

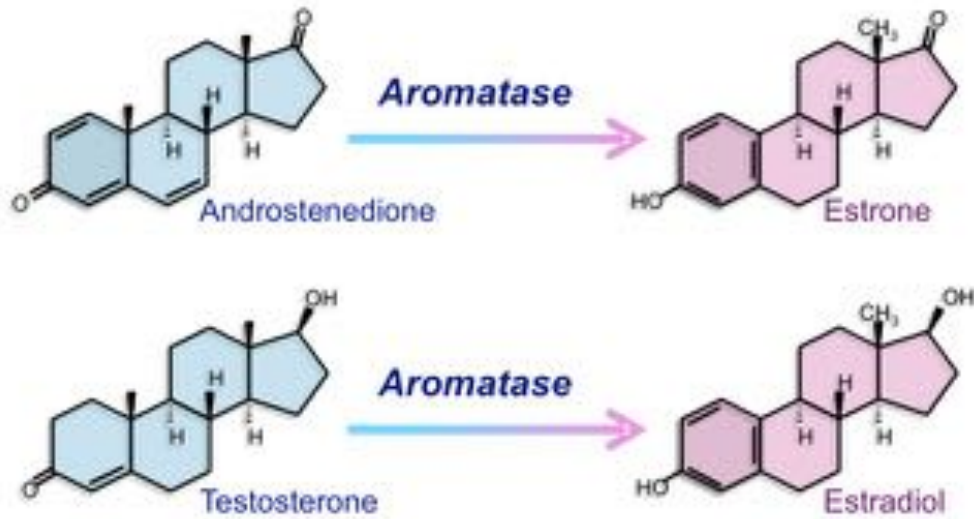
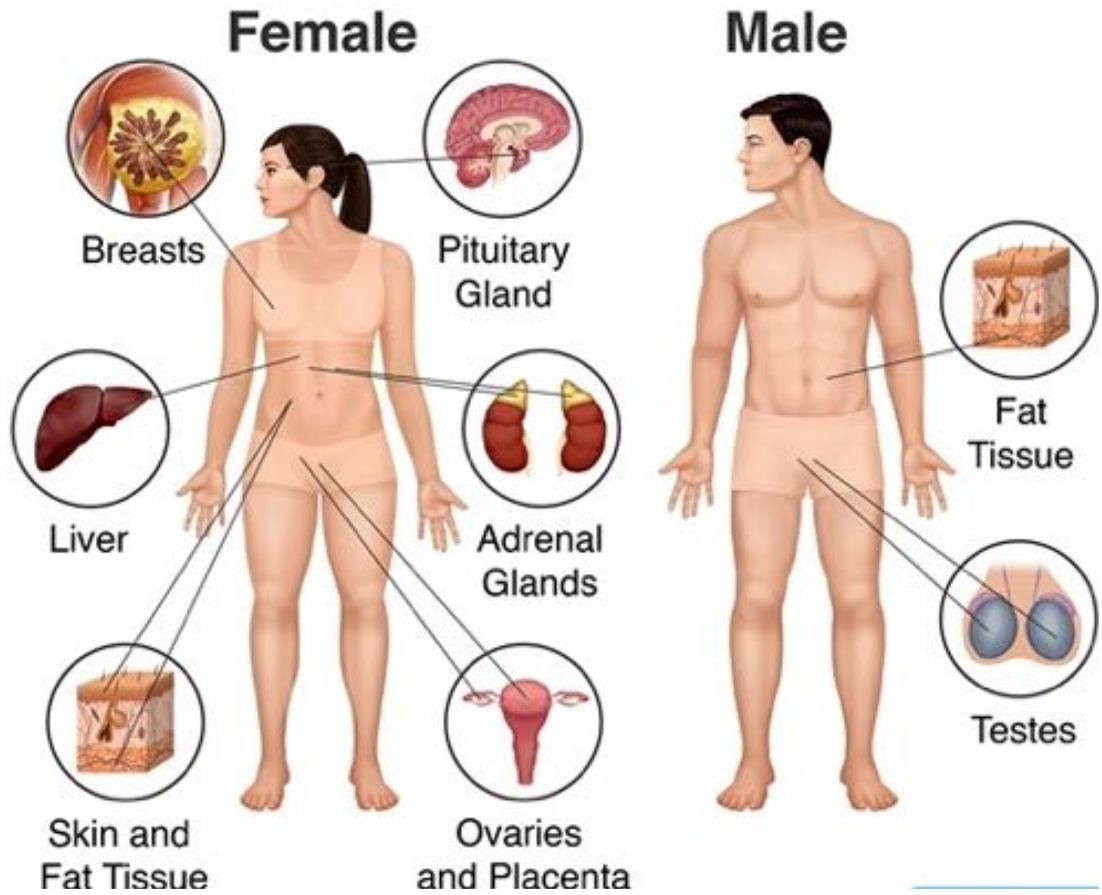
*Does the food we eat, and its
processing, impact our
hormonal balance and cancer
risk?*

Deborah J. Clegg, PhD

**Vice President for Research
Professor, Internal Medicine
Texas Tech University Health Sciences Center
El Paso, TX**

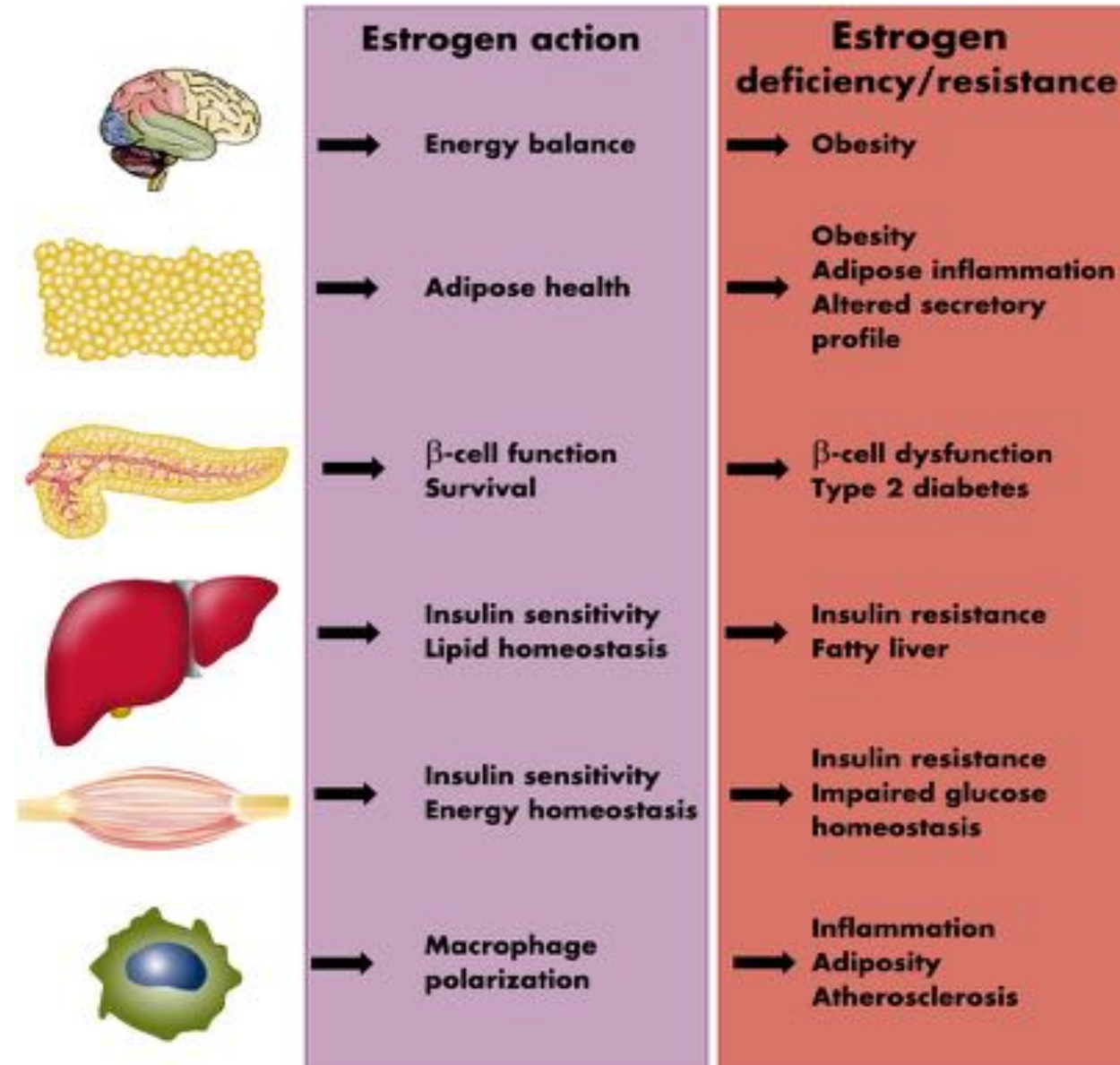
Origin of Estrogens

Estrogen Production in the Body

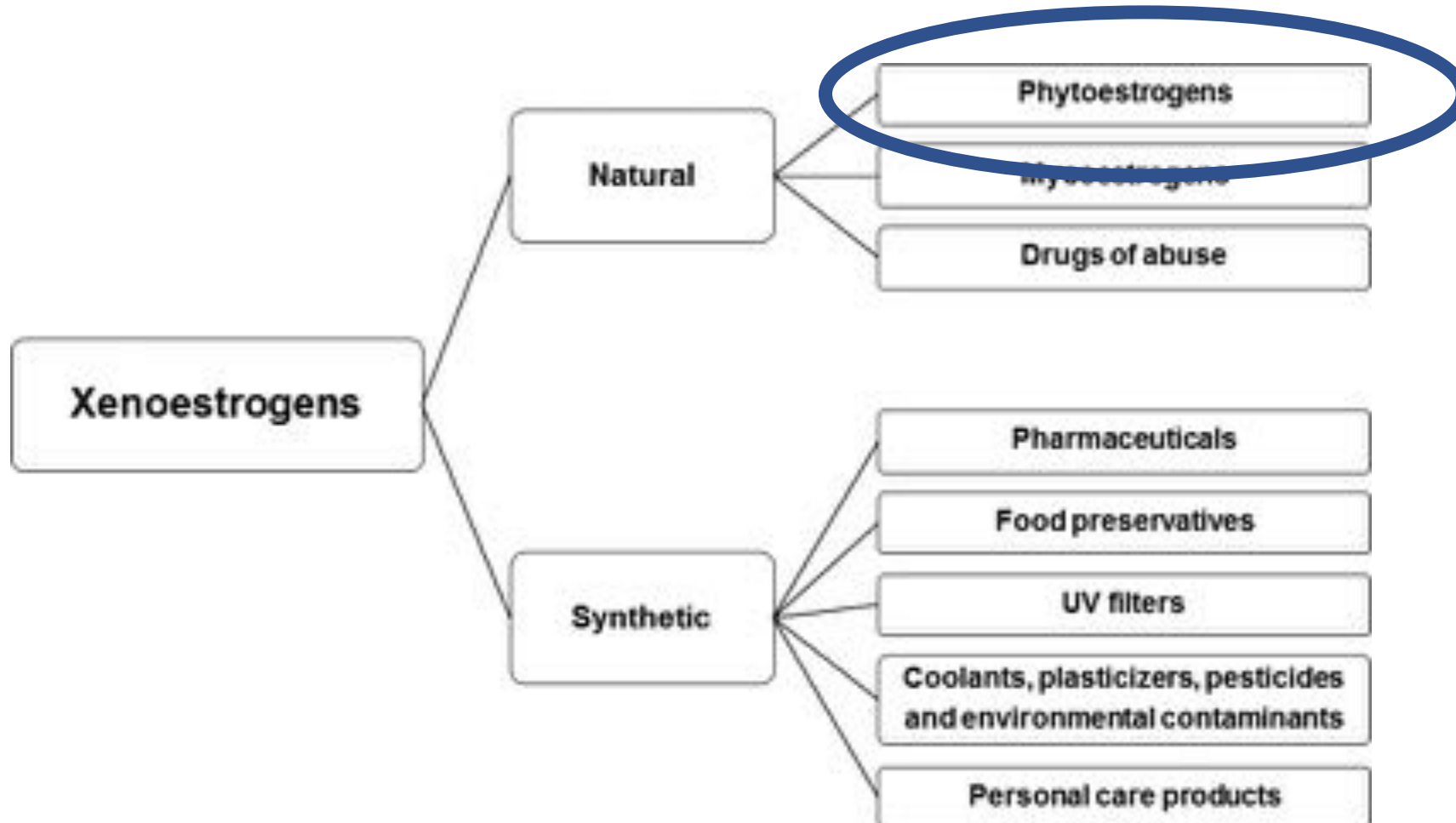


Aromatase Expression In Male Organs and Tissues	++++	++
	Testis Adipose tissue Muscle	Brain Liver Breast Skin Endothelium Gastric parietal cells

Function of Endogenous Estrogens



Xenoestrogens



What are the Similarities Between Phytoestrogens and Xenoestrogens?

- Phytoestrogens and Xenoestrogens are two foreign estrogens that are produced outside of the human body.
- They exert estrogen-like activity.
- Both compounds have wide applications as pharmaceuticals.....
- Both compounds may have beneficial and adverse effects....

Phytoestrogens



WHAT:

Phytoestrogens are plant nutrients found in soy products, grains, beans, and some fruits and vegetables. When consumed regularly during childhood, phytoestrogen consumption is linked to a decreased risk of breast cancer.

FOUND:

Phytoestrogens are found in foods such as whole grains, dried beans, peas, fruits, broccoli, cauliflower, and especially in many soy products.

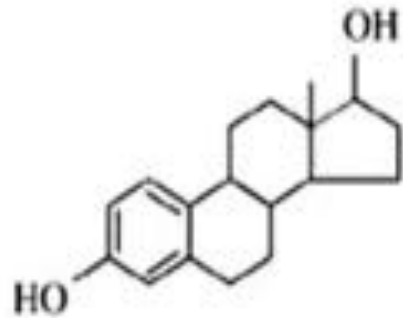
SCIENCE:

Overall, phytoestrogen consumption is believed to be protective against breast cancer. But, some research suggests women with HER-2-positive tumors and pre-menopausal women at high risk should avoid them.

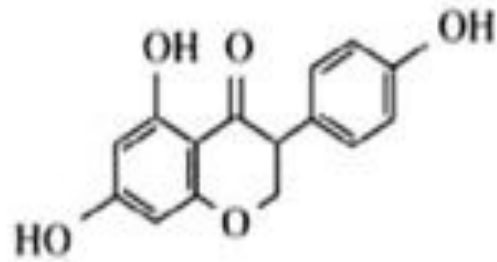
TOP TIPS:

It is best to avoid highly processed soy. Limit intake of concentrated isoflavones, including genistein, in favor of less-processed options such as tofu, edamame and tempeh.

