REVIEW ARTICLE

Distinctive Detoxification: The Case for Including the Microbiome in Detox Strategy

Jocelyn Strand, ND

Abstract

Exposure to environmental toxins contributes to both acute and chronic illnesses, and is of growing concern. The importance of the microbiome to gastrointestinal (GI), as well as systemic health, has been the topic of much research recently. The microbiome influences health, and can either be a source of beneficial metabolites, or contribute to poor health. Dysbiosis, particularly in the GI tract, or oral cavity is a source of endogenously produced toxicity in the form of proinflammatory mediators—most notably lipopolysaccharide (LPS). LPS is cleared by the liver from enterohepatic circulation, and contributes to its workload. Bacterial overgrowth has been shown to be a contributing factor to liver disease. Further influences of the microbiome on detoxification include the Gut-Liver axis and biofilm production. Botanicals can have beneficial effects on microbial balance, favoring probiotic abundance, while addressing pathogen load. Additionally, plants offer antioxidant, biofilm disruption, antiinflammatory and immunomodulatory activities. Inclusion of botanical medicine to modulate the microbiome is a novel therapeutic target to reduce endogenously produced toxins and total toxic load.

Jocelyn Strand, ND, Director of Clinical Education and Research, Biocidin Botanicals, Duluth, MN, USA.

Corresponding author: Jocelyn Strand, ND
E-mail address: drstrand@biocidin.com

One of the foundational therapeutics in functional medicine is supporting detoxification for patients. With respect to 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 toxic load and disease.

A bidirectional relationship exists between the gut and the liver, which is governed by the microorganisms populating the gastrointestinal (GI) tract—and is referred to as the gut-liver axis (GLA). This relationship explains why deeper cleansing occurs 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 be an obstacle to a lasting therapeutic effect.

Toxins and Chronic Disease

The debate is ongoing regarding the effects of nature vs nurture—genetics vs environment. The field of epigenetics, which describes the effects of environmental factors on the behavior of genes, has shown that the environment carries vastly more weight than inherited genes under most circumstances. The most influential environmental factors are toxic exposure and total toxic load.

According to the World Health Organization, chronic, noncommunicable 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 can contribute to chronic disease. The environmental contributors to chronic disease include:

1. toxic elements
2. naturally occurring substances
3. pesticides
4. persistent organic pollutants
5. volatile organic compounds
6. plastics

The mechanisms of toxicity in chronic disease include:

1. oxidative stress
2. endocrine disruption
3. genotoxicity
4. enzyme inhibition
5. dysbiosis

Genetics may predispose individuals to chronic disease, but this can't account for the rapidly increasing prevalence of chronic illnesses within just a generation or two. The case is compelling for pervasive environmental factors as underlying causes of chronic illness. As Judith Stern of the University of California at Davis states, "Genetics load 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.

Healthy Microbiome

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

1. hydration
2. nutrient synthesis
3. protection against pathogens from a barrier effect
4. training of the immune system
5. immune reserves for systemic defenses
6. production of short-chain fatty acids

Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are metabolites produced primarily in the colon via enzymatic conversion or fermentation of indigestible dietary residue by gut bacteria. 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 the composition of the gut microbiota.[3] A healthy microbiome is a 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 the 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 GI tract can create damage to the mucosa and the tight junctions of the gut, leading to increased intestinal permeability and allowing translocation of bacterial metabolites into the adjacent lymphatics and blood flow, where it travels by means of 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. Some studies have shown that LPS is cleared within minutes following injection and is primarily localized in the liver. Fairfield and Schnabl found that the resulting inflammatory cascade can cause collateral damage to hepatocytes and to their ability to participate in detoxification.[6]

The effects of LPS are so significant that it can be considered a cofactor for liver injury. Murine research has shown that LPS can augment injury from hepatotoxins. In mice with a sterile gut—no LPS, damage due to exposure of hepatotoxins was found to be mitigated.[7] Similarly, in alcoholic liver disease, LPS was also a cofactor. Rats fed ethanol (no LPS present) developed a fatty liver. However, when LPS was introduced, hepatic necrosis occurred.

