

Detox Diet Trends

Hope Barkoukis, PhD, RD, LD
 School of Medicine
 Case Western Reserve University
Hope1215@aol.com

Categories of Detox diets

No universal 'core' components	No universal agreement on supplemental strategies
Fasting- short/long term	Anti-oxidant/vitamin supplements/high dose
Slow introduction of foods/restriction	botanical supplements/ High dose
GI products	Specialty products
Hydro-therapy/ chelation	Special 'cleanses'

Some Popular Detox Diets	"Purported" Mechanism
Martha's Vineyard Diet Detox-Roni Delux	22 daily F/V →flush toxins
Raw Food-5 Step Plan Natalia Rose	100% raw diet→ sluggish system, "live enzymes"
Wild Rose Herbal D-tox Terez Willard	Variety of herbal combinations/ 12 days-liver detox
Fasting/herbals	"flushing" system

Any validity?

Screening techniques-
'cutting edge of science'
or
just plain crazy?

"Are you toxic" popular assessment tests: If you have 4 or more factors you 'need to detox'

Source: internet. Will not disclose exact website to not increase exposure to blatant quackery

- Fatigued?
- Feel dizzy, trouble concentrating?
- Cracking joints, back pain, AM stiffness?
- Frequent headaches, generalized aches?
- Sinus problems?
- Exposed to coffee, candy, soda, chemicals, sedatives, stimulants?
- Do you eat fatty, fried, or processed foods?
- Need to lose weight?
- Have auto-immune disorders?

Limitations in 'popular' 'detoxification' profile assessments

NIH: Detoxification Capacity Profile

Challenge Compound	Detoxification Process	Result	Reference Limits
Caffeine	Phase I: Oxidation (CYP2E1/3A4)	Caffeine Clearance	0.7 0.5 - 1.6 mL/min/kg
Salicylic Acid	Phase II: Conjugation with Glycine	o-Hydroxyphenol acid	53 30 - 53 % recovery
		Salicylic Acid	20 16 - 36 % recovery
Acetanilophen	Phase II: Conjugation with Glucuronic Acid	Acetanilophen Glucuronide	1.1 0.7 - 1.6 % recovery

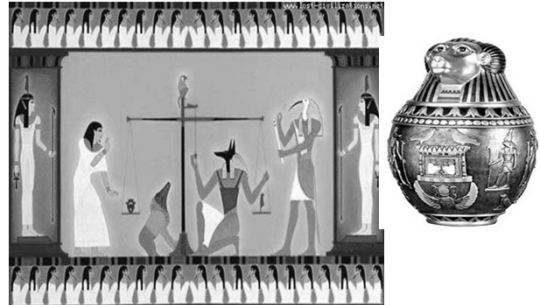
Phase	Result	Reference Limits
Phase I/Phase II - glylytation	1.3	1.3 - 3.5
Phase I/Phase II - sulfation	3.0	3.5 - 13.0
Phase I/Phase II - glucuronidation	36.0 H	1.9 - 4.2

Percentile Rankings by Quintile

Quintile	1st	2nd	3rd	4th	5th
25%					
40%					
50%					
60%					
80%					
90%					


Urine Lipid Paroxide 31.1 H

Liver has historically been viewed as the 'life force'



Ancient rituals of Egypt & canopic jar- Liver as a sacred organ

Liver detox 'products, supplements, treatments' not new, but now million \$\$ industry