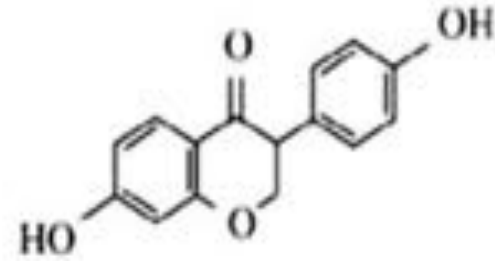
Similarity Between Estrogens and Phytoestrogens



17-β-estradiol



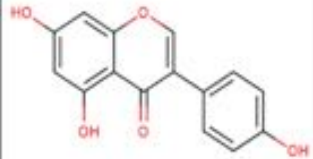
Genistein



Daidzein

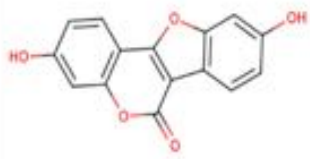
Examples of the Most Common Dietary Phytoestrogens

Isoflavones



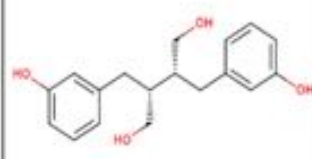
- Genistein
- Daidzein
- Glycitein
- Biochanin

Coumestans



- Coumestrol
- Wedelolactone
- Plicadin

Lignans



- Enterodiol
- Enterolactone
- Pinoresinol
- Secoisolariciresinol
- Matairesinol
- Sesamin

Isoflavones commonly found in soy

- genistein and daidzein are widely marketed as dietary supplements

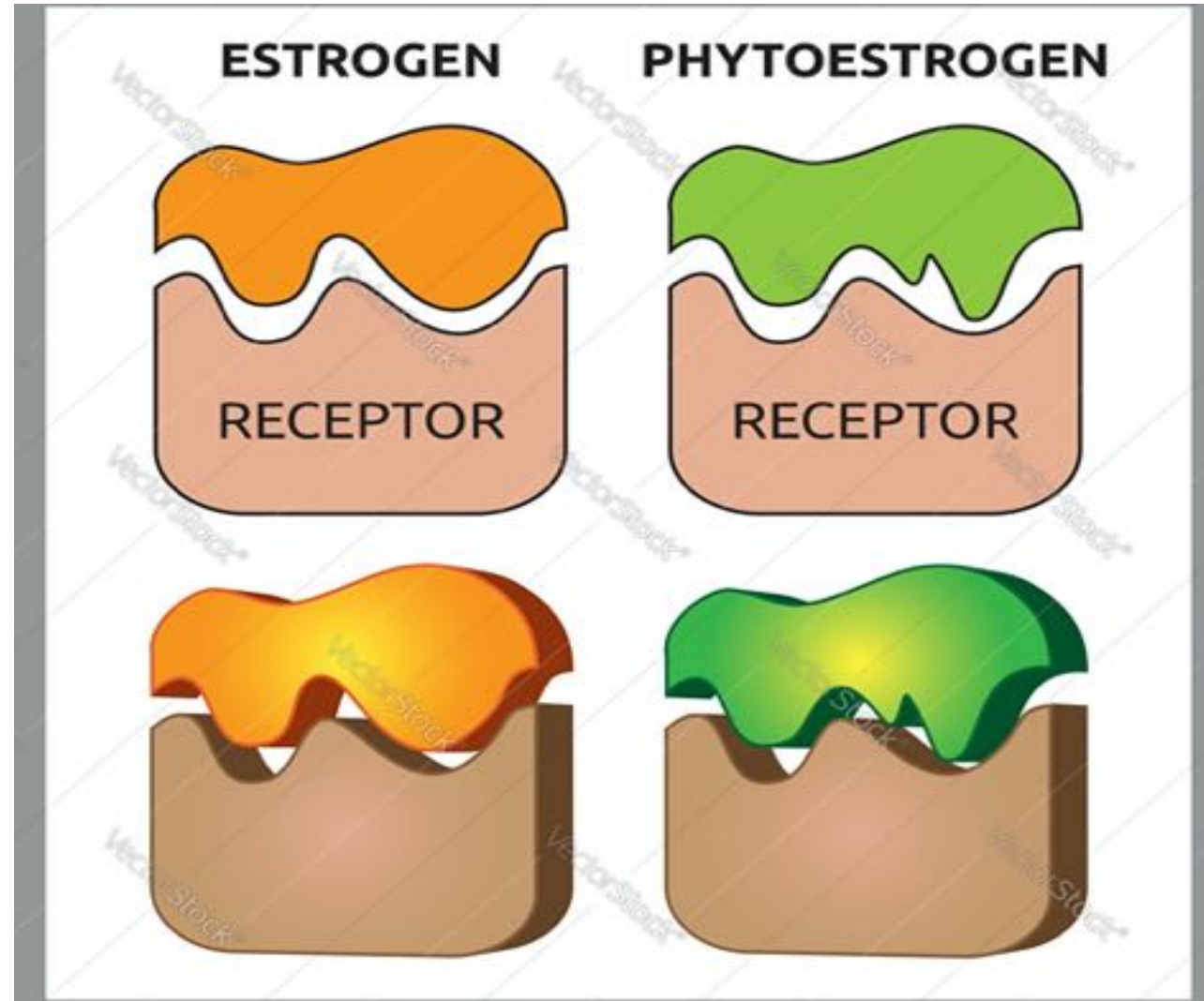
Coumestans commonly found in broccoli and sprouts

- have estrogenic activity that is 30 to 100 times greater than that of isoflavones

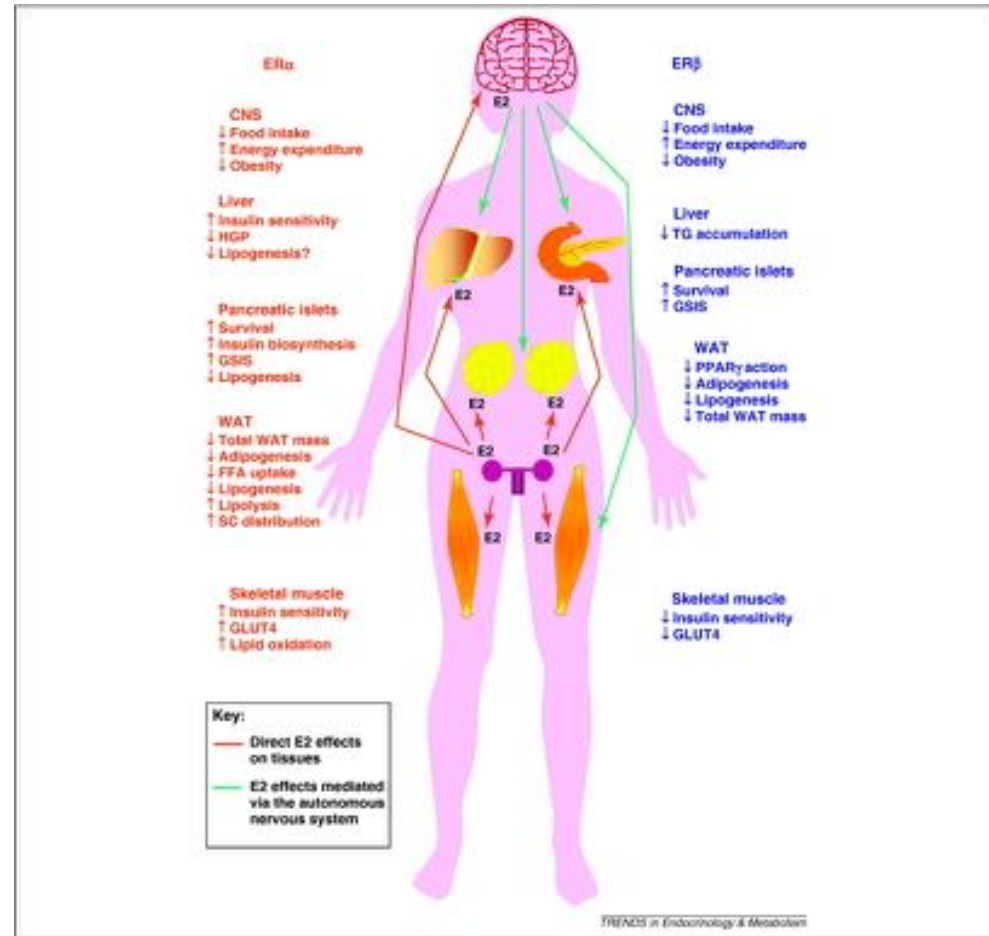
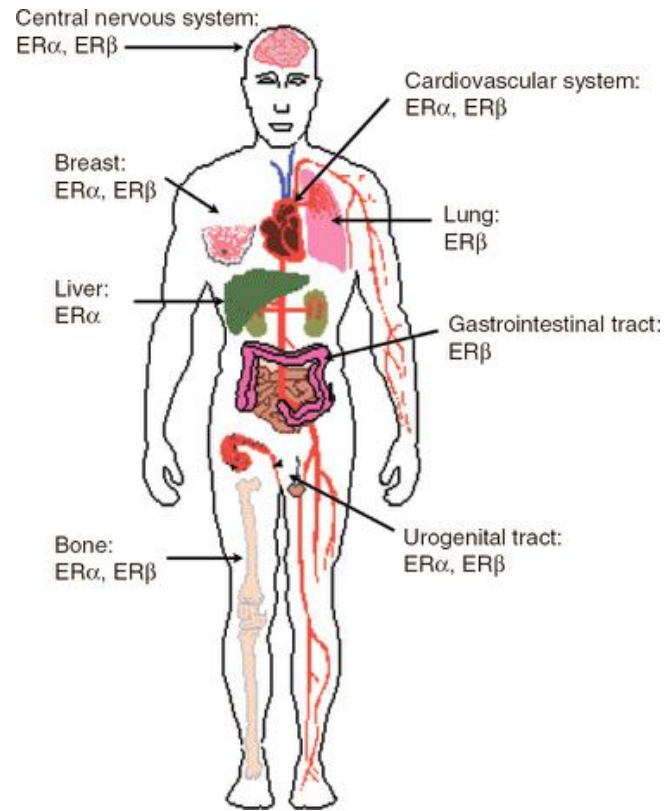
Lignans large group of low molecular weight polyphenols

- found in plants, particularly seeds, whole grains, and vegetables

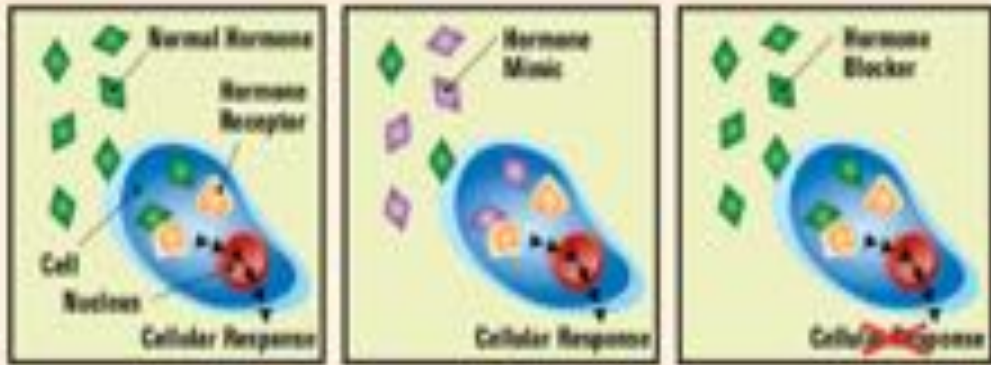
Similar BUT *Different* Binding Affinity to the Estrogen Receptors with Phytoestrogens



Location of Estrogen Receptors



Similar BUT *Different* Binding Activity of the Estrogen Receptors with Phytoestrogens



Phytoestrogens can also activate:

Serotonergic receptors

Insulin-like growth factors receptors

Free radical binding and modification of tyrosine kinases

Cycle adenosine monophosphate (cAMP)

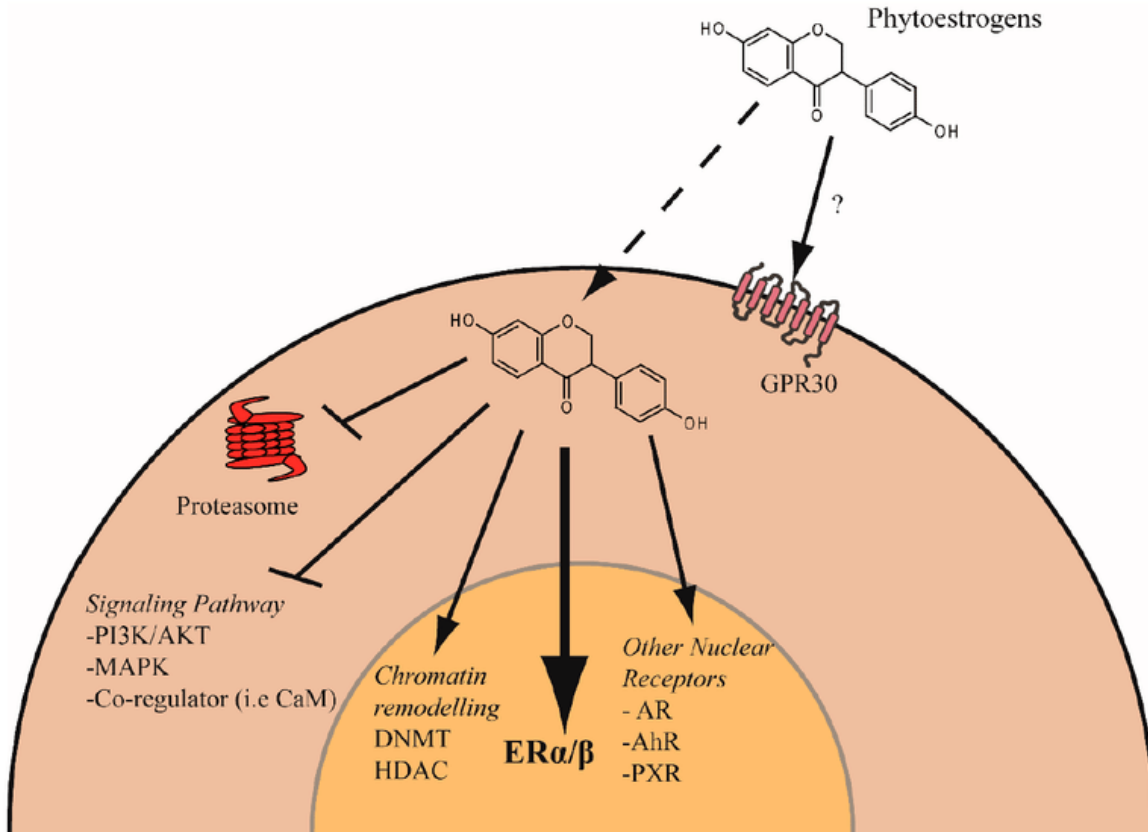
Phosphatidylinositol-3 kinase (PI3K)

DNA methylation

Affect histone and RNA expression

When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right).

