GASTROINTESTINAL PROCESSES

Symptoms and Clinical Considerations

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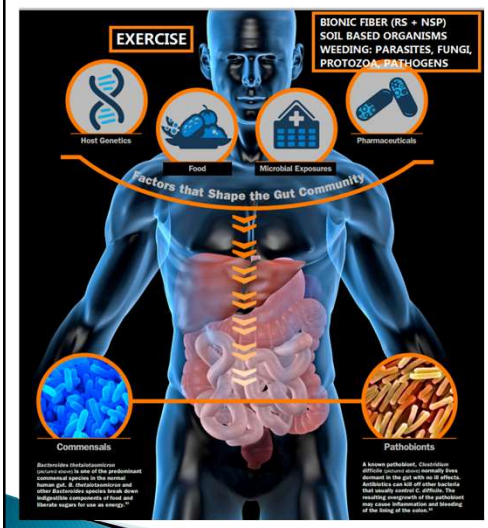
Gastrointestinal: Definitions



- Dysbiosis- microbial imbalance on or inside the body
  - This could be a pathological imbalance or a beneficial imbalance
  - In the context of health care this term normally indicates some negative impact on the human
- SIBO- Small Intestinal Bacterial Overgrowth- increased numbers and/ or abnormal type of bacteria in small intestines

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Microbial Shift Disease/Dysbiosis/SIBO

- A shift in microbial balance can begin to breakdown the barrier system within the GI tract (sometimes termed "leaky gut" or increase intestinal permeability)
  - This will lead to elevations of pro-inflammatory compounds often times chronic which can trigger alterations in pain thresholds, disruption of endocrine function and causal links in mood disorders
- There is bidirectional communications between the gut and the CNS

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Microbial Shift Disease/Dysbiosis/SIBO

- Vagal nerve afferent stimulation and possibly direct transport vessel to the brain *Acta. Neuropathol. 128, 805–820 (2014), Med. Hypotheses. 68, 1252–1257 (2007).*
- Disruption of neuro-immune cross talk *Immunol. Res. 63, 38–57 (2015).*
- "Leaky gut"- releasing compounds such as LPS endotoxins into circulation which stimulate systemic and CNS inflammation
  - Alter phase I (CYP450- enzymes) detoxification strategies of the body
- Increased neurotoxin exposure

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Dysbiosis

- Dysbiosis contributes to immune, metabolic, and neurologic dysfunction and resultant clinical disorders
  - Prevention of pathogen penetration into the lamia propria is via goblet cells and their production of mucins, which forms a protective mucous layer Cell. 2014 Feb 27;156(5):1045-59
    - Microbiota also regulates general functions of the GI: mucous production via the goblet cells is regulated by the microbiota on the intestinal epithelium and thus can be disrupted by dysbiosis Ann Nutr Metab. 2013;63 Suppl 2:28-40

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Additional Diseases/Symptoms

- Low immune status (sIgA)
- Insomnia
- Increased risk of mood disorders- anxiety, depression, PTSD
- Cognitive decline
- Inflammatory bowel disease
- Poly-neuropathy
- Cancer

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Allergies and Asthma

- Regulation of a proper, or improper immune response
  - "HYGEINE HYPOTHESIS"- the lack of exposure to different infectious agents early on in life as well as symbiotic organisms does not properly balance the immune response and thus leading to a potential up-regulation in Th2
- Antibiotics, diet, stress, and lifestyle can all alter the microbiome leading to altered mucosal immunity

Allergy Asthma Clin Immunol. 2015; 11

7

Secretory IgA (sIgA)

- Est. 80% of total body sIgA is in the gastrointestinal tract
  - 1st response to enteric pathogenic microbes
- sIgA mechanism: binds to proteins (epitopes) on microbes

FEMS Immunol Med Microbiol (2001)30:31-35
Clin Microbiol Rev (2006)19:315-37
JPEN (2012)36:1065-175

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GI Environment

- Not all patients exposed to a pathogenic microbe with develop disease
  - Patients biochemical individuality and genetic uniqueness play a large role in the pathogenesis of disease
- On the other hand, some otherwise benign commensal microbes can cause dramatic responses which can result in disease