WAKE UP YOUR LIVER BILE — WITHOUT CALOMEL

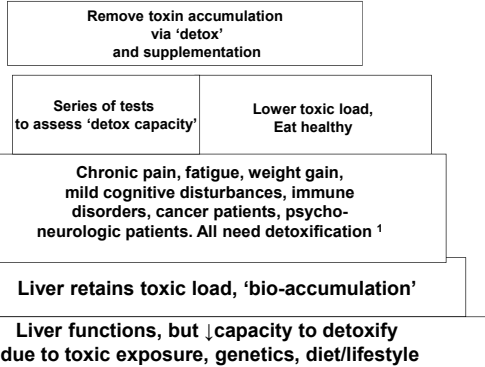
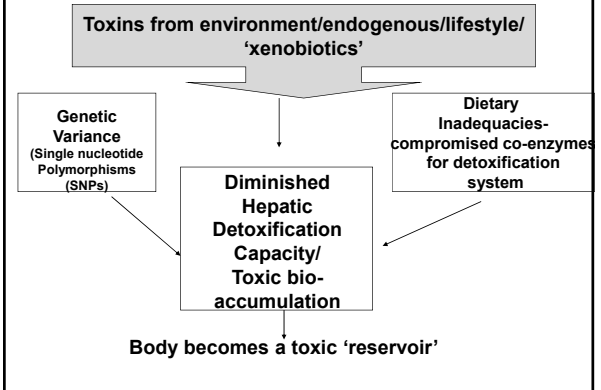
— And You'll Jump Out of Bed in the Morning Razin' to Go

The liver should pour out ten pounds of bile into the food you swallow every day. If this bile is not flowing freely, your food doesn't digest. You get constipation, liver, which poisons it, retained and your liver soon, make that the world looks black.

A mere movement doesn't get at the cause. It takes these good, old Carter's Little Liver Pills to act these ten pounds of bile flowing freely and make you feel "up and up". Directions, prices, get answers in making bile flow freely. Ask for Carter's Little Liver Pills by name. 10¢ and 25¢.

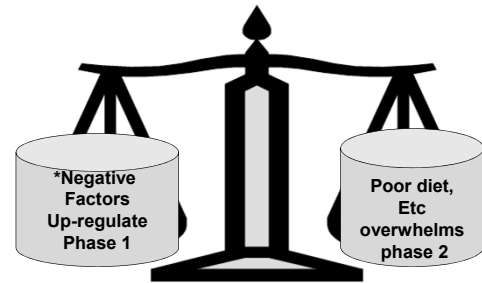
Right: 1939 Advertisement in Life Magazine; Left: York, England bill board: source Landmarks in Hepatology, 2004

Underlying hypothesis- detoxification strategies:

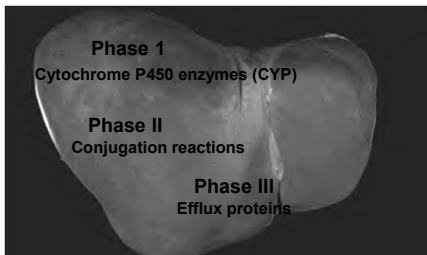


¹ Bennett, P. Working up the toxic patient: practical intervention & treatment strategies. 13th Internat Symposium of The Institute of Functional Medicine.

Hypothesis: Imbalance between phase 1 and phase 2 causes toxic overload

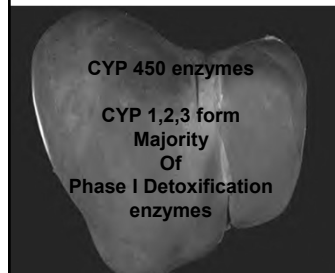


Hepatic detoxification requires a three step process:



The Liver-Biology & Pathophysiology, Wiley & Blackwell, 5th Edition, 2010

Phase I detoxification

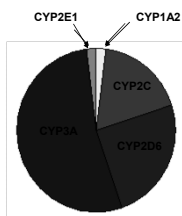


Transformation of the Original compound Via Oxidation, Reduction, Hydrolysis

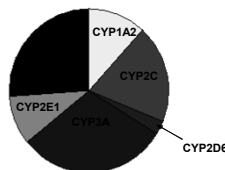
Up to date database for P450: <http://drnelson.utmem.edu/cytochromeP450.html>
The Liver, Biology & Pathobiology, Wiley-Blackwell, 5th Edition, 2010

CYP 450s

Role in detoxification



Relative Quantities of P450s in Liver



Shimada T et al. *J Pharmacol Exp Ther* 1994;270(1):414.

