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Powering Natural Medicine

A PUSH-CATCH SYSTEM THAT ENABLES EFFECTIVE DETOXIFICATION

BY DR. CHRISTOPHER SHADE, PHD,
AND CARRIE DECKER, ND

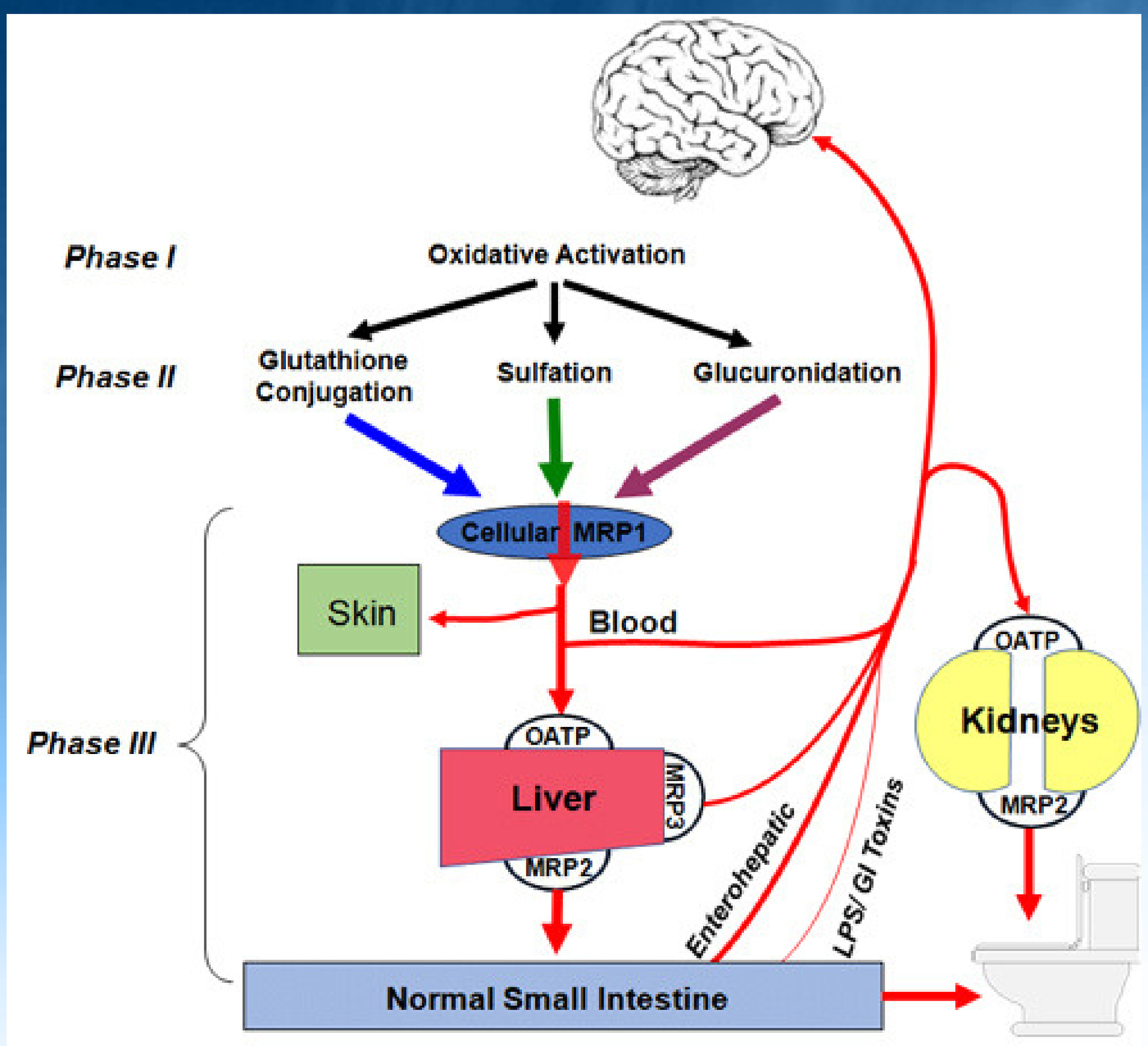
The human body is exposed to environmental toxins every day from a wide array of sources: particulate matter and diesel fumes in the air,[1,2] heavy metals and other contaminants in the water,[3,4] pesticide and herbicide residues found on foods,[5,6] and even substances like bisphenol A (BPA) via contact with the skin.[7] On a continuous basis, the body must work to eliminate toxic substances that are taken in. If intake exceeds removal, the toxins accumulate within the tissues and cells. These toxins tax our antioxidant systems, which must be upregulated in attempts to reduce cellular damage and death.[8] But even with upregulation, the antioxidant protection system is often depleted by repeated insults and toxin exposure, and this depletion may contribute to disease processes.[9] Chronic exposure to environmental toxins and toxic heavy metals is associated with the development of many types of cancer, respiratory disease, cardiovascular disease, diabetes, infertility, allergies, autoimmune disease, and many other conditions.[10,11,12,13]

Detoxification is the process by which the body eliminates substances that are both endogenous (such as hormones) and exogenous (such as medications, pollutants, metals, and other substances). In addition to cleaning up the diet and eliminating sources of toxicity, the use of chelating substances, antioxidant support, and therapeutic sweating are often the mainstays of detoxification protocols. However, these basic strategies, despite being crucial, lack consideration for other factors such as chronic infections, cholestasis, and enterohepatic recircu-lation of toxic substances that significantly impair the body's ability to detoxify. To comprehensively support detoxification, one must consider and address not only the glutathione system and its enzymes; liver, kidney, and gastrointestinal function; but also infections or dysbiosis, cholestasis, and the removal of toxins from circulation.

Stages of Detoxification

The process of detoxification consists of three phases, although many people are only familiar with the first two of these. Phase I reactions involve the oxidation, reduction and hydrolysis of substances via enzymes from the cytochrome P450 (CYP450) family.14 It is Phase I metabolism that converts many drugs into their active compounds, and converts some chemicals into more toxic metabolites. Phase II metabolism involves the conjugation of toxins, creating larger, inactive, water-soluble molecules. Phase II reactions include sulfation, glucuronidation, and glutathione conjugation (see Figure 1).15

Figure 1:
In a healthy state, toxins are processed and removed from the cells and organs via enzymes and transporter proteins, and leave the body primarily via the skin, urine, and feces.