Gut-Liver Axis (GLA)

The gut-liver axis describes a bidirectional pathway in which the GI tract, microbiome, and 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. BA are antimicrobial and prevent the overgrowth of microorganisms and many resultant proinflammatory bacterial metabolites. Reduction in the formation and release of BA is associated with overgrowth of microorganisms in the small intestine. Alterations of BA homeostasis that lead 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 BA are reabsorbed via enterohepatic recirculation. Microbiota modify the remaining 5% into secondary BA,[9] which are highly toxic, and excess levels can 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 BAs are mitigated by the production of SCFAs exerting their anti-inflammatory effect.[10]

Bacterial Overgrowth and Liver Disease

The destruction of liver tissue resulting from dysbiosis is illustrated by the connection between small intestinal

Table 1. Percent death following exposure to various concentrations of Biocidin for a period of 4 hours at 37° C wth 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%	78.0%	82.7%	99.8%
	Planktonic	0%	99.1%	55.9%	91.0%	99.9%
P. aeruginosa	Biofilms	0%	92.1%	99.9%	99.9%	N/A
	Planktonic	0%	93.3%	99.9%	99.9%	N/A
C. albicans	Biofilms	0%	99.9%	99.9%	99.9%	99.99%
	Planktonic	0%	95.6%	96.3%	95.9%	99.7%

bacterial overgrowth (SIBO) and liver disease. Patients with chronic liver disease (CLD) have SIBO significantly more often than controls do. The association of SIBO and CLD isn't confined to patients with advanced disease, suggesting that SIBO isn't 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 the risk of nonalcoholic fatty liver disease.[12]

Biofilms

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, including aerobic and anaerobic bacteria and/or fungal species. More than 80% of all microbial infections have developed biofilms within two weeks of 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 biofilms depend 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, solvents, 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 including heavy metals, hydrocarbons, industrial waste, and wastewater.

The molecules produced by biofilm communities contain glycoconjugates, such as glycoproteins, glycopeptides, peptidoglycans, glycolipids, LPS, 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, the result is 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 recalcitrant disease.[15] Evaluation of the oral microbiome is a powerful tool for reducing circulating endotoxins.

Botanicals and the Microbiome

Herbal medicines have been used 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.[17] That trial used an array of botanicals and essential oils.

Using the antipathogenic 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, Echinacea 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 1).

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

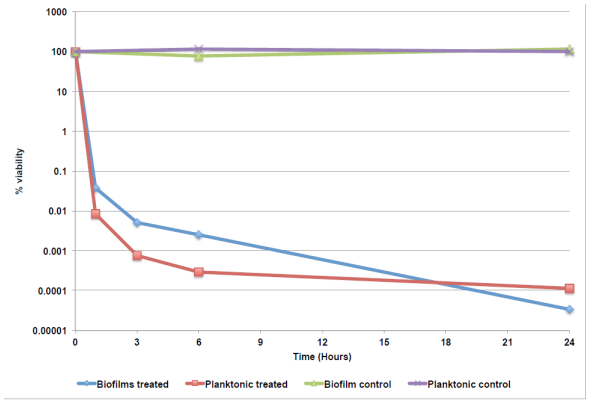
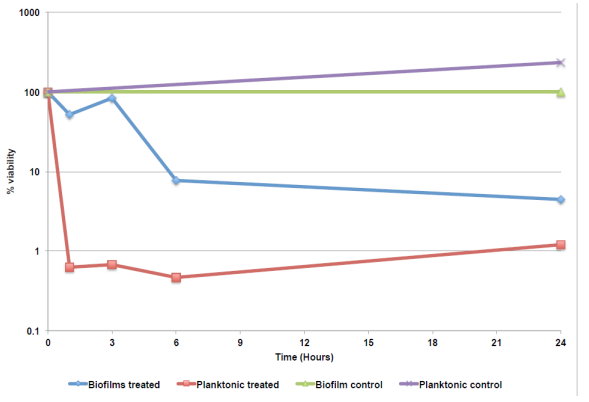


Figure 2. *C. albicans* biofilm exposed to 25% Biocidin® for a period of 24 hours.



Botanicals and Biofilms

Botanicals accomplish the control of biofilms through several methods. One is through the inhibition of quorum sensing, which 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.[18]

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 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 (Figure 1).[19]

Botanicals and LPS

Another recent pilot study has illustrated 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, and aloe, it reduced immune markers associated with LPS exposure after six weeks of application. The potential therapeutic effects of reducing LPS- associated inflammation is far-reaching (Figure 2).