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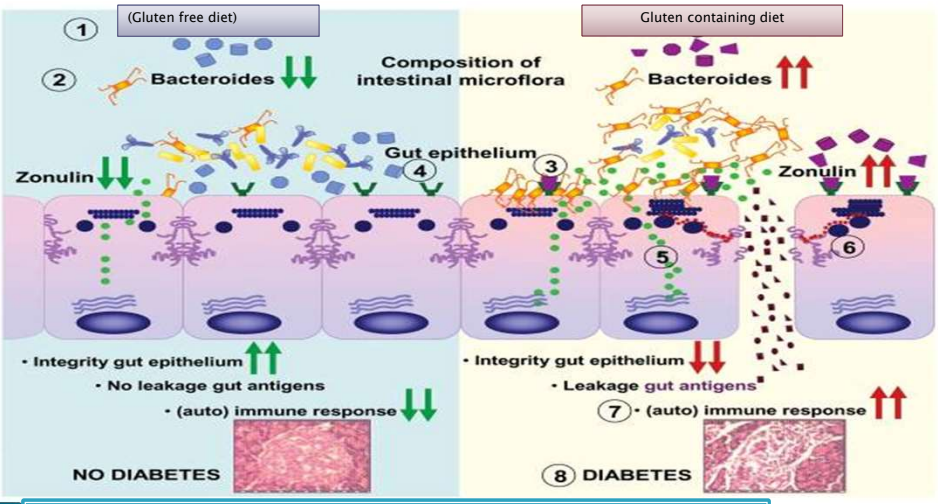
Intestinal Permeability and Diabetes



Imbalanced microflora that favors Bacteroides over *Bifidobacterium* and *Lactobacillus* activates zonulin which dissembles tight junctions

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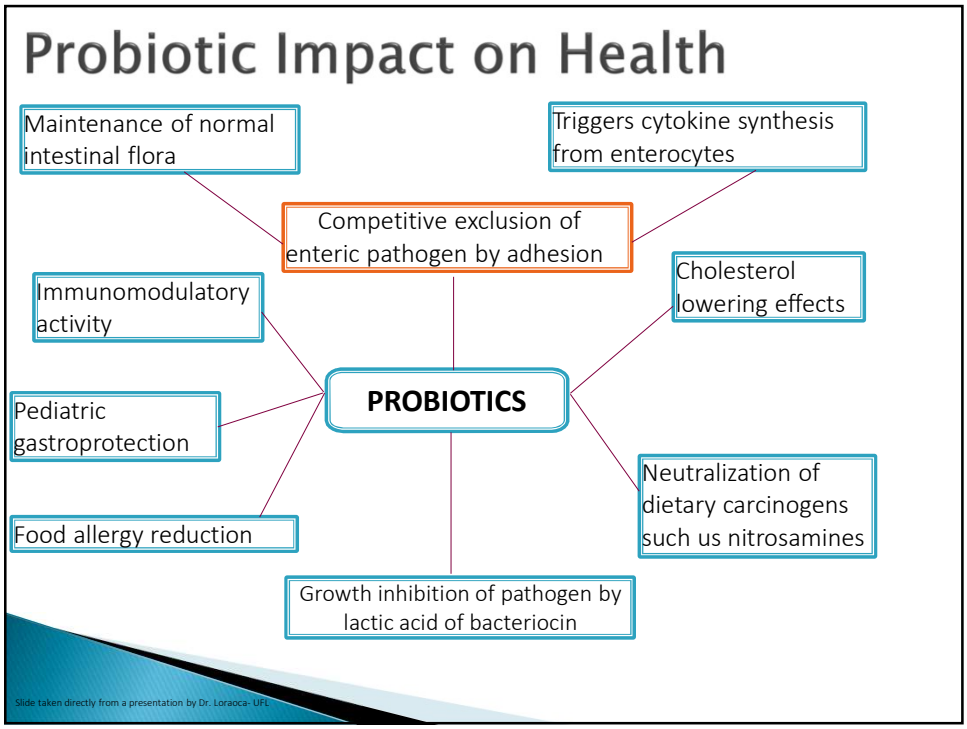

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Probiotics and GI Inflammation

- Lactobacillus species can reduce inflammation as proved by the reduction of serum studies of nuclear factor-kappa (NF-kB).
  - Further studies have been performed in human models diagnosed with ulcerative colitis and the effects of oral supplementation of *Lactobacillus* [species] were remarkable. The anti-inflammatory effect of the oral probiotics was greater than the group who received sulfasalazine, a common anti-inflammatory for autoimmune IBD

World Journal of Gastroenterology : WJG. 2010;16(33):4145-4151.

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Probiotics and GI Inflammation

- Reduction of inflammation → reduction of IL-6, leukocyte recruitment and myeloperoxidase activity
  World Journal of Gastroenterology : WJG. 2010;16(33):4145-4151.
  - Probiotics may also stimulate GSH production: ROS and hydroxyl radical scavenger *Mazidi et al., 2017; Asemi et al., 2013; Hegazy et al., 2010*
- *Mazidi et al.* conducted a large meta-analysis of random control trials on the effects of probiotics and their impact on C-reactive protein. This study demonstrated that probiotics do in fact significantly lower C-reactive protein.