Phytoestrogen Activation of Estrogen Receptors



Potential Anti-Cancer Mechanisms of Phytoestrogens

Phytoestrogens are able to **inhibit mitogenic pathways** via ER β or PI3K/MAPK, which in turn inhibit cancer cell proliferation and invasion

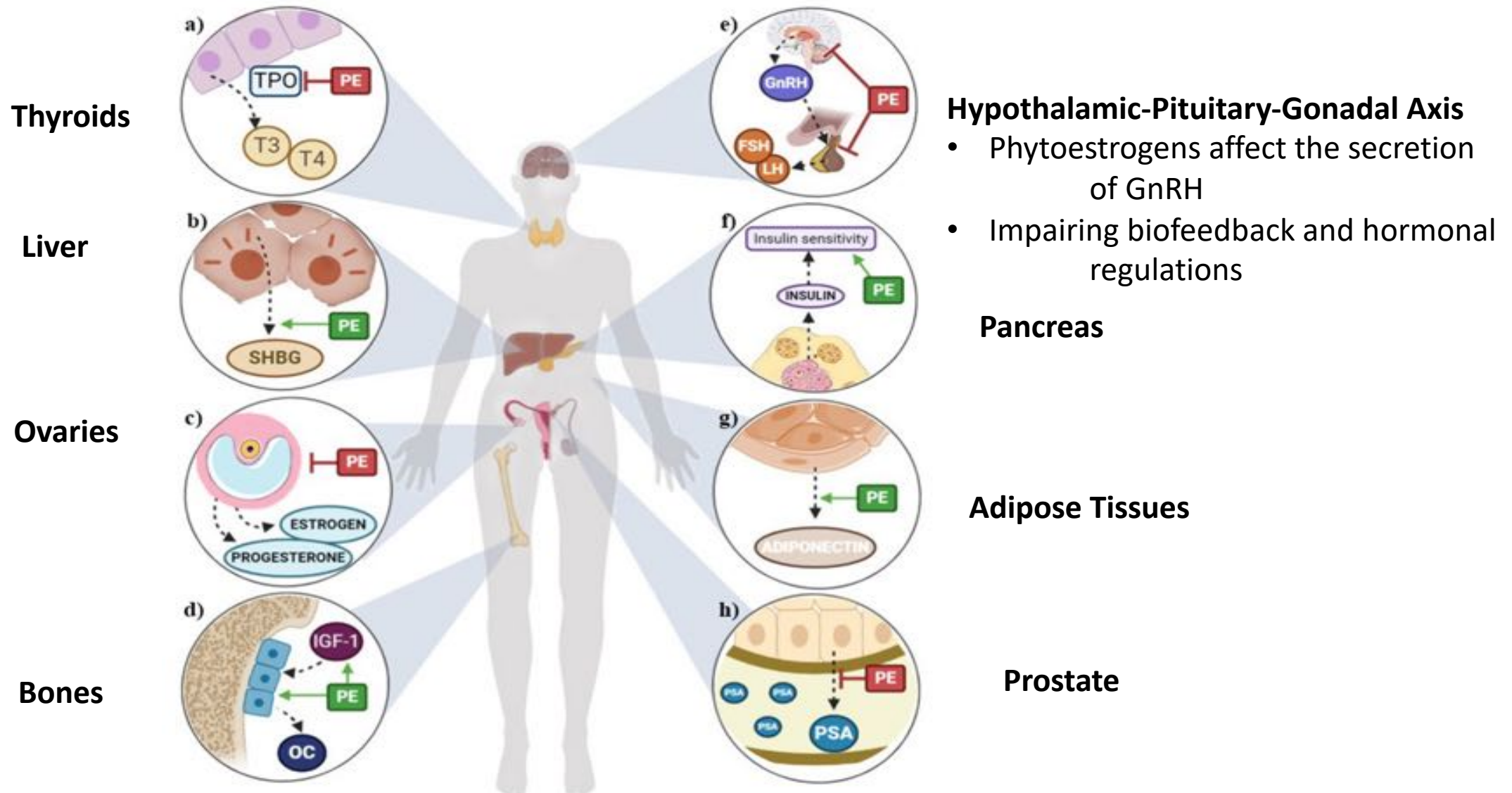
Phytoestrogens can cause **epigenetic modifications**, such as demethylation of CpG islands within the promoters of tumor suppressor genes which can contribute to cell growth arrest

Phytoestrogens **can inhibit proteasomes** as a mechanism which may decrease cancer cell survival

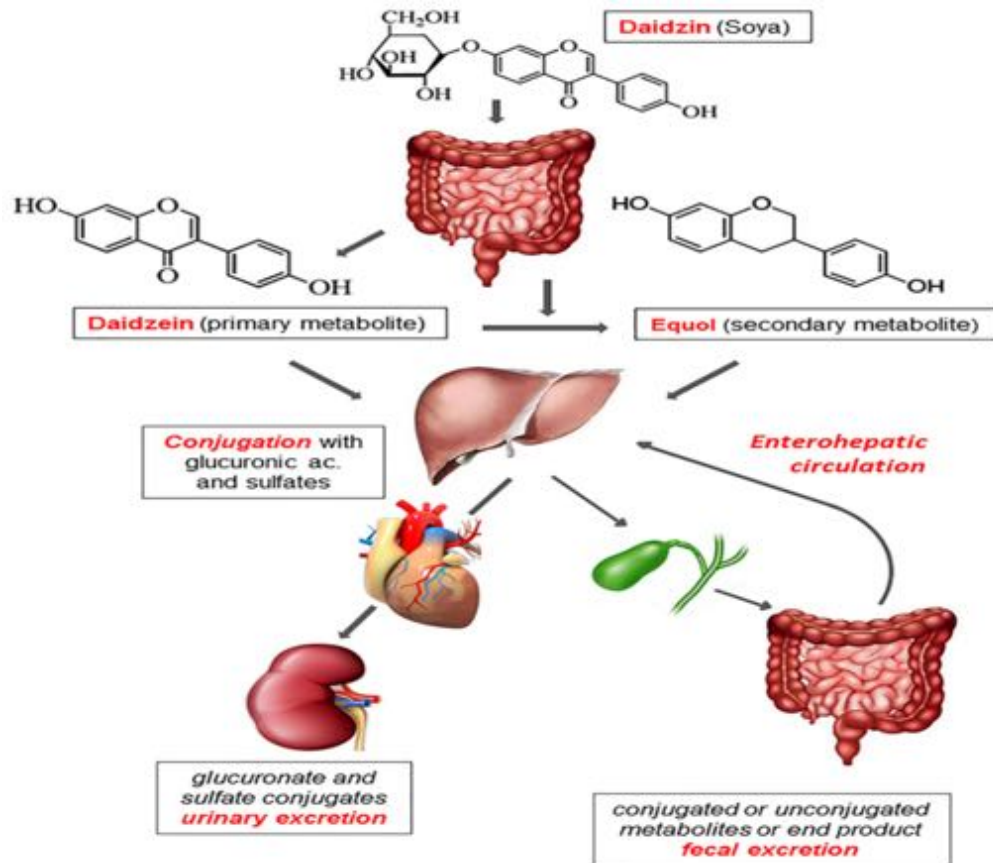
Potential Positive and Negative Impact of Phytoestrogens

- Phytoestrogens have been thought to lower the risk of:
 - Osteoporosis
 - Cardiometabolic diseases
 - Cognitive dysfunction
 - Breast and prostate cancer
 - Menopausal symptoms
- Phytoestrogens are also described as endocrine disruptors
- Beneficial vs harmful effects of phytoestrogens depend on:
 - Exposure (type, amount consumed, bioavailability)
 - Ethnicity
 - Hormonal status (age and physiological condition)
 - Health status of the consumer

Potential Health Outcomes of Phytoestrogens



Phytoestrogen Bioavailability



Absorption, metabolism, and excretion of phytoestrogens.

- Daidzin, contained in soy products, is hydrolyzed by the bacterial beta-glucosidase generating aglycones (primary metabolites)
- Colonic microflora is capable of transforming aglycones into secondary metabolites and bacterial end-products that are eliminated with feces
- Both primary and secondary metabolites undergo either glucuronidation or sulfidation by intestinal epithelial cells and hepatocytes
- Once in the bloodstream, these conjugated products reach target tissues and later on are excreted in urine or bile
- In the bile, they can be absorbed again by the intestine (enterohepatic circulation) or are excreted in feces as bacterial end-products or unconjugated forms

Where Do Phytoestrogens Come From?

ESTROGENS IN MEAT

Even with growth hormone and antibiotic use in "Traditional Steak," the hormone levels in meat is nowhere compared to plant-based foods.

Hormone levels in food:

nutritionwithjudy



* 20-Hydroxyecdysone
† Estrogenic activity

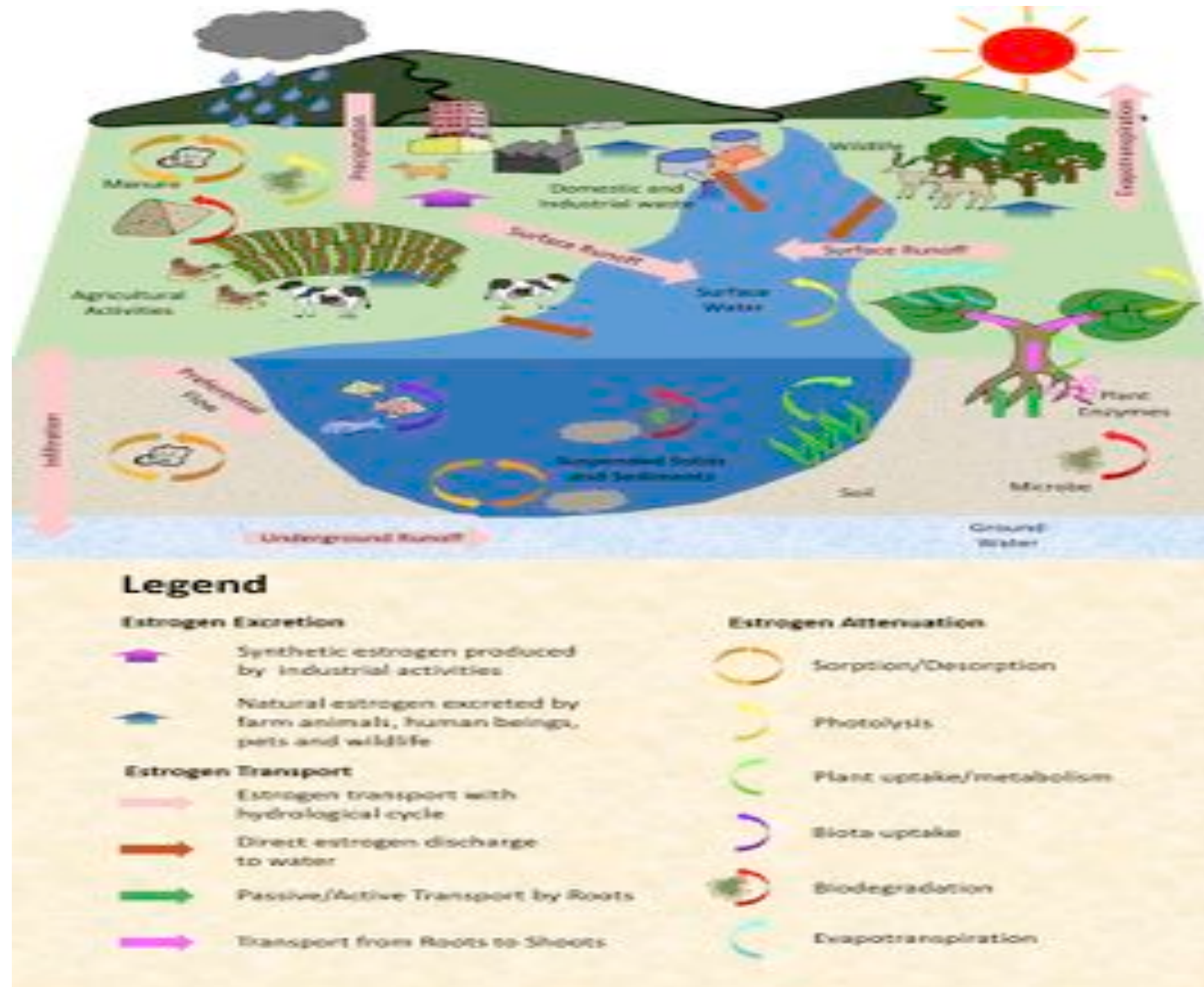
- Traditional Steak (12 oz): 7.6 ng
- Natural Steak* (12 oz): 5.2 ng
- Quinoa: 27,000,000 ng
- Tofu (3 oz): 19,000,000 ng
- Spinach (Raw): 975,000 ng

*Natural steak is defined as animals with no use of antibiotics or growth hormone injections.

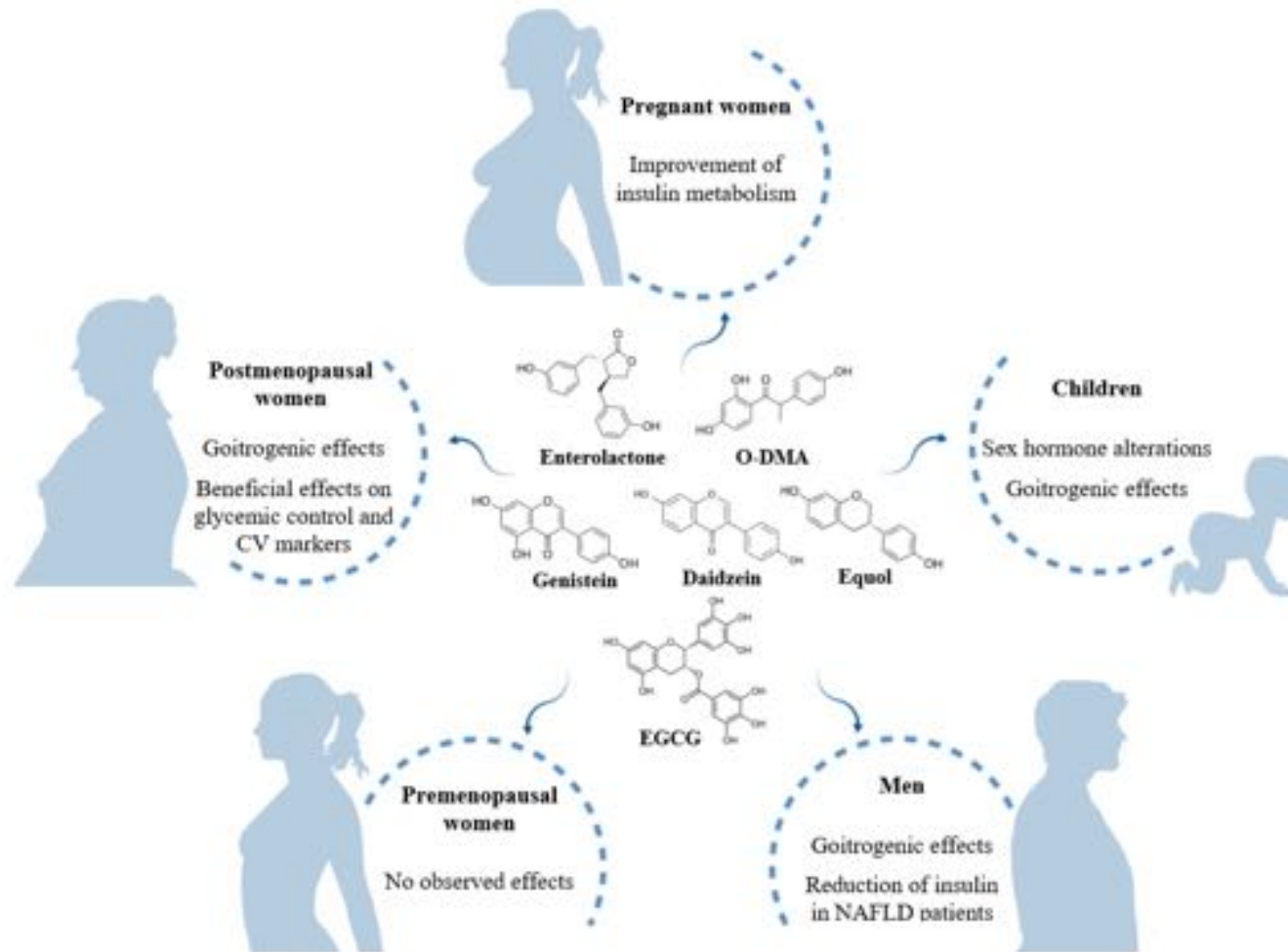
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nwj

Where Do Phytoestrogens Come From?