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

References

1. Sears ME, Genuis SJ. Environmental determinants of chronic disease and medical approaches: recognition, avoidance, supportive therapy, and detoxification. *J Environ Public Health*. 2012;2012:356798. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3270432/ doi:10.1155/2012/356798
2. Mohajeri MH, Brummer RJM, Rastall RA, et al. Mohajeri1 MH, Brummer RJM, Rastall RA, Weersma K, Harmsen HJM, Faas M, Eggersdorfer M. The role of the microbiome for human health: from basic science to clinical applications. *Eur J Nutr*. 2018;57(S1)(suppl 1):S1-S14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5962619/pdf/394_2018_Article_1703.pdf doi:10.1007/s00394-018-1703-4
3. Feng W, Ao H, Peng C. Gut microbiota, short-chain fatty acids, and herbal medicines. Front. Pharmacol: Ethnopharmacology. November 23, 2018. https://www.frontiersin.org/articles/10.3389/fphar.2018.01354/full doi:10.3389/fphar.2018.01354
4. Mohammad S, Thiemermann C. Role of metabolic endotoxemia in systemic inflammation and potential interventions. Front Immunol: Inflammation. January 11, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7829348/pdf/fimmu-11-594150.pdf doi:10.3389/fimmu.2020.594150
5. Pérez-Hernández EG, Delgado-Coello B, Luna-Reyes I, Mas-Oliva J. New insights into lipopolysaccharide inactivation mechanisms in sepsis. *Biomed Pharmacother*. 2021;141:111890. https://www.sciencedirect.com/science/article/pii/S0753332221006727 doi:10.1016/j.biopha.2021.111890
6. Fairfield B, Schnabl B. Gut dysbiosis as a driver in alcohol-induced liver injury. JHEP Rep. 2021 Apr; 3(2):100220. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7868813/ doi:10.1016/j.jhepr.2020.100220
7. Su GL. Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation. *Am J Physiol Gastrointest Liver Physiol*. 2002;283(2):G256-G265. https://journals.physiology.org/doi/full/10.1152/ajpgi.00550.2001 doi:10.1152/ajpgi.00550.2001
8. Blesl A, Stadlbauer V. The gut-liver axis in cholestatic liver diseases. *Nutrients*. 2021;13(3):1018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8004151/ doi:10.3390/nu13031018
9. Guzior DV, Quinn RA. Review: microbial transformations of human bile acids. *Microbiome*. 2021;9(1):140. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8204491/ doi:10.1186/s40168-021-01101-1
10. Zeng H, Umar S, Rust B, Lazarova D, Bordonaro M. Secondary bile acids and short chain fatty acids in the colon: A Focus on colonic microbiome, cell proliferation, inflammation, and cancer. *Int J Mol Sci*. 2019;20(5):1214. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429521/pdf/ijms-20-01214.pdf doi:10.3390/ijms20051214
11. Shah A, Shanahan E, Macdonald GA, et al. Systematic review and meta-analysis: prevalence of small intestinal bacterial overgrowth in chronic liver disease. *Semin Liver Dis*. 2017;37(4):388-400. https://pubmed.ncbi.nlm.nih.gov/29272899/ doi:10.1055/s-0037-1608832
12. Fialho A, Fialho A, Thota P, McCullough AJ, Shen B. Small intestinal bacterial overgrowth is associated with nonalcoholic fatty liver disease. *J Gastrointestin Liver Dis*. 2016;25(2):159-165. https://pubmed.ncbi.nlm.nih.gov/27308646/ doi:10.15403/jgld.2014.1121.252.iwg
13. Kumar A, Alam A, Rani M, Ehtesham NZ, Hasnain SE. Biofilms: survival and defense strategy for pathogens. *Int J Med Microbiol*. 2017;307(8):481-489. https://pubmed.ncbi.nlm.nih.gov/28950999/ doi:10.1016/j.ijmm.2017.09.016

14. Bhatt P, Verma A, Gangola S, Bhandari G, Chen S. Microbial glycoconjugates in organic pollutant bioremediation: recent advances and applications. *Microb Cell Fact*. 2021;20(1):72. https://pubmed.ncbi.nlm.nih.gov/33736647/ doi:10.1186/s12934-021-01556-9
15. Yoo Y-J, Kim AR, Perinpanayagam H, Han SH, Kum K-Y. Candida albicans virulence factors and pathogenicity for endodontic infections. *Microorganisms*. 2020;8(9):1300. https://pubmed.ncbi.nlm.nih.gov/32858856/ doi:10.3390/microorganisms8091300
16. Kleinstein SE, Nelson KE, Freire M. Inflammatory networks linking oral microbiome with systemic health and disease. *J Dent Res*. 2020;99(10):1131-1139. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7443998/pdf/10.1177_0022034520926126.pdf doi:10.1177/0022034520926126
17. Chedid V, Dhalla S, Clarke JO, et al. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Glob Adv Health Med*. 2014;3(3):16-24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030608/ doi:10.7453/gahmj.2014.019
18. Aumeeruddy-Elalfi Z, Ismael IS, Hosenally M, Zengin G, Mahomoodally MF. Essential oils from tropical medicinal herbs and food plants inhibit biofilm formation in vitro and are noncytotoxic to human cells. 3 Biotech. Sep 2018; 8(9):395. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6119553/
19. Liu Q, Meng X, Li Y, Zhao C-N, Tang G-Y, Li HB. Antibacterial and antifungal activities of spices. *Int J Mol Sci*. 2017;18(6):1283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5486105/ doi:10.3390/ijms18061283