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Probiotcs

Probiotics also lower inflammatory proteins such as IL-8 and TNF-α, effectively reducing intestinal permeability and that cascade of events described previously.

Lactobacilli strains have been noted to inhibit IL-8 production in colorectal adenocarcinoma cells (Caco-2), which were induced by TNF-α. Lactobacilli colonies that were stressed via antibiotics and sonication preserved their inhibitory actions; although heat treated Lactobacilli did not. These results further exemplify the preventative anti-inflammatory effects of lactobacillus.

Ren, Da-Yong, Chang Li, Yan-Qing Qin, Rong-Lan Yin, Shou-Wen Du, Fei Ye, Hong-Feng Liu, Mao-Peng Wang, Yang Sun, Xiao Li, Ming-Yao Tian, and Ning-Yi Jin. Lactobacilli Reduce Chemokine IL-8 Production in Response to TNF-α and Salmonella Challenge of Caco-2 Cells. *BioMed Research International.* (2013): 1-9.

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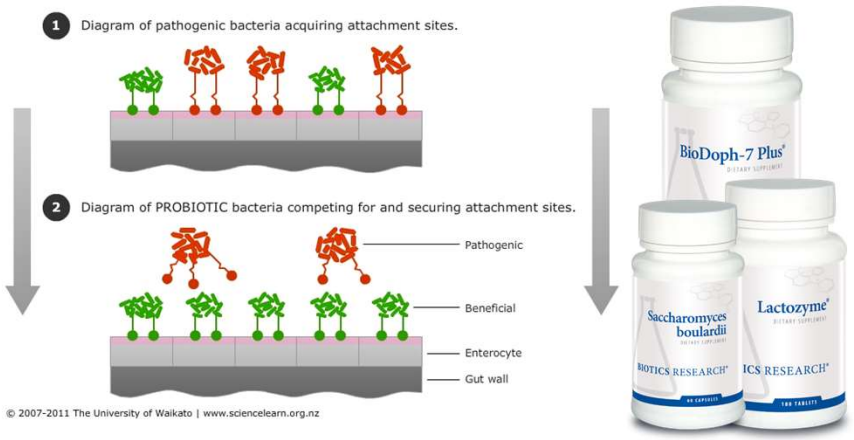
Probiotics and Pathogenic Microbes



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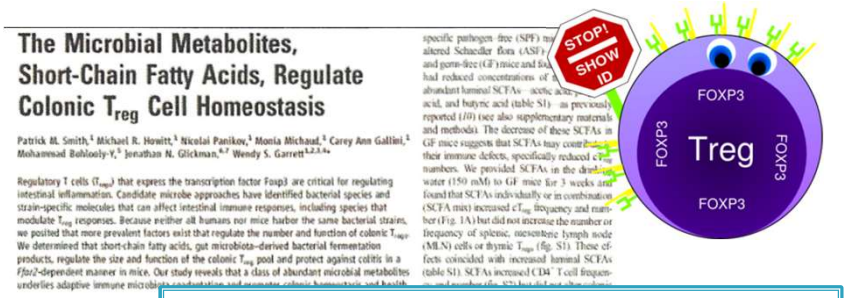
Short Chain Fatty Acids (SCFA)


The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic T_{reg} Cell Homeostasis

Patrick M. Smith,[1] Michael R. Howitt,[1] Nicolai Panikov,[1] Monia Michaud,[1] Carey Ann Gallini,[1] Mohammad Bohlooly-Y,[1] Jonathan N. Glickman,[6,7] Wendy S. Garrett[1,2,3,4,5]

Regulatory T cells (T_{reg}) that express the transcription factor Foxp3 are critical for regulating intestinal inflammation. Candidate microbe approaches have identified bacterial species and strain-specific molecules that can affect intestinal immune responses, including species that modulate T_{reg} responses. Because neither all humans nor mice harbor the same bacterial strains, we posited that more prevalent factors exist that regulate the number and function of colonic T_{reg}. We determined that short-chain fatty acids, gut microbiota–derived bacterial fermentation products, regulate the size and function of the colonic T_{reg} pool and protect against colitis in a *Ffar2*-dependent manner in mice. Our study reveals that a class of abundant microbial metabolites underlies adaptive immune microbiota coordination and promotes colonic homeostasis and health.

