Distinctive Detoxification

The case for including the microbiome in detox strategy

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One of the foundational therapeutics in functional medicine is supporting detoxification for our patients. When we think of toxicity, endogenous (internally produced) toxins don't necessarily spring to mind. But the microbiome is a source of metabolites and inflammatory mediators that can either support health and detoxification or contribute to our toxic load and disease. There is a bidirectional relationship between the gut and the liver governed by the microorganisms populating the GI tract, referred to as the gut-liver axis (GLA). It explains why we see deeper cleansing when detoxification protocols are combined with a microbial balancing cleanse. Additionally, biofilms, produced by microorganisms, can be an ongoing source of toxins. If left unaddressed, they can create a continual source of toxic exposure and an obstacle to lasting therapeutic effect.

Environmental Determinants of Chronic Disease

There is an ongoing nature vs. nurture (genetics vs. environment) debate. But the field of epigenetics (which describes the effect of environmental factors on the behavior of genes) has proven that the environment carries vastly more weight than the inherited gene under most circumstances. The most influential environmental factors are toxic exposure and total toxic load.

According to the World Health Organization, chronic, non-communicable diseases are rapidly becoming a global epidemic. Neurocognitive, metabolic, autoimmune, and cardiovascular diseases are on the rise. Genetics, lifestyle, and nutrition are not the only underlying causes. Early life, ongoing exposures, and bio-accumulated toxicants also contribute to chronic disease.

ENVIRONMENTAL CONTRIBUTORS TO CHRONIC DISEASE:
Toxic Elements
Naturally Occurring Substances
Pesticides
Persistent Organic Pollutants

Volatile Organic Compounds
Plastics

MECHANISMS OF TOXICITY IN CHRONIC DISEASE:
Oxidative Stress
Endocrine Disruption
Genotoxicity
Enzyme Inhibition
Dysbiosis

Genetics may predispose individuals to chronic disease, but this cannot account for the rapidly increasing prevalence of chronic illnesses within just a generation or two. There is a compelling case for pervasive environmental factors as an underlying cause of chronic illness. As Judith Stern of the University of California at Davis states, “Genetics loads the gun, but environment pulls the trigger.” [1] One of the most influential environmental factors is the prevalence of toxicity. The microbiome plays a pivotal role in governing the metabolism of exogenous (externally produced) and endogenous toxins. Let’s take a closer look.

A Healthy Microbiome Benefits the Host

Beneficial bacteria play a variety of important roles in human health, and dysbiosis (microbiota imbalance) plays a significant role in the pathogenesis of intestinal and extraintestinal illnesses.[2] The influence of the microbiome affects multiple areas influencing detoxification. These include:

- Hydration
- Nutrient Synthesis
- Protection against pathogens by a barrier effect
- Training of the immune system
- Immune reserves for systemic defenses
- Production of short-chain fatty acids

Short-Chain Fatty Acids

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3270432/
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5962619/pdf/394_2018_Article_1703.pdf

Short-Chain Fatty Acids (SCFAs) are metabolites produced primarily in the colon via enzymatic conversion or fermentation by gut bacteria of indigestible dietary residue. They are key mediators for communication between the host and gut microbes. SCFAs produced by microbes can influence host immunity and metabolism, including promoting T regulatory cell function and reducing risk of inflammatory disease. They also affect gut integrity by decreasing the luminal pH, enhancing absorption of some nutrients, exerting beneficial effects against intestinal inflammation, and protecting intestinal epithelial integrity. Finally, SCFAs have a direct impact on gut microbiota composition.[3] A healthy microbiome is requisite for the robust production of SCFAs.

Lipopolysaccharides

Lipopolysaccharides (LPS) are found on the outer shell of gram-negative bacteria and are a potent endotoxin contributing to various diseases. LPS is one of many pathogen-associated molecular patterns (PAMPs) and initiates a potent cytokine response (from macrophages and Kupffer cells in the liver), resulting in inflammation through binding of toll-like receptors (TLRs) and direct binding. Even small amounts of LPS due to bacterial infection are sufficient to elicit an inflammatory response.[4]

Inflammation resulting from LPS in the lumen of the gastrointestinal (GI) tract creates damage to the mucosa and the tight junctions of the gut, leading to increased intestinal permeability, allowing translocation of bacterial metabolites into the adjacent lymphatics and blood flow where it travels via the portal vein and must be cleared by the cells in the liver.[5]