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Phase III is often neglected in discussions of detoxification. However, it is critical. Phase III involves the process of transport and elimination of toxic substances through cellular membranes. The primary proteins that play a role in Phase III are multidrug resistance protein (MRP) 1, 2, 3, and 4, organic anion transport proteins (OATP), and P-glycoprotein (P-gp).16 These proteins also regulate the movement of molecules through barrier tissues, such as the blood-brain barrier.17

The work horses for detoxification are:
1) MRP1, the transmembrane transporter serving most cells in the body for exporting toxins to circulation,
2) OATP, the basolateral membrane transporter which moves toxin conjugates from the blood into the hepatocytes or renal tubule epithelial cells, and
3) MRP2, the apical transporter that moves toxin conjugates (and some bile salts) into the bile canaliculus or renal proximal tubule lumen.

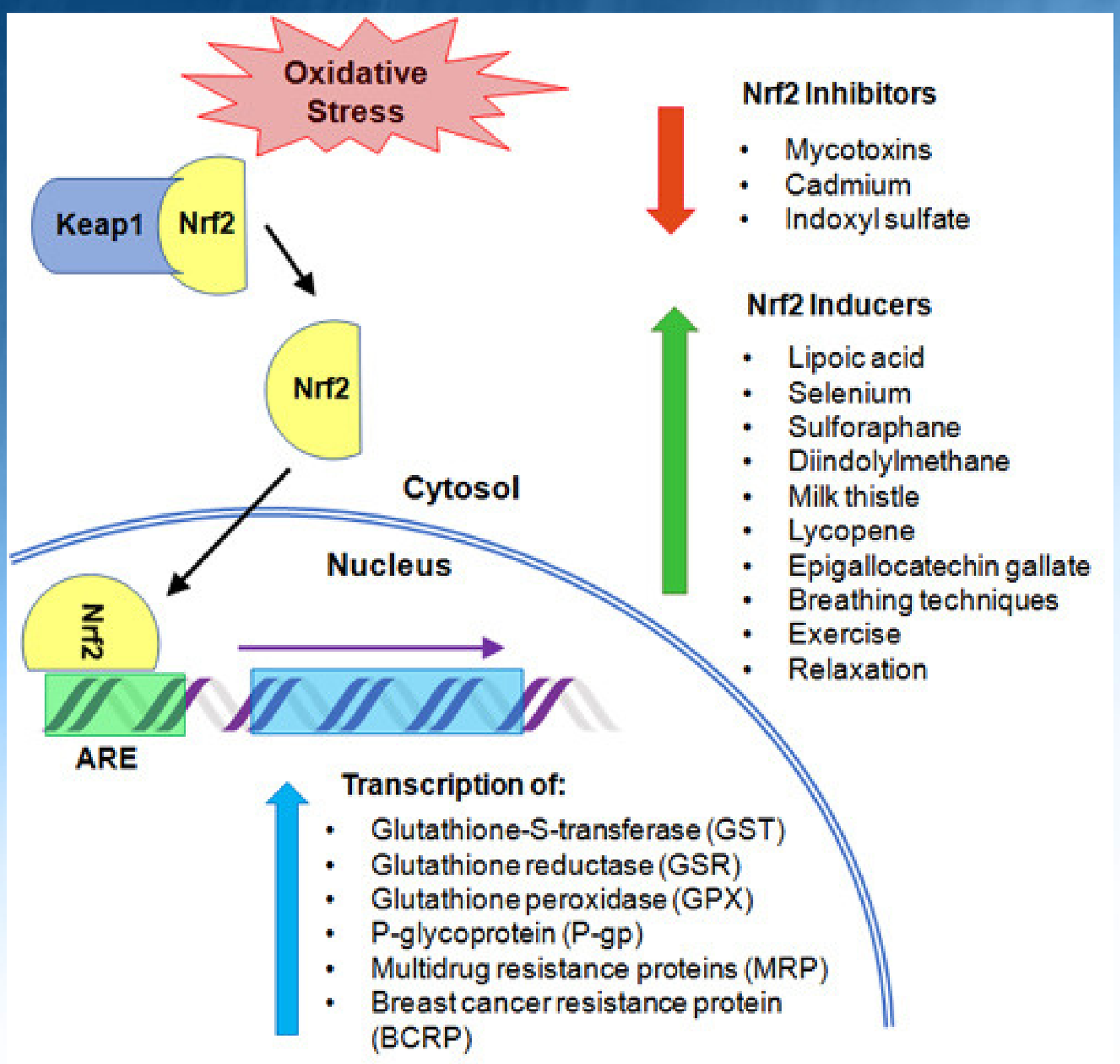
MRP3 and MRP4 are basolateral transporters that move toxin conjugates and bile salts from hepatocytes into the blood. All of the enzymes and transporters required for detoxification are present at a basal level, but many have increased expression in a coordinated fashion when stimulated by drug or toxin exposure.18,19

Although the process of detoxification occurs in every cell of the body, the liver, kidneys, and intestines are primary tissues in which higher levels of detoxification occur.20 Many are familiar with the importance of the liver and kidneys as organs of detoxification, yet neglect awareness of the role of the intestines, the mucosal lining of which expresses high levels of the proteins important for all phases of detoxification.21,22 When any of these systems are impaired, a backup in processing of toxins will occur, with a greater burden being placed on other organs.

Nrf2: The Cellular Detoxification On-Switch

Nrf2 (short for nuclear factor E2-related factor) is a cellular switch that orchestrates antioxidant, detoxification, and cellular defenses. Nrf2 is present in the cytosol of the cell (see Figure 2), and responds to oxidative stress by translocating to the nucleus and binding to the promoter region of genes that encode the transcription of critical components of detoxification known as the antioxidant response element (ARE).23 In addition to elevated levels of reactive oxygen species (ROS), the Nrf2/ARE pathway is activated by a reduced cellular antioxidant capacity, and by exposure to toxic substances like air pollution and heavy metals.24,25

Figure 2:
Oxidative stress causes Nrf2 to dissociate from binding protein (Keap1) in the cytosol and translocate to the nucleus where it binds the promoter region (ARE), leading to transcription of detoxification enzymes and proteins. Various substances have been shown to have an inhibitory or inducing effect on the Nrf2/ARE pathway.



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When activated, the Nrf2/ARE pathway can switch on over 200 genes that help the cell generate protective molecules (see Figure 2).26 This includes antioxidant elements, detoxification enzymes, and proteins required for glutathione synthesis and recycling such as glutathione S-transferase (GST), glutathione reductase (GSR), and glutathione peroxidase (GPX).27-30 Nrf2 also upregulates proteins responsible for Phase III detoxification (P-gp, BCRP, and MRP2) and the transfer of toxic substances out of the cell and central nervous system.