T_{reg} cells are critical for regulating intestinal inflammation

Bacterial fermentation products (SCFA) regulate the size and function of T_{reg} cells

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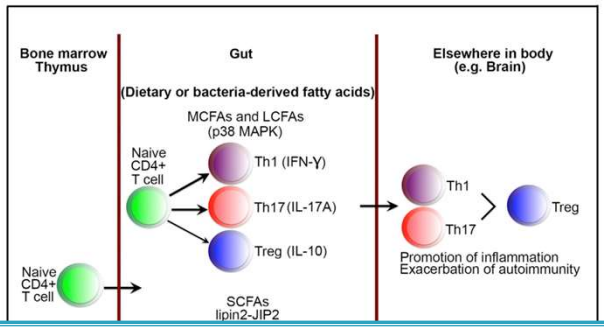
Published in final edited form as:
Immunity. 2015 October 20; 43(4): 629–631. doi:10.1016/j.immuni.2015.09.014.

Short, but Smart: SCFAs Train T Cells in the Gut to Fight Autoimmunity in the Brain

Yangzom D. Bhutia[1] and **Vadivel Ganapathy**[1,*]



The findings indicate that modification of gut microbes and their metabolism are viable targets for treatment of not only multiple sclerosis but potentially also other autoimmune diseases. The goal of such a strategy is to promote generation of SCFAs in the gut so as to drive the differentiation of naive CD4+ T cells into Treg cells and not into Th1 and Th17 cells. This can be achieved with the use of appropriate types of dietary fiber that have the ability to support the growth and proliferation of SCFA-producing gut microbes.

Cruz Ramos H, Hoffmann T, Marino M, et al. Fermentative Met… …acillus subtilis: Physiology and Regulation of Gene Expression. Journal of Bacteriology.

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SCFA and the GUT

Psyllium (Plantago ovato) (seed)
Mannitol
Kelgin (Sodium alginate)
Apple Pectin
Peppermint (Mentha piperita) (leaf)
Flax Seed (Linum usitatissimum)
Anise (Pimpinella anisum) (seed)
Bromelain (from Pineapple)
Celery (Apium graveolens) (seed)
Lactobacillus acidophilus (DDS-1)
Aloe Vera (Aloe barbadensis) (aerial part) (extract)
Prune (Prunus domestica) (fruit)

Butyric Acid
Calcium
Magnesium
Panthothenic Acid
Vitamin A

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Protective Substances in the GI: Mucous and SIgA

- Bio-Ae-Mulsion Forte: 100,000-300,000IU/day in acute phase
  - Maintenance for gut health- 10,000IU/day or 1 drop of Bio-Ae-Mulsion Forte (12,500IU)
- Okra
- L-Glutamine (can go up to 1 gram per 1 kg (2.2lbs) of body weight)
- Aloe
- Zinc: 10-25mg/day *Cent Eur J Immunol. 2014; 39(2): 165–169.*
  - Zinc carosine is the ideal form for GI issues

Halpern, Georges, Zinc Carnosine Nature's Safe and Effective Remedy For Ulcers, Square One Publishers, May 1, 2005

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GI RESOLVE

- Easy-to-mix and great-tasting powdered formula
- Updated product featuring ingredients backed by the most current scientific literature
- Cleanest GI repair formula on the market
- No flavors, colors, gums, sweeteners or other additives.
- *"Use the Best, Ditch the Rest"*

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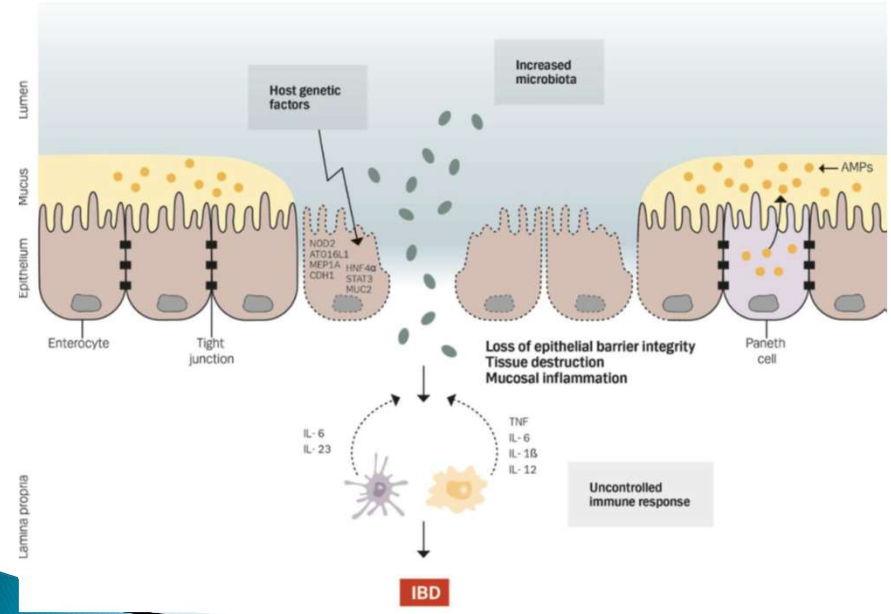

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L-GLUTAMINE

- **GI-*Resolve*™**contains 4 grams of the amino acid, glutamine
- Important energy source for the gastrointestinal tract and precursor for growth to the intestinal lining cells
- Helps maintain the integrity of the intestinal tract and enhances the protective mucosal lining
- Regulates intestinal barrier function in times of stress and other catabolic conditions
- Shown to stimulate the growth of the small intestinal mucosa and also enhances ion transport by the gut

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N-Acetyl Glucosamine (NAG)/Shellfish-Free!

