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WHAT EXACTLY IS PHASE III OF DETOXIFICATION?

While many functional medicine practitioners are familiar with phases I and II of detoxification, which involve functionalization and conjugation of toxins through various biochemical processes[1], many practitioners are unfamiliar with, or overlook the critical phase III detoxification pathway.

Phase III of detoxification is the final stage of physiological detoxification within the body involving the movement of toxins out of liver, kidney, and intestinal cells into the stool and urine for excretion.

The movement or filtration of toxins is a critical aspect of phase III detoxification. A requirement for phase III includes optimal bile production and fluidity, supporting the transport and elimination of toxins through membrane-bound cellular proteins, including the multidrug resistance protein (MRP), organic anion transport proteins (OATP), and P-glycoprotein.

The kidneys and intestines also play pivotal roles in phase III detoxification. These organs benefit from drainage support and binding agents to ensure elimination of toxins.

Detoxification strategies that fail to support phase III can result in toxin recirculation, uncomfortable detox reactions, and collateral damage to patients' health.

Phase III Support: Bile, Bitters, Binders, and Phosphatidylcholine

Proper bile flow is the foundation of Phase III detoxification and support the transport and elimination of toxins. Read on to learn more about bile and supplementation to support phase III detoxification.

Bile

Bile is a fluid produced in the liver and secreted by the gallbladder. It is made up of several components, including bile acids, salts, phospholipids, cholesterol, and water. Bile supports the digestion of dietary fats, regulates the composition of the gut microbiome, and is a component of phase III detoxification.

Fascinating research indicates that the cellular transporters that move bile acids and salts in and out of the intestine also transport toxins.[2,3] Therefore, sluggish bile flow, known as cholestasis, slows toxin efflux and impedes successful detoxification. Various factors drive cholestasis, including gallstones, biliary disease, chronic liver disease, certain medications, excess estrogen, and endotoxin, or lipopolysaccharide (LPS).[4,5] In addition to directly impacting phase III of detoxification, poor bile flow drives gastrointestinal dysbiosis and conditions such as small intestinal bacterial overgrowth (SIBO), which further increase the body's toxic burden.[6]

Bitters

Bitter herbs, also known simply as "bitters," have been an intrinsic part of life throughout human history. Traditional Chinese Medicine has a long, rich history of using bitter herbs for conditions ranging from diabetes to arthritis.[7] Swedish bitters, a combination of aloe, rhubarb, saffron, myrrh, gentian, zedoary, and agarikon, have been consumed in Europe as an herbal tonic since the 15th century.[8]

Today, we can use bitter herbs such as dandelion, solidago, myrrh, milk thistle, and gentian, to support bile flow and phase III detoxification at a cellular level.

For example, guggulsterone, a bitter compound found in myrrh resin, stimulates the human bile salt export pump (BSEP), located in cell membranes. BSEP stimulation is a major phase III detoxification mechanism.[9,10] Silymarin, a constituent of milk thistle seeds, enhances bile salt production and biliary excretion.[11] Silbinin and silychristin, additional constituents of milk thistle seeds, stabilize the membrane-bound bile acid export pump (BSEP) and multidrug resistance protein 2 (MRP2) transporters, facilitating the excretion of bile acids and toxins.[12,13]

Binders

Binding agents or 'binders' are a key component of Phase III detoxification. Binders support toxin elimination by adsorbing toxins. Different from absorption, adsorption is the chemical process of attracting, binding, and accumulating particles on a surface. At an atomic level, adsorption involves the sharing of electrons between the surface of the "adsorbent," such as activated charcoal,

and the "adsorbate," the substance being adsorbed. Therefore, ingesting binders allows toxins to be chemically "captured" in the gut and eliminated, rather than recirculated.

Toxins that are transported from the liver to the intestine can be reabsorbed into systemic circulation through a process called enterohepatic circulation. Recirculating toxins wreak havoc on numerous body systems. For example, mycotoxins can cause cellular damage when recirculated between the intestine, bloodstream, and liver. Endotoxin, also known as lipopolysaccharide (LPS), is a bacterial toxin released by gram-negative bacteria. If not eliminated properly, it can travel through the enterohepatic circulation, triggering widespread inflammation and symptoms such as cognitive dysfunction, headaches, joint pain, and malaise.[14,15]

Conversely, when a binder is present in the intestine, it can capture toxins, such as mycotoxins and LPS, and prevent their reabsorption via the enterohepatic circulation.

