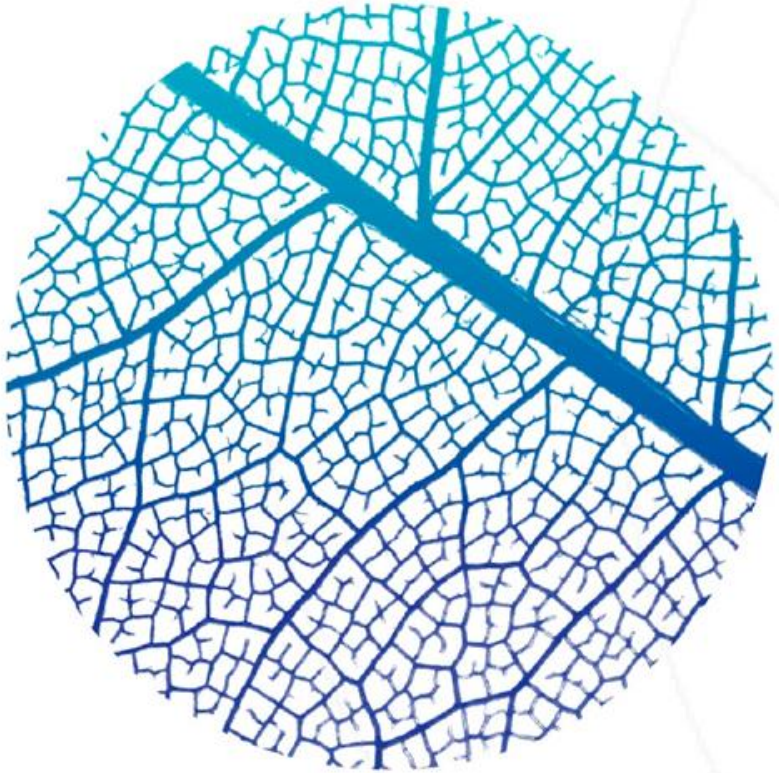


HISTAMINE RISING

THE ROLE OF DYSBIOSIS & GI DYSFUNCTION IN HISTAMINE DYSREGULATION

JOCELYN STRAND, ND

HISTAMINE BASICS & CLINICAL RELEVANCE

HISTAMINE 101

Histamine is a powerful biogenic amine that binds to a family of receptors on target cells in various tissues, mediating numerous biological reactions.

Histamine is synthesized by the decarboxylation of histidine by histidine decarboxylase. This becomes important later!

Histamine is produced in basophils and mast cells.

- Visceral hypersensitivity
- Promotes sensitization to painful stimuli
- Promotes inflammatory cell accumulation (neutrophils, macrophages, T-lymphocytes)
- Impairs epithelial barrier via modulation of tight junction proteins
- GI dysmotility

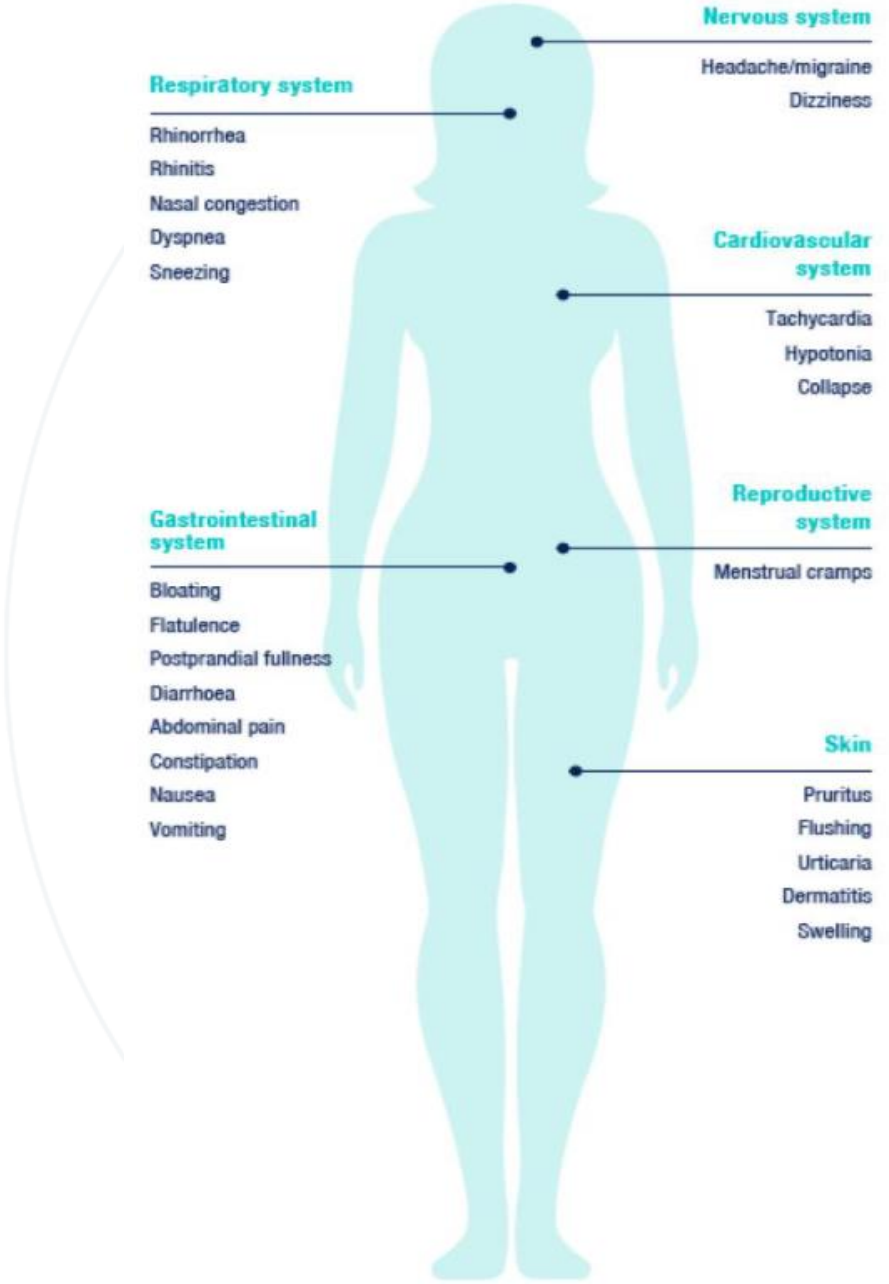
HISTAMINE RECEPTOR ACTIVITY

Histamine Receptor	Location	Effects	Drugs
H1	Widespread CNS: Tuberomammillary nucleus Peripheral: Airway smooth muscles, blood vessels, sensory nerves	Nociception, Pruritus, Vasodilation, Vascular Permeability, Hypotension, Flushing, Tachycardia, Bronchoconstriction, Mediate effects related to Asthma: Mucosal Edema, Smooth Muscle spasms, Inflammation, Mucous secretion, Regulate: Sleep/Wake cycles (circadian rhythm, Food intake, Thermal regulation, Emotions/Aggressive behavior, Locomotion, Memory and Learning	Gen 1: Diphenhydramine, Dimenhydrinate, Hydroxyzine, Promethazine, Pheniramine, Meclizine, Buclizine, Cyproheptadine, Cetirizine, Clemastine, Ketotifen Gen 2: Terfenadine, Loratadine, Ebastine, Cetirizine, Rupatadine, Mizolastine, Emedastine, Azelastine, Bilastine Gen 3: Desloratadine, Fexofenadine, Levocetirizine
H2	CNS: Cerebral cortex, dorsal striatum, hippocampal formation, dentate nucleus of cerebellum Peripheral: Gastric mucosa parietal cells, vascular smooth muscle cells, uterine cells, heart cells, neutrophils, mast cells	Gastric acid secretion, vascular permeability, hypotension, flushing, headache, tachycardia, bronchoconstriction	Cimetidine, Ranitidine, Famotidine, Nizatidine
H3	Mainly in CNS histaminergic neurons	Inhibit neurogenic sympathetic vasoconstriction in nasal mucosa, Nociception, Modulate histamine release from mast cells and cerebral neurons	Clobenpropit, Ciproxifan, Conessine, Betahistine, Pitolisant
H4	Bone marrow, dendritic cells, eosinophils, neutrophils, mast cells, T-cells	Role in differentiation of myeloblasts, promyeloblasts, immune function and chemotaxis, Itch perception, cytokine production and secretion, role in inflammatory and autoimmune disorders	

https://www.ncbi.nlm.nih.gov/books/NBK557790/?report=printable
https://pharmafactz.com/medicinal-chemistry-of-antihistamines/
https://en.wikipedia.org/wiki/H3_receptor_antagonist#:~:text=Examples%20of%20selective%20H3,349%2C821%2C%20betahistine%2C%20and%20pitolisant.

HISTAMINE PHYSIOLOGY

- Neurotransmission
- Gut motor function
- Fluid transport
- Modulate permeability of intestinal mucosa
- Affect mucosal ion secretion
- Modulate inflammation via action on submucosal and primary afferent neurons
- Participates in:
  - Cell proliferation
  - Differentiation
  - Hematopoiesis
  - Embryonic development
  - Secretion of hormones



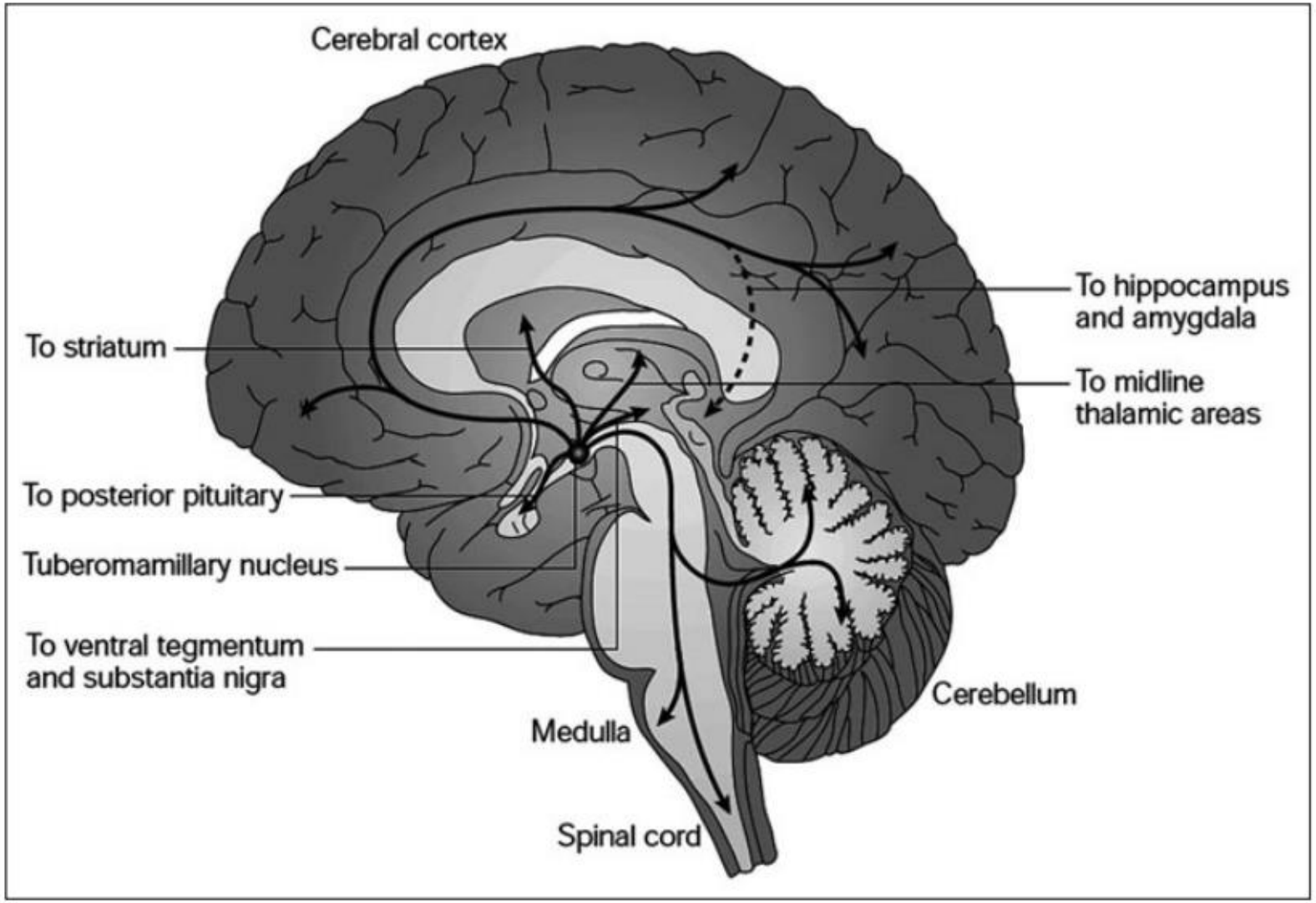
Many important effects – but balance is essential!