Summary of the Effects of Dietary Phytoestrogens at Different Life Stages

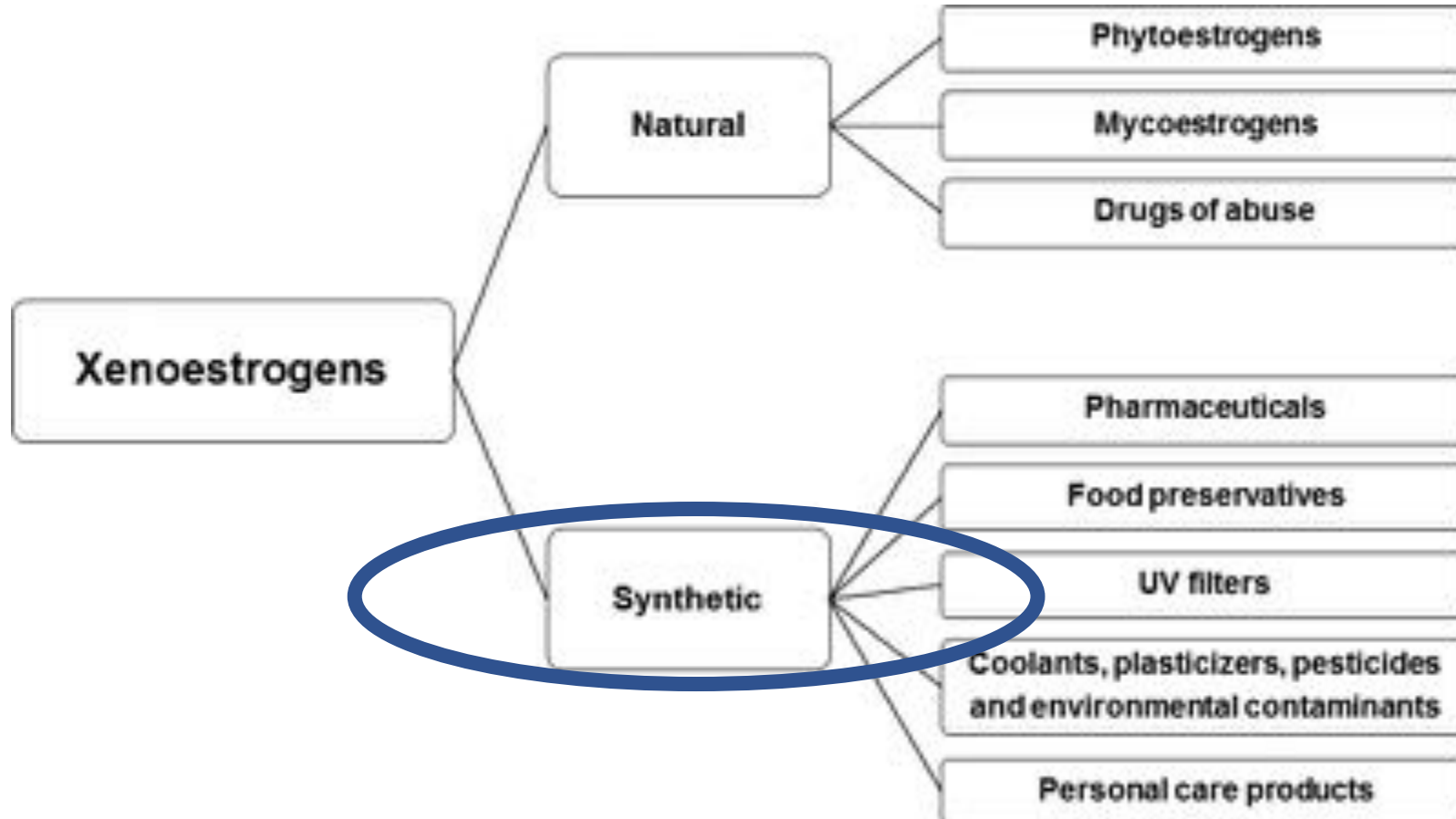


Association between dietary phytoestrogens and endocrine biomarkers is ***inconclusive***.

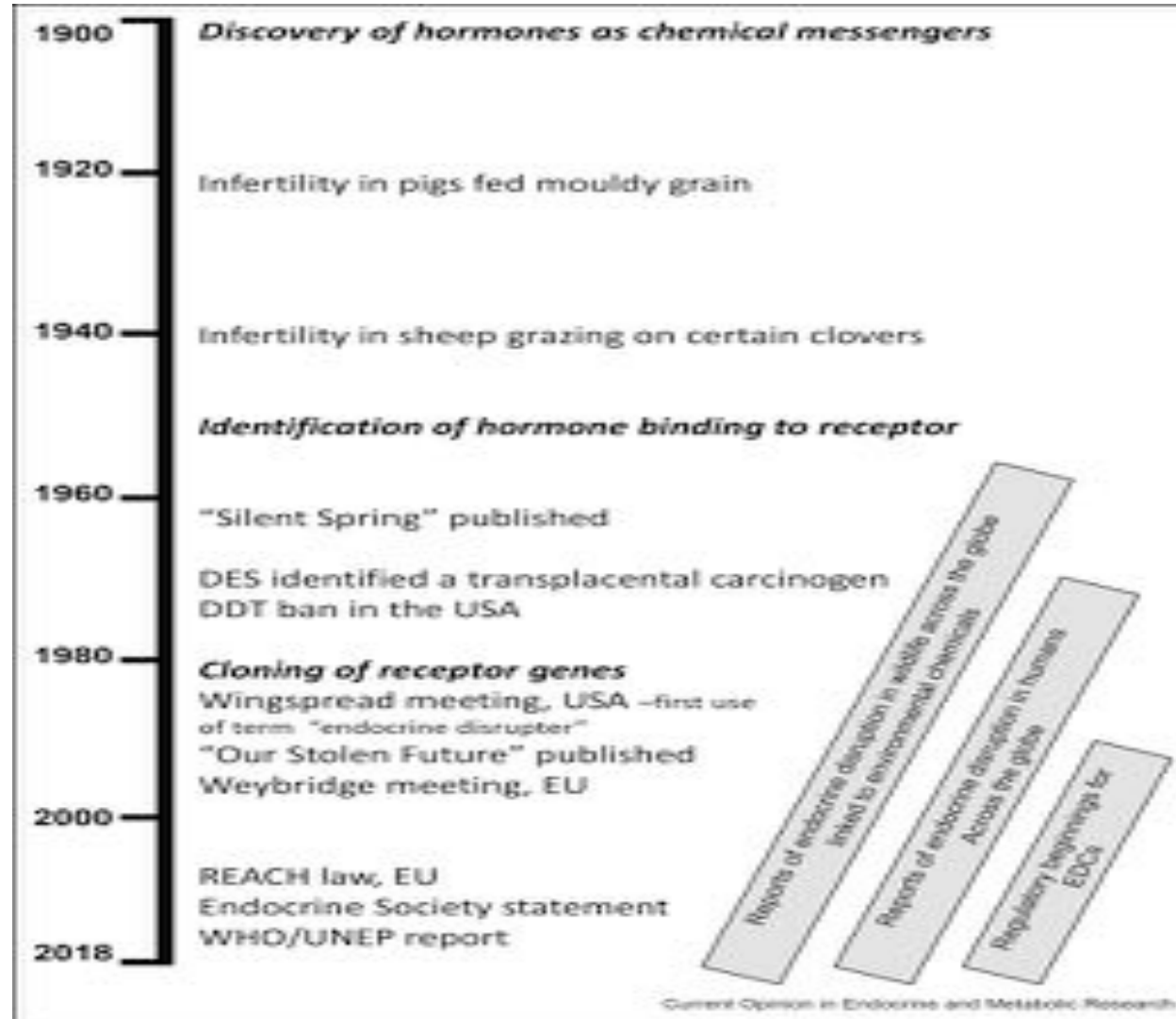
The disparity in results may be due to:

- Differences in type and concentration of compound
- Phytoestrogen bioavailability
- Circulating vs urinary excretion of metabolites
- Most studies done in postmenopausal women
- Little known about their impact during pregnancy
- Impact of phytoestrogens on pubertal development poorly studied

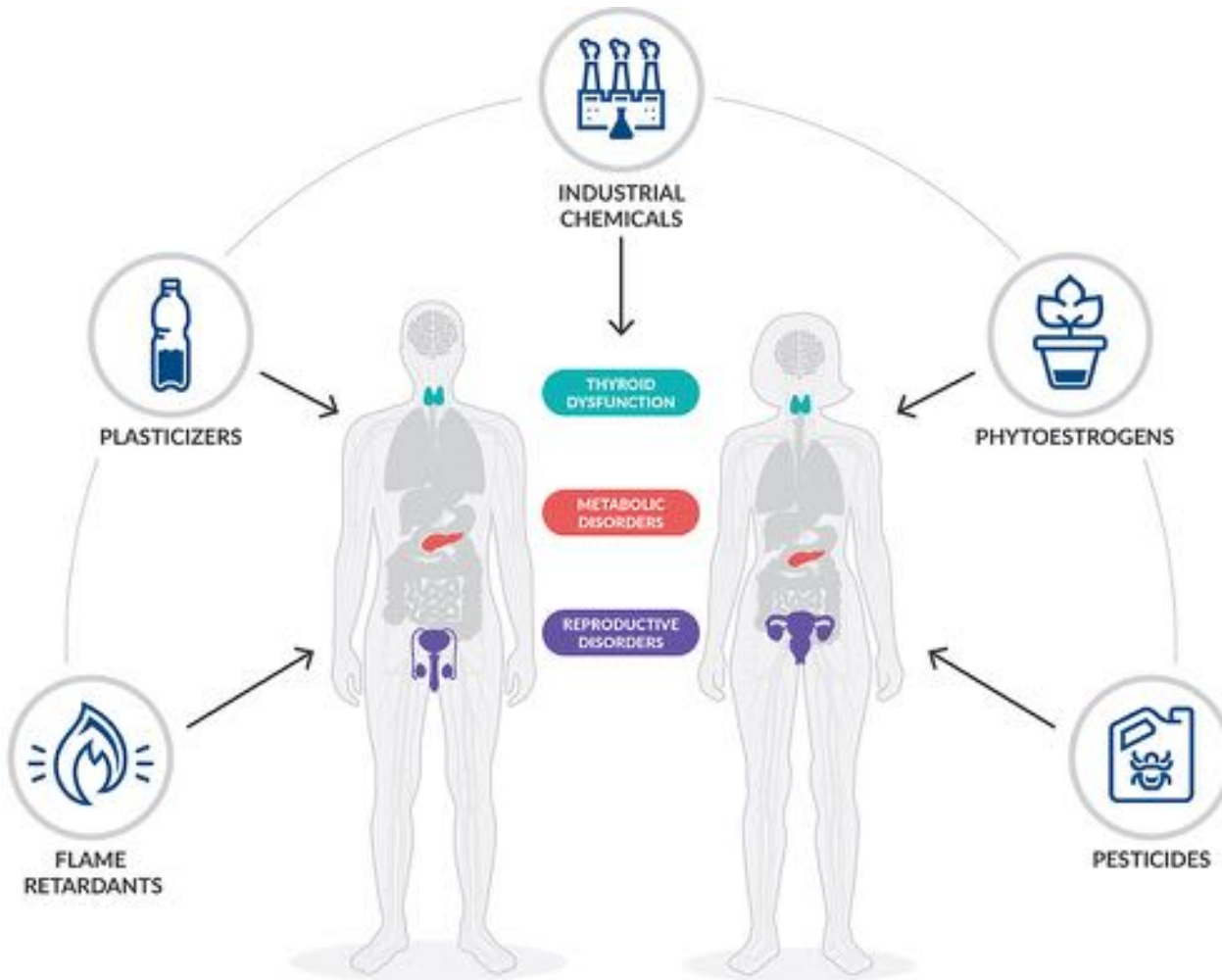
Xenoestrogens



Chronology of Knowledge of Xenoestrogens



Sites and Sources of Xenoestrogens



Dichlorodiphenyldichloroethylene (DDE) and other organochlorine pesticides found in maternal blood and placental tissue represents a dangerous prenatal exposure hazard for fetuses, due to chronic bioaccumulation and poor elimination

DDE has a higher affinity and lipophilicity and is not easily catabolized by organisms

Dichlorodiphenyltrichloroethane (DDT), stimulates membrane estrogen receptors and plays an important role in the propagation of DDT-induced apoptosis during the early stages of neural development

Lake Apopka in Florida is seriously affected by DDT and its metabolites

Male crocodiles have a micropenis, various abnormalities of the testes due to exposure of DDT and DDE

Where do Xenoestrogens Come From?