Net result from Phase I: Biologic reactive intermediate (BRI) compounds formed



"Remains impossible to accurately assess human exposure or level of toxicity from BRI"

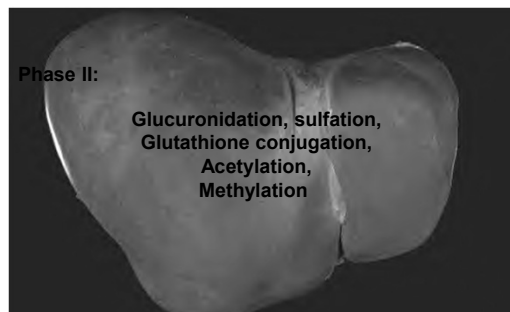
Current Drug Metabolism 9:344, 2008

Summary: Biologic reactive intermediates:

Current Drug Metabolism 9:344, 2008; *J Gastro. & Hepatology* 23:366,2008

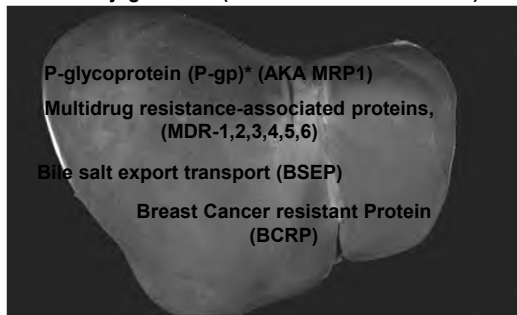
- BRI presence alone is not an accurate indicator of human toxicity;
- Toxicity is determined by dose, and the collective series of reactions & outcomes;
- Various herbals such as comfrey tea, kava root, germander, pennyroyal, black cohosh have BRI which do have capacity for hepato-toxicity

Phase II: goal- create inactive, water soluble compounds- conjugates



The Liver-Biology & Pathophysiology, Wiley & Blackwell, 5th Edition, 2010

Phase III: efflux protein system- responsible for removing conjugates out (from intra-to extra-cellular)



The Liver-Biology & Pathophysiology, Wiley & Blackwell, 5th Edition, 2010
Current Drug Metabolism 10(5):482, 2009

What factors influence hepatic detoxification system?
Evidence based data: factors influencing CYP450 -Phase II
The Liver-Biology & Pathophysiology, Wiley & Blackwell, 5th Edition, 2010

- Ethnicity
- Age
- Disease
- Environment/lifestyle
- Drugs
- Genetic variation
- Dietary factors

Factors Influencing Activity and Level of CYP Enzymes

Nutrition	1A1;1A2; 1B1, 2A6, 2B6, 2C8,9,19; 2D6, 3A4,5
Smoking	1A1;1A2, 2E1
Alcohol	2E1
Drugs	1A1,1A2; 2A6; 2B6; 2C; 2D6; 3A3, 3A4,5
Environment	1A1,1A2; 2A6; 1B; 2E1; 3A3, 3A4,5
Genetic Polymorphism	1A; 2A6; 2C9,19; 2D6; 2E1

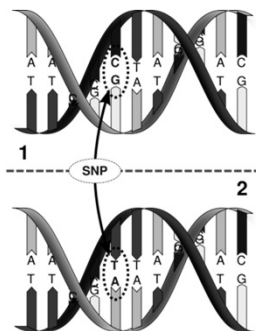
Red indicates enzymes important in drug metabolism
Adapted from: S. Rendic Drug Metab Rev 34: 83-448, 2002 17

* Not necessarily fully inclusive, key examples

Some Dietary interactions & CYP450s Current Drug Metabolism 9:1010,2006; Toxicology in Vitro 20:187,2006

- Smoked foods (polycyclic aromatic hydrocarbons) increase CYP1A activity
- Cruciferous vegetables (brussels sprouts, cabbage, broccoli): alter activity of selected CYP isoenzymes
 - Indole-containing vegetables (cabbage, cauliflower) upregulate CYP1A
 - Isothiocyanate-containing vegetables (watercress) inhibit CYP2E1
- Organosulfur compounds (garlic) inhibit CYP2E1 and induce CYP1A, CYP3A and phase II enzymes
- Grapefruit juice phytochemicals influence CYP3A activity
- Flavinoids- influence CYP 3A4, 1A2,2E1,3A4, phase II & membrane bound transporters

Genetics influence CYP450s, so need to understand genetics "basic": What is a SNP?