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8308327/

HISTAMINE & THE BRAIN

Histamine in brain diseases:

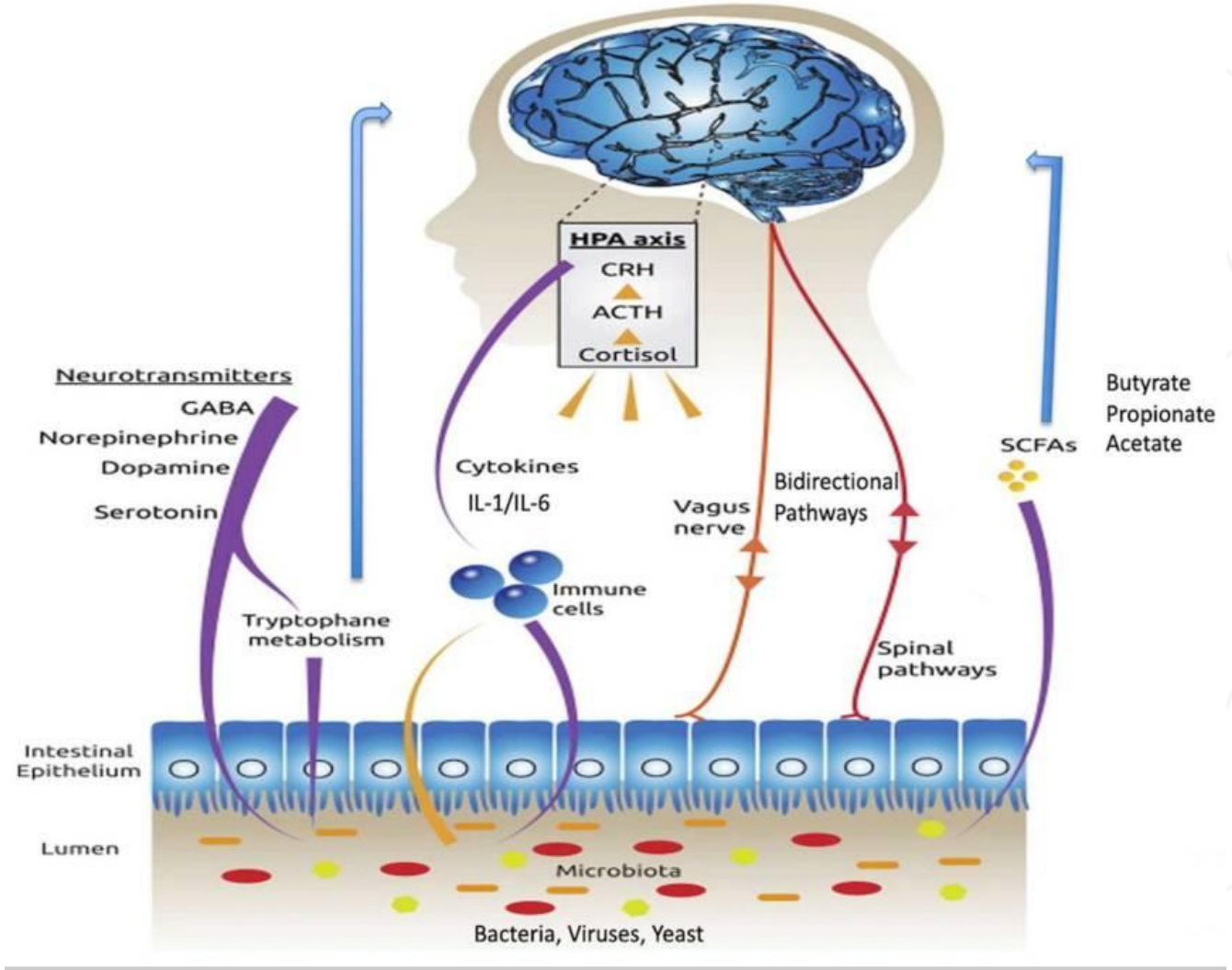
- Sleep-wake cycle
- Alzheimer's disease
- ADHD
- Schizophrenia
- Parkinson's
- Epilepsy
- Brain injury
- Pain



https://pubmed.ncbi.nlm.nih.gov/21618891/

HISTAMINE & “LEAKY BRAIN”

“Clinical, epidemiological, and immunological evidence suggest that enteric microbiota extensively and profoundly influences the gut-brain relationship (i.e., mental state, emotional regulation, neuromuscular function, and regulation of the HPA).”

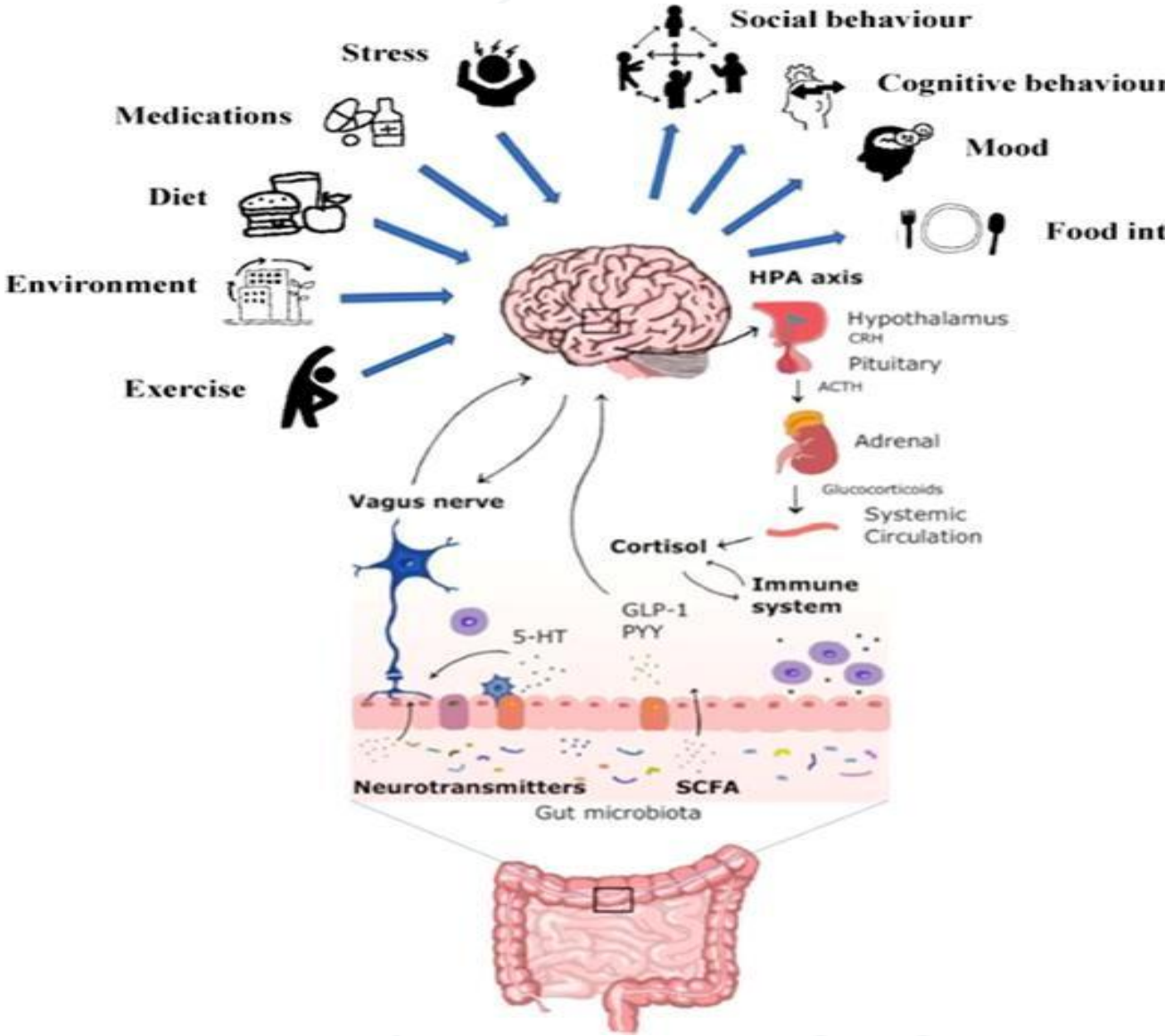


https://pubmed.ncbi.nlm.nih.gov/21618891/
https://pubmed.ncbi.nlm.nih.gov/24997034/

LEAKY BRAIN – RISK FACTORS

Risk factors for disruption in the GBA

- Medications
  - Antibiotic use – maternally or in infancy
  - Antidepressants – may have antimicrobial effects
- Early life stress – affects HPA axis and microbiome development
- Chronic stress – disrupts intestinal barrier integrity and microbiome composition
- Poor diet
- Environmental toxins and exposures



https://www.sciencedirect.com/science/article/abs/pii/S0963996921007924

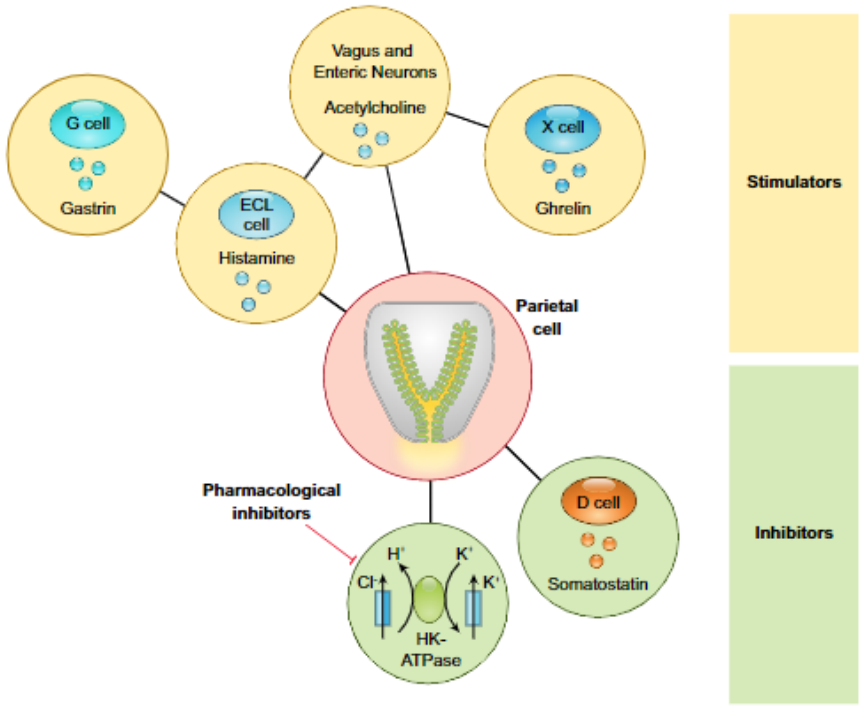
HISTAMINE – ESSENTIAL FOR GUT HEALTH

Physiological Reviews

Review Article

THE PHYSIOLOGY OF THE GASTRIC PARIETAL CELL

GRAPHICAL ABSTRACT



AUTHORS

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KEYWORDS

acid secretion; growth factors; mucosal homeostasis; parietal cell; stomach

Parietal cells are responsible for gastric acid secretion, which aids in the digestion of food, absorption of minerals, and control of harmful bacteria. However, a fine balance of activators and inhibitors of parietal cell-mediated acid secretion is required to ensure proper digestion of food while preventing damage to the gastric and duodenal mucosa. As a result, parietal cell secretion is highly regulated through numerous mechanisms including the vagus nerve, gastrin, histamine, ghrelin, somatostatin, glucagon-like peptide 1, and other agonists and antagonists.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7327232/:

DIAMINE OXIDASE & HISTAMINE INTOLERANCE

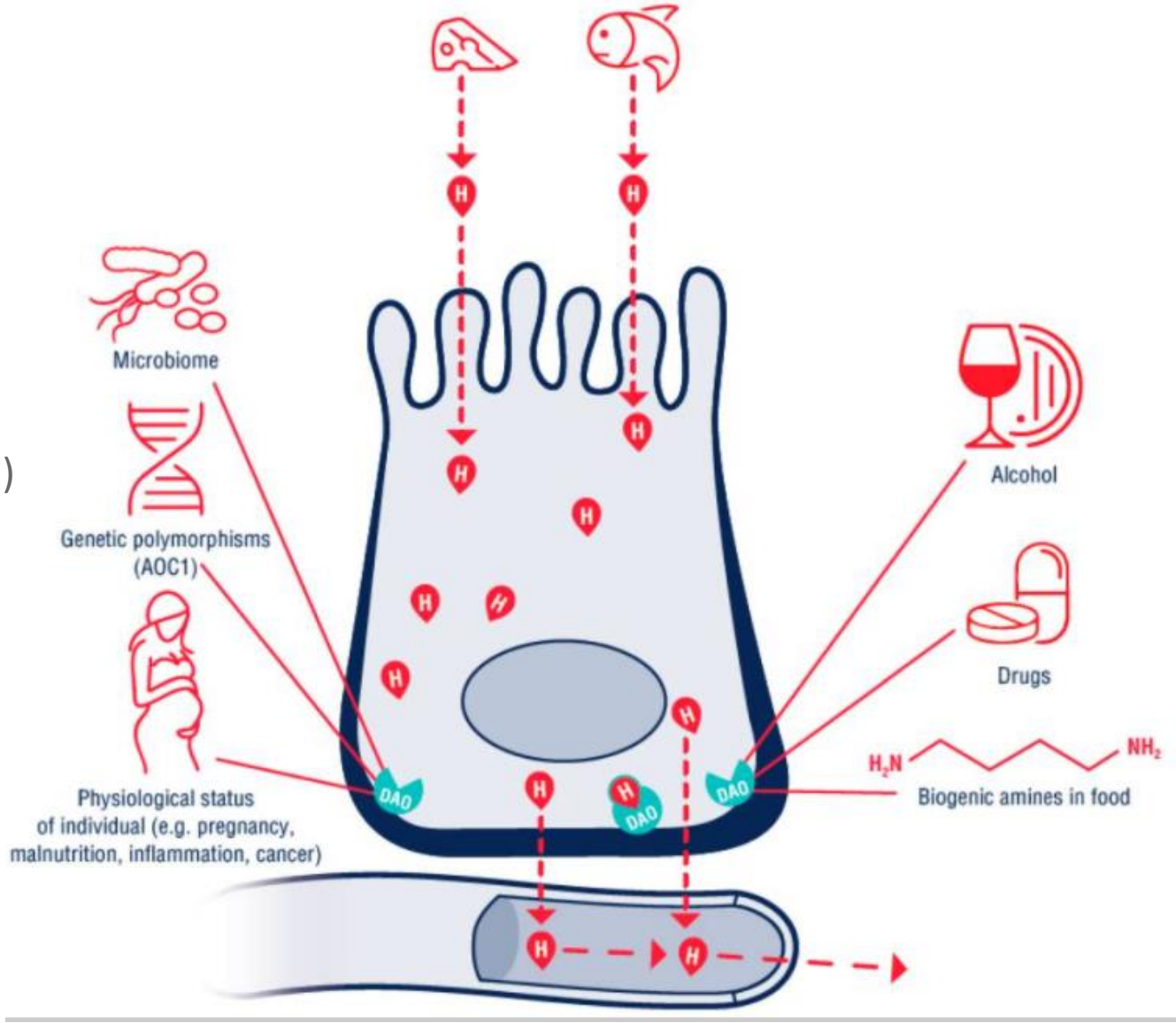
HISTAMINE & THE GUT

Diamine Oxidase – What is it?

- Extracellular enzyme that oxidizes and deaminates histamine into imidazole acetaldehyde
- DAO is histamine's vital counterpart
  - Primary enzyme responsible for keeping histamine levels in check
  - DAO degrades extracellular histamine
  - Mainly produced in the microvilli of the small intestine
- Low levels of DAO correlate with poor mucosal integrity and indicate poor gut function
- Atrophy of the microvilli can cause low DAO
- Low plasma DAO can be used to diagnose histamine intolerance

DAO MODULATORS

- High histamine foods – anything aged or fermented
- DAO blockers (alcohol, OTC drugs, many prescription medications)
- Antihistamines! This quick fix can create problems
- Host health (pregnancy, nutrient status, inflammation)
- Genetic polymorphisms
- The microbiome



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8308327/

HISTAMINE INTOLERANCE

- HIT – a.k.a Enteral Histaminosis
- Non immunologic
  - Food allergy 1-2% of the population
  - Food intolerance (i.e., lactose, histamine, fructose) 20% of adults in the US
- HIT is most often a result of impaired DAO activity
- 90% of NCGS (non-celiac gluten sensitivity) and HIT
- 97% of HIT patients have 3+ organ systems involved and an average of 11 symptoms

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8308327/

GOOD BUGS GONE BAD

SOME MICROBES PRODUCE
HISTAMINE TOO – EVEN THE GOOD GUYS

MICROBIAL CONTRIBUTIONS TO THE HISTAMINE POOL

M. SCHINK[1], P.C. KONTUREK[2], E. TIETZ[1], W. DIETERICH[1], T.C. PINZER[3], S. WIRTZ[3], M.F. NEURATH[3], Y. ZOPF[1]

MICROBIAL PATTERNS IN PATIENTS WITH HISTAMINE INTOLERANCE

[1]First Department of Medicine, Hector Center for Nutrition, Exercise and Sports, Friedrich-Alexander-Universitaet Erlangen-Nuernberg, Erlangen, Germany; [2]Second Department of Medicine, Thuringia-Clinic Saalfeld, Saalfeld/Saale, Germany; [3]First Department of Medicine, Friedrich-Alexander-Universitaet Erlangen-Nuernberg, Erlangen, Germany

Histamine intolerance represents a controversially discussed disorder. Besides an impaired degradation of orally supplied histamine due to diamine oxidase (DAO) deficiency, a deranged gut flora may also contribute to elevated histamine levels. Our aim was to determine the intestinal bacterial composition in patients with proven histamine intolerance in comparison to other food intolerances and healthy controls. A total of 64 participants were included in the study, encompassing 8 patients with histamine intolerance (HIT), 25 with food hypersensitivity (FH), 21 with food allergy and 10 healthy controls (HC). All lasma histamine and DAO serum acterial composition by 16s rRNA patients showed elevated levels of nd a significantly reduced alpha- r abundance of Bifidobacteriaceae 0.036). Also significantly reduced erved in the HIT patients, whereas occurrence of Proteobacteria and st a dysbiosis and intestinal barrier dysfunction in histamine intolerant patients, which in turn may play an important role in driving disease pathogenesis.

Key words: *dysbiosis, food intolerance, gastrointestinal microbiome, histamine, intestinal barrier, diamine oxidase, lactic acid bacteria*

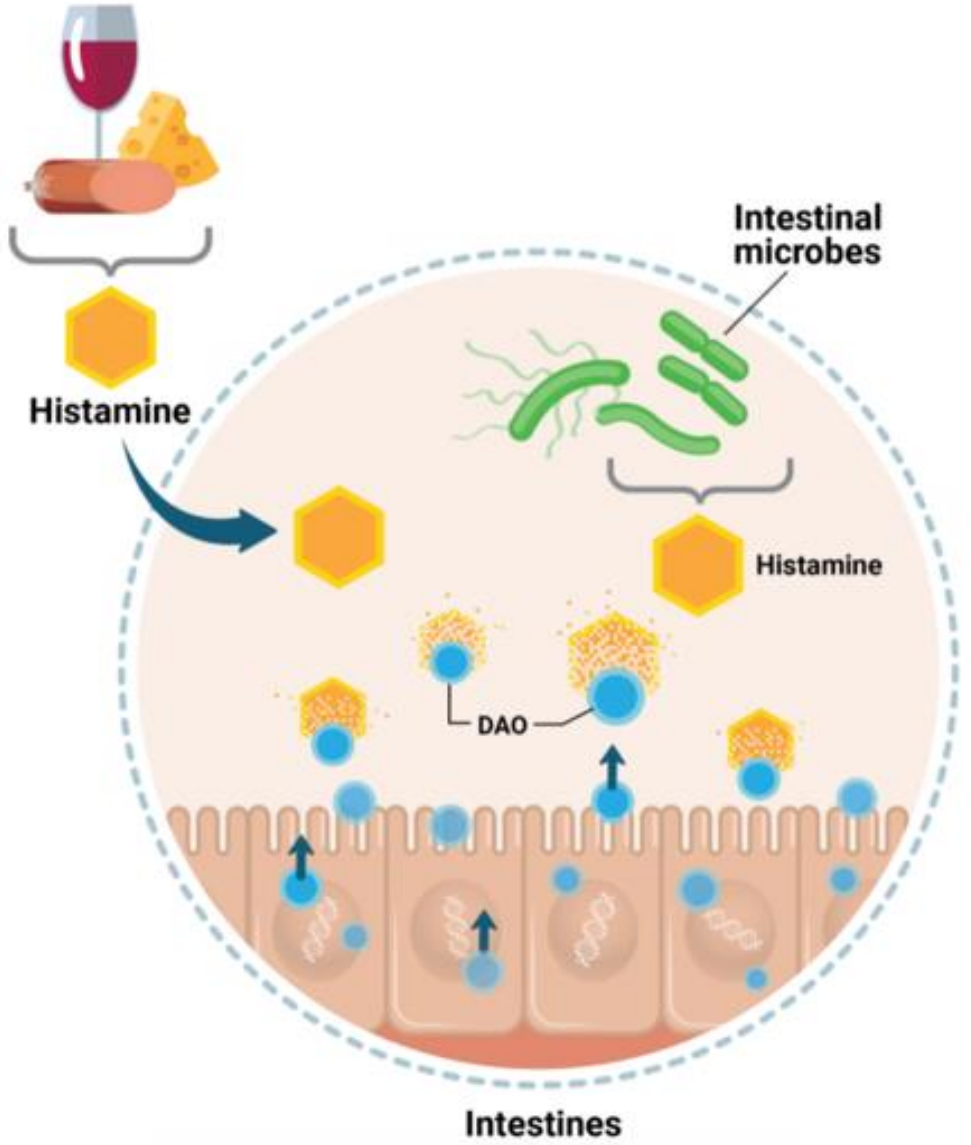
”Histamine intolerance represents a controversially discussed disorder. Besides an impaired degradation of orally supplied histamine due to diamine oxidase (DAO) deficiency, a deranged gut flora may also contribute to elevated histamine levels.”

https://www.jpp.krakow.pl/journal/archive/08_18/pdf/10.26402/jpp.2018.4.09.pdf

HISTAMINE EFFECTS IN THE GI TRACT

The Microbiome – a source of endogenous histamine production

- Those with Histamine Intolerance (HIT) have lower diversity in the microbiome
- Controls had higher levels of *Bifidobacterium*
- HIT participants had higher levels of *Proteobacterium*
- Some probiotic species produce histamine



Graphic Courtesy of Seeking Health

MICROBES MATTER MOST

WHY DO MICROBES MATTER MOST?

