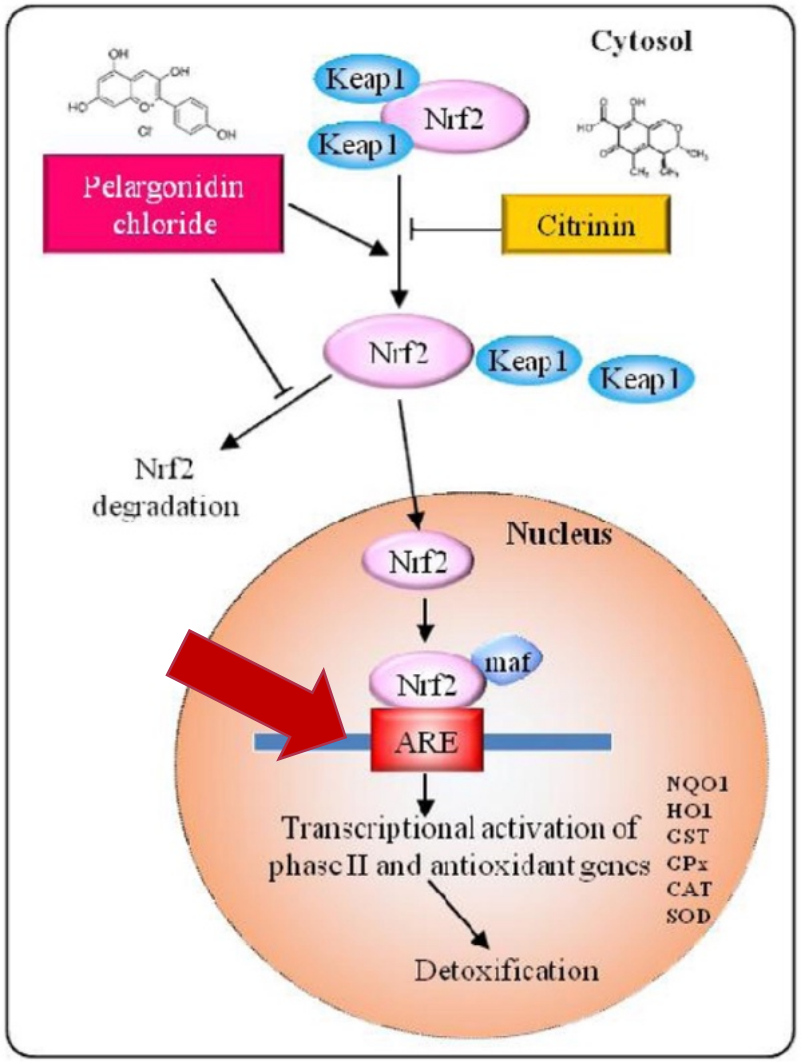
Keap1-Nrf2 & ARE*

Nrf2 is a transcription factor

Protein binds to AREs → activates certain gene sequences

Involving mechanisms such as:

- **Glutathione (GSH) and thioredoxin (TXN) antioxidant systems, SOD (superoxide dismutase)**
- **Phase I and Phase II detoxification enzymes**
- Modulation inflammation via NF-*κ*B.
- NADPH regeneration
- Heme metabolism
- Involved with autophagy, intermediary metabolism, stem cell quiescence, and unfolded protein response.
- **Affects mitochondrial function**, nutrient uptake, and is implicated in a multitude of diseases.



**ARE = Antioxidant Response Element*
Front. Pharmacol., 27 November 2017

Int J Mol Sci. 2020;21(13):4777
Oxid Med Cell Longev. 2016

Nutr Rev. 2017;75(6):442-455
Oxid Med Cell Longev. 2020

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Balance

Nrf2 & Detox/ROS neutralization

Inflammation

Nrf2: Detoxification & Antioxidant

The Nrf2-mediated signaling pathway protects against environmental insults and endogenous stressors

Oxidative stress is a common status defined as the imbalance between ROS production and antioxidant capacity in cells

Nrf2 coordinates inducible expression of ARE, influencing various function **including antioxidation, anti-inflammation, detoxification enzymes**

J Nutr Biochem. 2015;26(12):1401–1413. doi:10.1016/j.jnutbio.2015.08.001
Sheng Li Xue Bao. 2015 Feb 25;67(1):1-18
Oxid Med Cell Longev. 2019;2019:7090534

Dietary Phytochemicals & Nrf2

Sulforophane (cruciferous veggies)

EGCG (Catechins, green tea)

Grape seed

Resveratrol

Curcumin (turmeric)

Pomegranate (ellagitannins)

Cacao (polyphenols)

Quercetin (onions, watercress, apple and others)

Alkyl catechols (Traditionally fermented “ancient” and wood-fire smoked foods)

Crit Rev Food Sci Nutr. 2018;58(8):1260-1270

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Promoting Nrf2

Nutrients that promote Nrf2:

- Phenolic antioxidants
- Vitamin E (gamma- and delta-tocopherols and tocotrienols)
- Omega-3 Fatty Acids (DHA and EPA)
- Vitamin A (Carotenoids, lycopene)
- Isothiocyanates from cruciferous vegetables
- Sulfur compounds from allium and cruciferous vegetables
- Terpenoids (cannabis flowers)

Other Nrf2 promoting factors:

- Low level oxidative stress (hormesis)
- Exercise
- Caloric restriction (IF, FMD, fasting)

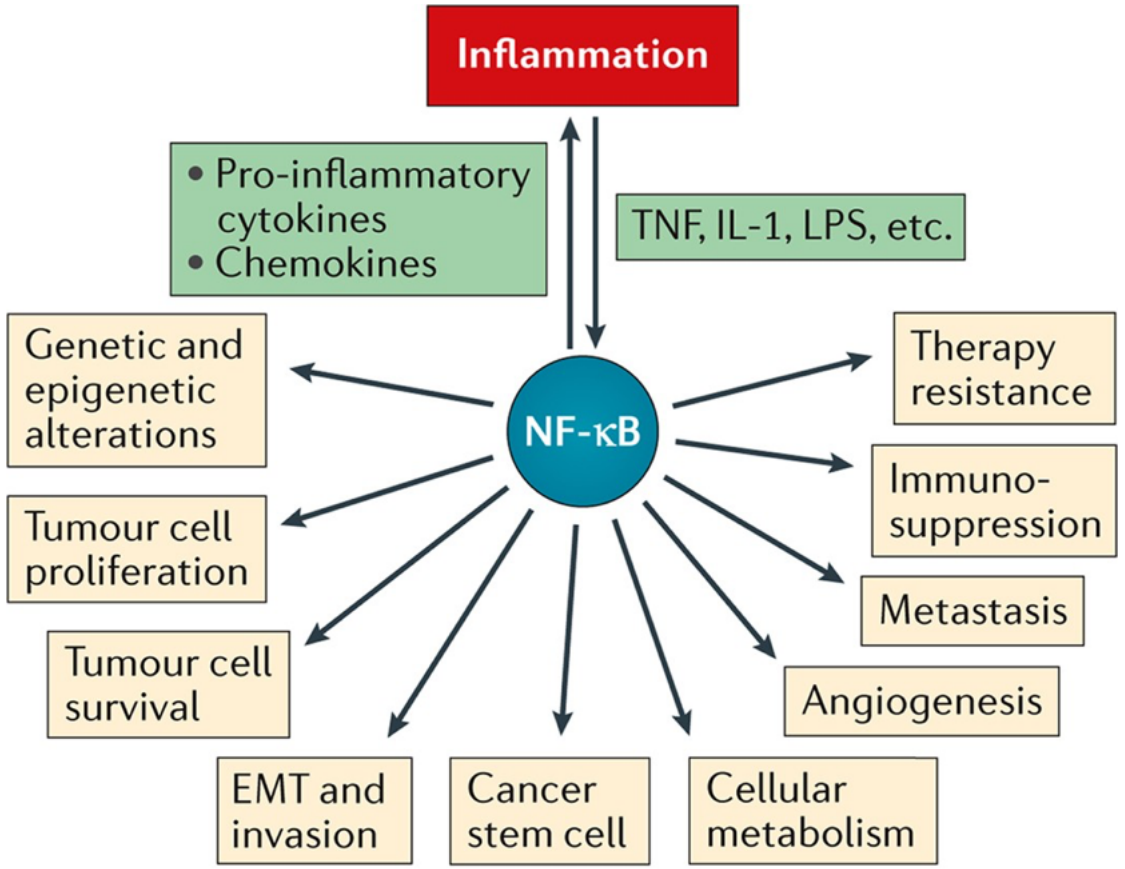
J Nutr Biochem. 2015;26(12):1401–1413
Sheng Li Xue Bao. 2015 Feb 25;67(1):1-18

Nuclear factor-κB (NF-κβ)