- Glycosaminoglycans, normally attached to mucin, help form the protective barrier that separates bacteria from the intestinal epithelium. In certain digestive challenges, there is a widespread breakdown of glycosaminoglycans.
- NAG is a naturally-occurring monosaccharide derivative of glucose and precursor for epithelial glycosaminoglycan synthesis.
- Helps improve symptoms in patients with inflammatory bowel disease (IBD).
- May also support the growth of beneficial gut bacteria such as *Bifidobacterium bifidum*.
- A Bonus! Found to “delay aging” --increased lifespan in aging mice.
- N-Acetyl Glucosamine (NAG)/Shellfish-Free!

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MSM

- Methylsulfonylmethane(MSM) is an oxidized form of dimethyl sulfoxide, an organic sulfur compound from lignan, known for its support of healthy inflammation pathways and the healing of the gastric mucosa
- MSM inhibits NF-kappaB
- Downregulates mRNA for interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) *in vitro*
- Case studies of patients with joint impairment showed improved symptoms for comfort and flexibility following supplementation with MSM
- Reduces colonic inflammatory markers
- Increases levels of glutathione
- Provides strong antioxidant benefits

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ALOE VERA LEAF

- **GI-*Resolve*™** includes *Aloe vera* leaf extract to support a healthy intestinal lining
- Reduces oxidative stress and support a healthy inflammatory response in rats with gastropathy
- Inhibits colonic myeloperoxidase (MPO) activity, which is a marker for inflammation
- Shows both strong antioxidant properties and spasmolytic effects

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OKRA *Abelmoschus sculentus*

- A mucilaginous herb
- Potent antioxidant properties
- Exhibits strong gastroprotective effects
- May have anti-lipidemic effects as well as anti-diabetic mechanisms *Rat study: J Pharm Bioallied Sci. 2011 Jul-Sep; 3(3): 397–402.*

MUCILAGE, OKRA." INTERNATIONAL RESEARCH JOURNAL OF PHARMACY."
Gemede HF, Haki GD, Beyene F, Rakshit SK, Woldegiorgis AZ. Indigenous Ethiopian okra (Abelmoschus esculentus) mucilage: A novel ingredient with functional and antioxidant properties. Food Sci Nutr. 2018 Feb 2;6(3):563-571.
Ortaç D, Cemek M, Karaca T, Büyükokuroğlu [illegible] Özdemir ZO, Kocaman AT, Gönеş S. In vivo anti-ulcerogenic effect of okra (Abelmoschus esculentus) on ethanol-induced acute gastric mucosal lesions. Pharm Biol. [illegible]:56(1):165-175.

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Licorice (DGL)

- Taken from a Biotics promotional piece:

"The licorice in GI-Resolve™ has been processed to remove glycyrrhizin, which has been associated with sodium and water retention."

- DGL may have a protective effect on the GI track from the carcinogenic process *Oncotarget. 2016 Nov 1; 7(44): 71960–71973.*
- Effective against H. pylori *J Res Med Sci. 2013 Jun; 18(6): 532–533.*

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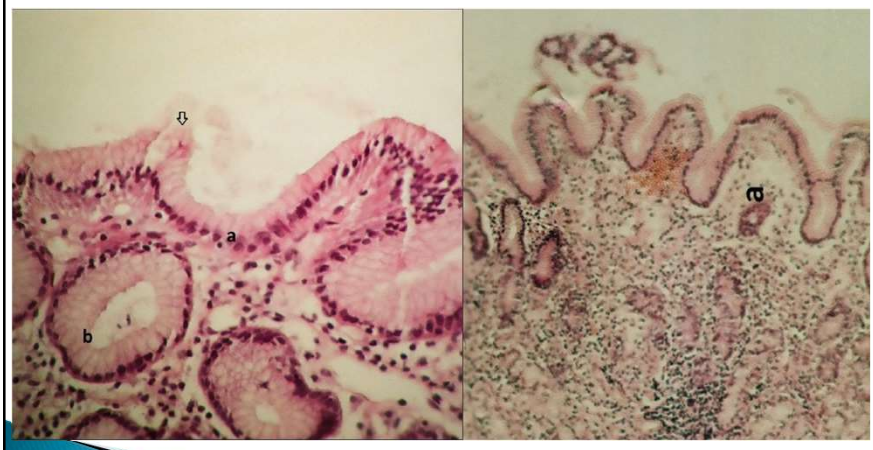
Licorice (DGL)– 250mg t.i.d. for 30 days

Before Treatment After Treatment



J Res Med Sci. 2013 Jun; 18(6): 532–533.