Factors that Impede Detoxification

Nrf2/ARE Pathway:

Studies have shown that the ability to upregulateNrf2 a nd its antioxidant-supporting action declines with age, which may be one reason the elderly are more susceptible to damage from environmental pollutants.31 Ochratoxin A, one of the most common mycotoxins found in foods and water-damaged houses, acts as a Nrf2 inhibitor (see Figure 2).32 Indoxyl sulfate, a uremic toxin that is increased in the blood with chronic kidney disease and exposure to toxic heavy metals such as cadmium, also acts as a Nrf2 inhibitor, further contributing to accelerated renal damage at the level of the tubules.33-35

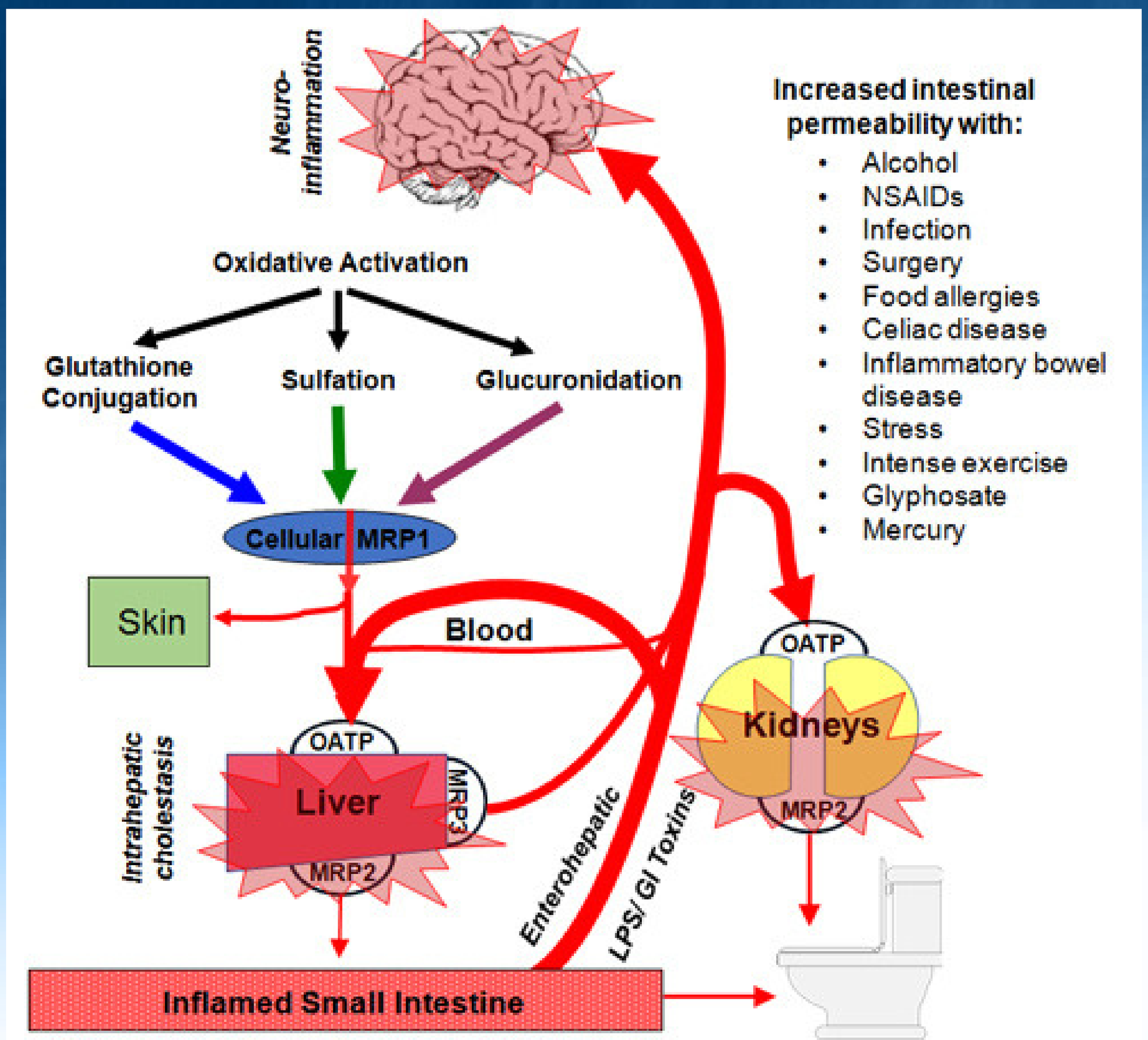
Endotoxin:

Lipopolysaccharide (LPS), also known as endotoxin, is associated with the outer membrane of gram-negative bacteria. Increased intestinal permeability, aka "leaky gut," allows for increased translocation of LPS from the gut into circulation. Damage to the intestinal barrier is common and can occur with infection, surgery, stress, intense exercise, celiac disease, food allergies, non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol use (see Figure 3).36-38

Toxins, including heavy metals, pesticides, and herbicides such as glyphosate, also have been shown to lead to inflammation and/or increased permeability.39-43 With exposure to mercury, inflammation and increased intestinal permeability may occur due to oxidative stress and glutathione depletion.44

Figure 3:

Gastrointestinal inflammation and increased intestinal permeability allow for endotoxin (LPS) to be released from bacteria in the gut into circulation. Endotoxin and related inflammatory cytokines block detoxification pathways by downregulating the detoxification enzymes and Phase III transporters, as well as contributing to cholestasis and kidney damage.



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Endotoxin and the associated inflammation leads to glutathione depletion, further contributing to cellular damage as toxins are no longer efficiently transported out of the cells, or protected from oxidative stress.45,46

Exposure to endotoxin and the cascade of inflammatory cytokines it triggers also has the effect of downregulating expression of some of the important CYP enzymes and Phase III transporters.47,48

Endotoxin exposure has a dramatic effect on the urinary elimination of mercury, acting synergistically with the heavy metal to further induce kidney damage.49

Endotoxin also has an effect of rapidly and dramatically reducing bile flow by suppressing expression and function of hepatobiliary transporters (Figure 4b).50

Cholestasis:

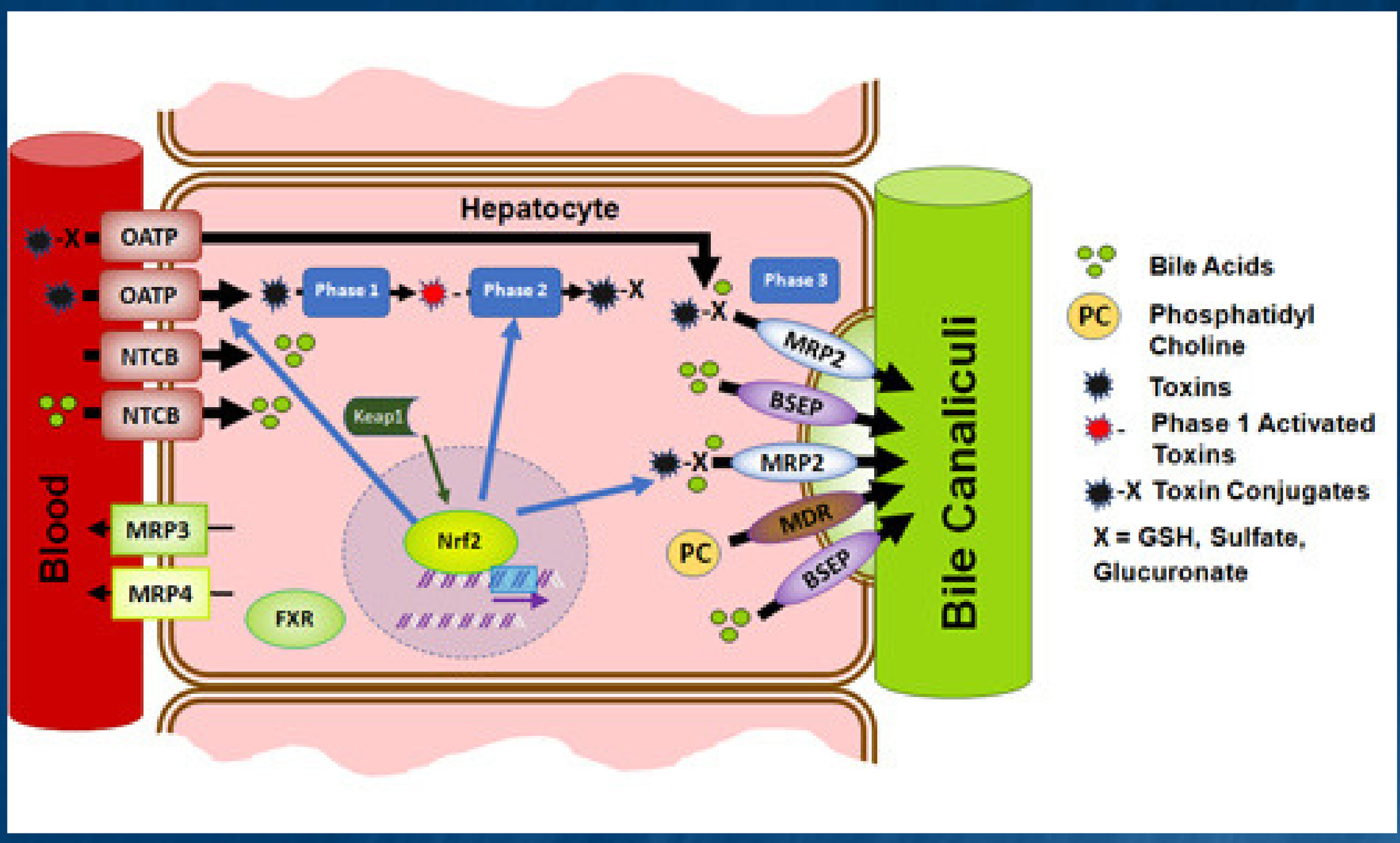
Bile plays a role in the human body not only for the emulsification and digestion of fatty substances, but also regulates many critical facets of physiology including glucose and cholesterol metabolism as well as thyroid hormone activation.51,52

Along with bile salts, the body secretes cholesterol and phospholipids as well as toxins out of the liver and into the intestines, where they either move out of the body or are reabsorbed via enterohepatic circulation.

Bile salts have an impact on the gastrointestinal flora and promote normal gastrointestinal motility.53,54 Because of these many important functions, diminished bile flow can have a serious and broad ranging impact on health.

Figure 4a:

Normal functioning hepatocyte. FXR remains in the cytosol until activated by bile acids. Oxidative stress causes Nrf2 to dissociate from Keap1 in the cytosol and bind ARE in the nucleus, increasing transcription of detoxification-related enzymes and proteins.



Bile acids are normally secreted from hepatocytes across the canalicular membrane via the bile salt export protein (BSEP), as well as the Phase III transporter MRP2.55 BSEP and MRP2 are from the same superfamily of transporters known as ATP-binding cassette (ABC) transporters, which also includes the Phase III transporters MRP1, MRP3, MRP4, BCRP, and P-gp. Very importantly, BSEP and MRP2 have an interdependent expression, and under normal conditions are colocalized in the apical membrane of the hepatocytes lining the bile canaliculi (see Figure 4a).56 The binding of bile salts to nuclear bile salt receptors, including farnesoid X receptor (FXR),57 pregnane X receptor (PXR),58 the vitamin D receptor (VDR),59 and possibly the xenobiotic receptor, constitutive androstane receptor (CAR),60 increases the expression of transporters for their efflux from the cell, and also regulates their uptake and biosynthesis (see Figure 4a).61

The rate limiting step in bile salt excretion is transport at the canalicular membrane, as there is a high concentration gradient to overcome in order to excrete bile salts into the bile acid pool.62 There are many factors which can inhibit or limit bile acid production and secretion. Substances such as estrogen (in excess), certain medications (including antidepressants), endotoxin, and related inflammatory cytokines are capable of inducing cholestasis by impairing the function of the bile acid transport proteins.63-66 Though often triggered by inflammatory responses, cholestasis also induces an inflammatory response, leading to ROS- and surfactant-induced hepatocyte damage and death due to intracellular bile sale accumulation.67,68 This failure to move bile salts into the bile canaliculus is termed intrahepatic cholestasis.