- A single nucleotide Polymorphism*;
- A change in a single Nucleotide;
- A gene variant;

*occurs in more than 1% of humans

CYP2D6 - numerous Polymorphisms

- Approximately 80 nucleotide polymorphisms are known
- Four phenotype subpopulations of metabolizers*
 - Poor metabolizers (PM)
 - Intermediate metabolizers (IM)
 - Extensive metabolizers (EM)
 - Ultrarapid metabolizers (UM)
- Variations according to racial background
- More than 65 commonly used drugs are substrates

* The Pharmacological Basis of Therapeutics, Goodman & Gilman, 2005

Abbreviated summary- Consequences of variant CYPs

- Influences rate of detoxification, and therefore the efficacy, duration, and peak of drug response
- Drug-drug/drug-dietary interactions/Affects ADR (adverse drug reactions)
- But, no evidence to suggest ‘toxin bio-accumulation’ in your liver due to CYP450s’ variances’

Non validated mechanism: hepatic ‘toxin over-load/ bio-accumulation’ theory

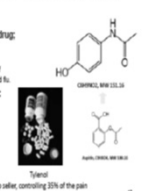
Use Acetaminophen as a case study example- Concept: if ‘toxins’ exceed liver’s capacity, result = liver dysfunction

Acetaminophen- safe at appropriate doses, hepato-toxic at high doses

Acetaminophen (APAP)

Over-the-counter drug:
relieving pain,
relieving fever,
relieving the symptoms of
allergies, cold, cough, and flu.

Co-administrations:
Sedative
Antibiotics
Vasodilators
Sedatives
Antacids
Anesthetics

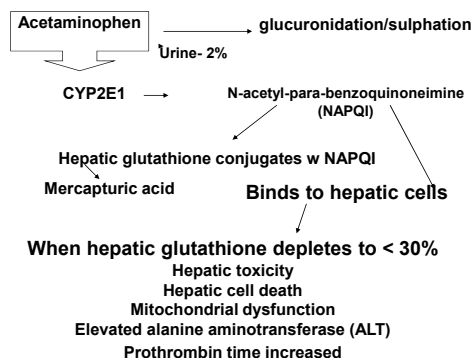


The yellow, crescent-shaped 324 of the pain killer market in North America

Acetaminophen Toxicity

- Acetaminophen overdose results in more calls to poison control centers in the United States than overdose with any other pharmacologic substance.
- The American Liver Foundation reports that 35% of cases of severe liver failure are caused by acetaminophen poisoning which may require organ transplantation.
- N-acetyl cysteine is an effective antidote, especially if administered within 10 h of ingestion [NEJM 319:1557-1562, 1988]
- Management of acetaminophen overdose [Trends Pharm Sci 24:154-157, 2003]

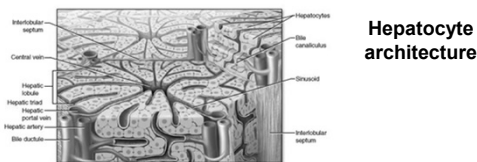
The Pharmacological Basis of Therapeutics, Goodman & Gilman, 2005



Human & Experimental Toxicology, 22:453, 2003

Scientifically sound analogy to debunk the ‘liver is a toxic dump’/bio-accumulation theory

- Liver is metabolically active ≥ 500 functions, precise architecture to fulfill those functions;
- ** If toxins were to exceed liver’s capacity to detoxify, hepatic damage/cell death would occur;
- Net result: markers of hepatic inflammation, injury, death would be manifested in various biomarkers→ hepatic destruction