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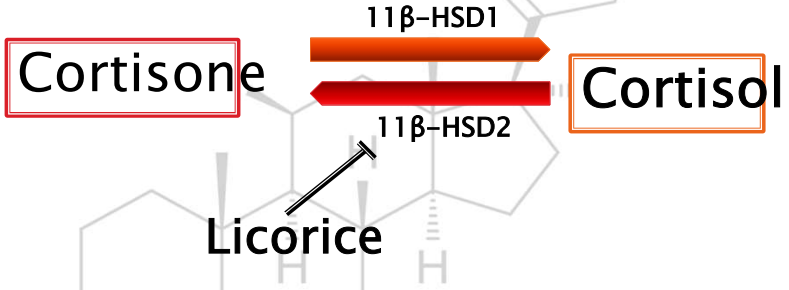
Cortisol and Cortisone

- Glycyrrhizin from licorice will preferentially inhibit 11β-HD2 thus stabilizing the free active form→ cortisol



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- Coats and soothes the intestinal lining
- Strong antioxidant activity results in cytoprotective mechanisms that supports the healing of tissues damaged by inflammation
- A randomized double-blind, placebo-controlled clinical trial revealed a significant improvement in symptom scores compared to the placebo group in the support of esophageal and gastric health

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"Water Runs Right Through Me"

- This is a common complaint that is usually sign of a poor aldosterone response and may serve as a surrogate marker of "adrenal health"
  - Licorice root inhibits 11β hydroxysteroid dehydrogenase II which increases aldosterone thus resorbing more sodium and H_20, lessening the amount of filtrate
    - Licorice can also bind to mineral-corticoid receptors *J Clin Endocrinol Metab. 2004 Apr;89(4):1973-6.*
    - Inhibits hepatic degredation of aldosterone by blocking 5β reductase *Steroids. 1990 Feb; 55(2):52-8.*

Ther Adv Endocrinol Metab. 2012 Aug; 3(4): 125–138.

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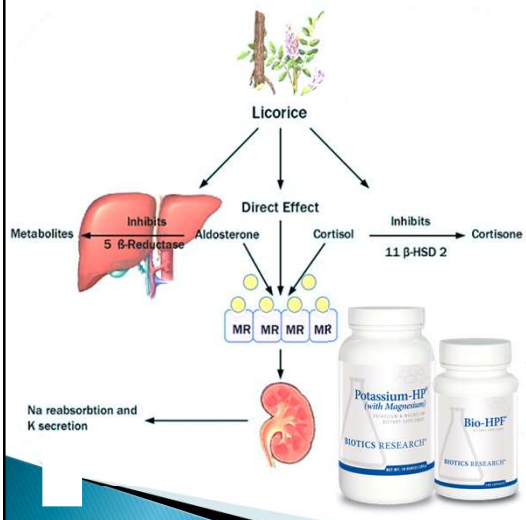
Licorice Root



Aldosterone can be increased by increasing potassium intake. Aldosterone's responsibility is fluid retention thus aiding in the balance of potassium and sodium. Thus increasing potassium will trigger aldosterone activity.

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Zinc Carnosine –Featuring PepZinGI

World J Gastroenterol. 2006 Oct 14;12(38):6178-81.

Polaprezinc protects human colon cells from oxidative injury induced by hydrogen peroxide: relevant to cytoprotective heat shock proteins.

Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair

Raymond J Playford [1], Tania Marchbank [1,2], Dan Murray [3]

Plymouth University Peninsula School of Medicine & Dentistry, Plymouth, UK; [2]Queen Mary University of London,UK; XSTO Solutions LCC, New Jersey

United States Patent Number: 5,238,931
"Inflammatory Bowel Disease Preventive and Curative Agent Containing Zinc L-Carnosine Salt as Active Ingredient

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Zinc Carnosine –Featuring PepZinGI

- Key ingredient supported by dozens of scientific papers
- A nutrient known for its mucosal-protective properties and restorative effect on gastrointestinal dysfunction, such as ulcers
- Zinc carnosine activates the Nrf2 signaling pathway, supporting a healthy inflammatory response
- With over 17 years as a prescription product, Zinc Carnosine has a strong track record of safety, efficacy and scientific merit
- Ushers in a new era of evidence-based dietary supplements and natural medicine for clinical gastroenterology
- Captures the synergy of L-carnosine and zinc, both associated with:

1. Antioxidant properties
2. Membrane stabilization
3. Tissue repair

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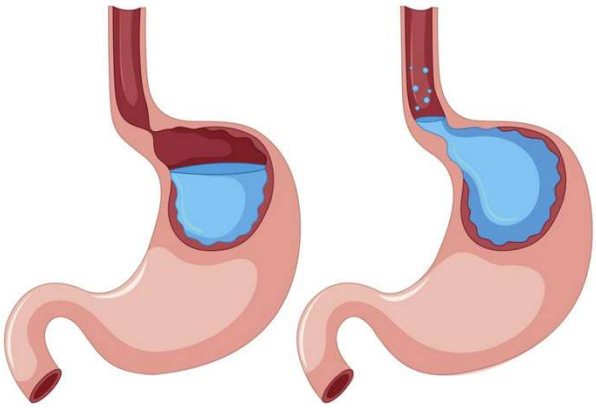

Gastroesophageal reflux (GERD)

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Acid Reflux & GERD Stats

- People with acid reflux more than twice a week, are classified as having gastroesophageal reflux disease (GERD).
- Up to 10% of adults in US have daily heartburn, and 44% have this symptom monthly.
- Approximately 25-30% of adults in the US have GERD.*
- Babies hospitalized for GERD increased 42% from 1998 to 2005.**
- Children ages 2-17 hospitalized for GERD increased 84% in the same timeframe.**

*www.Medscape.org **National Institute of Diabetes and Digestive and Kidney Diseases El-Serag HB, Sweet S, Winchester CC, Dent J Update on the epidemiology of gastroesophageal reflux disease, a systematic review. Gut.

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Low Stomach Acid (Hypochlorhydria)

- Incomplete solubilization of essential minerals
- Increased risk of bone fractures Bacterial overgrowth
- Impaired absorption of vitamin B12 Incomplete protein digestion • Chronic indigestion
- Normal pH is 1.5-3.5

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Acid Reflux Medications

Ironically, most recommendations for Acid Reflux address ways to decrease stomach acid:

- Antacids to neutralize acid
- Protein Pump Inhibitors to decrease production of HCl

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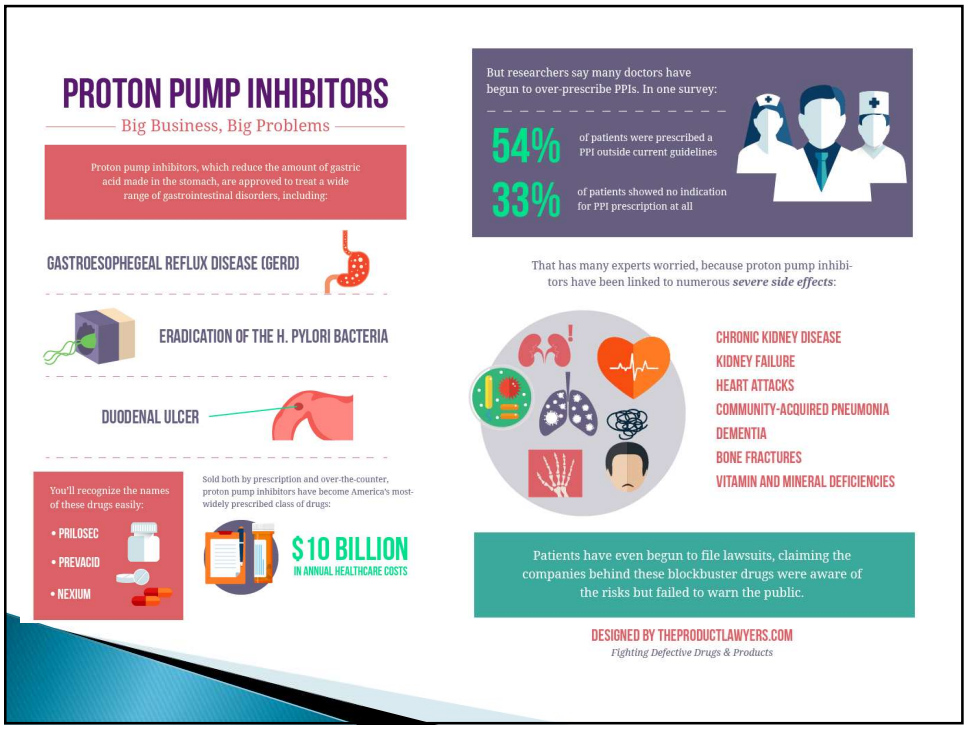

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Long-Term PPI Use

- PPIs resolve symptoms, but people become dependent on them and long-term use associated with:
  - Risk of fractures
  - Hypomagnesemia
  - Clostridium difficile-associated diarrhea (Seto Microbiome Study showed lower microbial diversity)
  - Vitamin B12 deficiency
  - Acute interstitial nephritis (AIN)
  - Dementia
  - 7-fold increase incidence of SIBO

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PPIs and GI Infections

PPIs can increase a person's risk of developing gastrointestinal infections, with the most common causative agent being *Clostridium difficile*.