- Our bodies are host to literally *trillions* of microbes – more than the stars in the Milky Way, more than our own cells. As they go about their lives, they influence ours.
- Only in the last few decades have we begun to understand the magnitude of these small passengers. **The term "microbiome" (first used in the scientific community in the late 1980s) surged in public awareness over the last 20 years.** It describes the microorganisms coexisting in our bodies – bacteria, viruses, fungi.
- Scientists eager to explore this new realm have provided a wealth of research – **over 100,000 studies**. Proof of the vital role microbes play in whole-body health. They simultaneously foster the development of immune competence and tolerance. Providing us with benefits we are only beginning to grasp – **hydration, nutrient synthesis, protection against invaders, tissue healing**, and more. In short, we need them.

DYSBIOSIS – THE LPS/HISTAMINE CONNECTION

- LPS enhances H1 receptor function in endothelial cells (of prostaglandin I2 (PGI2), PGE2, and interleukin-6 (IL-6))
- LPS increases histamine 4-15 fold depending on the tissue
- LPS upregulates the activity of histidine decarboxylase
- Basophils show a sixfold increase in histamine with LPS exposure
- LPS causes mast cell degranulation – exacerbating asthma
- LPS-mediated mast cell activation activates NKs and IFN-γ secretion
- Stabilization of brain mast cells alleviates LPS-induced neuroinflammation by inhibiting microglia activation

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075511/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC416330/pdf/iai00286-0130.pdf
https://www.nature.com/articles/s41598-019-51716-6
https://www.sciencedirect.com/science/article/abs/pii/0090122985901849
https://pubmed.ncbi.nlm.nih.gov/22581748/
https://www.jimmunol.org/content/185/1/119.long
https://www.frontiersin.org/articles/10.3389/fncel.2019.00191/full

Molds and Mycotoxins

Symptoms of mold toxicity

- **Pathognomonic (highly specific symptoms)**
  - **Electric shock-like sensations**
  - **Ice pick-like pains**
  - **Vibrating or pulsing sensations running up and down the spinal cord**

- **Other symptoms include:**

Muscle weakness	Fatigue with cognitive impairment	Sensitivity to light
Numbness and tingling	Joint & muscle pain	Chronic sinus congestion
Disequilibrium	Headaches	Excessive thirst
Dizziness	Gastrointestinal symptoms	Sensitive to light touch
Severe anxiety & depression	Chest tightness & pain	Metallic taste in the mouth

The Microbiome & Mycotoxins

Microorganisms from the gut have been reported to exhibit the capacity for degrading and modifying the toxicity of mycotoxins.

- The most frequent mechanism is chemical transformation of mycotoxins by enzymes present in the microbes, or excreted by the microbes into the gut.

- Certain gut microbiota have constituents in their cell wall which can “bind” mycotoxins, thereby reducing their absorption.

- However, cases of activation into compounds that are more toxic than the parent compound are also known. Notably, the activation of “masked mycotoxins” by hydrolases before their absorption.

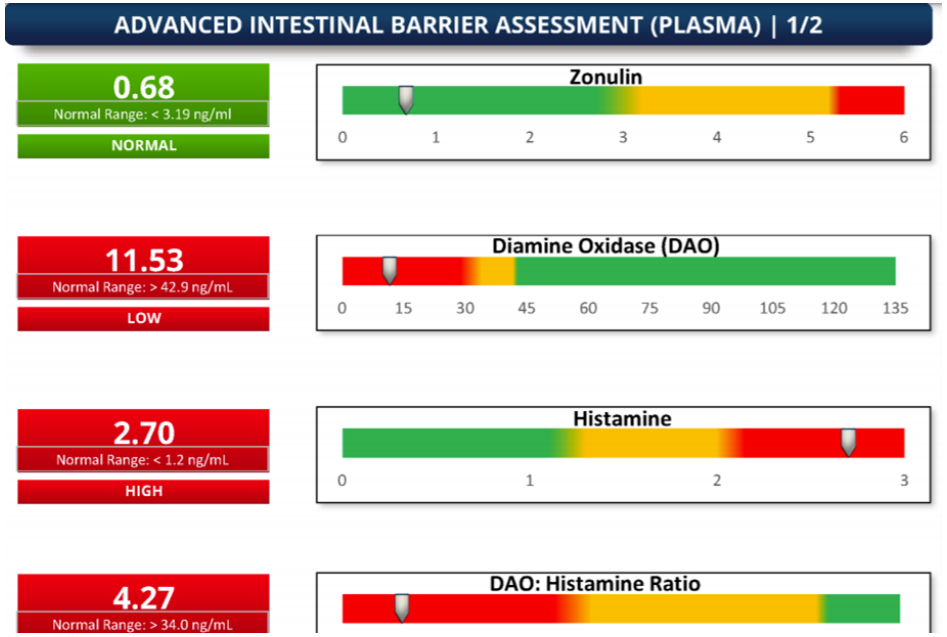
- Some mycotoxins can alter the composition of the gut microbiota.
  - Direct effects of mycotoxins on the microbes because of antimicrobial properties
  - Indirect effects secondary to the toxic effect of mycotoxins on the cells present in the gut

PILOT RESEARCH

BOTANICALS, BINDERS & HISTAMINE

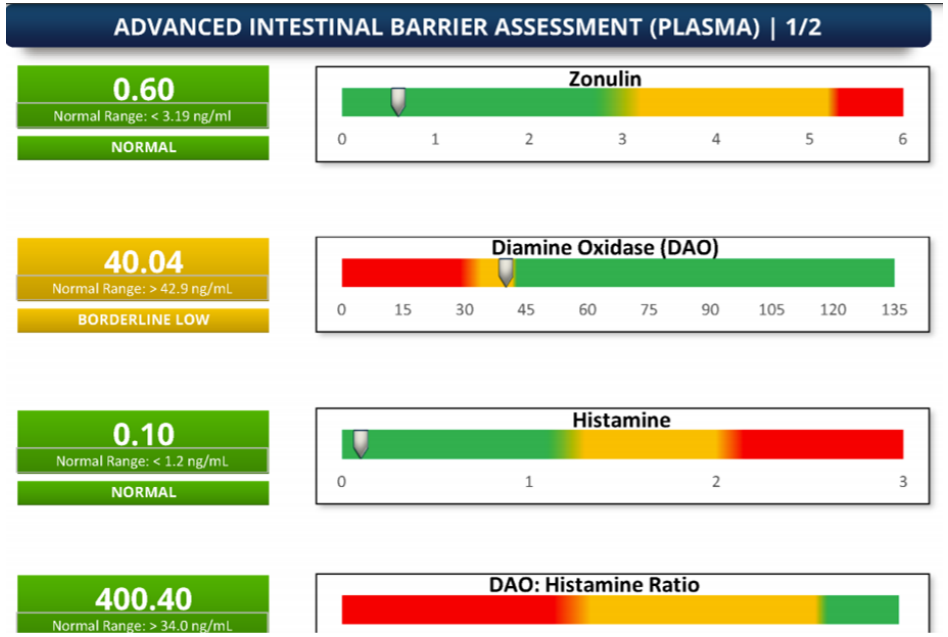
Participant #1

Pre-test 5/11/21



Participant #1

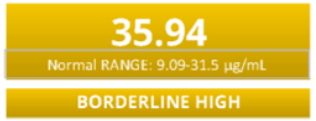
Post-test 6/23/21

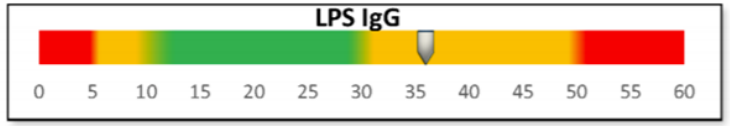


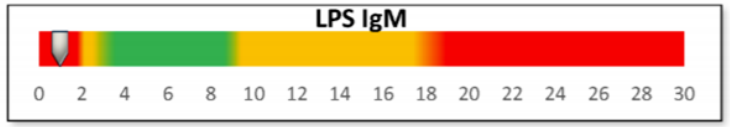
BOTANICALS, BINDERS & LPS

Participant #1

Pre-test 5/11/21







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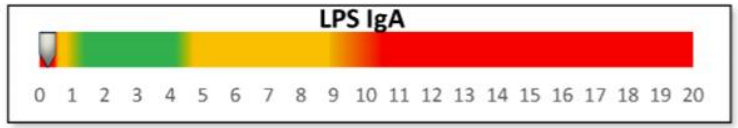
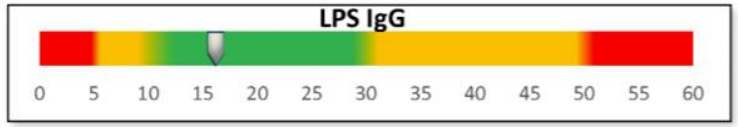
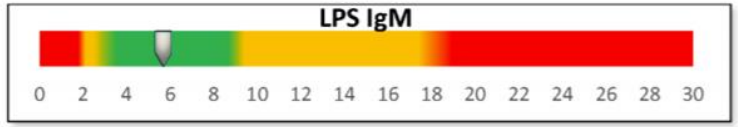