LPS and the Liver

Removal of intestinal products by the liver is vital in protecting systemic tissues and organs from inflammatory damage. Those products include bacterial endotoxins (LPS), bacterial exotoxins (cytolysin), fungal exotoxins (candidalysin) and other PAMPS from microorganisms - many of which promote hepatocellular injury. Studies show that LPS is cleared within minutes following injection and primarily localized in the liver. The resulting inflammatory cascade causes collateral damage to hepatocytes, and their ability to participate in detoxification.[6]

The effect of LPS is so significant that it can be considered a cofactor for liver injury. Murine research shows that LPS augments injury by hepatotoxins. In mice with a sterile gut (no LPS), damage due to exposure of hepatotoxins was mitigated. Similarly, in alcoholic liver

[3] Frontiers | Gut Microbiota, Short-Chain Fatty Acids, and Herbal Medicines | Pharmacology (frontiersin.org)
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7829348/pdf/fimmu-11-594150.pdf
[5] https://www.sciencedirect.com/science/article/pii/S0753332221006727
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7868813/

disease, LPS is also a cofactor. Rats fed ethanol only developed fatty liver. However, when LPS was introduced, it resulted in hepatic necrosis.[7]

Gut-Liver Axis (GLA)

The Gut-Liver Axis describes a bidirectional pathway in which the gastrointestinal system, microbiome, and the liver influence and depend upon one another. Disruption of the GLA results in loss of homeostasis, compensation, and eventual disease through elevated toxins and resulting inflammation.[8]

The liver plays a pivotal role in regulating the microbiome by releasing primary bile acids (BA) into the small intestine. Bile acids are antimicrobial and prevent the overgrowth of microorganisms and resultant proinflammatory bacterial metabolites. Reduction in the formation and release of BA is associated with overgrowth of microorganisms in the small intestine. Alterations of bile acid homeostasis leading to excessive intrahepatic accumulation of potentially toxic BAs and their metabolites are thought to play a pivotal role in mediating the hepatic injury of cholestatic diseases.

The vast majority (95%) of primary bile acids are reabsorbed via enterohepatic recirculation. Microbiota modify the remaining 5% into secondary BA.[9] Secondary BAs are highly toxic, and excess levels contribute to inflammation, cholestasis, gallstone formation and carcinogenesis. In the presence of a healthy microbiome (which also acts upon xenobiotics and other endogenous toxins), the effects of secondary bile acids are mitigated by the production of SCFAs exerting their anti-inflammatory effect.[10]

Small Intestinal Bacterial Overgrowth and Liver Disease

The destruction of liver tissue resulting from dysbiosis is illustrated by the connection between small intestinal bacterial overgrowth (SIBO) and liver disease. Chronic liver disease (CLD) patients have SIBO significantly more often when compared with controls. The association of SIBO and CLD is not confined to patients with advanced disease, suggesting that SIBO is not a consequence of advanced liver disease but may play a role in the progression of CLD.[11]

Gram-negative bacteria and the resulting elevation in LPS frequently accompanied by SIBO contributes to intestinal permeability, damaging the protective barrier, and increasing risk of non-alcoholic fatty liver disease.[12]

Biofilms

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[7] Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation | American Journal of Physiology-Gastrointestinal and Liver Physiology
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8004151/
[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8204491/
[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429521/pdf/ijms-20-01214.pdf
[11] https://pubmed.ncbi.nlm.nih.gov/29272899/
[12] https://pubmed.ncbi.nlm.nih.gov/27308646/

Biofilms are involved in the majority of clinical infections. They are communities of microbial cells surrounded by a secreted polymer called the "extracellular polymeric substance." They are composed of multiple organisms (aerobic and anaerobic bacteria and/or fungal species). More than 80% of all microbial infections have developed biofilms within two weeks from the onset of infection. Biofilm bacteria can resist up to 5000 times the antibiotic concentration that would typically be needed to resolve infections and, once established, are an ongoing source of reinfection. Biofilms in the GI tract often contain bacterial metabolites, as described above. In fact, LPS is part of the structure of biofilms.[13]

The composition of microbial biofilm depends on the environmental conditions in which the microbes reside. Biofilm is a survival mechanism for microorganisms and provides protection from environmental stress, acid, antimicrobials, UV, desiccation, predation, biocides, solvent, toxic chemicals, and other pollutants.[14]