The natural world offers a variety of binding agents, including activated charcoal, bentonite clay, and chitosan. For example, activated charcoal contains millions of tiny pores that adsorb toxins in the gut, including metals, bacterial endotoxin, and mycotoxins.[16,17] Hospitals and emergency rooms have long used activated charcoal to treat cases of poisoning in children and adults. Activated charcoal is often made from coconut shells or bamboo. It is well-tolerated and readily excreted in the stool.

Chitosan, another potent binding agent, is a water-soluble polysaccharide derived from the outer skeleton of shellfish. Despite being derived from shellfish, chitosan has not been found to trigger allergenicity in shellfish-allergic individuals because the allergenic proteins have been removed. Chitosan binds heavy metals and microbes and may also support the growth of beneficial gut bacteria, which play crucial roles in the immune system.[18,19]

When detoxing, it is best to utilize a combination of binders to capture an array of toxins, as different natural binders have different affinities and capacities for toxin removal.

PC

Phosphatidylcholine (PC) is the predominant lipid building block of cellular and organelle membranes. It is also an integral part of bile and is thus necessary for detoxification.

PC insufficiency reduces bile flow and may slow down toxin elimination.[20] Furthermore, when PC is in short supply, hepatic cell membranes suffer damage from the free radicals generated during detoxification. PC deficiency also causes lipids to accumulate in the liver, hindering detoxification and promoting inflammation.[21]

The Kidneys: Unsung Heroes of Detoxification

The kidneys are the unsung heroes of detoxification, processing an extraordinary array of toxins via their tiny tubules. These delicate organs filter an astonishing 150 quarts of blood daily, ridding the body of various fat and water-soluble toxins including endogenous toxins like ammonia, urea, creatinine, and toxins derived from phase II hepatic detoxification. The kidneys also regulate the elimination of exogenous contaminants like heavy metals.[22] Alongside the liver and the gastrointestinal system, the kidneys play a crucial role in phase III detoxification; however, their small size and fragile structure make them susceptible to damage directly by toxins and through the detoxification process.

The kidneys use several processes to filter toxins from blood and prepare them for elimination in the urine. First, the glomeruli, tiny clusters of looped blood vessels in the kidneys, filter out many small- and medium-sized substances. The proximal tubules of the kidneys harbor active transporters, including the vital MRPs that usher toxins from the blood into the urine. Finally, passive diffusion of some toxins, namely fat-soluble toxins, also occurs in the renal tubules.

Botanicals for Kidney Support

Incorporating kidney-supporting botanicals to detoxification protocols may protect them from toxin-induced damage and support the urinary elimination of toxins. Several Western herbs and herbs from Traditional Chinese Medicine (TCM) have been found to support the kidneys, including dandelion leaf, Fu ling, and He Shou Wu.

In TCM, dandelion leaf is considered an anti-toxin herb. It is rich in phytochemicals, including β-sitosterol, α-amyrin, l, quercetin glycosides, chicoric acid, and sesquiterpene lactones. β-sitosterol has been found to inhibit kidney damage in rats exposed to toxic industrial solvents, while chicoric acid prevents chemotherapy-induced kidney damage by upregulating the antioxidant Nrf2 pathway.[23]

Fu ling *(Poria cocos)* is a medicinal mushroom used for over 2,000 years in TCM.[24] Fu ling has diuretic effects and aids detoxification by inhibiting the kidney's water transporter, renal aquaporin-2.[25]

He Shou Wu *(Polygonum multiflorum)*, another treasured herb in the TCM herbal compendium, also supports the kidneys. It contains a compound called 2,3,5,4'-Tetrahydroxystilbene-2-O-β-D-glucoside (THSG) that is structurally similar to resveratrol and has been shown to protect the kidneys against synthetic chemical toxicity while reducing the expression of genes involved in kidney fibrosis through the Nrf2 antioxidant pathway.[26] Interestingly, He Shou Wu also demonstrates hepatoprotective effects, decreasing inflammatory activity in the liver.[27]

Conclusion

Phase III detoxification is the culmination of numerous biochemical and physiological processes that transform harmful contaminants, making them available for elimination. However, when phase III detoxification and the excretion pathways are overlooked, toxins may recirculate in the body, continuing to degrade health. By supporting phase III detoxification and the two primary excretion pathways, bile and kidney elimination, we can improve detoxification outcomes dramatically.

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