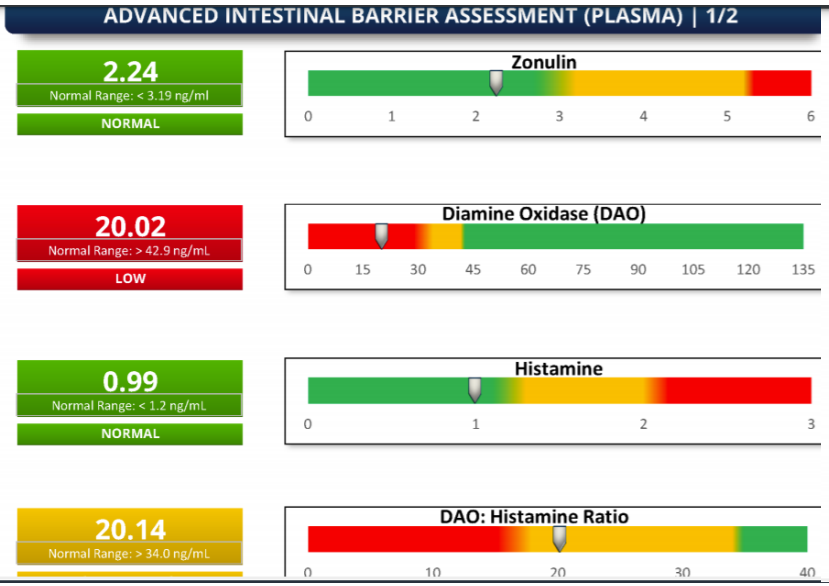




BOTANICALS, BINDERS & HISTAMINE

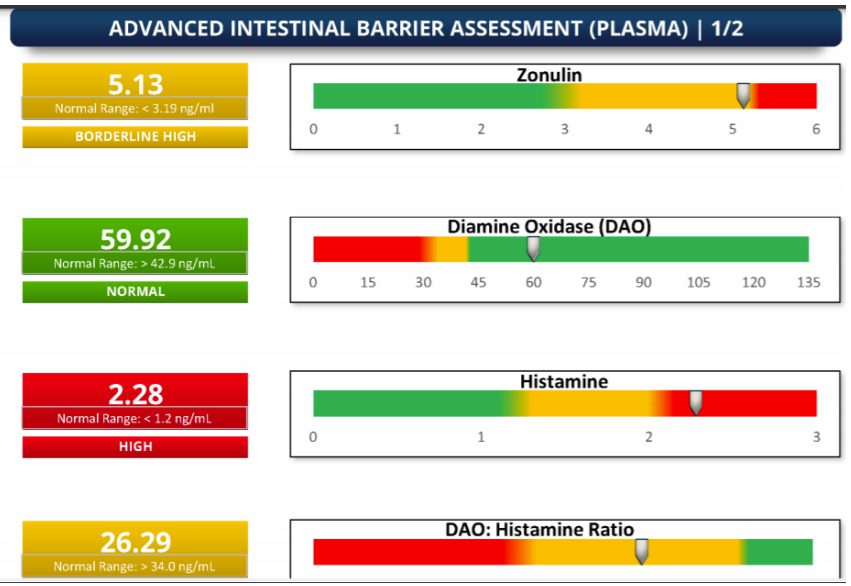
Participant #2

Pre-test 4/27/21



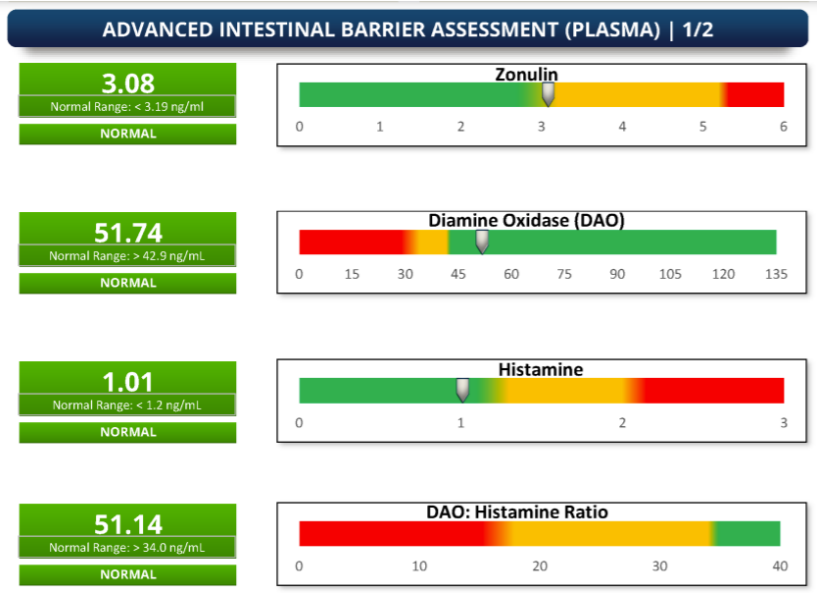
Participant #2

Post-test 06/08/21



Participant #2

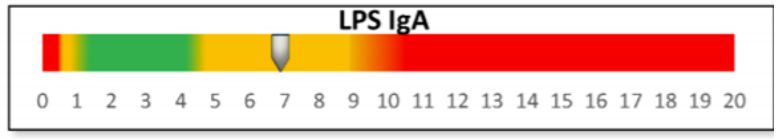
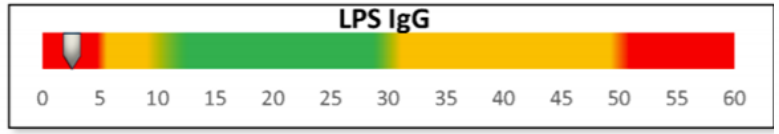
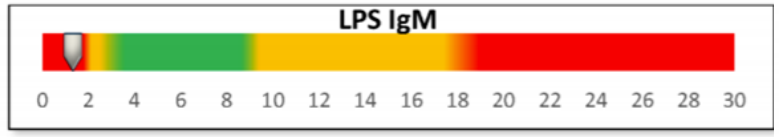
Post-test 07/16/21



BOTANICALS, BINDERS & LPS

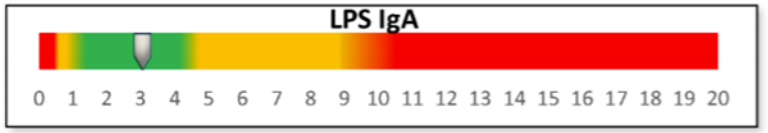
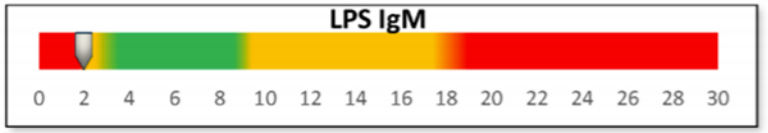
Participant #2

Pre-test 04/27/21

6.87 Normal RANGE: 0.83-4.47 µg/mL BORDERLINE HIGH	
2.57 Normal RANGE: 9.09-31.5 µg/mL LOW	
1.32 Normal RANGE: 2.5-9.4 µg/mL LOW	

Participant #2

Post-test 06/08/21

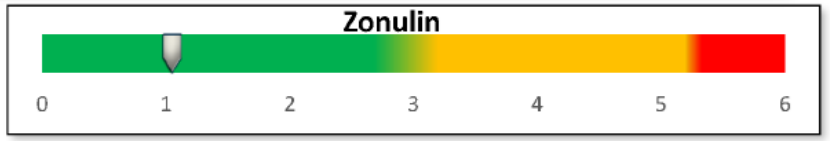
3.04 Normal RANGE: 0.83-4.47 µg/mL NORMAL	
6.16 Normal RANGE: 9.09-31.5 µg/mL BORDERLINE LOW	
1.98 Normal RANGE: 2.5-9.4 µg/mL LOW	

BOTANICALS, BINDERS & HISTAMINE

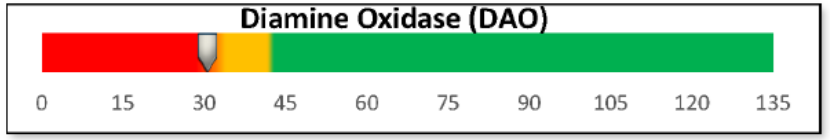
12/10/21

ADVANCED INTESTINAL BARRIER ASSESSMENT (PLASMA) | 1/2

1.05
Normal Range: < 3.19 ng/ml
NORMAL

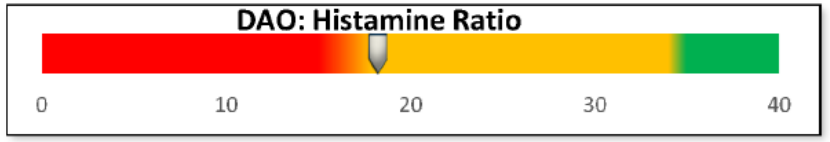


30.54
Normal Range: > 42.9 ng/mL
LOW



1.68
Normal Range: < 1.2 ng/mL
BORDERLINE HIGH

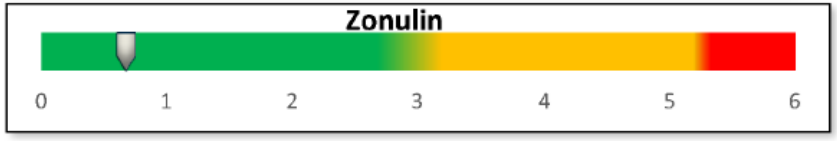
18.21
Normal Range: > 34.0 ng/mL
BORDERLINE LOW



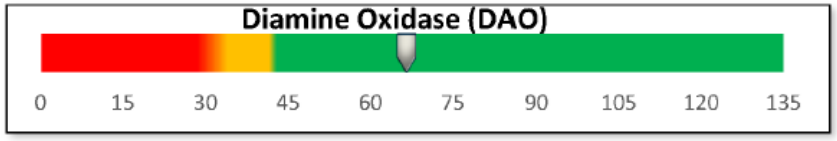
03/08/22

ADVANCED INTESTINAL BARRIER ASSESSMENT (PLASMA) | 1/2

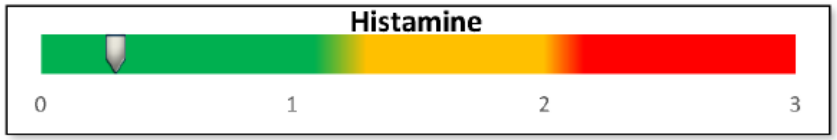
0.67
Normal Range: < 3.19 ng/ml
NORMAL



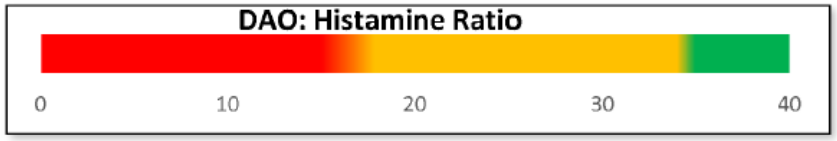
66.57
Normal Range: > 42.9 ng/mL
NORMAL



0.30
Normal Range: < 1.2 ng/mL
NORMAL



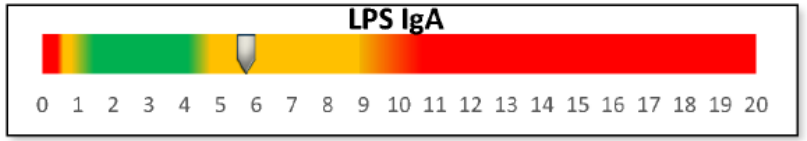
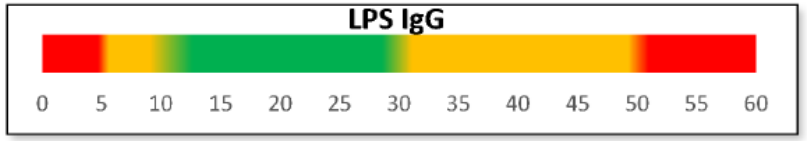
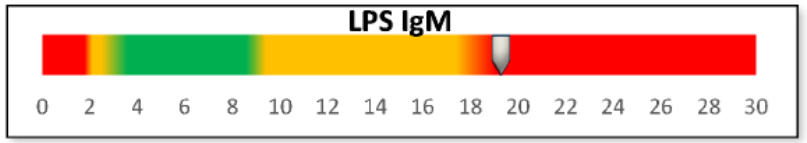
224.14
Normal Range: > 34.0 ng/mL
NORMAL



BOTANICALS, BINDERS & LPS

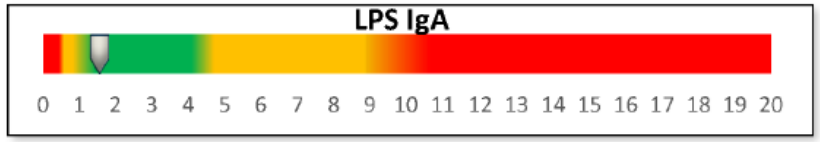
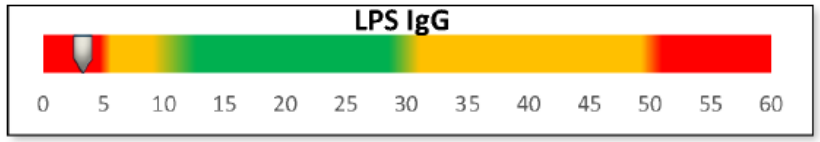
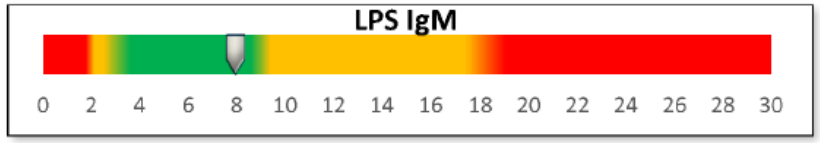
12/10/21

ADVANCED INTESTINAL BARRIER ASSESSMENT (PLASMA) | 2/2

5.71 Normal RANGE: 0.83-4.47 µg/mL BORDERLINE HIGH	LPS IgA 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	
74.58 Normal RANGE: 9.09-31.5 µg/mL HIGH	LPS IgG 0 5 10 15 20 25 30 35 40 45 50 55 60	
19.27 Normal RANGE: 2.5-9.4 µg/mL HIGH	LPS IgM 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	