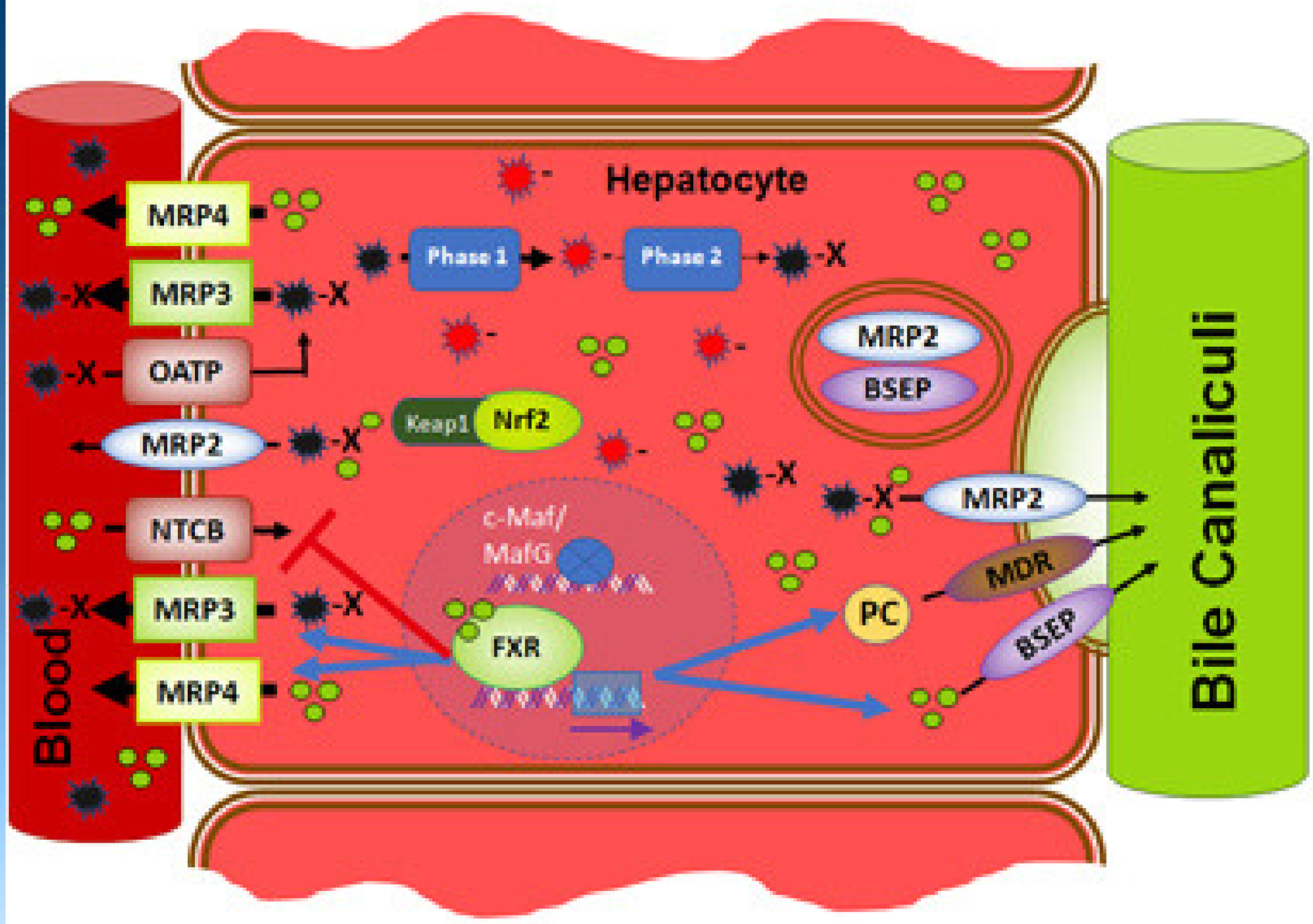
Cholestasis is toxistasis

With cholestasis, not only is there reduced biliary excretion of bile, but, due to coregulation of BSEP and MRP2, detoxification is impaired as well. There is a reduction of transport of toxins out of the cell by the Phase III proteins, a reduction of Phase II metabolism, and decreased hepatocellular synthesis of GSH, in part due to the blocking of Nrf2 binding to ARE (see Figure 4b).69-71 In cholestasis, a decreased expression of BSEP and the Phase III transporter MRP2 is seen at the canalicular membrane.72 The Phase II estrogen metabolite, estradiol-17β-d-glucuronide (E217βG), triggers internalization of both BSEP and MRP2,73 while LPS causes relocation of MRP2 to the basolateral membrane.74 Each of these factors negatively impacts the ability of the hepatocyte to transport toxins out into the bile. OATP, which serves to transport bile acids and toxins from the blood into the hepatocyte, decreases. An additional protein in the ABC transporter family, MRP3, upregulates in cholestasis, protecting the hepatocytes from toxin-related damage and death.75

However, rather than serving to transport toxins out into the bile canaliculi as MRP2 does, it eliminates them from the cell back into the blood and neighboring cells (see Figure 4b).76 With the additional relocation of MRP2 to the basolateral membrane there are now two pumps moving toxins and toxin conjugates back into the blood during cholestasis. This is likely the mechanism of "detox reactions" or "Herxheimer reactions" experienced during unbalanced detoxification protocols and points to therapeutic interventions to remedy those reactions or prevent them in the first place.

Figure 4b:

In cholestasis, there is reduced levels of BSEP and MRP2 at the canalicular membrane due to internalization and relocation. Binding of bile salts to FXR inhibits NTCB transport of bile acids into the cell and increases transcription of BSEP and MRP3 and 4 to lower intracellular bile acid concentration. Nrf2 is blocked from binding ARE by c-Maf/MafG, leading to reduced Phase II inactivation of toxins as well as diminished glutathione synthesis.



The kidney reflexively adapts in attempts to support bile salt removal from the blood in cholestasis by a variety of mechanisms.77 Passive glomerular filtration increases, while at the level of the tubules, active secretion of bile increases, and tubular reabsorption of bile acids is repressed.78 MRP2 is one of the specific proteins that have increased expression in the kidney, protecting the organism by increasing renal bile salt and toxin elimination.79 In severe biliary obstruction, acute renal failure may occur.80 In the intestines, with biliary obstruction, the expression of MRP2 in the enterocytes, where it also serves to transport toxins out, is dramatically reduced.81 The intestinal reabsorption of bile also adapts in cholestasis, as a bile acid transporter that contributes substantially to enterohepatic reabsorption in the duodenum is also downregulated.82

Clinical Manifestations of Cholestasis/Toxistasis

A range of conditions including biliary obstruction, pregnancy, chronic viral hepatitis, cirrhosis, primary biliary cholangitis, and primary sclerosing cholangitis may lead to cholestasis. Cholestasis related to extrahepatic or intrahepatic biliary obstruction is suggested by gastrointestinal symptoms including right upper quadrant pain or tenderness which may be prolonged, epigastric tenderness, discomfort or nausea after meals, and stool changes possibly including evidence of gross fat malabsorption (see Table 1a). Symptoms often are exaggerated with consumption of meals containing a high amount of fat. General or isolated pruritis, localized to the palms or soles of feet, is common, and often worse at night or pre-menstrually in women.83 Depending on the cause of cholestasis, there also may be symptoms of fatigue and impaired memory and concentration.84,85 These symptoms, however, mirror those of toxemia and point to the liver "backfire" (basolateral toxin transport dominating over canalicular transport, Figure 4b) described previously as being causal. Laboratory findings and imaging which may suggest cholestasis are found in Table 1b.