NF-κβ is a transcription factor that modifies inflammatory responses

Activation of NF-κB is primarily initiated by bacterial endotoxins such as lipopolysaccharide (LPS) and pro-inflammatory cytokines such as TNF and IL-1

NF-κB activation induces various target genes associated with cancer (and other metabolic disease including T2D, CVD, osteoporosis etc…)



Nature Reviews | Immunology

Nat Rev Immunol 18, 309–324 (2018)

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NF-κB Oxidative Stress Transcription Factor

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor which regulates the expression of genes involved in immune and inflammatory responses

Oxidative stress production and antioxidant capacity is part of a protective response, however…

Overproduction of ROS plays a role in the pathogenesis of various inflammatory diseases due to imbalanced immune response

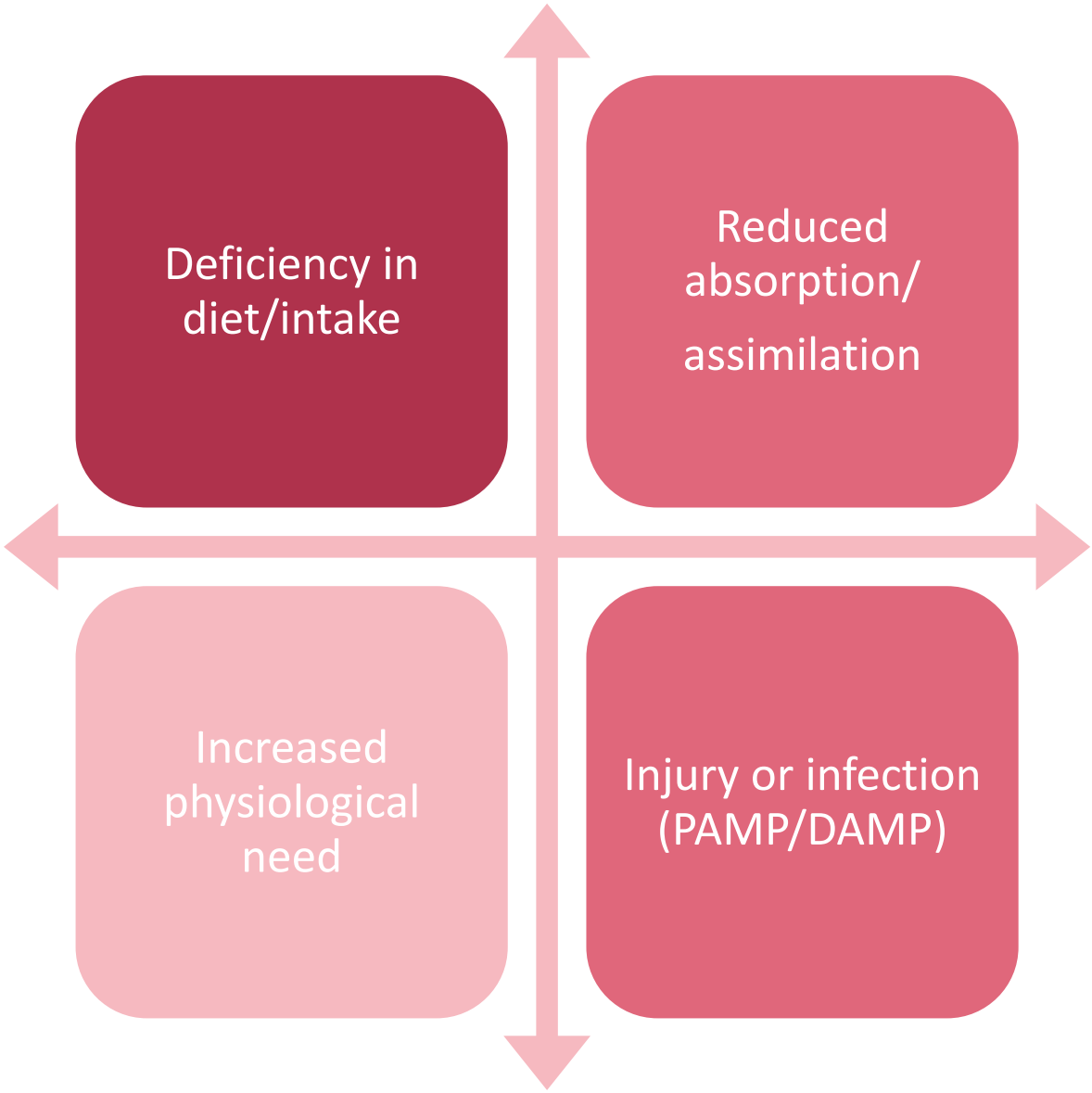
Free Radic Biol Med. 2018 Sep;125:3-14

Nutrient Targets for Biotransformation

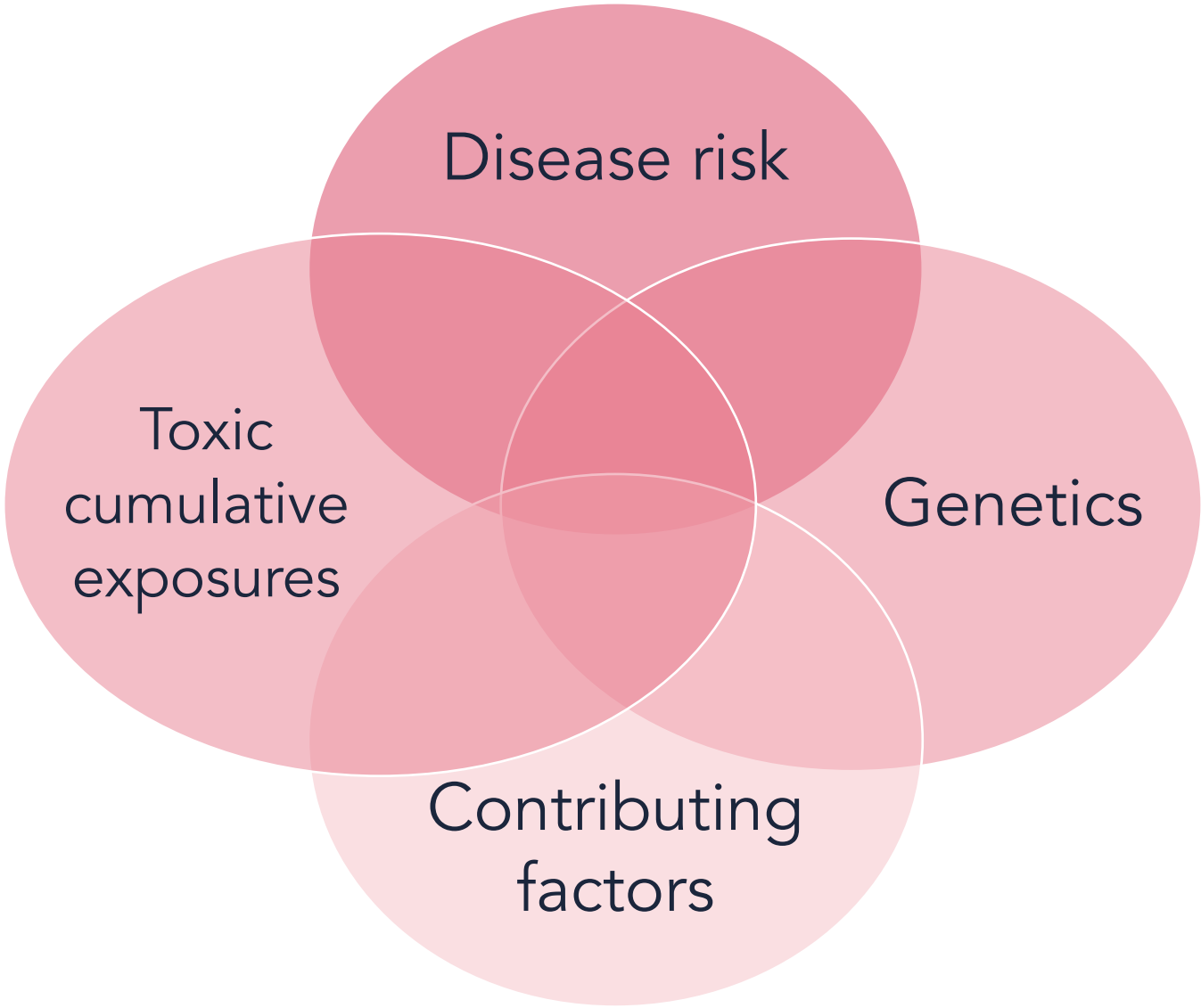
Nutrient Status Impact on Detoxification