In a study of **1,815 people**, it was noted that those who took PPIs had a substantial increase in bacteria within the *Stretptococcus*, *Enterococcus*, *Staphylococcus*, and *Eschericha coli* families.

This study demonstrated that significant disruption in the gut microbiome are present in people who use PPIs. These changes can cause dysbiosis and can predispose users to a higher risk of developing C. difficle infections

Imhann, Floris, Marc Bonder, and Arnau Vich Villa, et al. Proton pump inhibitors affect the gut microbiome. *Gut.* (2016);65(5): 740–48.

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Products for GERD

Powdered products are ideal for GERD as they can have action above the stomach, the esophagus, as they are ingested.

- L-glutamine powder
- Aloe leaf- liquid or powder
- Deglycyrrhized licorice (DGL)
- Okra

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Additional Products for GERD

- HCL Ease: for GERD- dosing in-between meals as well as during may help
- Hydro-Zyme: commonly 2-4 with each meal
  - Can dose up to "stomach tolerance"; Higher dosages look at Betaine HP
- Gastrazyme: 3-4 t.i.d.
  - Can also be used to lessen offensive odor of BM, can also add B12-2000 (hydroxocobalamin)
- Berberine HCL: 2-3 t.i.d. w/meals

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SIBO, FUNGI, PARASITES

- WHEN, WHY, HOW?

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4 STRATEGIES FOR GI WAR

Starve, Kill, Eliminate, Restore

1) STARVATION
- ❑ Diet, free of processed food

2) KILLERS:
- ❑ ADP
- ❑ Dysbiocide
- ❑ FC Cidal
- ❑ Caprin
- ❑ Berberine

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3) ELIMINATION:
- ❑ Mg Zyme
- ❑ Lax Ease
- ❑ Vitamin C tolerance
- ❑ Colonics

4) RESTORATION/HEALING:
- ❑ BioDoph 7
- ❑ Bio Dophilus FOS powder, capsules
- ❑ Butyric CalMag
- ❑ IAG
- ❑ EFA

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What should I eat?

General Rules

1) Eat food that existed before modern times
2) Eat food in the form closest to the way it appears in nature

3) VEGETABLES: any and all! Restrict starches such as potatoes.
4) FRUITS: Better to eat those with a lower glycemic index, Grapefruit, Kiwi, Apples, Strawberries, Cherries, etc.
5) GRAINS: ideally gluten-free, Quinoa, Millet, Buckwheat, Rice, Teff
6) NUTS: Eat FRESH and RAW. Keep Refrigerated! Walnuts, macadamia nuts, almonds, brazil nuts, and hazelnuts are best.
7) LEGUMES: Lentils, Peas, Beans, fermented soy like Tempeh.

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Vegetarian Diet

LOW IN:
- Calcium
- Vitamin D
- Vitamin B12
- Protein
  - Methionine, Taurine, NAC, MSM, Lysine needed for proper bone mineral density

VEGAN diet further devoid of sulfur containing amino acids

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What about MEAT?

- BEEF – NO cow product of any kind
  - cancer-inducing peptides
  - Difficult to digest
  - Large protein molecule
- PORK – full of parasites and protozoa
  - Parasites can bypass blood-brain barrier
- LAMB, GOAT, SHEEP
- CHICKEN – dark meat better
- Frequency?

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PROTOCOLS

Food Allergies

- IAG
- Bio C Plus
- Biomega 1000
- Hemp Oil

CONSTIPATION

- Lax ease
- Mg Zyme 2 bid

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GI TRACT SUPPORT

- GI Resolve 1 scoop bid E
- HCL Ease (for acid) 3 bid after meals
- Bio 6 Plus 1-2 with each meal
- Hydro Zyme 2 at the beginning of each meal
- Bio Doph 7 – 1 bid E
- Veggie Zymes 2 with each meal
- Lax Ease 2-4 qd E (constipation)
- Mg Zyme 3 bid F (constipation)
- IPS 2 bid E
- Colon Plus 2 bid E with at least a glass of water
- Explain food combining principles and water/food separation principle

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