Table 1a: Signs and Symptoms of Cholestasis

Right upper quadrant pain or tenderness
Discomfort or nausea after meals
Pruritis, often worse at night
Epigastric tenderness
Fat malabsorption
Stool changes, especially pale stool
Jaundice
Fatigue
Impaired memory and concentration

Table 1b: Labs and Imaging Suggestive of Cholestasis

Elevated serum aminotransferases[86]
Elevated alkaline phosphatase, particularly if marked elevation with respect to aminotransferases[87]
Elevated gamma-glutamyl transpeptidase[88]
Elevated bilirubin
Elevated 5′-nucleotidase[89,90]
Elevated serum bile acids[91]
Biliary sludge or gallstones shown on imaging

A "Push-Catch" Strategy to Maximize Liver Detoxification Pathways

Successful and effective detoxification requires not just support for the phases of detoxification, but also the implementation of a proper directionality to progressively mobilize and eliminate toxins from the cells and tissues, and then from the body as a larger entity. As described previously, much of this is controlled at the canalicular membrane of the hepatocyte; however, it also involves the efficient binding of toxins in the upper GI tract. With a rapid delivery system, such as nanoscale lipid-based deliveries, it is possible to supplement nutraceuticals to support detoxification phases and stimulate bile flow (the "push") and then, within 30 minutes, follow with solid-phase toxin binders (the "catch").

This Push-Catch strategy creates an efficient and discreet detoxification cycle that can be done once per day or can be repeated multiple times per day for more rapid detoxification. Importantly, because of the focus on directionality, "detoxification symptoms" are minimized or eliminated. Though many combinations of compounds can be used, the following are core concepts.

Glutathione Support

Glutathione is central to multiple cell functions, such as detoxification, free-radical control, immune balance, and cell growth. Because glutathione is lost during removal and elimination of mercury and other toxins from the cell, it also can become chronically depleted in settings of toxicity.92 Many conditions such as autoimmune disease,93 chronic infections,94,95 and autism96 are also associated with lower levels of glutathione, which sheds light on why individuals who experience one of these are often extremely vulnerable to additional insults and toxicants.97 Furthermore, liver concentrations of glutathione are five-fold higher than other cells in the body. Glutathione support is thus a cornerstone of detoxification protocols.

Typical oral supplementation of glutathione has low bioavailability, and minimally impacts intracellular levels.98 N-acetylcysteine (NAC), which supports the production of glutathione by providing the precursor L-cysteine, also has limited ability to support intracellular glutathione levels as the conversion of L-cysteine to glutathione is often poor.99-101 Because of this, intravenous glutathione, and alternate oral glutathione delivery forms, such as liposomes and S-acetylglutathione, are often utilized.102,103

Another important mechanism to consider in detoxification protocols is inducing the endogenous cellular production of glutathione and the related antioxidant-supporting and chemoprotective (detoxifying) enzymes and proteins via the Nrf2/ARE pathway (see Figure 2).

Sustained activation of Nrf2 has been shown to counteract hepatic injury and bilirubin elevation associated with cholestasis.104 Although Nrf2 is maintained at a basal level, it has a half-life of approximately 15 minutes and is constantly degraded in cells not experiencing stress.105,106 Natural substances that have been shown to induce Nrf2 include lipoic acid (especially the R-form), selenium, diindolylmethane (DIM), sulforaphane, lycopene, milk thistle, and epigallocatechin gallate (EGCG).107-111 Importantly, lifestyle factors also have the ability to affect Nrf2 induction. Activities such as relaxation, breathing techniques, and exercise have the effect of inducing Nrf2.112-114

Hepatoprotection and Biliary Support

Some of the medications which improve symptoms and biochemical markers of liver injury in settings of cholestasis have mechanisms that include supporting the detoxification pathways. Ursodeoxycholic acid (UDCA), a primary medication used in settings of cholestasis, may have a protective effect via co-regulation of Phase III transporter expression. UDCA stimulates hepatic BSEP, and also co-stimulates hepatic, intestinal, and renal MRP2.115 UDCA, as well as S-adenosylmethionine (SAMe), prevents the cholestasis-induced blockage to Nrf2/ARE binding, increasing synthesis of detoxification-related enzymes and glutathione.71,116 Rifampicin, a medication that is used primarily as an antibiotic, but also for pruritis associated with cholestatic liver disease,117 enhances bile acid detoxification by increasing expression of CYP3A4 (Phase 1), UDP-glucuronosyltransferases (Phase 2), and MRP2 (Phase 3).118

Many natural substances support detoxification by improving biliary elimination of toxins. Phosphatidylcholine, the predominant phospholipid building block of cellular membranes, is a crucial constituent of bile. As phosphatidylcholine comprises over 90% of the total bile phospholipids content,119 inadequate intake contributes to impaired biliary excretion of bile and toxins, and promotes cholesterol crystallization and gallstone formation.120

This further promotes liver damage by obstruction of the small bile ducts. Increased intake of phosphatidylcholine has been shown to enhance biliary lipid secretion, preventing cholestasis and subsequent liver damage.121,122 Although small amounts of choline can be synthesized from methionine or serine, it is considered an essential nutrient and must be obtained from the diet.123 A recent study showed that only 8% of US adults meet the recommended adequate intake (AI) of choline, with vegetarians, postmenopausal women, and men at greater risk of inadequacy.124,125

Bitter Herbs

Well known for their generally stimulating effect on digestive system function, bitter herbs play an important role in promoting adequate biliary secretion. Digestive bitters which have hepatoprotective effects and/or support the formation and elimination of bile include gentian, dandelion, myrrh, and milk thistle. Some of these botanicals also have specific mechanisms by which they have been shown to support detoxification pathways.

Gentian (Gentiana lutea) is one of the strongest herbal bitters that is often utilized in digestive bitter formulations. Gentian has been shown to have a choleretic effect, normalizing bile volume in the setting of liver injury.126 As a liver protective agent, gentian has been observed to increase levels of GSH, GSR, GPX, and superoxide dismutase which were otherwise reduced by alcohol or acetaminophen-induced oxidative damage.127,128

Dandelion (Taraxacum officinale) simultaneously stimulates the production of bile by the liver (choleretic), the flow of bile into the small intestine (cholagogue), and also has hepatoprotective effects.129 In the setting of alcohol-induced oxidative stress, supplementation with dandelion root extract has also been observed to increase hepatic antioxidant activity, including GSH, GST, GPX, and GSR.130

Myrrh (Commiphora myrrha) has a complex profile of use and is perhaps most recognized for its antimicrobial effect.131,132 Myrrh also acts as an anesthetic, anti-inflammatory, antioxidant, and cholesterol-lowering agent.133 In Ayurvedic medicine, myrrh is used as a detoxifier and female reproductive tonifying agent, helping to move stagnant blood.134 Myrrh, and its close relative guggul (Commiphora mukul), contain molecules known as guggulsterones that have diverse biological activities. The guggulsterones are the bioactive agents responsible for the cholesterol-lowering effect, as well as anti-inflammatory and anti-oxidative properties.135 Guggulsterones have been shown to increase the transcription of BSEP as well as induction of the detoxification-promoting nuclear transcription factor PXR.