- Co-factors
- Antioxidants
- Minerals
- Fiber

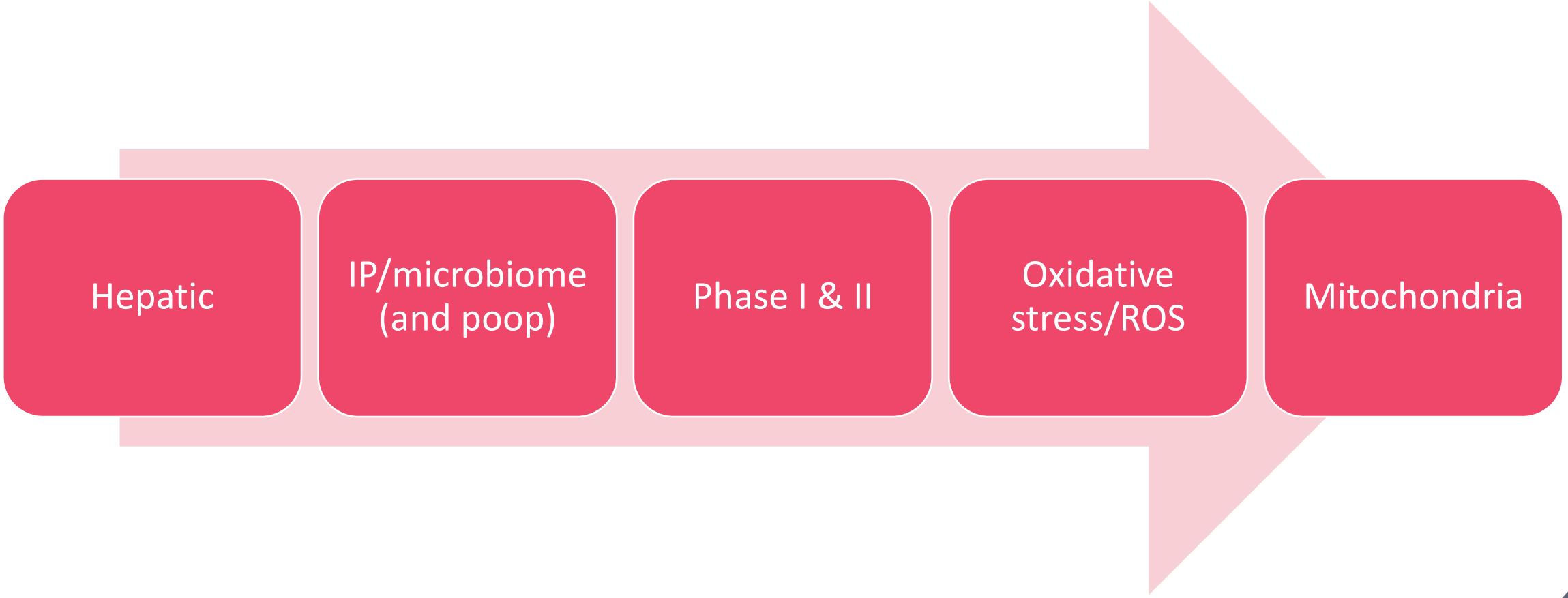
Factors Contributing to Nutrient Deficiency



Implications in disease



Detoxification Targets



Biotransformation classes

Oxygen radicals/ROS	• Superoxide dismutase • Catalase • Glutathione peroxidase
Ammonia	• Urea cycle enzymes • Renal citrate synthetase

Phase I – oxygenase systems	• Microsomal cytochrome P450
	  • performing dealkylation, oxidation, and removal of sulfur, halogen and azo groups
	• Flavin-containing monooxygenase
	• Oxidation-reduction via alcohol dehydrogenase
	• Aldehyde and ketone oxidase and reductase
	  • via xanthine oxidase, glutathione peroxidase, and monoamine oxidase

Phase II – conjugation reactions	• Glutathione transferase • Sulfation via sulfotransferases • Thiotransferases • Glycine conjugation (glycination forming peptide bonds) • Taurine conjugation • Glucuronidation • Acetylation • Methylation

Important Antioxidant/Detoxification Compounds

Major antioxidants

- Ascorbate (vitamin C)
- Vitamin E
- Vitamin A/β-carotene
- Riboflavin
- Selenium
- Zinc
- Copper
- Manganese
- Glutathione
- Isoflavones

Building blocks or cofactors

- Glycine, Mg (glutathione building block)
- Selenium, copper, zinc (glutathione peroxidase)
- Riboflavin (glutathione reductase)
- Copper, Zinc, Manganese (SOD)

Glutathione: The master antioxidant

Low glutathione (GSH)

- Reduced antioxidant capacity and ROS
- Reduced energy production
- Reduced detoxification capacity
- Compromised GI barrier
- Altered immune response

Precursors of GSH

- Cysteine
- Glycine
- Glutamine
- Serine
- Taurine
- N-acetylcysteine (NAC)

Nutritional considerations

- Diet rich in protein, colorful fruits and vegetables
- Digestive support (see 5R)
- NAC and AA building blocks
- Micronutrient cofactors (Vitamin C & E, Mg, Se, Zn, B2, B5, B6, and folate)
- Alpha lipoic acid, curcumin, milk thistle

Detox Cocktail

Supplement Facts

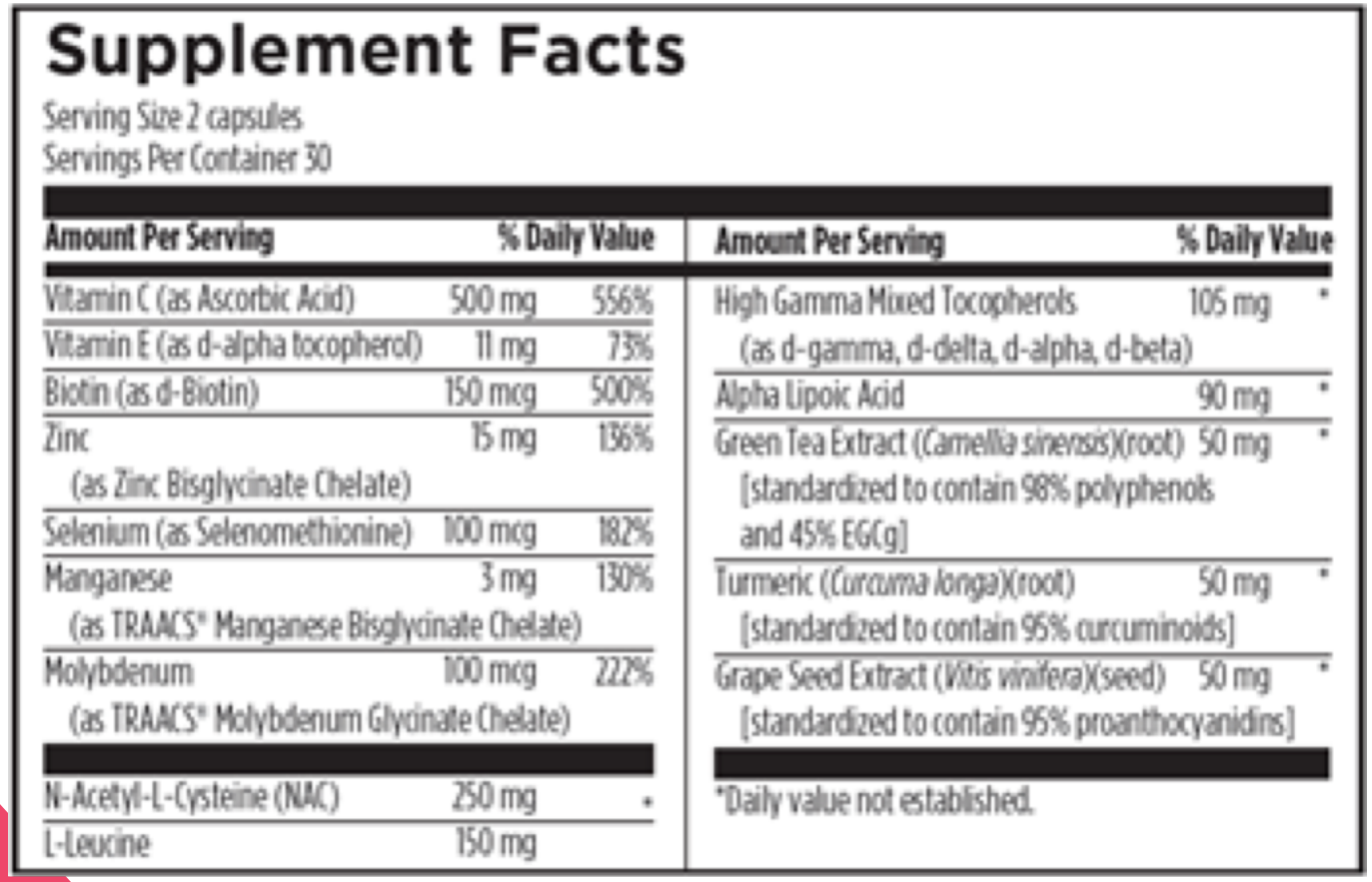
Serving size 2 capsules
Servings per container 60