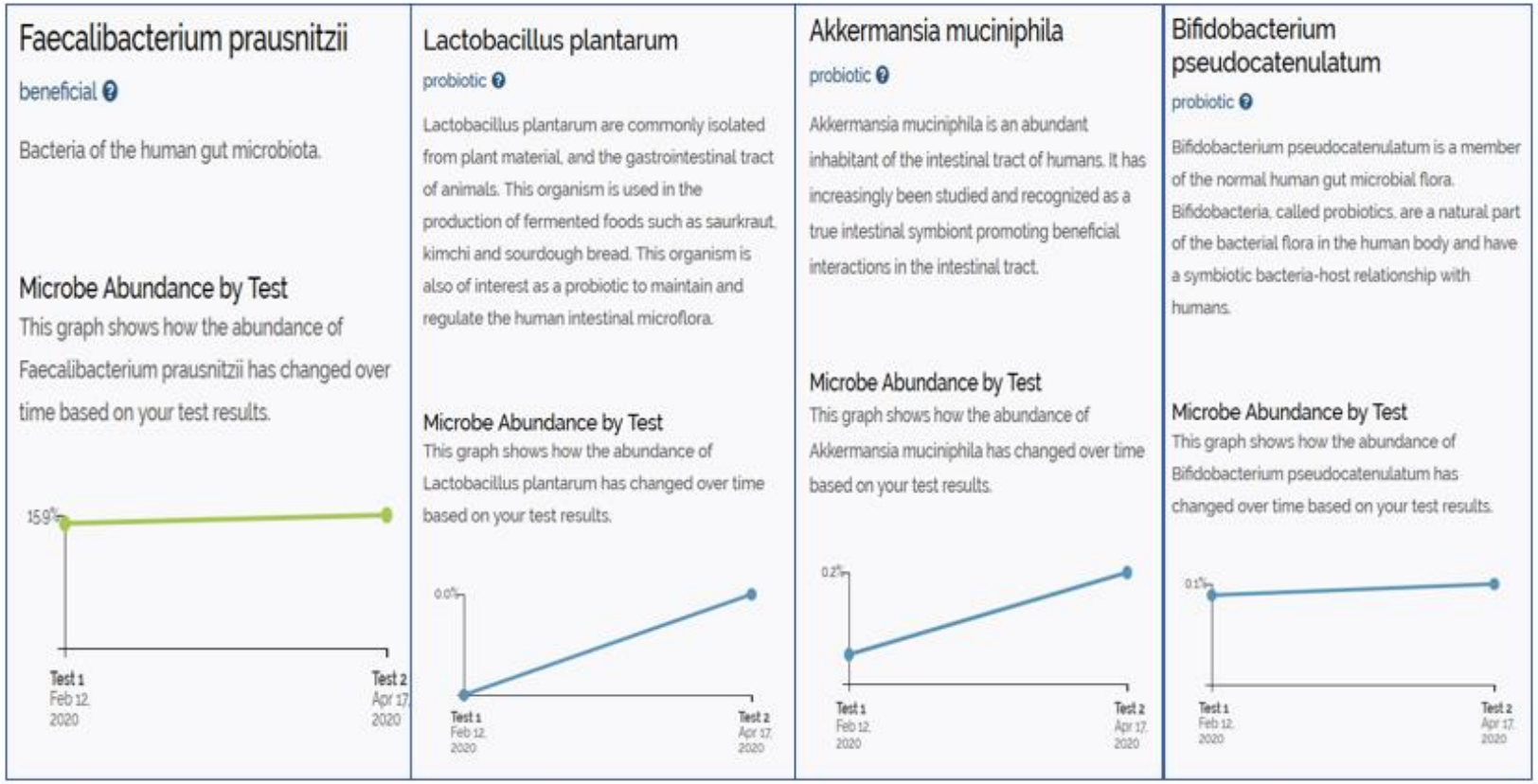
03/08/22

ADVANCED INTESTINAL BARRIER ASSESSMENT (PLASMA) | 2/2

1.55 Normal RANGE: 0.83-4.47 µg/mL NORMAL	LPS IgA 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	
3.27 Normal RANGE: 9.09-31.5 µg/mL LOW	LPS IgG 0 5 10 15 20 25 30 35 40 45 50 55 60	
7.93 Normal RANGE: 2.5-9.4 µg/mL NORMAL	LPS IgM 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	

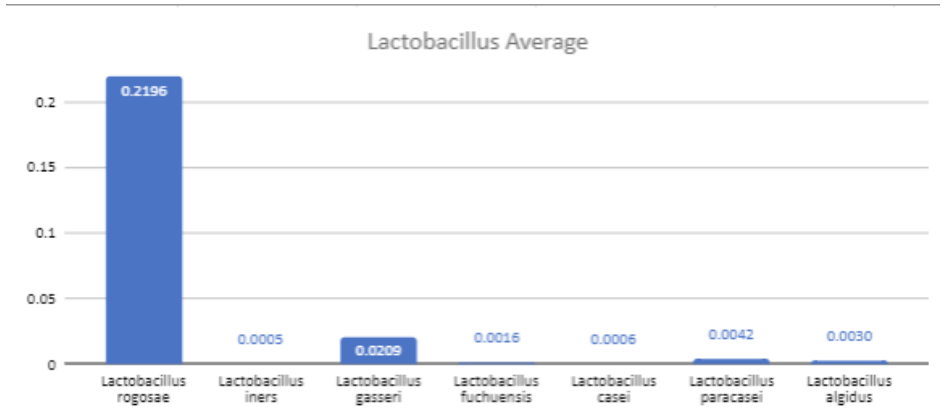
BOTANICALS & THE MICROBIOME

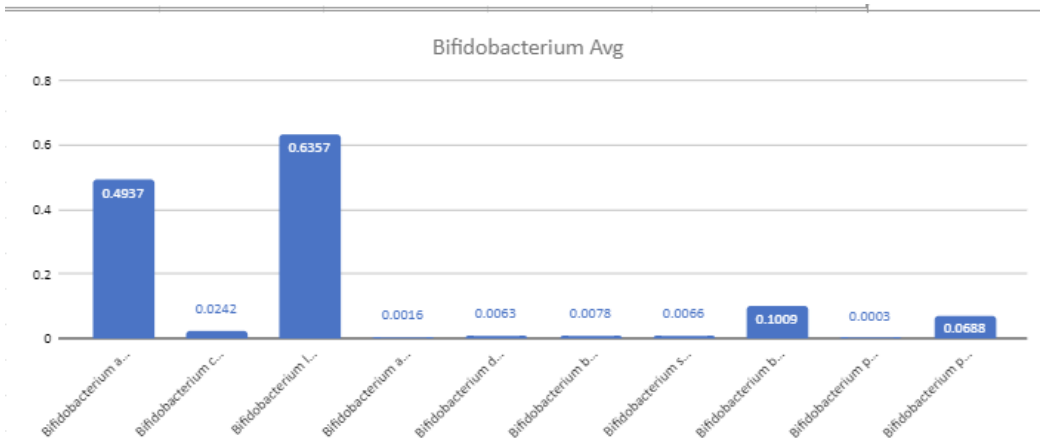
- Pilot study was completed in 2020 with 13 participants using a biocidal botanical formula and binders for 8 weeks at maximum dosing.
- 69% (9/13) of the participants had an increase in probiotic abundance.
- 73% (8/11) of the participants had an increase in *Akkermansia muciniphila*.



BOTANICALS & THE MICROBIOME

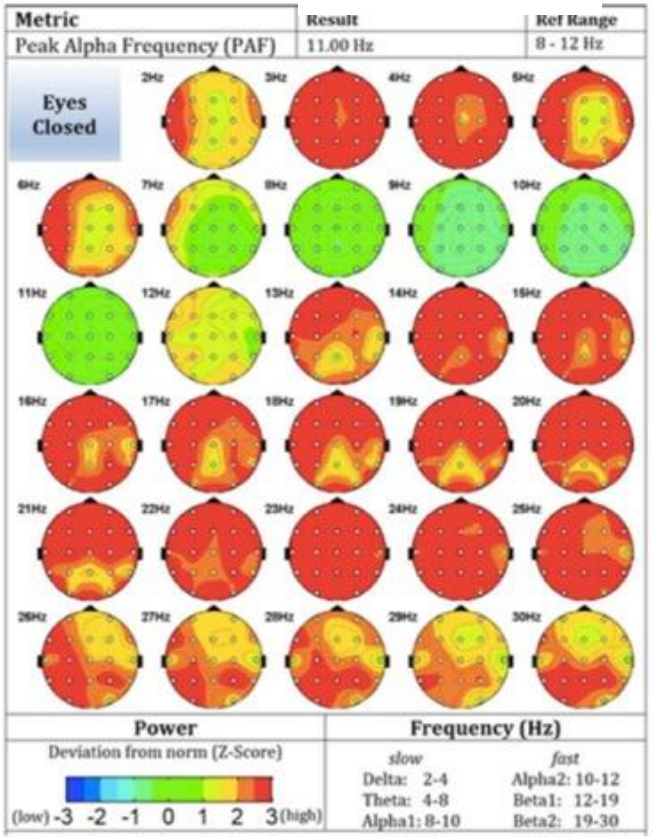
Probiotic Organisms Abundance(%):	23000064	23000099	23000065	23000096	23000070	23000078	23000061	23000068	23000057	23000090	23000101	23000060	23000084	23000085	23000055	23000051	23000052	23000054	23000088	24000359	23000083	24000366	23000086	24000499	23000076	23000077
Akkermansia muniiciphila	0%	0.33%	0.05%	0.19%	0%	0%	0.94%	11.26%	0.06%	1.31%	0.03%	1.36%	0.28%	2.13%	0.00%	0.00%	0.45%	1.38%	0.56%	0.00%	3.91%	4.15%	0.48%	0.05%	0.45%	0.19%
Oxalobacter formigenes	0.03%	0.10%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.00%	0.02%	0.00%	0.00%	0.00%	0.00%	0.13%	0.07%			0.03%	0.07%
Bifidobacterium pseudocatenulatum	0.09%	0.04%	0.08%	0.09%	0.01%	0.03%	0%	0%	0.16%	0.35%	0%	0%	0%	0%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00%	0%		0.25%			
Bifidobacterium longum	0.27%	0.04%	0%	0%	0.33%	0.32%	0.20%	0.13%	0.67%	3.45%	0%	0%	0.94%	0.75%	0.00%	0.00%	0.07%	0.06%	0.00%	0.00%	0.02%	1.01%	1.43%	2.19%	0.01%	
Lactococcus lactis	0.00%	0.01%	0.01%	0.02%	0.01%	0%	0.14%	0.11%	0.02%	0.07%	0.08%	0.25%	0.14%	0.02%	0.03%	0.13%	0.02%	0.05%	1.00%	0.01%	0.01%	0.22%	0.02%		0.03%	0.02%
Bifidobacterium pseudolongum	0.01%	0.00%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.05%		0.20%		
Lactobacillus plantarum	0%	0%	0%	0.01%	0%	0%	0%	0%	0%	0%	0%	0.02%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.03%				
Bifidobacterium bifidum	0%	0%	0%	0%	0.26%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%		0.02%			
Streptococcus thermophilus	0%	0%	0%	0%	0.01%	0%	0.04%	0.01%	0%	0.06%	0.73%	0.08%	0.07%	0%	0.03%	0.04%	0.03%	0.00%	4.00%	3.30%	0.01%					0.02%
Bifidobacterium adolescentis	0%	0%	0%	0%	0%	0.08%	2.05%	1.51%	0%	0%	0%	0%	0%	0%	0.00%	0.00%	5.30%	2.84%	0.00%	0.00%	0.00%	8.29%	1.80%	6.25%		
Lactobacillus reuteri	0%	0%	0%	0%	0%	0%	0%	0.01%	0%	0%	0%	0%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
Bifidobacterium sp.12_1_47BFAA	0%	0%	0%	0%	0%	0%	0%	0%	0.02%	0.17%	0%	0%	0.03%	0.02%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%		0.01%		
Saccharomyces cerevisiae	0%	0%	0%	0%	0%	0%	0%	0%	0.04%	0%	0%	0%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
Bifidobacterium breve	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.04%	0%	0%	0%	0.02%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%			0.01%		
Lactobacillus paracasei	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.11%	0.03%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
Lactobacillus casei	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.01%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%			0.02%		
Lactobacillus rhamnosus	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.44%	0%	0%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%					
Bifidobacterium animalis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0.00%	0.00%	0%	0%	0.00%	0.00%	0.06%	0.00%	0.00%	0.00%	0.00%		0.01%			
Bacillus Subtilis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%												0.03%	0.00%			
Bifidobacterium Catenulatem																						0.02%	0.01%	0.01%		
Total Abundance	0.40%	0.52%	0.14%	0.31%	0.62%	0.43%	3.37%	13.03%	0.97%	5.45%	0.95%	2.19%	1.46%	2.94%	0.06%	0.19%	5.95%	4.33%	5.56%	3.31%	4.08%	13.84%	4.01%	8.73%	0.52%	0.30%