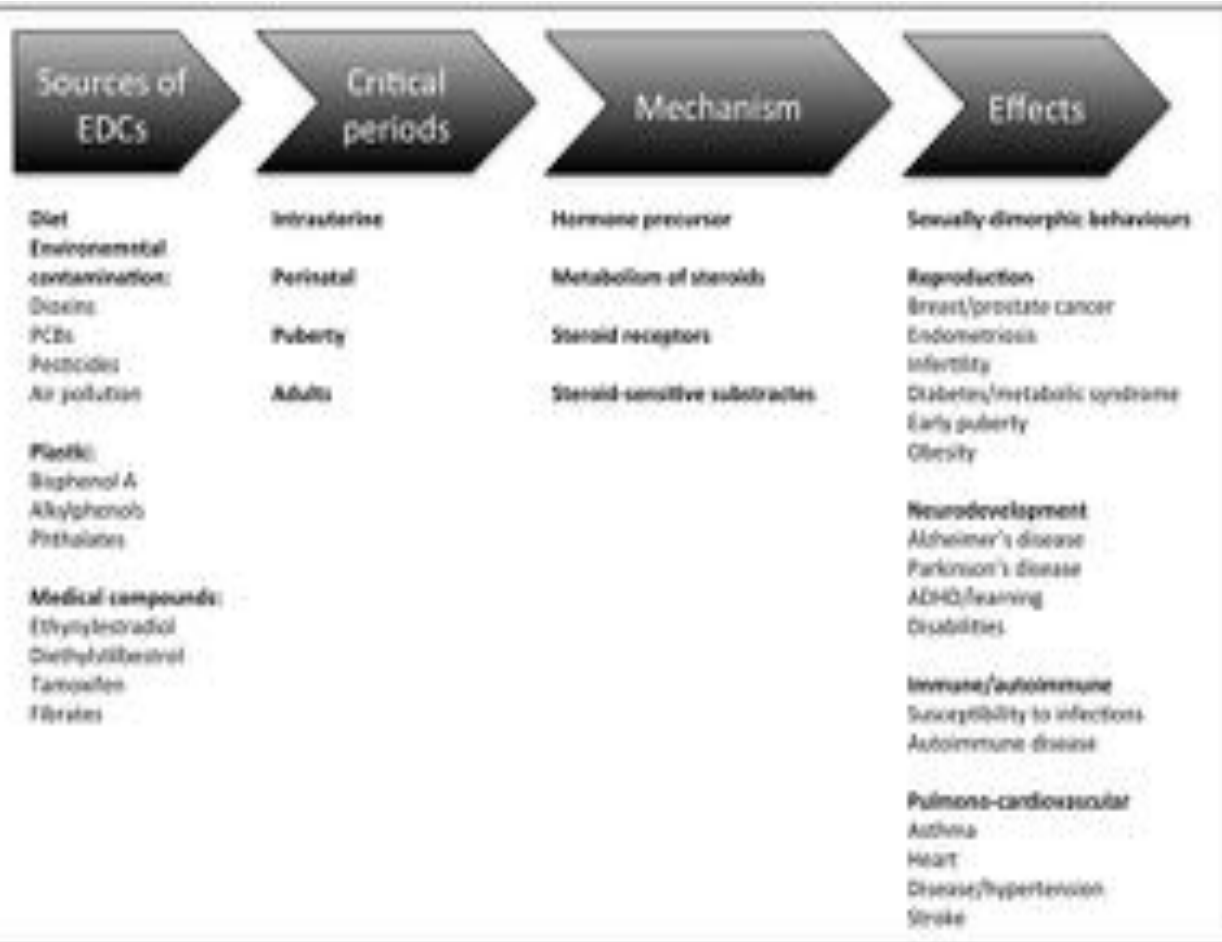


- As endocrine disruptors, XEs can be either synthetic or natural chemical compounds derived from sources, including diet, pesticides, cosmetics, plastics, plants, industrial byproducts, metals, and medications
- Xenoestrogens mimic the chemical structure of naturally occurring estrogen compounds even without structural similarity to estrogens
- Xenoestrogens exert effects via various pathways other than classical ER-signaling
- Xenoestrogens can weakly activate compounds that interfere with the hormonal balance
- Xenoestrogens exert tissue-specific and non-genomic actions when estrogen concentrations are relatively low

Routes of Exposure to Endocrine Disrupting Chemicals (EDC)



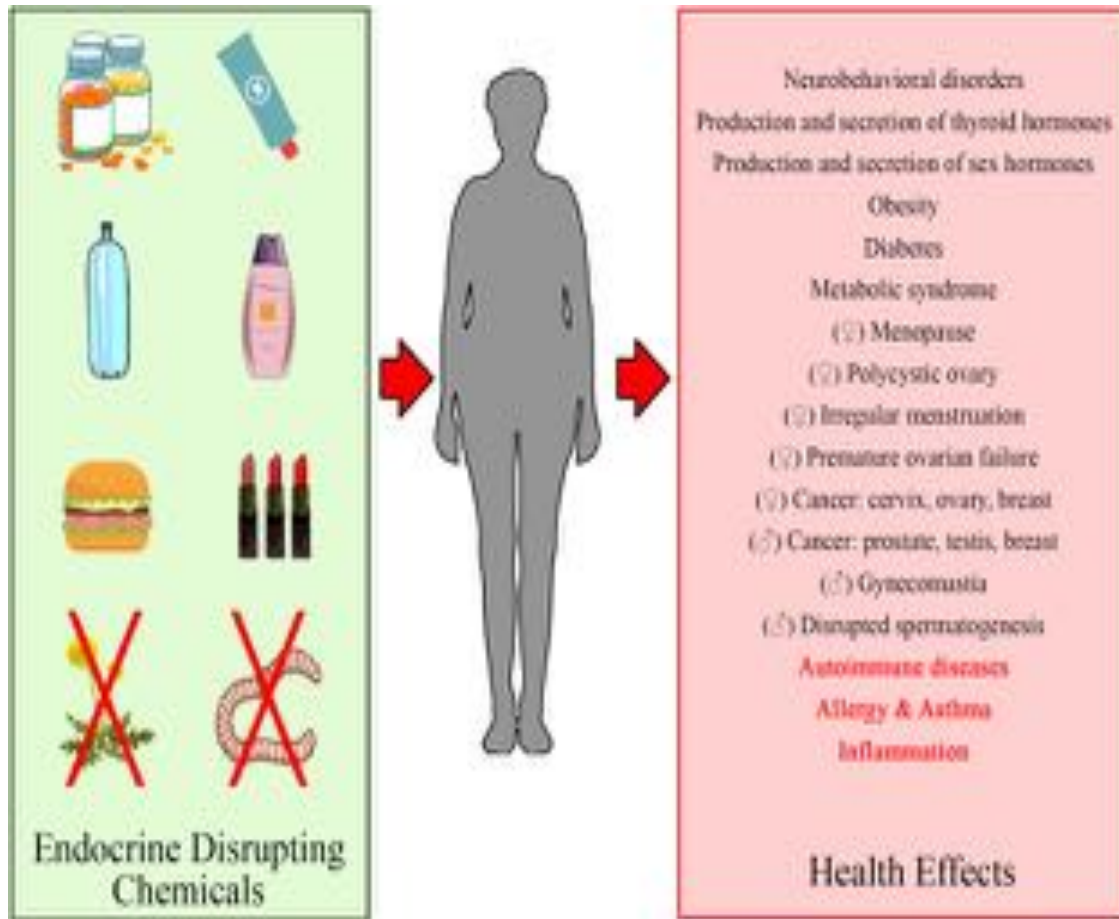
Critical Periods of Xenoestrogen Activity



Term Window

- Period of developmental susceptibility during which the developing organism can be altered by environmental factors resulting in structural, functional, and/or cellular changes
- Alterations during these 'windows' identified at late stages

Sites of Xenoestrogen Activity



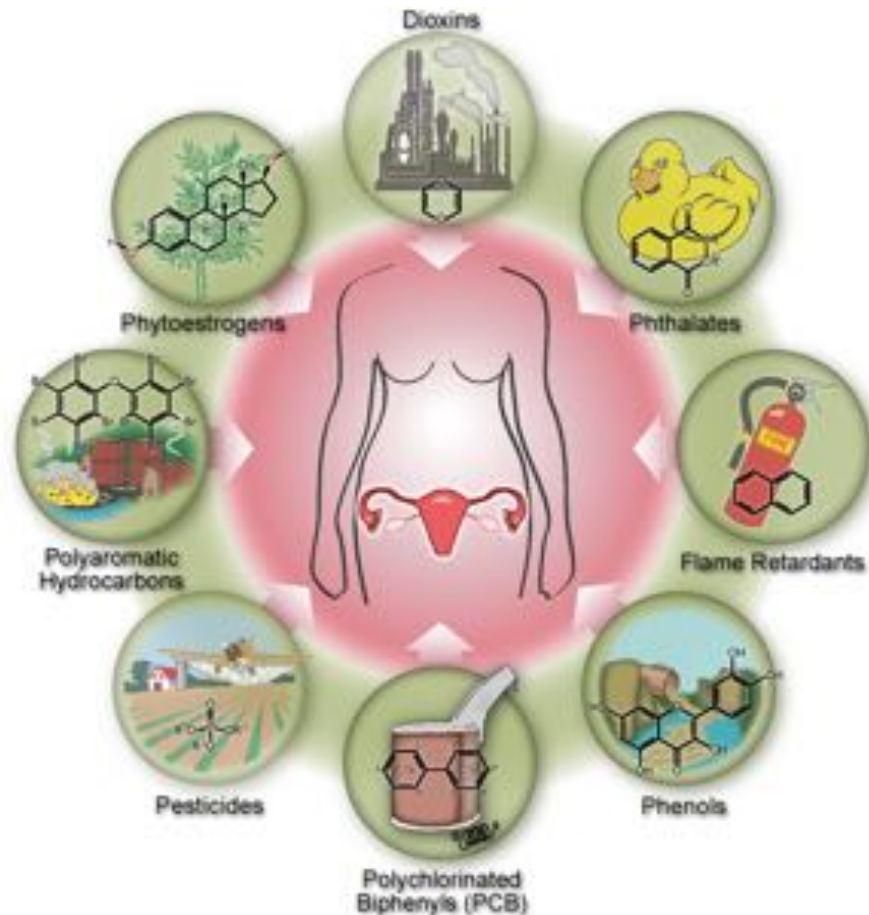
- Xenoestrogens have estrogenicity or anti-estrogenicity
- Can bind to receptors within the organism
- Manipulate differentiation and modulation of cell proliferation
- Impact apoptosis, cytokine production, and cell cycle progression

*** All of which should be controlled by the endogenous 17β -estradiol

Xenoestrogens Impact on Neurological Disorders

- [Polychlorinated Biphenyls](#) (PCBs) have been shown to cause neurological diseases to include:
 - long-term neurological deficits
 - problems with learning and memory function
 - slower reaction time
 - reduced color discrimination, and constricted visual fields
 - diminished vocabulary and verbal recall (Crinnion, 2011)
- Xenoestrogens such as DDT have been shown to interfere with neural development in pregnancy
- Children who have been exposed to PCBs during pregnancy through maternal consumption of fish have been shown to exhibit problems with intellectual functioning
- Children who have been exposed to PCBs have a poorer gross motor function and reduced visual recognition memory

Endocrine Disrupting Chemicals (EDC) and Their Impact on Female Reproduction



- Xenoestrogens interfere with the development of the female reproductive tract by competitively inhibiting estrogens and selectively binding to estrogen receptors
- Nine PCBs, three pesticides, a furan, and two phthalates slowly damage the follicular pool and are associated with earlier ages of menopause
- Xenoestrogens can lead to the formation of cysts in ovaries. This condition is known as polycystic ovary syndrome ([PCOS](#)) (Götz et al., 2001)
- Adolescents who resided in an area of substantial industrial development and PCB exposure underwent earlier menarche and thelarche than their unexposed peers

Xenoestrogens and Men's Health

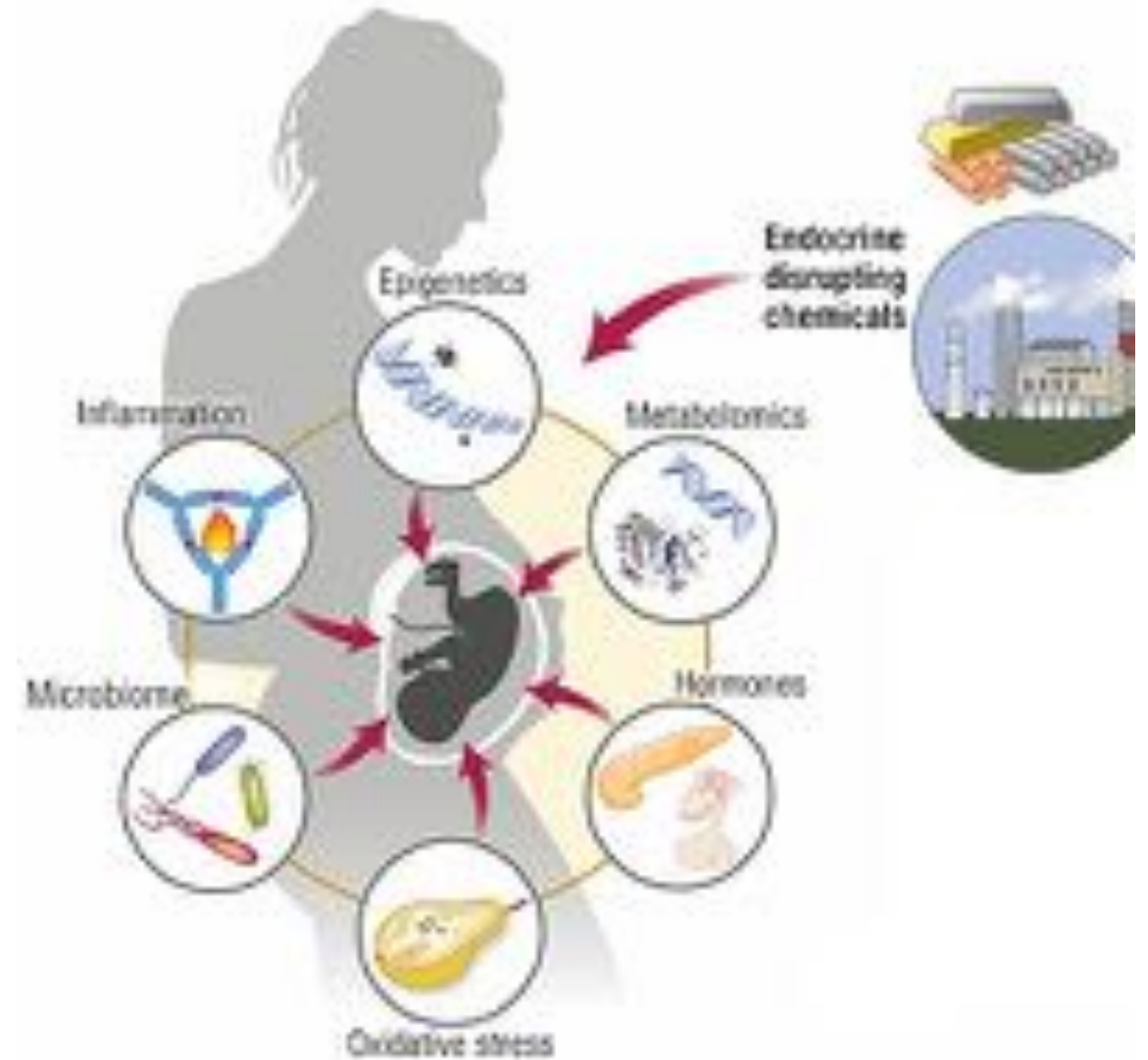
- Xenoestrogens increase the [risk of prostate cancer](#) by disrupting endocrine function in men and either cause or accelerate the development of prostate cancer (Prins, 2008)
 - Xenoestrogens which enhance prostate cancer include PCBs, inorganic arsenic, ultraviolet filters, BPA, and cadmium
 - Xenoestrogens exacerbate the growth of [prostate cancer cells](#) by interfering with the signaling actions of estrogen (Watson et al., 2019)
- There are reductions in testosterone levels which occur during aging in men resulting in increasing levels of estrogen which may be impacted by xenoestrogens
- Xenoestrogens have been found to be responsible for the decrease in both the quantity and quality of human sperm in the last five decades (Götz et al., 2001)
- Xenoestrogens impair the development of the testes and the male reproductive tract

Xenoestrogens Impact on Fetal Development

Xenoestrogens have been shown to negatively impact the development of a fetus (Paterni et al., 2017)

Exposure to xenoestrogens has been shown to have cancer-causing and mutating effects on the cells of a fetus (Palmlund, 1996)

Exposure to xenoestrogens while a woman is pregnant leads to changes in the genetic sequence in the placenta which negatively impacts fetal growth and development (Vilahur et al., 2014)



How Can You Minimize Your Exposure to Xenoestrogens?