	Amount Per Serving	%DV
Alpha lipoic acid (thioctic acid)	100 mg	*
N-Acetyl-L-Cysteine (free-form)	100 mg	*
Turmeric (*Curcuma longa*) extract (root) (standardized to contain 95% curcuminoids)	100 mg	*
Milk thistle (*Silybum marianum*) extract (seed) (standardized to contain 80% silymarin)	125 mg	*
Broccoli (*Brassica oleracea italica*) sprout concentrate (whole plant) (standardized to contain a minimum of 400 mcg sulforaphane)	100 mg	*
Artichoke (*Cynara scolymus l.*) extract (leaf)	125 mg	*
Taurine (free-form)	225 mg	*
Glycine (free-form)	225 mg	*
L-Glutamine (free-form)	225 mg	*
L-Methionine (free-form)	100 mg	*
Chlorella (*Chlorella spp.*) powder (cracked cell wall)	200 mg	*

*Daily value (DV) not established

- NAC → precursor to glutathione, chelator
- Taurine, glycine, methionine → AA precursors glutathione
- Alpha lipoic acid (ALA) → major antioxidant, free radical scavenger; chelator
- Broccoli → phase II detoxification support (sulforaphane)
- Artichoke → liver-protective (similar to milk thistle)
- Chlorella → increased antioxidant enzymes and metal binder/chelation

Another Detox Cocktail



Supplement Facts

Serving Size 2 capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin C (as Ascorbic Acid)	500 mg	556%
Vitamin E (as d-alpha tocopherol)	11 mg	73%
Biotin (as d-Biotin)	150 mcg	500%
Zinc (as Zinc Bisglycinate Chelate)	15 mg	136%
Selenium (as Selenomethionine)	100 mcg	182%
Manganese (as TRAACS® Manganese Bisglycinate Chelate)	3 mg	130%
Molybdenum (as TRAACS® Molybdenum Glycinate Chelate)	100 mcg	222%
N-Acetyl-L-Cysteine (NAC)	250 mg	*
L-Leucine	150 mg	

Amount Per Serving		% Daily Value
High Gamma Mixed Tocopherols (as d-gamma, d-delta, d-alpha, d-beta)	105 mg	*
Alpha Lipoic Acid	90 mg	*
Green Tea Extract (*Camellia sinensis*)(root) [standardized to contain 98% polyphenols and 45% EGCg]	50 mg	*
Turmeric (*Curcuma longa*)(root) [standardized to contain 95% curcuminoids]	50 mg	*
Grape Seed Extract (*Vitis vinifera*)(seed) [standardized to contain 95% proanthocyanidins]	50 mg	*

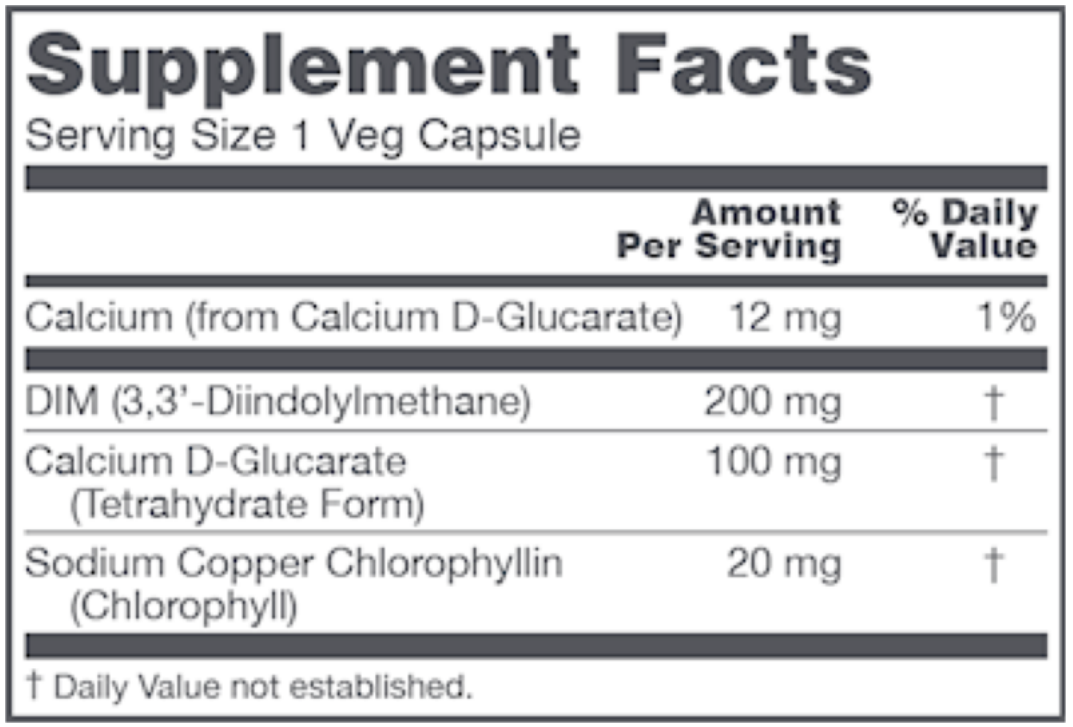
*Daily value not established.

Similar ingredients with additional antioxidant

Vitamin C, Vit E (mixed tocopherols), Manganese, MolyB, Selenium, Zinc

EGCG, Turmeric, ALA, Grape seed → modulates Nrf2, NF-κβ, PG, phase II pathways

Estrogen Detox Cocktails

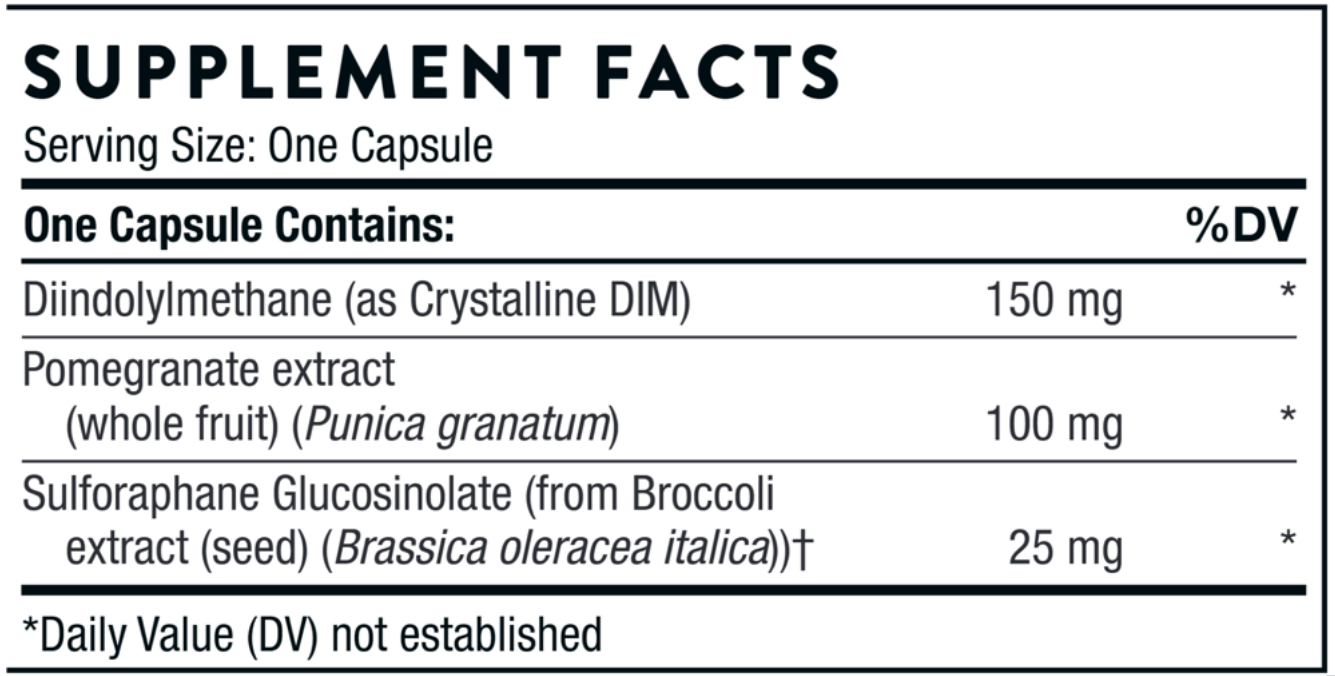


Supplement Facts

Serving Size 1 Veg Capsule

	Amount Per Serving	% Daily Value
Calcium (from Calcium D-Glucarate)	12 mg	1%
DIM (3,3'-Diindolylmethane)	200 mg	†
Calcium D-Glucarate (Tetrahydrate Form)	100 mg	†
Sodium Copper Chlorophyllin (Chlorophyll)	20 mg	†

† Daily Value not established.