Biofilms and Toxicity

Biofilms exist in the natural world, including on and in the human body, where they retain environmental toxicity and create toxic byproducts themselves. How sticky are they? They are used for the biochemical conversion of pollutants by sorption (heavy metals, hydrocarbons, industrial waste, and wastewater). The molecules produced by biofilm communities contain glycoconjugates such as glycoproteins, glycopeptides, peptidoglycans, glycolipids, lipopolysaccharides, and glycosides – many of which result in inflammation and contribute to toxicity in the body.[15] Failure to address biofilms can result in refractory illness, and an ongoing source of toxicity.[15]

Oral Health, Dysbiosis, and Biofilms

When LPS is produced in the gut, the liver clears it, protecting systemic tissues and organs. However, when gram-negative bacteria such as *Porphyromonas gingivalis* produce toxic metabolites in the mouth, it results in the direct translocation to adjacent blood flow and lymphatics. Oral dysbiosis and its resultant upregulation of inflammatory pathways is linked to diabetes, cardiovascular disease, Alzheimer's dementia, respiratory diseases, and more.[16]

Many of the microorganisms in the mouth participate in the production of biofilms, which are easily identified by the sensation of "fuzzy teeth." These biofilms have the same qualities and effects as those elsewhere in the body and, as such, are a source of toxicity and

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[13] https://pubmed.ncbi.nlm.nih.gov/28950999/
[14] Microbial glycoconjugates in organic pollutant bioremediation: recent advances and applications (nih.gov)
[15] https://pubmed.ncbi.nlm.nih.gov/32858856/
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7443998/pdf/10.1177_0022034520926126.pdf

recalcitrant disease.[17] Evaluation of the oral microbiome is a powerful tool for reducing circulating endotoxins.

Botanicals and the Microbiome

Herbal medicines have been utilized by humans to treat infection for thousands of years and provide a safe and effective option for addressing biofilms and dysbiosis. A study with nearly 400 people found that herbal remedies were as effective as Rifaximin (the most studied antibiotic related to SIBO) at treating symptoms. That trial used an array of botanicals and essential oils. [18]

Using the anti-pathogenic properties of more than one botanical in a combination or formula provides a broader spectrum and deeper activity against pathogens. The resulting formulations, or "biocidal combinations,'' are powerful allies that may be used to address infection.

Pilot testing at the University of Binghamton has illustrated remarkable broad-spectrum antimicrobial and antibiofilm activity (in vitro) with a combination containing Bilberry extract, Noni, Milk Thistle, Echinacea (Purpurea & Angustifolia), Goldenseal, Shiitake, White Willow, Garlic, Grapeseed extract, Black Walnut (hull and leaf), Raspberry, Fumitory, Gentian, Tea Tree oil, Galbanum oil, Lavender oil, and Oregano oil.

Table 2. % Death following exposure to various concentrations of Biocidin® for a period of 4 hours at 37°C with aeration

		0% biocidin®	25% Biocidin®	50% Biocidin®	75% Biocidin®	100% Biocidin®
S. aureus	Biofilms	0%	92.9%	88.4%%	95.0%	89.7%
	Planktonic	0%	99.2%	60.0%	91.9%	99.9%
K. pneumonia	Biofilms	0%	90.7%	78%	82.7%	99.8%
	Planktonic	0%	99.1%	55.9%	91%	99.97%
P. aeruginosa	Biofilms	0%	92.1%	99.99%	99.96%	N/A
	Planktonic	0%	93.3%	99.99%	99.97%	N/A
C. albicans	Biofilms	0%	99.96%	99.99%	99.98%	99.99%
	Planktonic	0%	95.6%	96.3%	95.9%	99.7%

Botanicals are Effective Against Biofilms

Botanicals accomplish control of biofilms through several methods. One method is through the inhibition of quorum sensing. Quorum sensing is cell signaling by bacteria and other organisms using autoinducers to determine gene expression, virulence, resistance, and development of biofilms. Botanicals shown to inhibit quorum sensing, such as Garlic and Oregano, are well known for their antimicrobial ability. This understanding of how they can combat biofilms highlights their clinical and historical significance.[19]