- Avoid cosmetic products that have toxic chemicals and [xenoestrogens](#)
- In particular, avoid parabens and phthalates as the cosmetics industry commonly uses these
- Use glass and/or ceramic ware to store food at home instead of plastic containers
- Avoid microwaving plastic containers which cause BPA leaching to occur
- Avoid placing your [plastic bottles](#) or containers in direct sunlight
- Limit your intake of fish, mainly canned fish which is high in mercury and PCBs
- Opt for pesticide-free [fruits and vegetables](#) where possible - if not, thoroughly wash your fruits and vegetables immediately after purchasing them



Xenoestrogens and the Literature

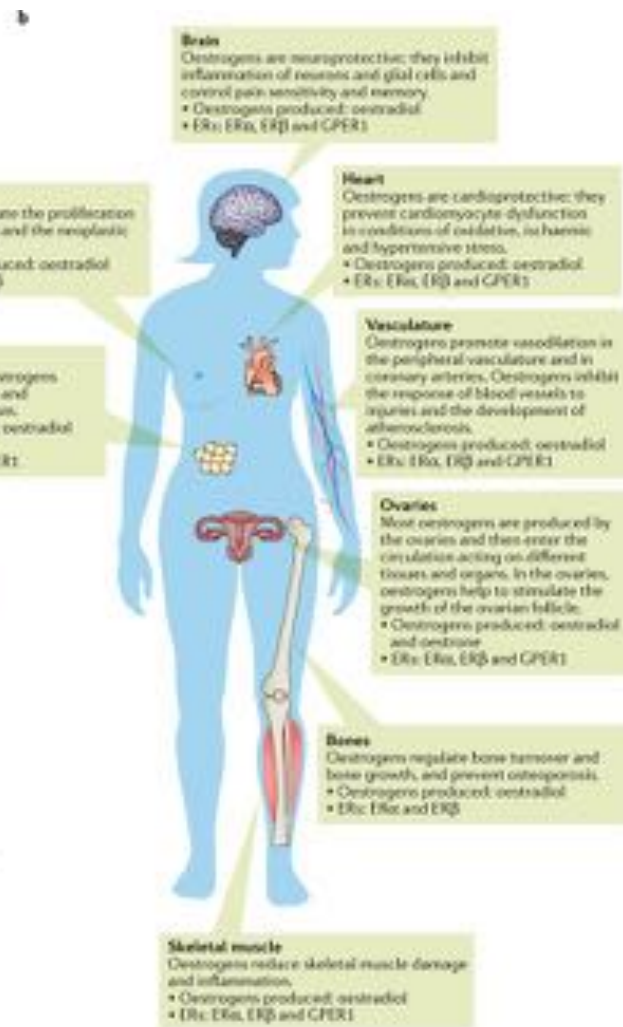
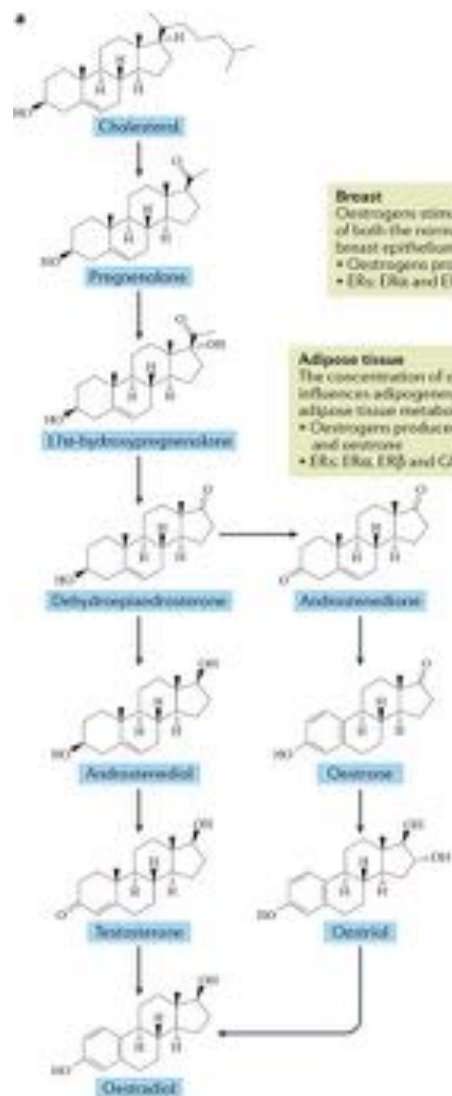
Research XEs has limitations because it is a moral hazard to conduct studies regarding the harmful effects of XEs on humans

Many of the studies reported in the literature are observational and in animals, thus limiting the application of the results to human

There are few, if any, randomized controlled trials found on the topic of XEs

Many of the beneficial and harmful effects of XEs, which have been accumulated in organisms, are dose-dependent and time-dependent, which may not be observed during a shorter period

More experiments are required to study the substances in the environment and in isolation



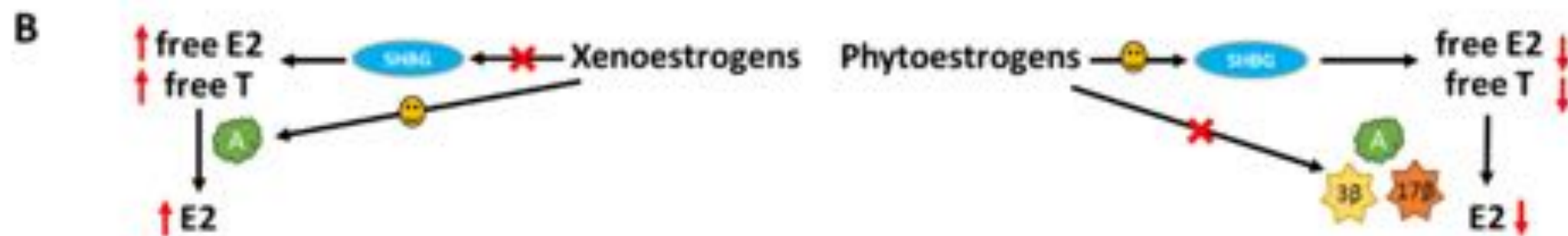
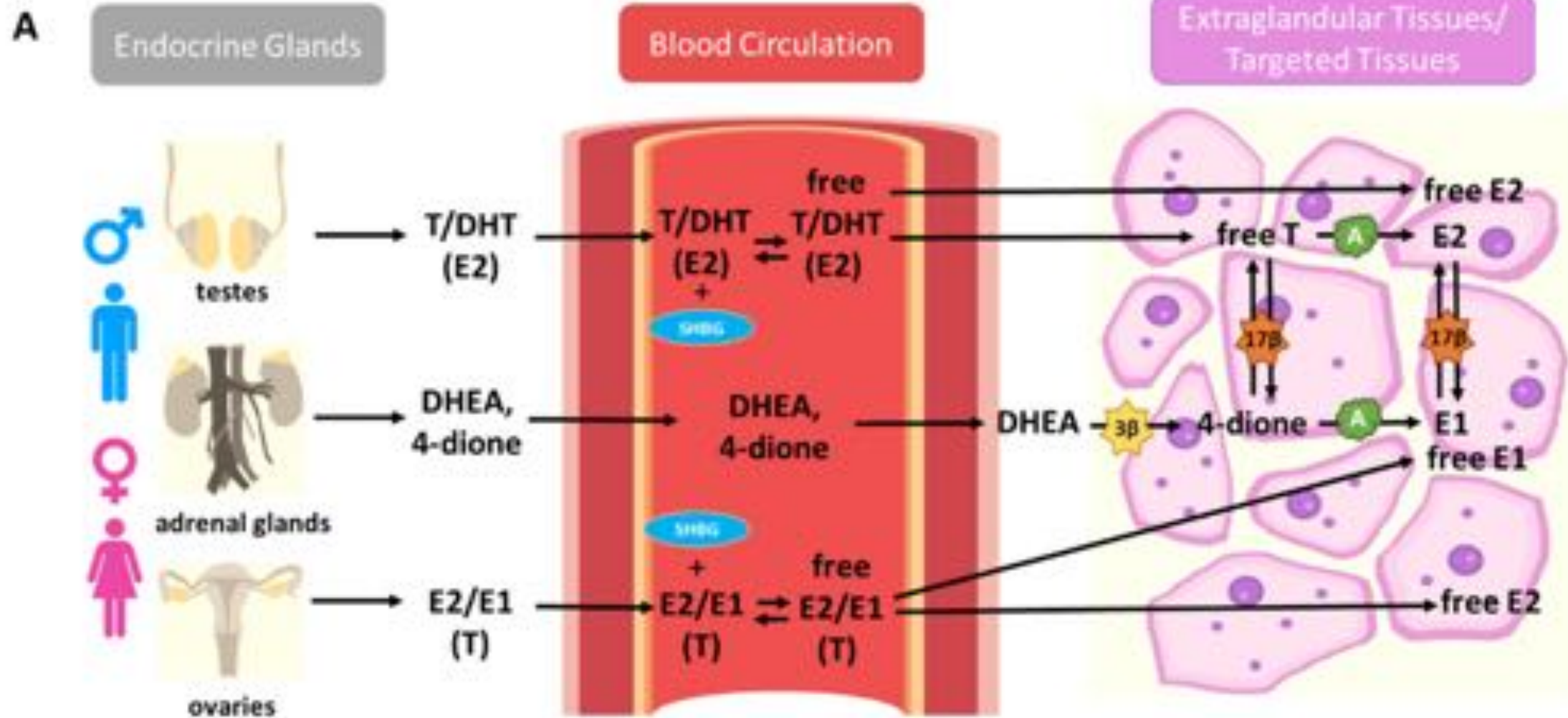
Breast
Estrogens stimulate the proliferation of both the normal and the neoplastic breast epithelium.
• Estrogens produced: estradiol
• ER α , ER β and ER δ

Adipose tissue
The concentration of estrogens influences adipogenesis and adipose tissue metabolism.
• Estrogens produced: estradiol and estrone
• ER α , ER β , ER δ and GPER

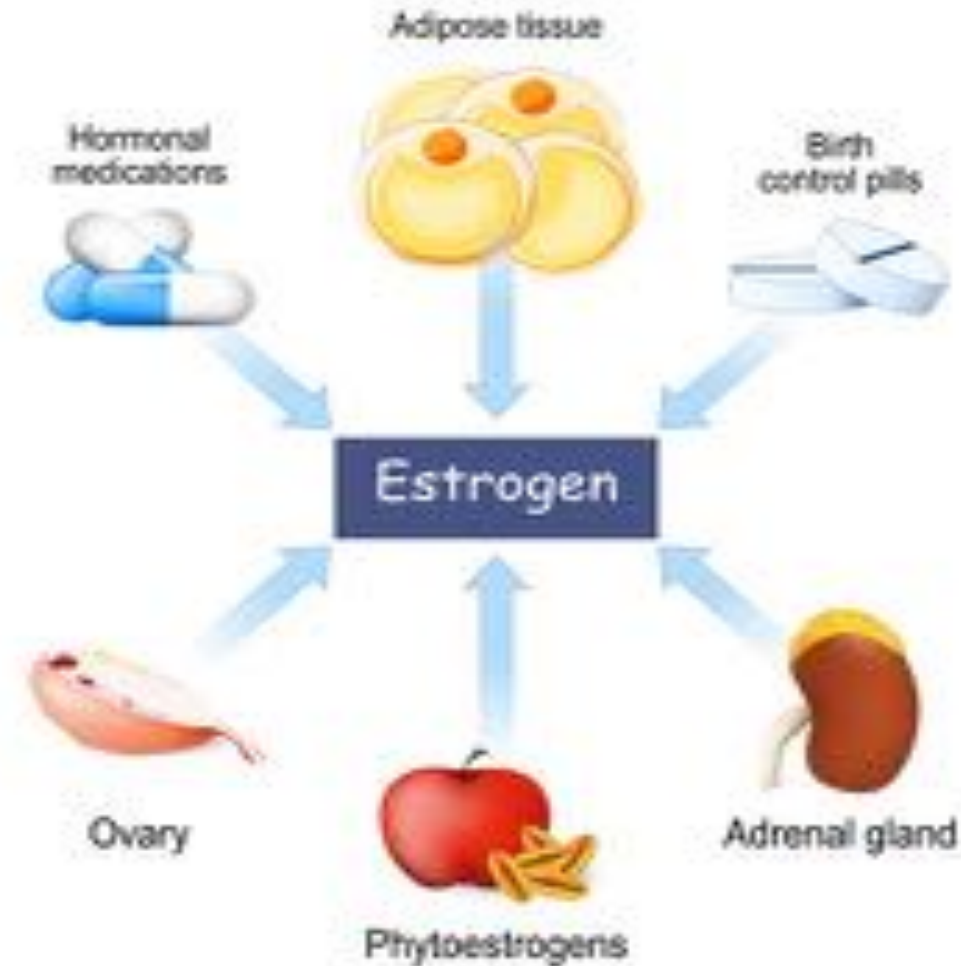
Selective estrogen receptor modulators (SERMs)

Tamoxifen, Raloxifene

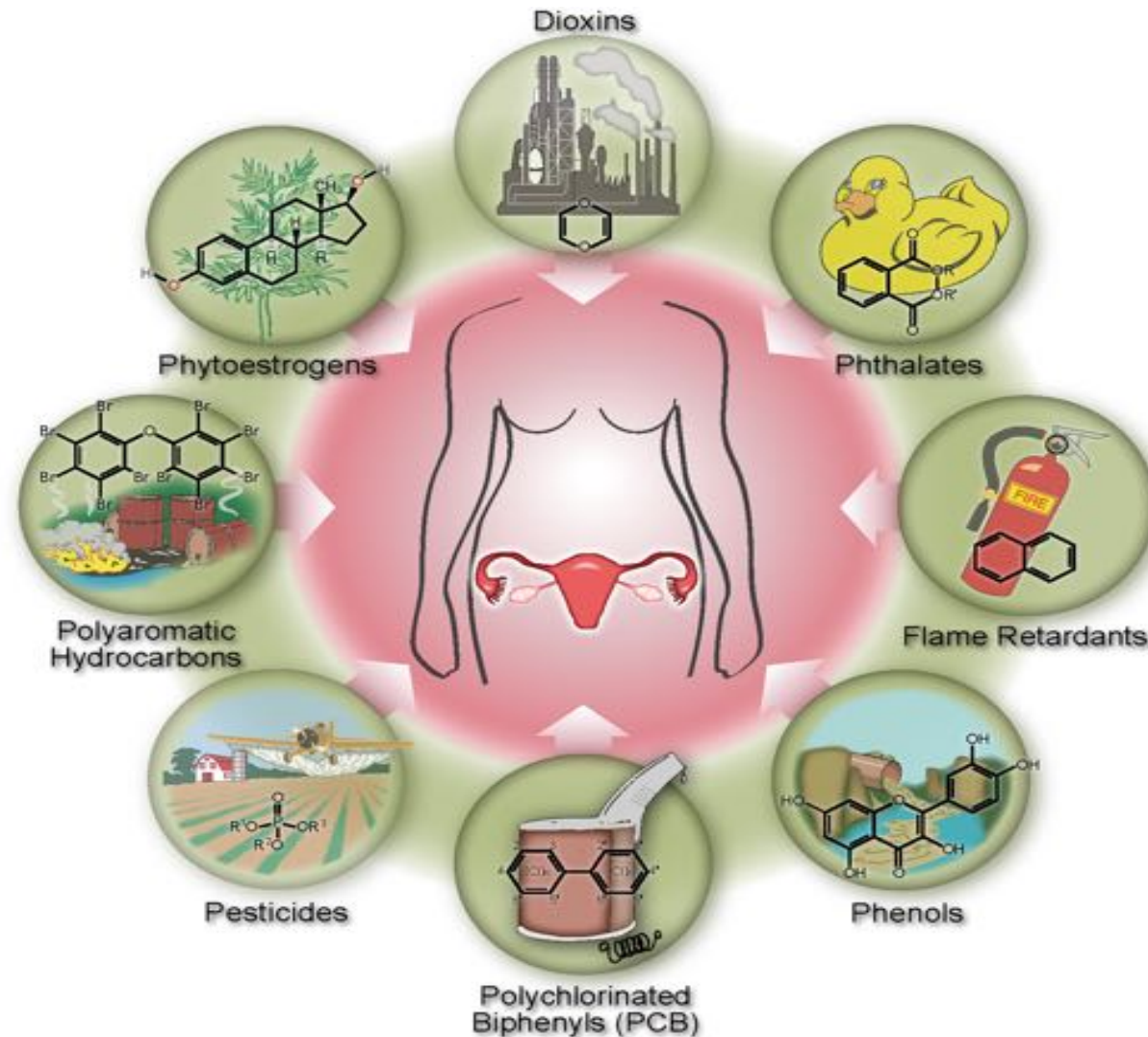
These are drugs that interact with estrogen receptors but have different effects on different tissues. They can show agonism or antagonism depending upon the tissue type.