SUPPLEMENT FACTS

Serving Size: One Capsule

One Capsule Contains:		%DV
Diindolylmethane (as Crystalline DIM)	150 mg	*
Pomegranate extract (whole fruit) (*Punica granatum*)	100 mg	*
Sulforaphane Glucosinolate (from Broccoli extract (seed) (*Brassica oleracea italica*))†	25 mg	*

*Daily Value (DV) not established

Supporting detoxification through nutrition & lifestyle

Detoxification isn’t a pill or tea

- Avoidance (limit exposure)
- Support energy pathways
- Neutralize oxidative stress
- Ensure gut integrity and microbiome balance
- Open lymphatic flow
- Protect the liver and kidneys
- Support cofactors and precursors through nutrition - hydration, micro- and macronutrient support
- 3 Ps all day every day!

The 3 Ps of detoxification

Caution

Dysbiosis (imbalance of bacteria in the gut)

- Some bacteria can “undo” Phase II conjugation
- Example: some bacteria make beta-glucuronidase, which removes glucuronides have been used to conjugate estrogens in Phase II

Constipation (slowed transit time of stool)

- Will lead to some toxins being reabsorbed or not removed quickly enough

Decreased kidney function

- Reduced ability to excrete bio-transformed compounds into the urine

Decreased liver/gallbladder function

- Impaired Phase I and II and impaired Phase III excretion of compounds through bile into the intestines

Detoxification Overview

Antioxidants + Phytonutrients

Reactive Inter-mediates

Phase I:

- Oxidation
- Reduction
- Hydrolysis
- Hydration
- Dehalogenation

B2, B3, B6, B12

Folate

Glutathione

BCAA

Flavonoids

Phospholipids

Phase II:

- Glucuronidation
- Sulfonation
- Methylation
- Glutathione Conjugation
- Amino Acid Conjugation
- Acetylation

Methionine, cysteine,

glutamine, glycine, taurine

B5, B12, folate,

Vitamin C

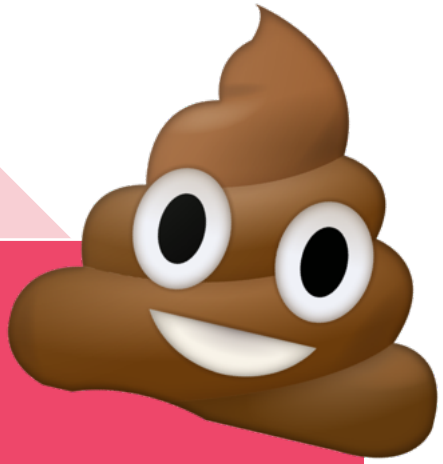
Choline

Glutathione

Magnesium

Phase III:

- Urine
- Bile
- Stool



Review Article

Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application

Romilly E. Hodges[1] **and Deanna M. Minich**[2,3]

[1] *University of Bridgeport, 126 Park Avenue, Bridgeport, CT 07748, USA*
[2] *Institute for Functional Medicine, 505 S. 336th Street, Suite 500, Federal Way, WA 98003, USA*
[3] *University of Western States, 2900 NE 132nd Avenue, Portland, OR 97230, USA*

Research into human biotransformation and elimination systems continues to evolve. Various clinical and *in vivo* studies have been undertaken to evaluate the effects of foods and food-derived components on the activity of detoxification pathways, including phase I cytochrome P450 enzymes, phase II conjugation enzymes, Nrf2 signaling, and metallothionein. This review summarizes the research in this area to date, highlighting the potential for foods and nutrients to support and/or modulate detoxification functions. Clinical applications to alter detoxification pathway activity and improve patient outcomes are considered, drawing on the growing understanding of the relationship between detoxification functions and different disease states, genetic polymorphisms, and drug-nutrient interactions. Some caution is recommended, however, due to the limitations of current research as well as indications that many nutrients exert biphasic, dose-dependent effects and that genetic polymorphisms may alter outcomes. A whole-foods approach may, therefore, be prudent.

6. Conclusions

Over the past decade, there has been investigation into nutrigenomic and epigenetic influences of food constituents on chronic diseases [201, 202]. Similarly, studies have revealed that exposure to and accumulation of toxins play a significant role in cardiovascular disease, type 2 diabetes, and obesity [203–207]. Thus, one's dietary intake and environmental influences may have large bearing on the incidence of chronic disease. In fact, these influences may be significant not just for the individual, but for several generations due to the transgenerational inheritance of epigenetic changes [208, 209]. Therefore, it would seem that designing clinical recommendations to maximize the effects of food and reduce the impact of toxins is essential. However, it is not without caution and critical thinking that a detoxification protocol should be assembled for patients by trained clinicians. There remain many unresolved issues regarding knowing how and what foods modulate detoxification pathways.

J Nutr Metab. 2015;2015:760689

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Compounds that modulate some CYP enzymes (phase I)

Enzyme	Food, beverage, or bioactive compounds *Food sources in italics*	Type of study	Dosages used and references
CYP3A	Rooibos tea	*In vivo*	Rooibos tea, 4 g/L simmered for 5 minutes, as sole beverage [69]
CYP3A1	Garlic	*In vivo*	30 to 200 mg/kg garlic oil [36] 80 and 200 mg/kg garlic oil 3 times weekly [70]
	Fish oil	*In vivo*	20.5 g/kg fish oil [36]: *note high dose used*
CYP3A2	Garlic	*In vivo*	200 mg/kg diallyl sulfide [8]
	Cruciferous vegetables	*In vivo*	50 mg/kg/d indole-3-carbinol [75]
CYP3A4	Curcumin *Turmeric, curry powder* [34]	*In vivo*	50 and 100 mg/kg curcumin [11]

(b)

Enzyme	Food, beverage, or bioactive compounds *Food sources in italics*	Type of study	Dosages used and references
CYP3A	Green tea	*In vivo*	45 mL/d/rat (avg. 150 g animal weight) green tea [33] 400 mg/kg green tea extract [71] 100 mg/kg/d green tea extract [56]
	Black tea	*In vivo*	54 mL/d/rat (avg. 150 g animal weight) black tea [33]
	Quercetin *Apple, apricot, blueberries, yellow onion, kale, alfalfa sprouts, green beans, broccoli, black tea,* and *chili powder* [47, 48]	*In vivo*	10 and 20 mg/kg [72]
CYP3A2	Cruciferous vegetables	*In vivo*	12 mg/kg/d sulforaphane [57]
CYP3A4	Grapefruit	Clinical	200 mL grapefruit juice 3 times daily [74]
	Resveratrol *Grapes, wine, peanuts, soy,* and *itadori tea* [32]	Clinical	1 g/d resveratrol [28]: *note high dose used*
	Garden cress	Clinical	7.5 g twice daily dose of garden cress seed powder [55]
	Soybean	*In vivo*	100 mg/kg soybean extract [7]
	Kale	*In vivo*	2 g/kg/d kale, as freeze-dried kale drink [51]
	Myricetin *Onions, berries, grapes,* and *red wine* [58]	*In vivo*	0.4, 2, and 8 mg/kg myricetin [58]

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Compounds that modulate Nrf2

Enzyme	Food, beverage, or bioactive compounds *Food sources in italics*	Type of study	Dosages used and references
Nrf2	Fish oil	Clinical	3 × 1 g/d fish oil containing 1098 mg EPA and 549 mg DHA [181]
	Lycopene *Tomatoes, rose hips, guava, watermelon,* and *papaya* [111]	Clinical	2 × 15 mg/d lycopene [181]
	Curcumin *Turmeric, curry powder* [34]	*In vivo*	200 mg/kg/d curcumin [155] 75 mg/kg/d curcumin [156] 50 mg/kg/d curcumin [157] 200 mg/kg/d curcumin [158]
	Cruciferous vegetables	*In vivo*	0.5 mg/kg/d sulforaphane [159] Diet of 15% crushed broccoli seed [160]
	Garlic	*In vivo*	50 and 100 mg/kg/d diallyl disulfide [161] 250 mg/kg/d raw garlic [162] 25 mg/kg S-allyl cysteine [163]
	Catechins *Tea* (especially *green tea*), *cocoa, legumes,* and *grapes* [182]	*In vivo*	5, 15, and 45 mg/kg epicatechin [164] 15 mg/kg epicatechin [165] 20 mg/kg Theaphenon E (95% EGCG) [166] 5, 15, and 30 mg/kg epicatechin [167]
	Resveratrol *Grapes, wine, peanuts, soy,* and *itadori tea* [32]	*In vivo*	10 mg/kg/d [168] 20 mg/kg/d [169]
	Ginger	*In vivo*	100 mg/kg/d [6]-shogaol [170] 10 and 100 mg/kg dried ginger extract [171]
	Purple sweet potato	*In vivo*	100 and 200 mg/kg anthocyanin extract from purple sweet potato [118]
	Isoflavones *Soy, kudzu root,* and *red clover* [183]	*In vivo*	80 mg/kg/d soy isoflavones [172] 60 and 120 mg/kg puerarin from kudzu root [173]
	Coffee	*In vivo*	2.0 mL/d coffee to an average animal weight of 200 g ± 10 g [174]
	Rosemary	*In vivo*	50 and 100 mg/kg carnosic acid [175] 5 mg/animal carnosol extract [176]
	Blueberry	*In vivo*	200 mg/kg blueberry [166] 0.6 and 10 g/day [177]
	Pomegranate	*In vivo*	1 and 10 g/kg pomegranate extract [178]: *note high doses used*
	Naringenin *Citrus* [179]	*In vivo*	50 mg/kg/d naringenin [179]
	Ellagic acid *Berries, pomegranate, grapes, walnuts,* and *blackcurrants* [42]	*In vivo*	Diet of 0.4% ellagic acid [166]
	Asthaxanthin *Algae, yeast, salmon, trout, krill, shrimp,* and *crayfish* [38]	*In vivo*	15 mg/kg astaxanthin [166]
	γ-tocopherol *Nuts, seeds, whole grains, vegetable oils,* and *legumes* [111]	*In vivo*	20.8 mg/kg γ-tocopherol [180]