Another method of biofilm control is by the inhibition of efflux pumps within cells, called "multidrug resistance pumps." Plants containing tannins, berberine, and certain phenolics have effects as efflux pump inhibitors, demonstrating marked synergy when combined with

[17] https://pubmed.ncbi.nlm.nih.gov/32858856/

[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030608/

[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6119553/

conventional antibiotics against a variety of both gram-positive and gram-negative organisms. Goldenseal, Black Walnut, White Willow, Raspberry Leaf, and Garlic are a few that have been studied.[20]

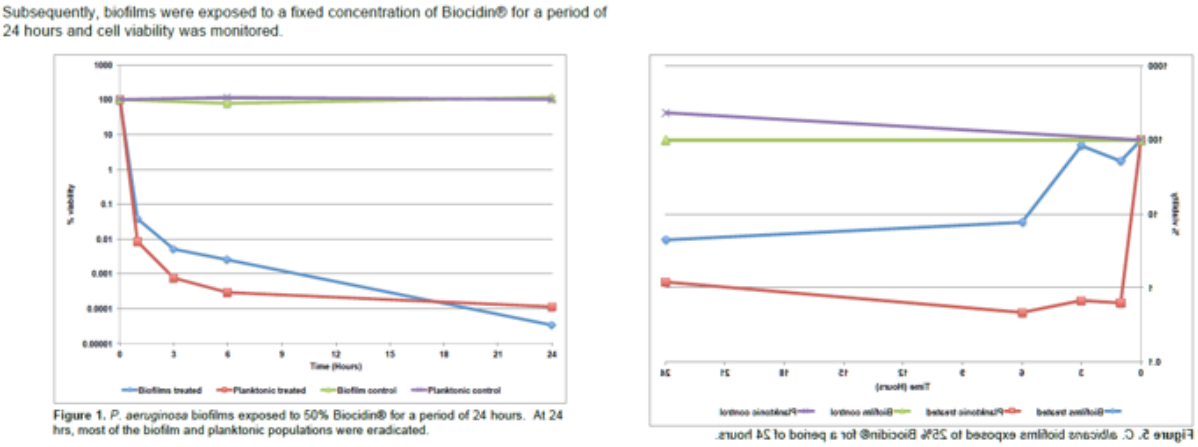


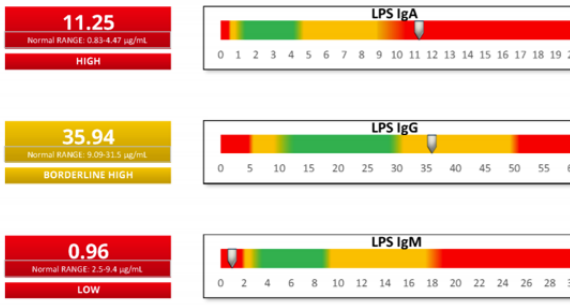
Figure 1. *P. aeruginosa* biofilms exposed to 50% Biocidin® for a period of 24 hours. At 24 hrs, most of the biofilm and planktonic populations were eradicated.

Botanicals and LPS

Another recent pilot study illustrates the effectiveness of a similar biocidal formula. When administered with a formula containing binding agents (activated charcoal, zeolite clay, silica, apple pectin, humic and fulvic acids, aloe), it reduced immune markers associated with LPS exposure after six weeks of application. The potential therapeutic effect of reducing LPS-associated inflammation is far-reaching.

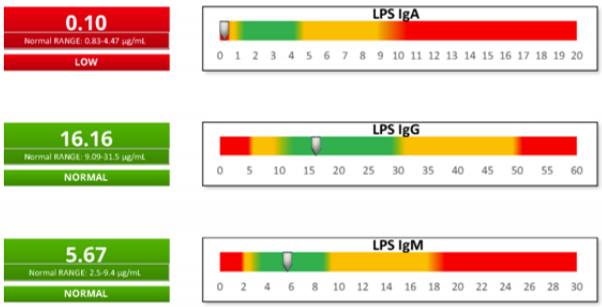
Participant #1

Pre-test 5/11/21



Participant #1

Post-test 06/23/21



When applying detoxification strategies in clinical practice, it is common to include nutrient therapy to supplement detox pathways in the liver and gut. Adding botanicals to

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5486105/

balance the microbiome in the gastrointestinal tract and oral cavity is a well-tolerated and effective way to uplevel the experience and deepen the effects – setting patients up for vitality and health.