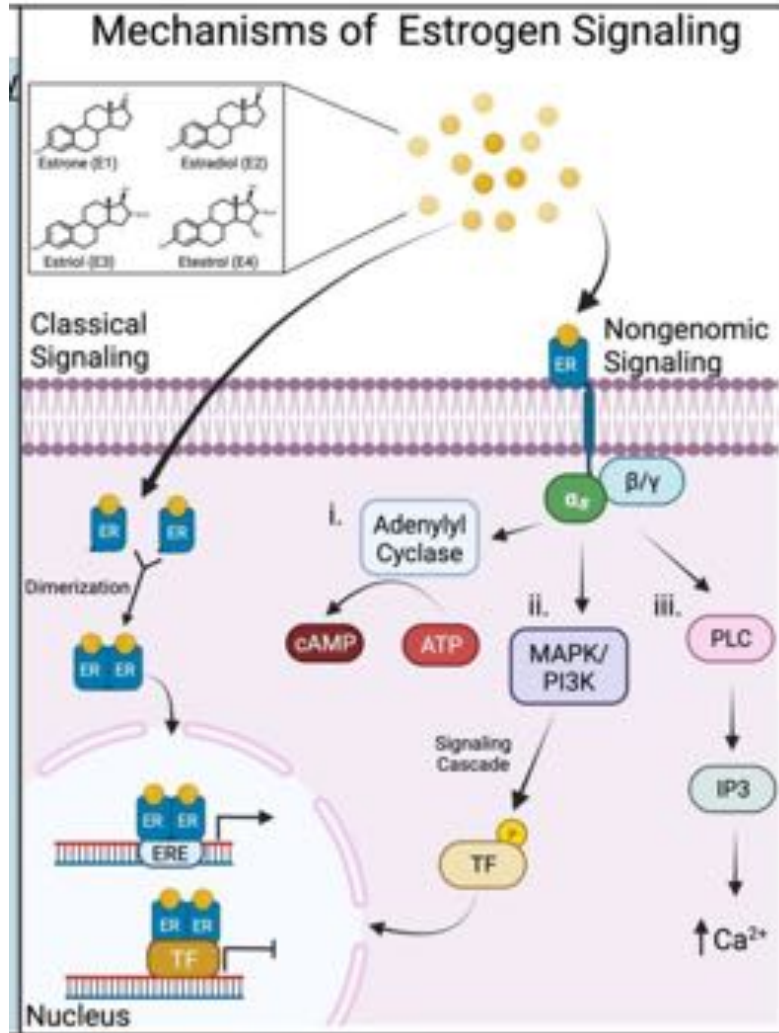
Origin of Estrogens and Phytoestrogens



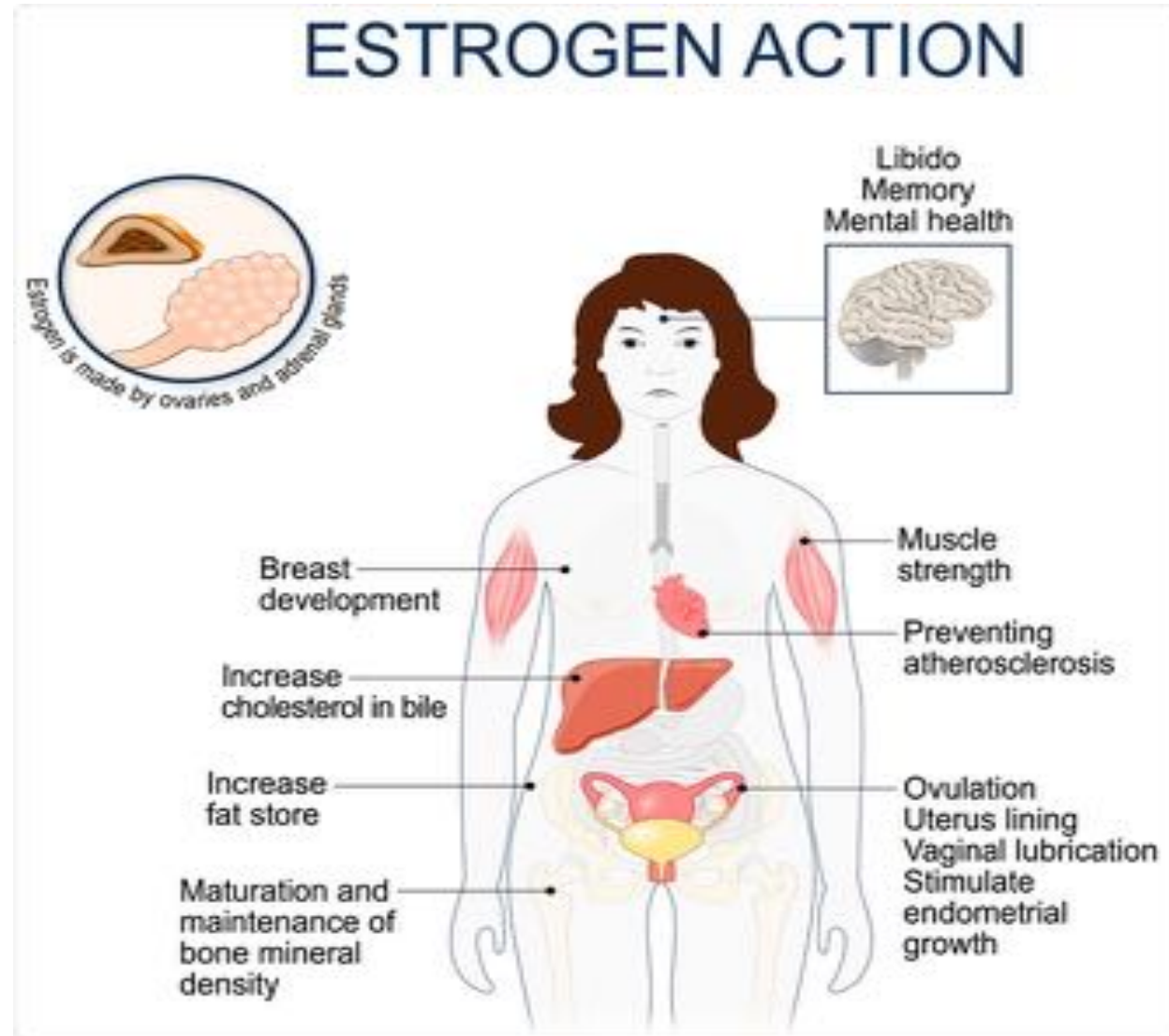
Where do Phytoestrogens/Xenoestrogens Come From?



Similar BUT *Different* Binding Affinity to the Estrogen Receptors with Phytoestrogens



Function of Endogenous Estrogens



Similarity Between Estrogens and Phytoestrogens

Types of Estrogen

There are two main types of estrogen hormones, steroidal and non-steroidal.

Steroidal:

Estrone (E1)

Estradiol (E2)

Estriol (E3)

Non-steroidal:

Natural Xenoestrogens

Phytoestrogens

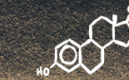
Mycoestrogens

Synthetic Xenoestrogens

SheCares

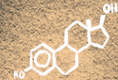
Types of Estrogen

Estrogen made by the body



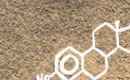
Estrone (E1):

Made in ovaries. Only estrogen hormone the body produces after menopause (in reduced amounts)



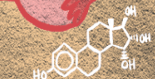
Estradiol (E2):

Made in ovaries during reproductive years



Estriol (E3):

Produced by placenta during pregnancy



Estetrol (E4):

Produced by fetus during pregnancy

Estrogen made outside the body

Synthetic estrogens:
Produced for medical use, like in birth control pills

Phytoestrogens:
Found in plants, like soybeans

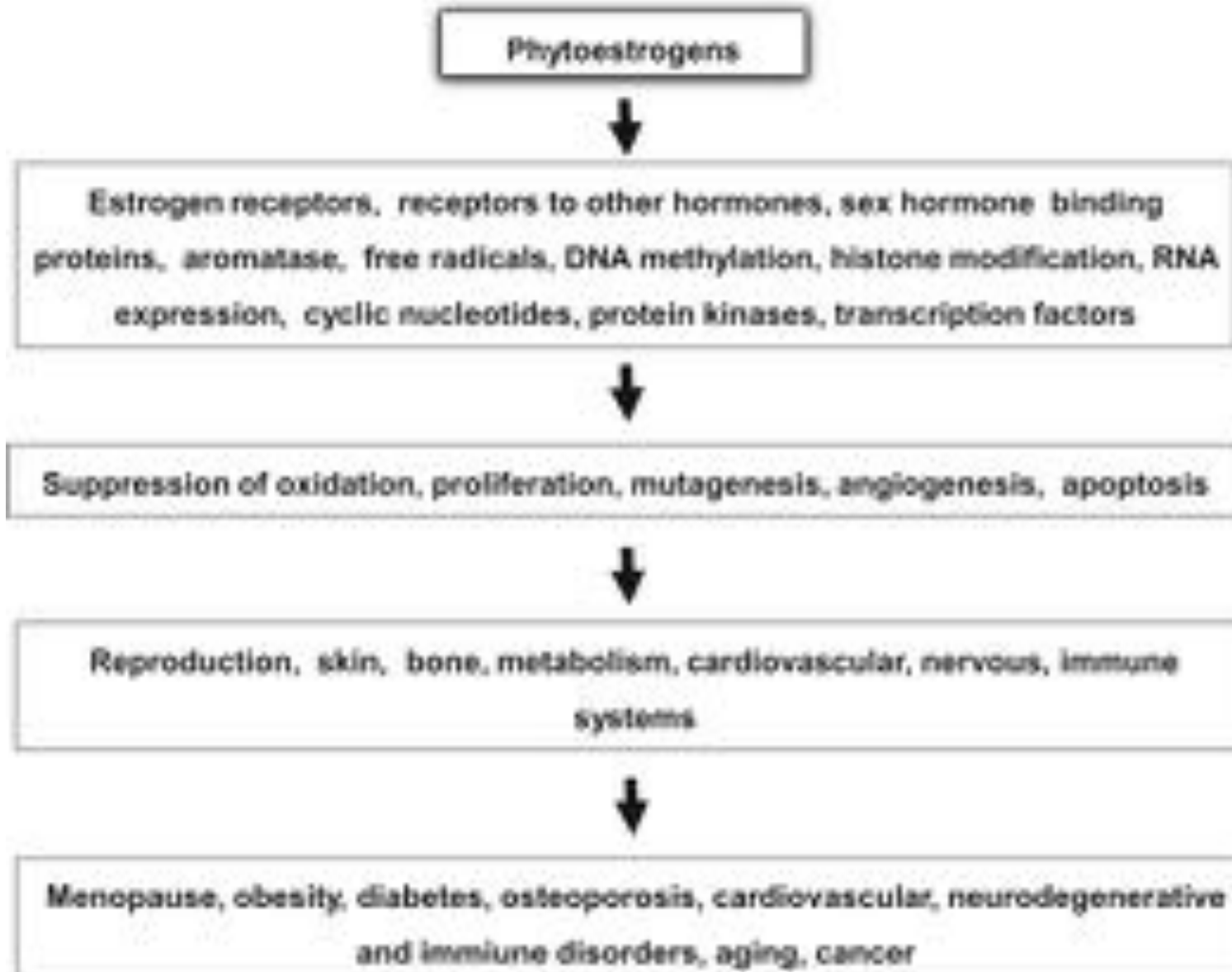
Xenoestrogens:
Pollutants from man-made products that act as endocrine disrupting agents

verywell

Estrogen Pharmacokinetics

- Estrogens and androgens are only biologically active in their free form
- Estradiol is extensively bound to SHBG
- SHBG binds to estrogens and androgens and affects steroidal activity
- Only a small fraction of estrogens are free and not bound
- *In vitro* studies suggest isoflavonoids stimulate the synthesis of SHBG by liver cancer cells
- Human data inconclusive
- Phytoestrogens inhibit aromatase and other enzyme synthesis of steroid hormones