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Top: Nutrients for methylation (phase II)

Bottom: Nutrients & foods for glutathione conjugation (Phase II)

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Table 9: Selected dietary sources of nutrients for methylation support (adapted from [111]).

Methionine	Meats, poultry, fish, shellfish, egg, nuts (especially Brazil nuts), seeds (especially sesame seeds and pumpkin seeds), spirulina, teff, soybeans Lower amounts found in other legumes and whole grains (especially teff and oats)
Vitamin B12	Meats and meat products (especially liver and kidney), poultry, fish, shellfish, and eggs
Vitamin B6	Meats, nuts (especially pistachio), garlic, whole grains, seeds (especially sesame and sunflower seeds), legumes (especially chickpeas and lentils), and prunes
Betaine	Quinoa, beets, spinach, whole grains (especially rye, kamut, bulgur, amaranth, barley, and oats) sweet potato, meats, and poultry
Folate	Beans and legumes (especially mung beans, adzuki beans, chickpeas, and lentils), liver, nuts (especially peanuts), seeds (especially sunflower seeds), spinach, asparagus, mustard greens, and avocado
Magnesium	Seeds (especially pumpkin seeds and sesame seeds), beans (especially soybeans), nuts (especially Brazil nuts and almonds), and whole grains (especially amaranth)

(c)

Vitamin B6	Turkey, pork, chicken, beef, amaranth, lentils, pistachio nuts, sunflower seeds, garlic, and prunes
Magnesium	Nuts, seeds, beans, and whole grains
Selenium	Brazil nuts, pork, turkey, lamb, chicken, and egg
Methionine	Turkey, pork, chicken, beef, egg, Brazil nuts, soybean, sesame seeds, and spirulina
Cystine	Pork, turkey, chicken, egg, soybean, spirulina, sesame seeds, and oats
Glycine	Turkey, pork, chicken, amaranth, soybean, peanuts, pumpkin seed, and beef
Folate (dietary form of folic acid)	Mung bean, adzuki bean, and other legumes, liver, sunflower seeds, quinoa, spinach, asparagus, avocados, mustard greens, and artichokes
Alpha-lipoic acid	Spinach, broccoli, tomato, peas, Brussels sprouts, and visceral meats [127, 128]
Functional foods	Turmeric, milk thistle, cruciferous vegetables, and artichoke [129–133]

Table 8: Amino acids used in phase II conjugation and selected food sources.

Glycine	Turkey, pork, chicken, soybean, seaweed, eggs, amaranth, beef, mollusks, peanuts, pumpkin seeds, almonds, duck, goose, mung beans, sunflower seeds, lentils, lamb, bison, lobster, and fish [111]
Taurine	Many cooked meats and fish supply taurine. Taurine is also synthesized in the body from cystine (requiring niacin and vitamin B6) and homocysteine (requiring additionally betaine and serine) [144]
Glutamine	Plant and animal proteins such as beef, pork, chicken, dairy products, spinach, parsley, and cabbage [145]
Ornithine	Ornithine is synthesized endogenously via the urea cycle, requiring arginine and magnesium [144]
Arginine	Turkey and pork are especially rich sources; also chicken, pumpkin seeds, soybean, butternuts, egg, peanuts, walnuts, split peas, mollusks, almonds, sesame seeds, lentils, fava beans, mung beans, pine nuts, beef, sunflower seeds, and white beans [111]

Curcumin *(Curcuma longa)*

Curcumin has been shown to induce phase I through CYP1A1, 1B1 and 3A4 in vivo (at least 50mg-100mg/kg+)

Induces UGT enzymes (glycosyltransferase → phase II)

Also, inducer of Glutathione S-Transferases (phase II conjugation)

Epigenetic modulator of methylation (phase II detoxification)

Nrf2 activator and antioxidant pathways

Inhibits the activation of free radical activated transcription factors such as NFκβ and nitric oxide synthase

It also modulates the proinflammatory cytokines and anti-inflammatory process including T-reg cells

Activity on Cyclooxygenase (COX) and Lipoxygenase (LOX) inflammatory mechanisms

Front Genet. 2019;10:514
Curr Mol Med. 2020;20(2):116-133

Arthritis Res Ther. 2008;10(4):R85
Crit Rev Food Sci Nutr. 2019;59(1):89-101
J Nutr Metab. 2015;2015:760689

Ginger *(Zingiber officinale)*

Bioactive phenolic compounds are mainly gingerols, shogaols, and paradols

Induces Nrf2

- 100 mg/kg/d [6]-shogaol
- 10 and 100 mg/kg dried ginger extract

In addition to Nrf2, modulates glutathione (GSH, GSTP1) and reduces ROS

Gingerols can inhibit LPS-induced COX-2 expression

Ginger extract can reduce the elevated expression of NFκB and TNF-α and support iNOS

J Nutr Metab. 2015;2015:760689
Chem Res Toxicol. 2014;27(9):1575-1585
Foods. 2019;8(6):185.
Int J Prev Med. 2013;4(Suppl 1):S36-S42
Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition

Cruciferous Veggies

Includes brassica family (ie broccoli, cabbage, Brussels sprouts, kale etc…). Great source of **fiber, protein, and long list of micronutrients**.

Rich sources of sulfur-containing compounds known as **glucosinolates**

Chopping or chewing raw cruciferous activates bioactive glucosinolate hydrolysis products via enzyme myrosinase → **isothiocyanates and indole-3-carbinol (I3C)**. These metabolites are also generated by microbiota and by cooking

Some CYP activity (CYP1A1), but major inducer of Phase II detoxification enzymes, including glutathione S-transferases (GSTs), sulfation, and methylation enzymes

Modulates Nrf2 and NFκB (reduces ROS, inflammation and acts as an antioxidant)

Go-to for estrogen-dominant cases that also need overall detoxification support (caution in supplementing I3C or DIM for low E1 cases)

J Nutr Metab. 2015;2015:760689
https://lpi.oregonstate.edu/mic/food-beverages/cruciferous-vegetables

DIM vs I3C

Active form

Indole-3-carbinol (I3C)

3,3’-diindolylmethane (DIM)

PubChem. Indole-3-carbinol. https://pubchem.ncbi.nlm.nih.gov/compound/3712
PubChem. 3,3’-Diindolylmethane. https://pubchem.ncbi.nlm.nih.gov/compound/3071

FUNCTIONAL MEDICINE
Continuing Education

Resveratrol *(3,5,4'-trihydroxystilbene)*

Upregulates Phase I (CYP1A1,2C9, 3A4) at higher doses (1g/day*)

**unlikely to reach those doses with wine!*

Phase II activity (UGT, SULT, GST)

Nrf2 modification, can reduce ROS activity

Powerful antioxidant and mitochondrial support

Powerful immune modulation via T-regs/Th2, pathogen response via NLRP3 inflammasome activation, stimulation of immune response (notably CTL and NK cells) and downregulation of cytokines

J Nutr Metab. 2015;2015:760689
Front Immunol. 2018 Dec 20;9:2992
Acta Virol. 2020;64(3):276-280

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG) is a flavanol/catechin found in high concentrations in green tea → also other tea varieties and fruits like cranberries, strawberries, blackberries, avocado and apple

Inducer of Nrf2 which in turn induced phase II detoxification

Hepato-protective → Reduces oxidative stress secondary to toxin exposure

Favorable modulation of virus-induced pathology via NLRP3 inflammasome pathway activation

J Nutr Metab. 2015;2015:760689
Antioxidants (Basel). 2020;9(8):659
Food Chem Toxicol. 2008;46(4):1271-1278
Nutrients. 2019;11(8):1862