Hepatocyte architecture

No data to support hepatic bio-accumulation of toxins occur on chronic basis; excessive toxin exposure would result in concurrent hepatic cell death secondary to inflammation, fibrosis, necrosis—and compromised hepatic functionality

The Liver, Biology, Pathophysiology, 5th Edition, 2010

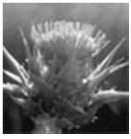
Popular Detoxification Menu...or toxin anyone?
 Thiamine, riboflavin - \geq 150mg
 B6, C, niacin- significantly higher than UL
 Choline, Zn, Mg- higher than UL
 Anti-oxidant cocktail, E, Beta-carotene, C
 Botanicals including
 Milk thistle extract,
 Broccoli extract,
 Dandelion root

Valid liver detox 'support'

- Role of nutritional factors...
- Life style factors....
- Botanicals....

Milk Thistle- Silybum marianum

- *No toxicity concerns, efficacy still not demonstrated*
- Active substance: silymarin (flavonolignans), from the seeds
- Many forms: capsules (~\$5 for 50), liquid extract
- Herbal remedy for over 2,000 years in Europe for liver and gallbladder disease
- Synonyms: Bull thistle, pig leaves, royal thistle, snake milk, St. Mary's thistle, wild artichoke




• USDHHS: <http://www.ahrq.gov/clinic/epcsums/milktsm.htm>
 • MayoClinic: http://www.mayoclinic.com/health/silymarin/NS_patient-milkthistle
 • NCCAM: <http://nccam.nih.gov/health/milkthistle/>

Herbal Liver 'detox' potions:

Natural Medicines DataBase- accessed via SCAN's member page; however, individual subscriptions available

- Herbal hepato-toxins:
- Chaso, Onshido, Lipokinetix®, Kombucha tea, germander, xiao-chai-hu-tang, Chinese green tea extracts (camellia sinensis)
- Commonly include:
- No efficacy reported, no hepatic toxicities, but drug interferences: yellow dock, dandelion root, burdock, licorice root* (electrolyte imbalance/BP)



NO DATA to support:
 Any technique, singular dietary component or combination of 'supplements', 'herbals', hepatic detox programs** will purify liver, enhance total hepatic detoxification activity, harmonize or 're-balance' liver. * No RCT has been conducted.

Dietary – phase I or phase II influence does not translate into entire hepatic detoxification alteration

Risks, concerns....



Beyond what you've heard before about
Supplement safety concerns,
DRI UL,
What is the potential harm?

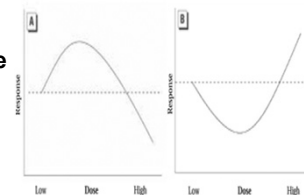
"Hormesis"

'dose' matters: dose either has a favorable
or harmful biologic effect

- Lower dose has opposite effect of a higher dose

- Results in response curve – J or U shaped curve

Figure 1. Schematic forms of the hormetic dose response. (A) The most common forms of the hormetic dose-response curve showing low-dose stimulatory and high-dose inhibitory responses (J- or inverted U-shaped curve). (B) The hormetic dose-response curve depicting low-dose reduction and high-dose enhancement of adverse effects (J- or U-shaped curve).



Mortality in RCT of anti-oxidant supplementation for primary & secondary prevention: systematic review & meta analysis. JAMA:297(8) 842, 2007

- Random effects meta-analysis & meta regression for co-variates, RCT, using vitamin C, selenium, Beta carotene, vitamin E- either alone or in combination
- Vitamin C, p=N/S for mortality, but vitamin E (RR= 1.04); Vitamin A (RR=1.16); beta carotene (RR=1.07) significantly increased mortality in low bias trials, where total n=180,938

RD's take away messages for detox diets:

- Check COI of authors before blindly accepting;
- Be aware of "scientific smooze";
- Expertise in hepatic P450, or detoxification system is not a pre-requisite to critical thinking in this realm;
- Familiarize yourself with validated status tests for micro-nutrients;
- Encourage food first approach, educate client on DSHEA, hormesis, plausibility;
- No supplement/extract can replace whole food benefits & may not be beneficial at all