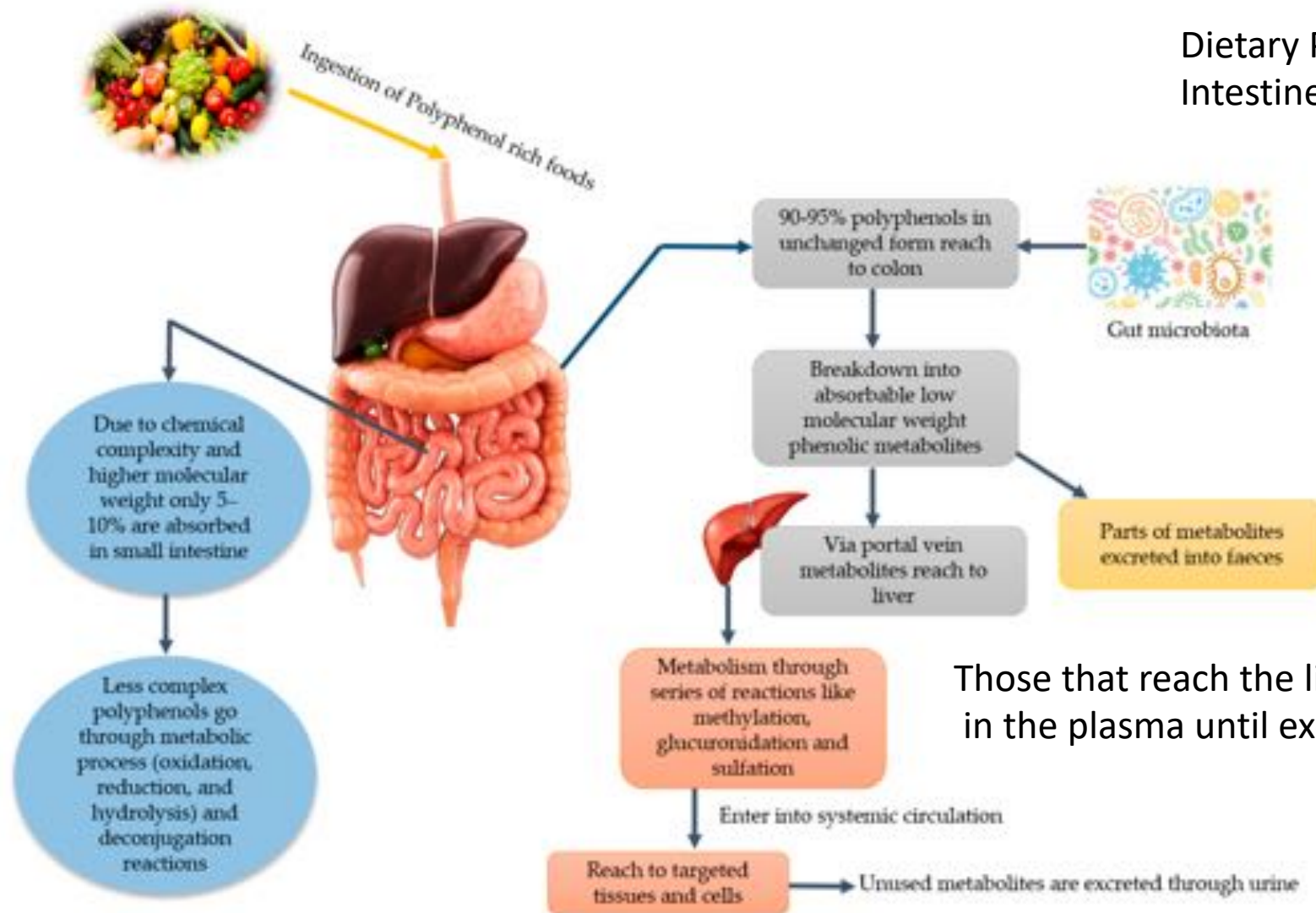
Phytoestrogen Mechanisms



Anti-Cancer Impact

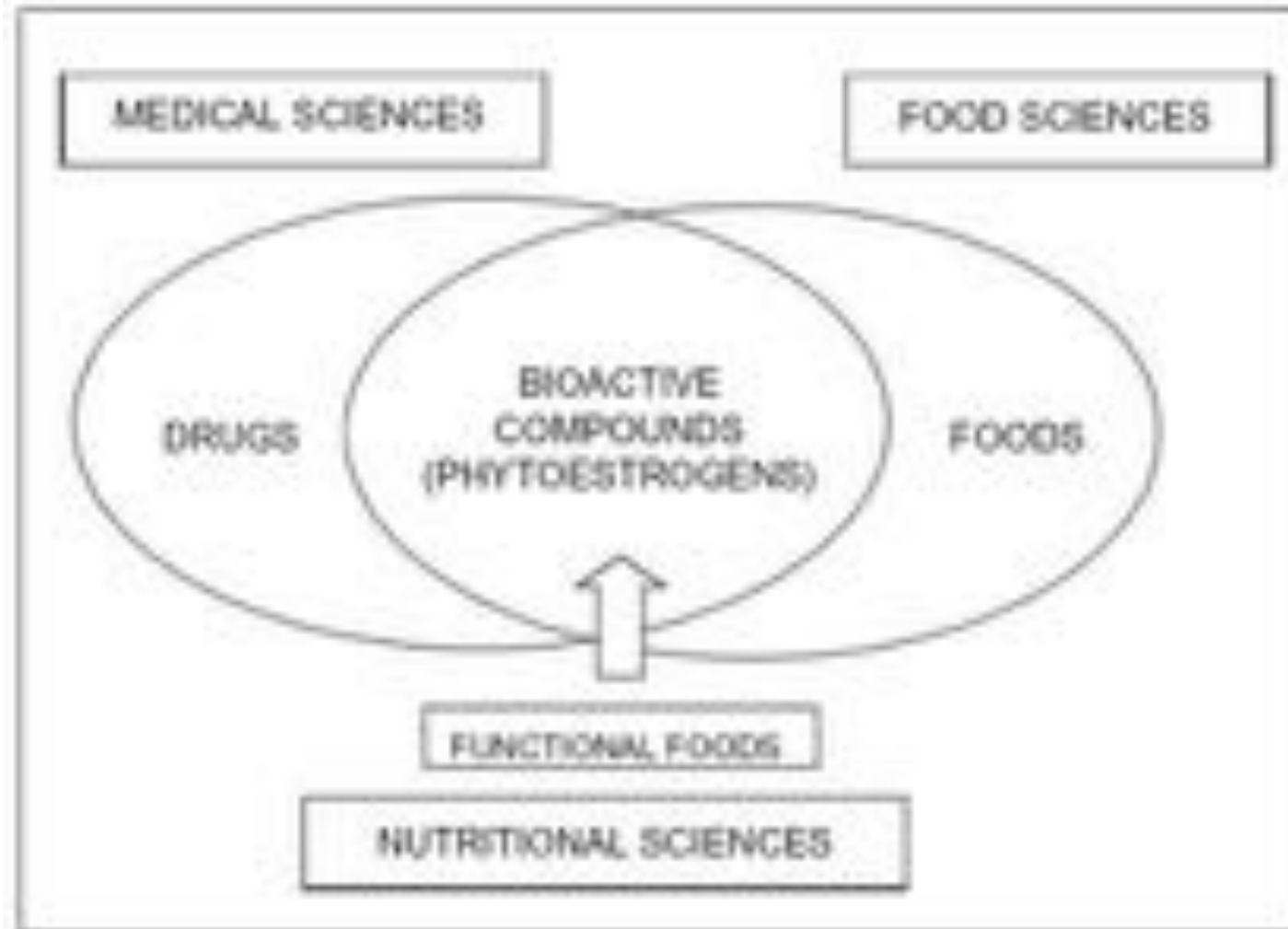
Phytoestrogen Bioavailability

Dietary Phytoestrogens are digested in the small intestine where they are poorly absorbed

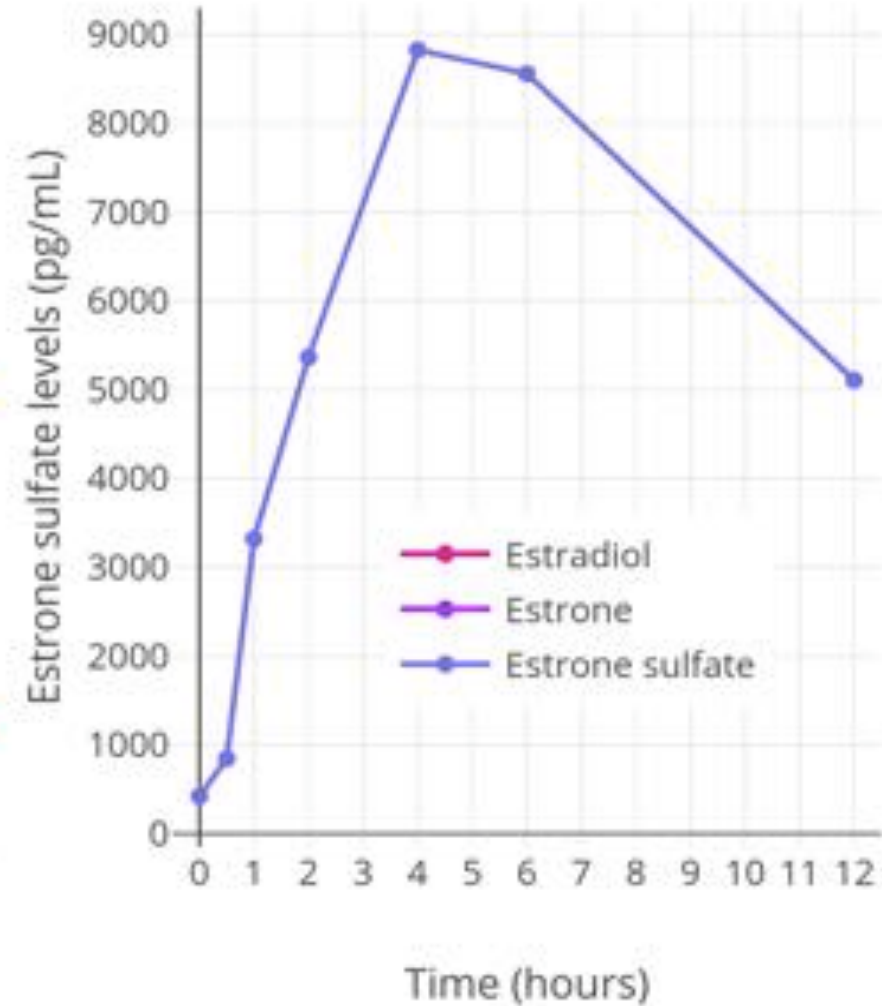
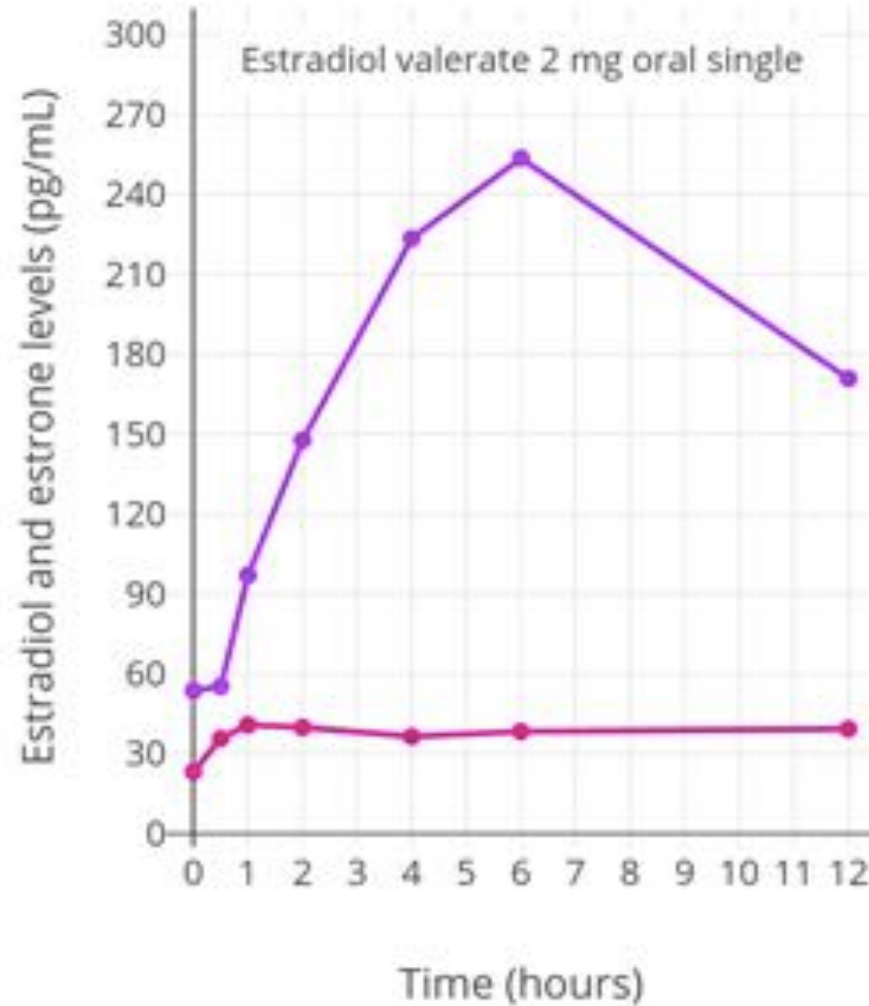


Those that reach the liver are conjugated and circulate in the plasma until excreted in the urine

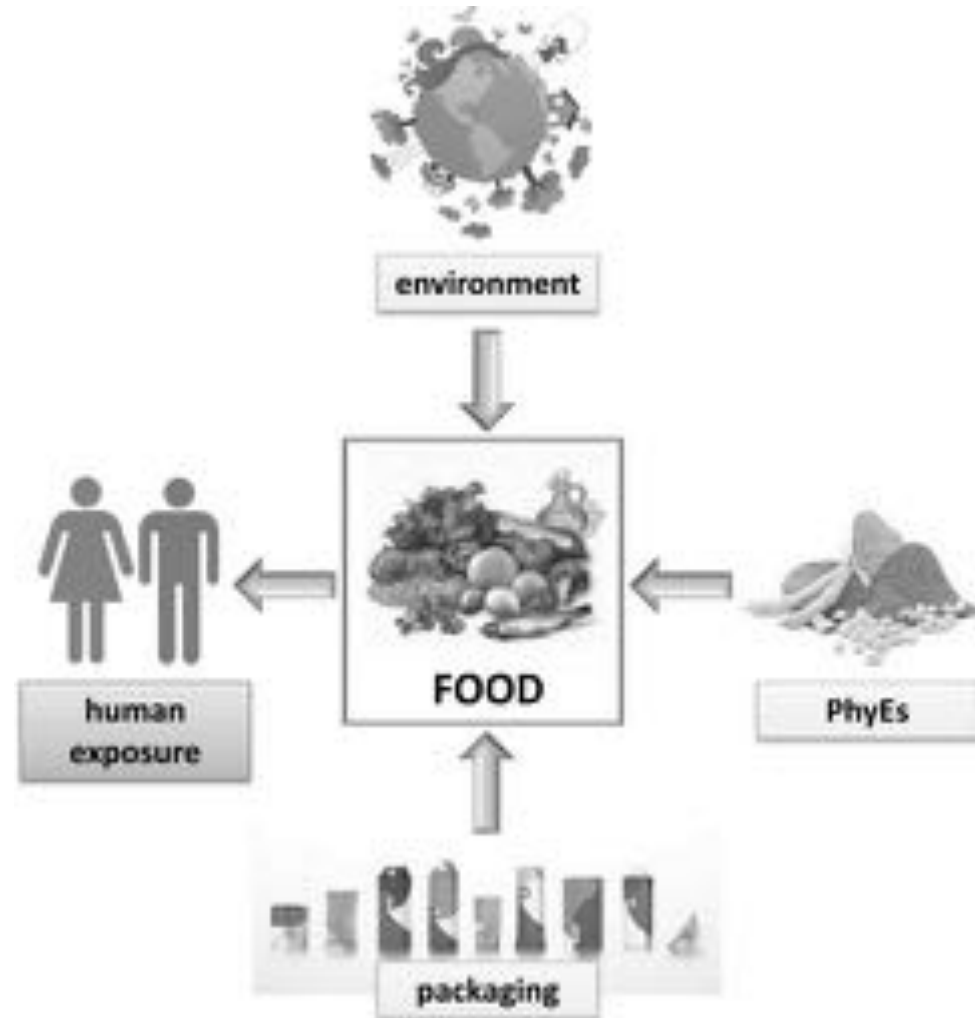
Potential Functions of Phytoestrogens



Oral Estrogen Bioavailability



Environment and Food Processing Impact Hormonal Balance



Xenoestrogens and Metabolic Effects in Men & Women

- Xenoestrogens are an independent risk factor for systemic inflammation and cardiovascular disease.
- Higher xenoestrogen levels are correlated with [metabolic dysfunction](#).
- Xenoestrogens such as aldrin, lindane, and DDE accumulate preferentially in humans
 - Accelerate the accumulation of fat, both inside and outside the blood vessels
 - Enhance the development of [obesity](#)
 - Increase coronary artery disease due to the accumulation of fatty plaque (Teixeira et al., 2015)