Coffee

Bioactive compounds include hydrocinnamic acids and polyphenols, including chlorogenic acid, diterpenes and trigonelline *and caffeine*

Phase I induction (CYP1A1, 3A4, 4B1 among others) – *major estrogen pathways*

Phase II via UGT, SULT, and Nrf2 modulator (2mL/d)

Known to have antioxidant, anti-inflammatory, and antiproliferative effects, cardioprotective (reduced stroke risk, antidiabetic), and neuroprotective (memory, focus)

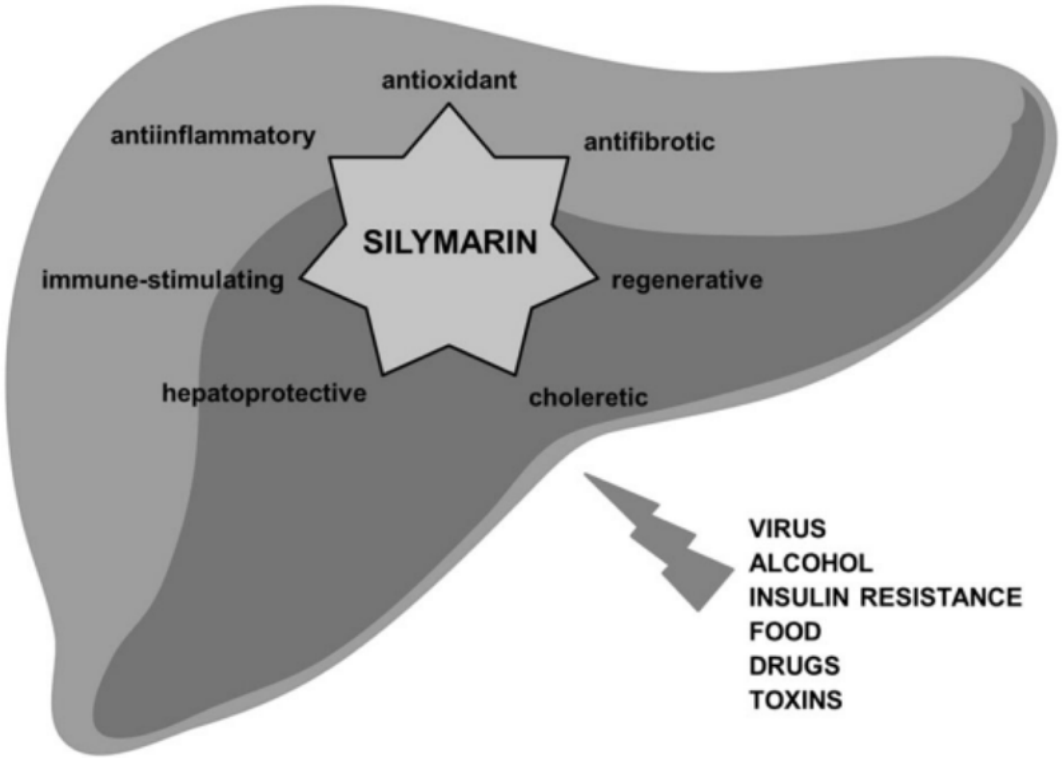
J Nutr Metab. 2015;2015:760689
Nutrients. 2020;13(1):88. Published 2020 Dec 29
Ind Crops Prod. 2022;175:114265

I Like big mugs, I cannot lie

- Phase I to phase II out of balance
- Impact of caffeine on mucosa and motility
- Sensitivity to caffeine and stimulating bioactive compounds in coffee
- Adrenal stress and catecholamine activation
- Other ingredients, dose, time of day, health goals

J Nutr Metab. 2015;2015:760689
Nutrients. 2020;13(1):88. Published 2020 Dec 29
Ind Crops Prod. 2022;175:114265

Milk Thistle *(Silymarin marianum)*



- Anti-inflammatory
- Anti-oxidant
- Reduces ROS
- Prevents the absorption of toxin
- Improves glucose metabolism and insulin resistance

Molecules. 2022;27(16):5327
Phytother Res. 2018;32(11):2202-2213

Mediterranean diet and inflammaging within the hormesis paradigm

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Nrf2, NF-κβ, Redox homeostasis (and of course microbiome modulation)

Table 1

Nutritional hormetins of typical Mediterranean foods able to activate specific stress-response pathways

Nutritional hormetin	Food item within traditional Mediterranean diet	Stress pathway
Phytochemicals (phenolic antioxidants, terpenoids, carotenoids, and allium-derived sulfur compounds)	Olives, legumes, leafy green vegetables, tomatoes, eggplant, fruits, garlic, and onion	Activation of nuclear factor erythroid 2 (Nrf2)
Resveratrol	Grapes, red wine	Regulation of redox homeostasis
		Activation of Nrf2 and sirtuin pathway
		Blocking of nuclear factor κB (NF-κB)
Vitamin E	Dried fruits, herbs, leafy green vegetables	Activation of heat shock response
		Down-regulation of NF-κB
n-3 polyunsaturated fatty acids	Fish, nuts	Activation of Nrf2
		Blocking of NF-κB
Fiber	Legumes, unrefined whole-grain cereals, fresh vegetables, fruits	Cooperation with cellular stress pathways (heat shock proteins)

Nutr Rev. 2017;75(6):442-455

PLOS | ONE

RESEARCH ARTICLE

Activation of the Nrf2 Cell Defense Pathway by Ancient Foods: Disease Prevention by Important Molecules and Microbes Lost from the Modern Western Diet

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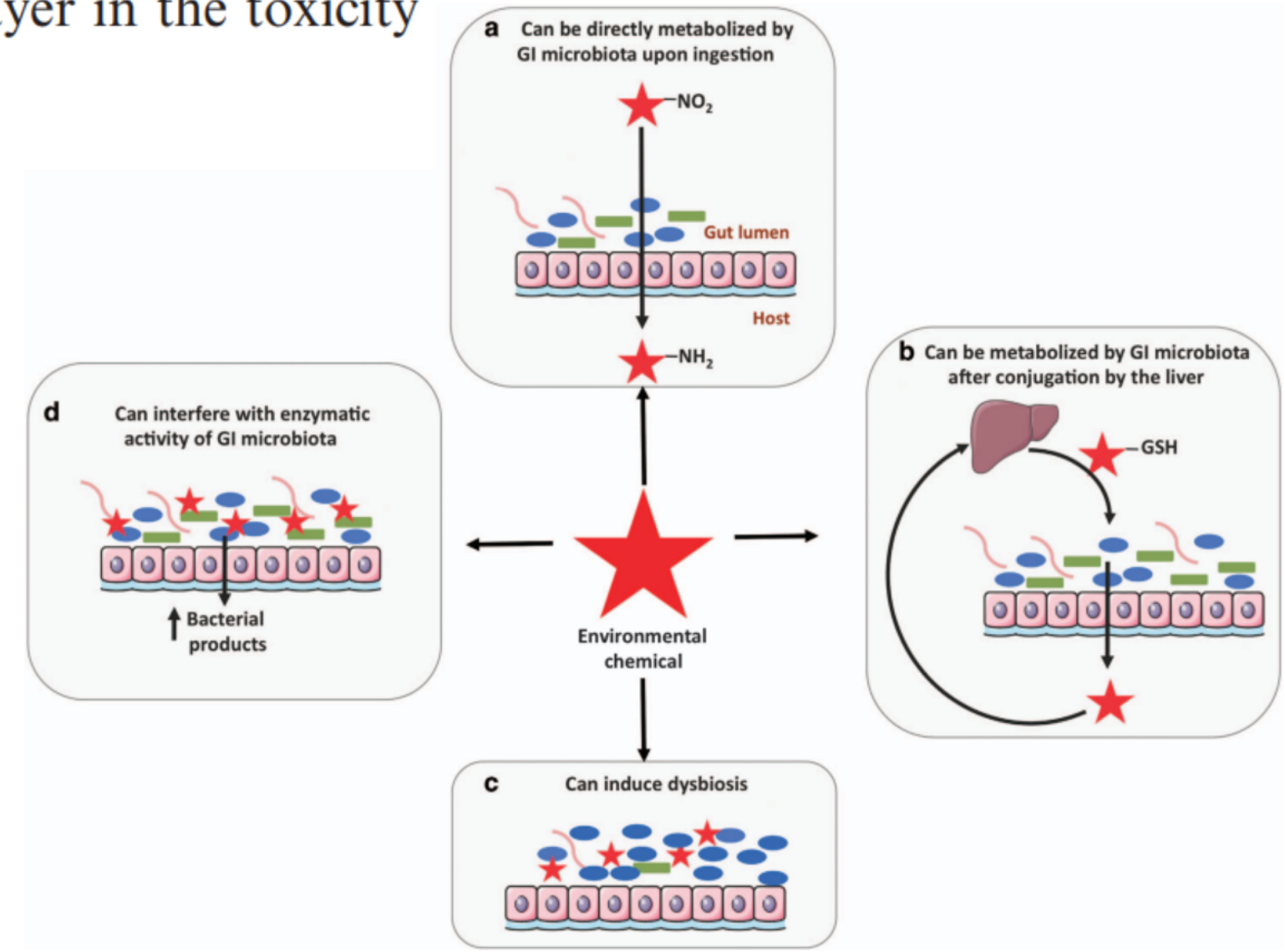
Lactobacillus plantarum, *Lactobacillus brevis*, and *Lactobacillus collinoides*, which are consumed from a diet rich in traditionally fermented foods and beverages, convert common phenolic acids found in fruits and vegetables to 4-vinylcatechol and/or 4-ethylcatechol.