Milk thistle (Silybum marianum) has been vastly studied for its anti-oxidative, anti-inflammatory, and hepatoprotective effects.136 Silymarin is the active complex extracted from the seeds of the plant, with the flavonolignan silybin, also known as silibinin, being the most biologically active moiety comprising 50% to 70% of silymarin. One of the most important mechanisms by which milk thistle supports detoxification, in addition to its antioxidant effects, is via its anti-cholestatic properties.137 Silibinin stabilizes BSEP in its hepatocyte membrane location, preventing cholestasis caused by BSEP internalization in the presence of substances like estrogen.138 When co-administered with estrogen, silymarin was shown to prevent the estrogen-induced decrease in bile-salt dependent bile flow.139 Silibinin and silymarin also have been shown to stimulate the nuclear bile salt receptor FXR in a dose dependent manner, which increases expression of BSEP and MRP2, and also may have other positive metabolic effects.140

Toxin Binders

Completing the process of detoxification requires intestinal binders for two reasons: 1) many toxins (methylmercury, cadmium, and mycotoxins being well-known, as well as others with increased intestinal permeability) are reabsorbed after excretion into the bile, and 2) endotoxin and other dysbiotic toxins derived from the gut can be prophylactically bound with non-absorbed sorbent substances like activated carbon. As translocation of endotoxin from the gastrointestinal tract to circulation not only directly causes inflammation and oxidative damage but also has a dramatic negative effect on detoxification, it is imperative to bind and remove it from the body. Supporting reduction of intestinal permeability is also an important aspect of detoxification strategies. However, because there is no universal toxin binder that has an equal affinity for all toxins (heavy metals, molds, plastics, and more), a combination of binders that span a breadth of possible toxin chemistries is necessary (see Table 2).

Table 2: Toxic Substances Bound by Common Binders

- Activated charcoal: Endotoxin, mycotoxins, pesticides and herbicides, volatile organic compounds (VOCs)
- Bentonite clay: Mycotoxins, bisphenol A (BPA), pesticides and herbicides, some metal binding, also has antibacterial activity
- Chitosan, a molecular mimic of Welchol: Ochratoxin, polychlorinated biphenyls (PCBs), phthalates, BPA, endotoxin, metals, also has prebiotic activity
- Thiol-functionalized silica: Heavy metals specific binder including mercury, lead, arsenic, and cadmium

Activated charcoal is well known for its ability to adsorb a wide variety of toxic substances, and is used for this purpose in many emergency settings when poisonous substances or medication overdoses have been ingested.141 One of the most important things about charcoal is that it is very effective at binding and removing endotoxin, a major contributor to blocked detoxification pathways.142-144

Activated charcoal also effectively adsorbs pesticides and herbicides,145 volatile organic compounds (VOCs) such as benzene,146 mycotoxins,147 and the intestinal precursor to indoxyl sulfate, a uremic toxin.148 Charcoal has also been observed to reduce pro-inflammatory cytokine production in settings of infection.149

Bentonite clay is particularly good at absorbing mycotoxins, including food-borne aflatoxin; aflatoxin's precursor mycotoxin sterigmatocystin, commonly found in water-damaged buildings;150,151 zearalenone, a mycotoxin with estrogenic effects commonly found on stored grains152; and fumonisin B1, a mycotoxin most often found on corn.153 Bentonite clay also strongly binds bisphenol A (BPA),154 as well as pesticides and herbicides,155,156 and cyanotoxins, a product of harmful algal blooms that may be found in contaminated drinking water or food.157 Bentonite clay has an affinity for some heavy metals such as lead,158 cadmium,159 and nickel,160 and has been shown to reduce the cadmium-induced toxicity and pro-inflammatory response in vivo as well.161,162 Bentonite clay also has intrinsic broad-spectrum antibacterial properties and has a healing effect on the gastrointestinal lining.163

Derived from shellfish, chitosan is the result of enzymatic treatment of chitin, a component of the shell. As a biomaterial with use in a variety of applications including as a vaccine adjuvant, chitosan has been observed to be safe for use in individuals with shellfish allergies.164,165 Chitosan acts similarly to the bile acid sequestrants cholestyramine (Questran) and colesevelam (Welchol),166 preventing the absorption of lipids by effectively binding to bile salts,167 but most importantly where detoxification is concerned, removing the many conjugated toxins excreted in the bile. One extremely harmful and common toxin, ochratoxin, a mold toxin found in many foods as well as water-damaged buildings,168,169 is very effectively bound and removed by chitosan.170,171 Chitosan also binds metals including mercury172,173 as well as polychlorinated biphenyls (PCBs), phthalates,174 and BPA.175 Chitosan, like charcoal, also is able to bind endotoxin.176,177

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Chitosan also has a prebiotic effect, promoting the growth of Bifidobacterium and Lactobacillus.178 Like bentonite clay, chitosan also has been demonstrated to have an antimicrobial effect.179

Although chitosan and bentonite clay have an ability to bind some heavy metals, they are not the most effective tools for this purpose. Thiolated resins are substances with covalently attached thiolic metal-binding groups which very tightly bind metals including lead, mercury, cadmium, and arsenic.180,181 The use of thiolated resins dates back to the 1970s when they were used to address methylmercury (MeHg) poisoning in Iraq, and were found to significantly reduce the half-life of MeHg from 61 to 20 days, performing even better than penicillamine, a medical metal-chelating agent.182,183 The thiol-functionalized silica intercepts MeHg and other metals trapped in enterohepatic circulation, binding them and escorting them out of the intestines.184

Because binders act locally in the gastrointestinal tract, they allow tissue-bound toxins such as metals to safely drain into the blood at a natural rate. This contrasts with many blood metal chelating agents, which may increase circulatory levels of metals and place a greater burden on the kidneys and liver in the process of elimination.185 With gastrointestinal binders, the work of the liver and kidneys to eliminate toxic substances including metals is diminished as enterohepatic reabsorption is interrupted. The ability of charcoal and chitosan to block initial absorption of endotoxin is an important aspect of the role of binders in effective detoxification protocols.

Nanoscale Delivery Systems Optimize Detoxification

In order to appropriately time the cellular and hepatobiliary flushing of toxins with a gastrointestinal binder to properly bind and eliminate them, a nutritional delivery system with rapid uptake and cellular delivery is necessary.

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Lipid nanoparticle delivery systems pose a feasible solution, as appropriately designed lipid-based vesicles have the potential for rapid uptake into circulation and greatly increased cellular delivery.186 However, not all liposomal and nanoemulsifed particles are able to deliver these benefits, as only appropriately sized particles with properly designed surface chemistry enable rapid intraoral absorption and enhanced cellular delivery.