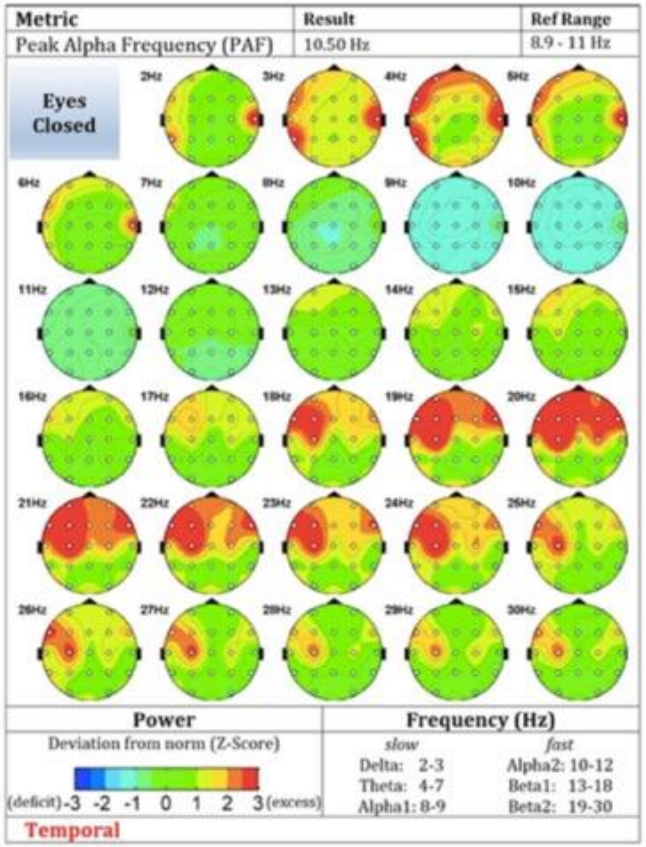


NEUROINFLAMMATION CASE STUDY

11.21.18 Baseline -



7.9.19 Post - Susan

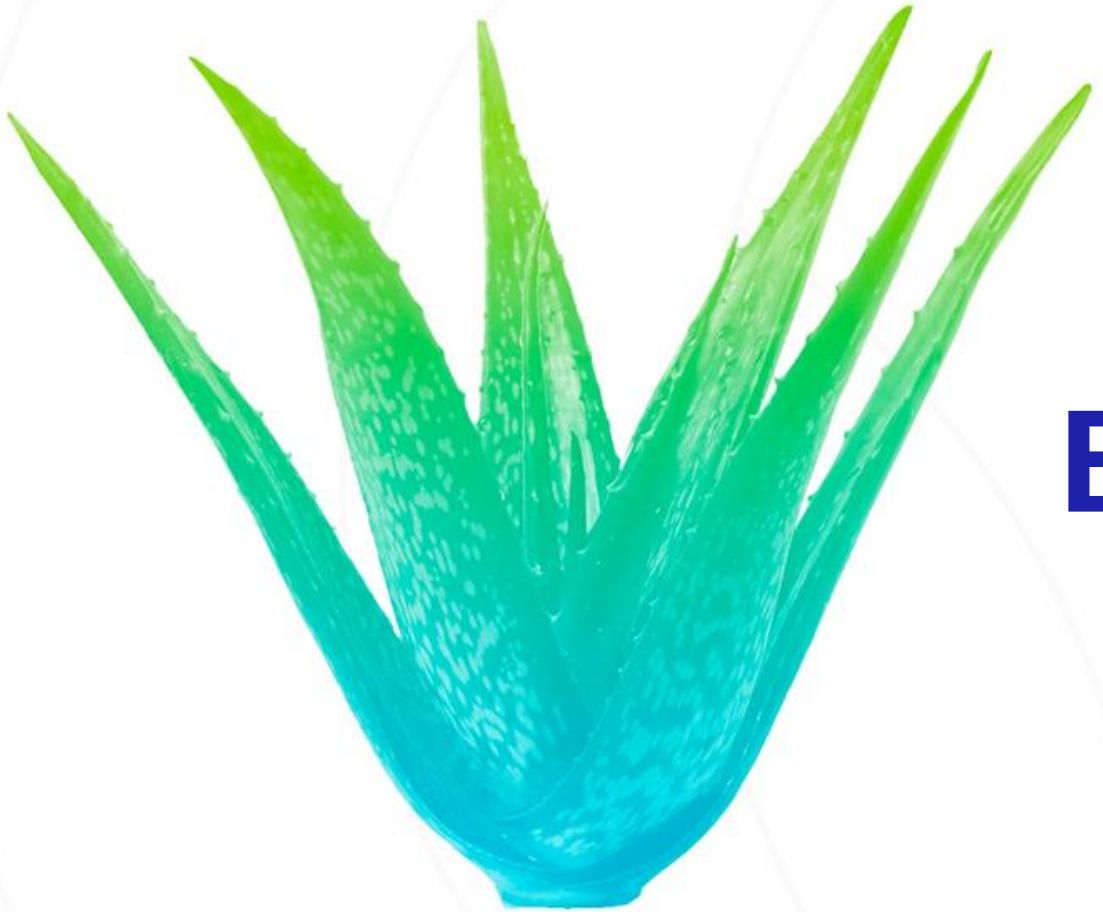


NeuroRead

Improved alpha peak

Much improved delta and theta power.

Much improved reduction in what is believed to be neuro-inflammation

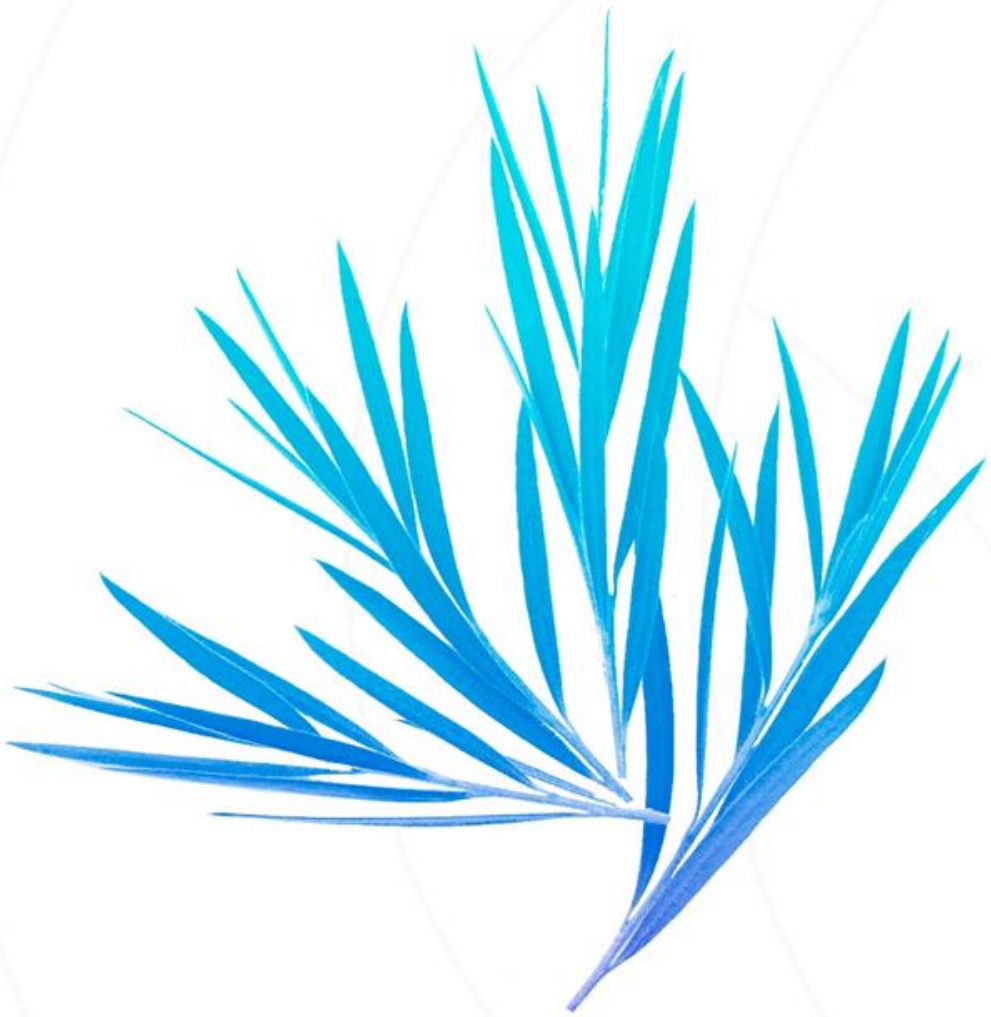


BIOFILMS

BIOFILMS IN CLINICAL PRACTICE

Proceed with caution!

- The extracellular matrix holds on to cellular and metabolic debris
  - Histamine
  - Exogenous toxins (heavy metals, organophosphates etc)
  - Microbes – new irritants
  - Oxalates
  - Anything that floats by!
- The ECM is composed of PAMPS
- There will likely be multiple organisms at play
- Use titration and binders to support patient comfort



ORAL DYSBIOSIS

ORAL LPS & HISTAMINE

Lipopolysaccharide stimulates histamine-forming enzyme (histidine decarboxylase) activity in murine dental pulp and gingiva

Noriaki Shoji [a], Atsushi Yoshida [a, b], Zhiqian Yu [a, b], Yasuo Endo [b], Takashi Sasano [a]

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https://doi.org/10.1016/j.archoralbio.2006.04.004

Summary

To examine the potential role of the histamine-forming enzyme, histidine decarboxylase (HDC), in oral inflammation and disease, we studied HDC activity in oral tissue after induction by bacterial agents. Following injection of *E. coli*-derived lipopolysaccharide (LPS) into mice, we measured the quantitative changes in HDC activity over time in dental pulp and gingiva. Oral tissue taken from individual mice was insufficient for detecting precise HDC activity, thus, we combined dental pulp