PLOS ONE | DOI:10.1371/journal.pone.0148042 February 17, 2016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757558/

REVIEW ARTICLE OPEN

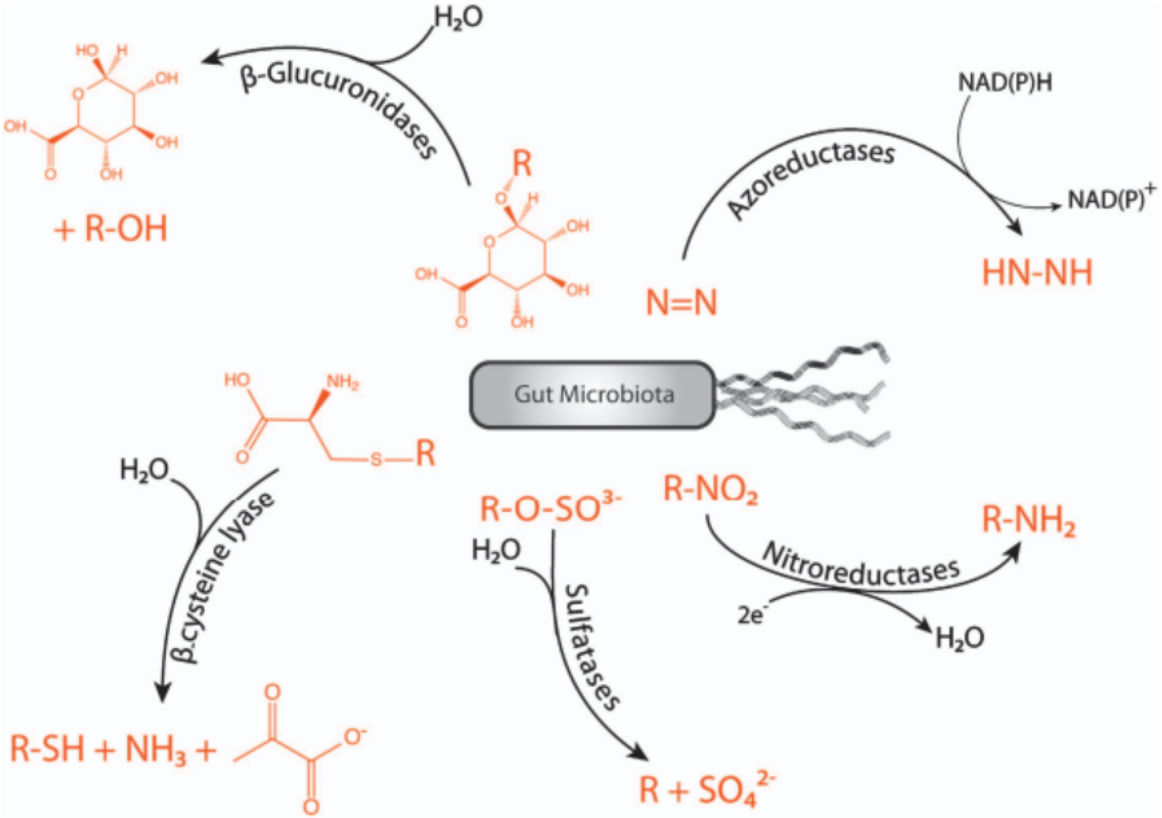
The gut microbiota: a major player in the toxicity of environmental pollutants?

Sandrine P Claus[1], Hervé Guillou[2] and Sandrine Ellero-Simatos[2]



NPJ Biofilms Microbiomes. 2016;2:16003. Published 2016 May 4

Xenobiotic-metabolizing enzymes of the GI microbiota



- Glucuronidases
- Nitro-reductase (amines –NO2)
- Sulfate hydrolysis
- Cysteine conjugation (glutathione formation)

NPJ Biofilms Microbiomes. 2016;2:16003. Published 2016 May 4

Heavy Metal Chelation (with food)

Cilantro *(Coriandrum sativum)*

- Reported to enhance mercury excretion
- Decreased lead absorption into bone and improved renal excretion

Chlorella (*Chlorella vulgaris* {CV})

- Supplementation contributed to reducing heavy metal levels
- SOD-1 regulation could induce antioxidant effects in these patients
- Promotes zinc-mediated antioxidant activity by increasing flavonoids, polyphenols, tocopherols, glutathione, and ascorbate (ASC) levels

Other compounds/mechanisms

- Multi-minerals
- Fiber (Modified citrus pectin, soluble fiber)
- Glutathione and NAC
- Selenium
- Taurine and methionine
- Alpha lipoic acid (ALA)

ScientificWorldJournal. 2013;2013:219840
J Toxicol Sci. 2011;36(1):121-126
Antioxidants (Basel). 2019;8(4):101

Avoidance

Reduce risk of exposure to xenobiotics

Lifestyle factors that impact toxic load

- Cooking method
- Air and water quality
- Pots and pans
- Sweating/sauna
- LED light therapy (mitochondria)
- Exercise
- Stress adaptation
- Sleep quality

FUNCTIONAL MEDICINE
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Products of Glycation and Lipidation

Glucose reacts non-enzymatically with amino groups of protein (via Maillard Reaction)

- Forms **Advanced Glycation End Products (AGEs)**
- Occurs during food preparation like bread baking
- AGE formation rate increase in diabetes (hyperglycemia) and renal failure (increased reactive carbonyl compounds RCOs)
- Accumulation of AGEs contribute to uremic toxicity (contributor to kidney disease)

Lipid oxidation reactions for **lipoxidation end products (ALEs)**

- Associated with increased cardiovascular risk and atherosclerosis (LDL) neurodegenerative diseases (Alzheimer's disease), and autoimmunity

Increase cardiovascular risk as a result of AGEs and ALEs

- Vascular stiffening
- Oxidative stress
- Cytokine stimulation and inflammatory response
- Leads to increased risk of CVD and renal disease with diabetes

Am J Lifestyle Med. 2017;13(4):384-404
Front Physiol. 2016;7:423

Avoidance Principles

Avoiding plastics (switching to glass containers, reusable bags, etc…)
Water filters (https://www.ewg.org/tapwater/)
Air purifiers (HEPA filters)
Regenerative/organic farming (produce, animal protein, fish etc…)
Switching personal care products and cleaning supplies
Avoiding fragrances (air fresheners, perfumes, etc…)
Sweeping/dusting frequently
Avoid “modern” products like memory foam, PVC furniture and flooring, nonstick cookware, etc…

Other lifestyle considerations

- Sauna
- Epsom salt bath
- LED red light therapy
- Dry brushing
- Lymphatic massage
- Acupuncture and cupping
- Circadian rhythm/sleep
- Exercise
- HPA-axis and Stress management

FUNCTIONAL MEDICINE
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Summary of Diet & Lifestyle Factors

Dietary factors

- Increase hydration (filtered water, teas)
- Increase fiber consumption
- Add a multi-mineral
- Consider adding
  - Glutathione or precursors (glycine, taurine, NAC)
  - Cofactors like niacin, B2, zinc, copper, and magnesium, selenium
  - Mitochondrial and antioxidants support (EGCG, resveratrol, curcumin, phenols, carotenoids, tocopherols)
- Cilantro and chlorella for heavy metals
- Supporting GI with personalized protocol (motility, integrity, and microbiome)

Lifestyle factors

- Infrared Sauna
- Dry brushing
- Lymph massage and dry brushing
- Exercise
- Support HPA-axis & Circadian rhythm
- Slowly exchange personal care and household products for “clean” swaps

Summary

You don’t need to be extreme to support detoxification → Avoid extreme protocols, juice cleanses or water fasts

Support the gut and microbiome (first and foremost)

Open the drain (lymph drainage, vascular circulation, 3P’s)

Use nutrition to bind toxins, compete with toxin absorption, and upregulate detoxification pathways

Leverage lifestyle modification that favorably modifies mitochondria, inflammation, and antioxidant elements

Although avoidance of all toxins is nearly impossible in this modern age, it remains our most powerful tool. That said, scare tactics add stress and stigma and don’t have a place in a comprehensive and well-rounded FxMed approach to detoxification

Thank You!

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