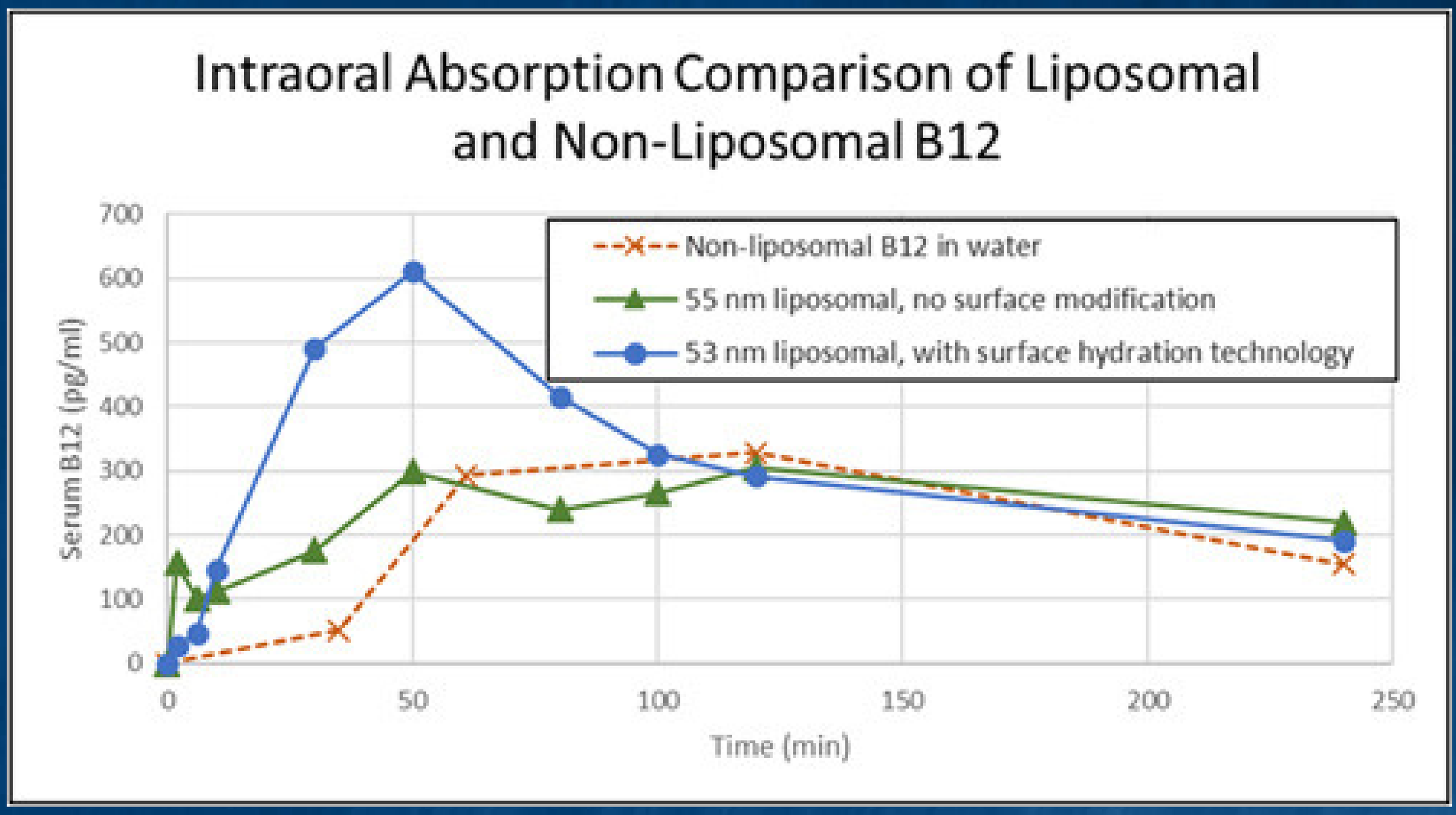
Particle size has a dramatic effect on systemic and cellular absorption, the capacity of the vesicles to extravasate from blood vessels and permeate into tissues, and the ability to evade immune system clearance.187 The consideration of each of these factors has led to the optimal sizing of lipid nanoparticle delivery systems in the range of 50 to 100 nm. As capillary pore size ranges from only 6 to 12 nm in endocrine glands to 50 to 180 nm in the discontinuous leaky capillaries,188 it is obvious that only the small liposomes will be able to permeate into the tissues through these openings.

Surface modifying techniques also can be used to improve the ability of lipid nanoparticles to traverse through the blood vessel endothelium and be absorbed by the tissues.189Particles utilizing surface hydration technology have been observed to dramatically increase intraoral absorption of liposomal particles, as shown in Figure 5, which compares delivery of B12 with and without surface modification to that of non-liposomal B12. Intelligently-designed surface modifications of lipid nanoparticles have also been shown to prolong the time a therapeutic agent is in circulation, reducing clearance by the mononuclear phagocyte system.190

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease. If pregnant, consult a physician before use.

Figure 5:

Comparison of B12 absorption intraorally in human subject.



Although absorption of the very small lipid nanovesicles primarily occurs intraorally, there always will be a percentage of the nanoparticle-containing liquid which is swallowed and experiences lower gastrointestinal absorption. In this setting, the lipid vesicle serves to protect the substances which it contains from degradation by the harsh gastric juices. These particles are absorbed via the lymphatics, which also allows for them to bypass first-pass hepatic metabolism, increasing bioavailability.191

In addition to their use in clinical applications for the delivery of drugs including anti-cancer, anti-fungal, and anti-inflammatory medications,192,193 lipid nanoparticle delivery systems have been shown to dramatically improve absorption of a variety of natural substances such as DIM and milk thistle, which otherwise have poor bioavailability.194-196

Liposomal delivery systems are becoming increasingly popular for delivery of substances such as glutathione because they protect it from breakdown in the digestive system, and, in cell culture studies, have been shown to dramatically increase intracellular delivery 100-fold over non-liposomal formats.197 Because optimally-sized liposomes with intelligent surface modifications prolong the time the therapeutic core remains in circulation, they are ideal for the delivery of many substances for which a prolonged systemic effect is desirable. Phosphatidylcholine, which forms the external membrane of lipid nanoparticles, also nourishes cellular membranes by providing necessary phospholipids for cellular repair.198

Although many products claim improved bioavailability via liposomal delivery, few are able to truly deliver the increased absorption these systems are capable of. However, with appropriately engineered lipid nanoparticle delivery systems, the rate of absorption, cellular delivery, and bioavailability of many medications and natural substances can be dramatically enhanced.

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