ORAL BIOFILMS

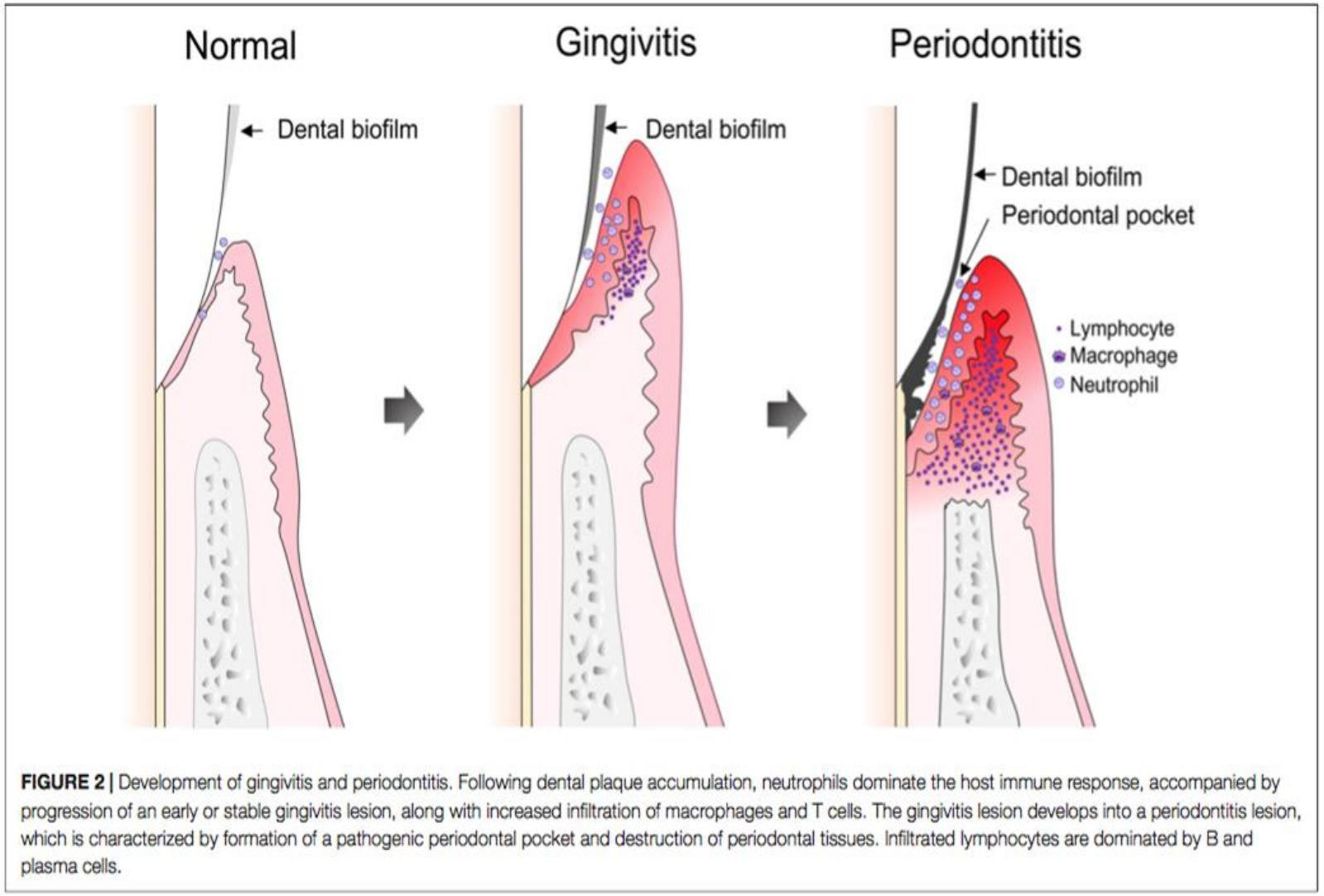


FIGURE 2 | Development of gingivitis and periodontitis. Following dental plaque accumulation, neutrophils dominate the host immune response, accompanied by progression of an early or stable gingivitis lesion, along with increased infiltration of macrophages and T cells. The gingivitis lesion develops into a periodontitis lesion, which is characterized by formation of a pathogenic periodontal pocket and destruction of periodontal tissues. Infiltrated lymphocytes are dominated by B and plasma cells.

Kriebel K, Hieke C, Muller-Hilke B, Nakata M, Kreikemeyer. Oral Biofilms for Symbiotic to Pathogenic Interactions and Associated disease – Connection of Periodontitis and Rheumatic Arthritis by Peptidylarginine Deiminase. Frontiers Microbio. Jan 2018; Vol.9: article 53.with permission.

THE POWER OF BOTANICALS

THE POWER OF BOTANICALS & THE MICROBIOME

Microbes are not an enemy to be eliminated, but an ecology to be nourished.

How do we do that?

By working with the gift of botanicals.

Plants have developed tools to grow and flourish under the same environmental stressors that we face.

They have an innate capacity to protect themselves – producing antimicrobial compounds, antioxidants, biofilm disruptors, and immune modulators.

(Yes, plants have immune systems, too!)

A Brief History of Plants as Medicine

- The origins of plants being used as medicines were instinctive.
- In ancient times, the knowledge and understanding of illnesses, and therefore treatments, was very limited.
- Everything was based on experience.
- Until the advent of iatrochemistry in the 16th century, plants were the source of treatment and prophylaxis.

1. Petrovska BB. Historical review of medicinal plants' usage. Pharmacogn Rev. 2012 Jan;6(11):1-5. doi: 10.4103/0973-7847.95849. PMID: 22654398; PMCID: PMC3358962

THE SYNERGY OF PLANTS

Each plant offers multiple activities.

When layered together in a formula – a powerful synergy occurs.

- Antimicrobial activity
- Activity against biofilms
- Protective antioxidant action
- Immunomodulation

The outcome is not additive but exponential!

Botanicals offer a graceful and mighty solution that cannot be duplicated. The power to achieve and maintain balance.

The power to thrive.

SYNERGY OF BOTANICAL FORMULAS

Scientific literature shows that individual botanicals have multiple activities, which may account for outcomes seen in a clinical setting.

- **Analgesic:** Black walnut, Galbanum oil, Noni, White willow bark
- **Antibacterial:** Black walnut, Garlic, Goldenseal, Noni, Oregano oil, Tea tree oil
- **Antifungal:** Echinacea, Galbanum oil, Lavender oil, Oregano oil, Shiitake, Tea tree oil
- **Anti-inflammatory:** Bilberry, Galbanum oil, Garlic, Gentian, Goldenseal, Grape seed, Lavender oil, Milk thistle, Noni, Oregano oil, Raspberry leaf, White willow bark
- **Antimicrobial:** Bilberry, Black walnut, Echinacea, Fumitory, Galbanum oil, Garlic, Gentian, Goldenseal, Lavender oil, Milk thistle, Noni, Raspberry leaf, Tea tree oil
- **Antioxidant:** Bilberry, Black walnut, Fumitory, Garlic, Gentian, Grape seed, Milk thistle, Noni, Raspberry leaf, Shiitake
- **Antiparasitic:** Black walnut, Galbanum oil, Garlic, Noni
- **Antiviral:** Echinacea, Galbanum oil, Noni
- **Biofilm disruptor:** Garlic, Oregano oil, Tea tree oil
- **Immunomodulatory:** Echinacea, Noni, Shiitake

BIOFILM CONTROL WITH BOTANICALS

Published research has shown the efficacy of botanicals to affect the following:

- **Quorum Sensing inhibition**
  - Garlic, oregano, bilberry, goldenseal
- **Initial Attachment Phase inhibition**
  - Oregano, lavender oil, tea tree oil, grapeseed, bilberry
- **Swarming Motility inhibition**
  - Grapeseed, bilberry
- **Efflux Pump inhibition**
  - Echinacea, gentian, goldenseal, shiitake, bilberry, black walnut, garlic, gentian, grapeseed, lavender oil, oregano oil, tea tree oil

ADDITIONAL TREATMENT STRATEGIES

SUGGESTED BINDERS

Microbial debris, metabolites, and immune waste need to be removed or a rebound immune/inflammatory response is likely. (**Herxheimer Reaction** or "**Healing Crisis**")

- **Zeolite Clay**: Chelating and binding agent to assist in removal of toxins and heavy metals.
- **Activated Charcoal**: Sourced from bamboo, it assists in binding and absorbing a variety of organic and inorganic compounds.
- **Aloe Vera Extract**: This anti-inflammatory inner leaf material soothes and promotes repair of the mucosal layer of the GI tract.
- **MMST Silica**: Another well known chelating agent to assist in binding toxins and metals.
- **Apple Pectin**: Another excellent chelating agent, with a broad affinity for various biotoxins.

ZEOLITE

Silica-rich zeolite powder (clinoptilolite)

- High CEC (cation exchange capacity)
- Large surface area
- Not technically a “clay”
- Unusually high silica content in order to increase binding capacity
  - Ammonium and other cations are held in the negatively charged lattice through CEC
  - Shown to bind ammonium and mycotoxins in feed
- 3rd party-tested for microbial contaminants and heavy metals
  - Aluminum is always detected in aluminosilicate minerals (it’s the ”backbone” of the molecules), but it is not bioavailable
  - All heavy metals are well under the EPA, USDA, and California Prop 65 established safe levels for daily consumption
- Studies on the ion exchange in clinoptilolite received extensive attention due to their selectivities for ammonia, some radioactive materials, and heavy metals

ALOE

Aloe Vera – Inner Leaf

- Acetylated long-chain polysaccharides in the aloe vera leaf observed to have hepatopr against aflatoxin B1
- Observed to activate a number of enzymes in the body, which are responsible for eliminating chemicals and pollutants through antioxidant status and carcinogen metabolism

MMST SILICA

- The oligomeric, high-aluminum-affinity form of soluble silica reduces aluminum availability from the human gastrointestinal tract
- Stabilized with acacia gum – no maltodextrin
- Converts easily into orthosilicic acid when ingested

HUMIC ACID

Apple Pectin

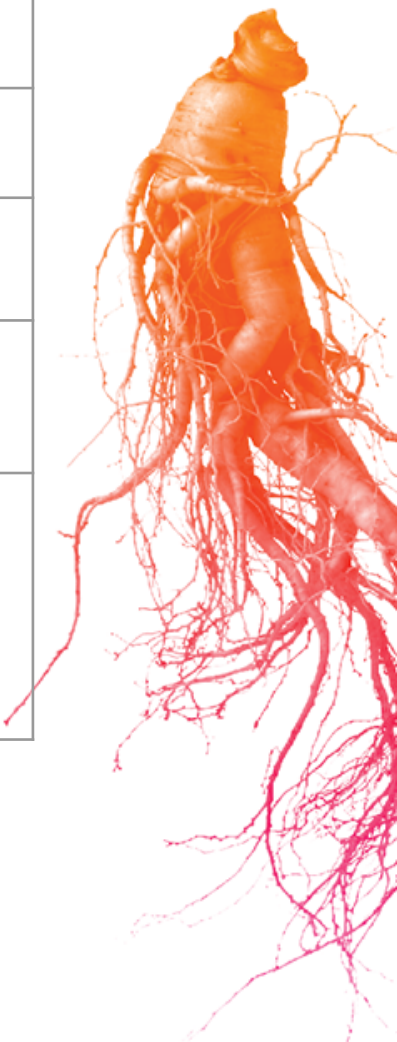
- Observed to reduce radiation load
- Pectin can vary, but promotes excretion of toxic metals to varying degrees
- Counteract some inflammatory effects of lectins
- Observed to decrease slow-transit constipation

Humic/Fulvic Mineral Powder

- High ratio of humic acid to fulvic acid
  - Humic acid acts as a binding site for chemi compounds such as:
    - Arsenite
    - Uranium
    - Polar pesticides
  - Fulvic acid (improves nutrient absorption)

SUPPLEMENTATION FOR HIT

Broad-spectrum antimicrobials	Biocidin® liquid, Biocidin® LSF
Binders	GI Detox™+, activated charcoal, zeolite
Diamine Oxidase – to replace for those low in endogenous DAO	Seeking Health or Xymogen
Antihistamine and mast cell stabilizing (nettles, quercetin, NAC, bromelain, vitamin C	D-Hist by Orthomolecular, Seeking Health
Directed nutrients to support histamine processing epigenetics	Histamine Block Plus by Seeking Health
Probiotics – be careful here!	Histamine-friendly probiotic, supports microbiome balance and a healthy gut response to ingested histamine: ProBiota HistaminX by Seeking Health



https://www.jpp.krakow.pl/journal/archive/08_18/pdf/10.26402/jpp.2018.4.09.pdf

HISTAMINE DETOX PATHWAY SUPPORT

Increase detoxification strategies:

- **Increase fluids** – water, lemon water
- **Alkalize** – Alka-Seltzer Gold, buffered vitamin C, or lemon-lime water at onset of symptoms
- **Support liver** – NAC, glutathione, milk thistle, dandelion root, etc.
- **Replenish minerals** – Trace minerals, magnesium, zinc, selenium, copper
- **Open drainage pathways** – Epsom salt bath, dry skin brushing, lymph drainage massage, castor oil packs, infrared sauna, enemas or coffee enemas, mild exercise, drainage remedies (homeopathic)
- **Bind toxins** – Full-spectrum binder with activated charcoal, zeolite clay, humic/fulvic acid, silica, pectin
- **Sauna** – Proceed with caution!
- **Sleep** – Commit to a consistent bedtime routine and wake up at the same time every day
- **Diet** – Eat low-inflammatory foods