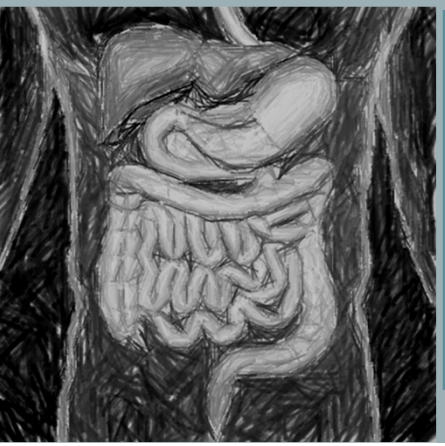
NUTRITIONAL SUPPLEMENTS FOR GUT HEALTH



Thomas Guilliams Ph.D.

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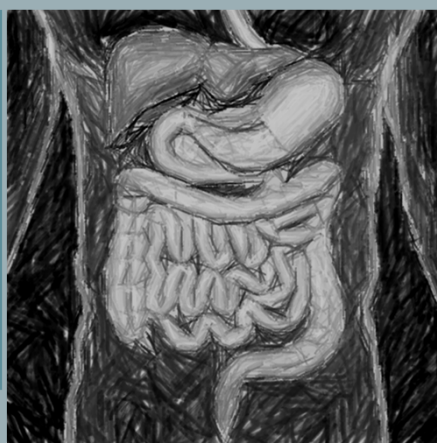
Founder/Director- The Point Institute



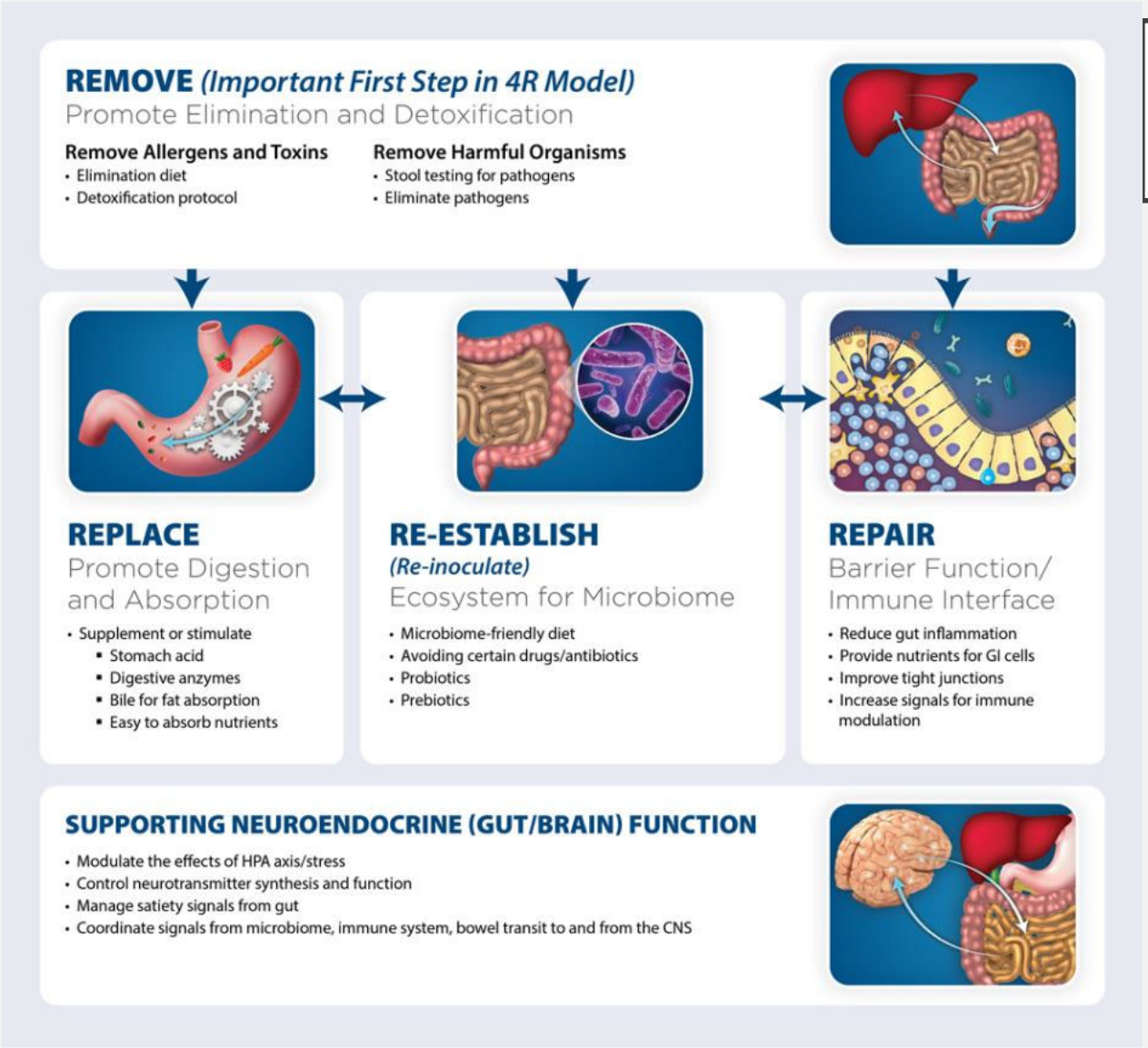
DISCLOSURE OF FINANCIAL RELATIONSHIPS

- Ortho Molecular Products
  - Consulting Fees
- Genova
  - Speaker Fees
- Off-Label Usage
  - None

LEARNING OBJECTIVES

- Discuss non-pharmacological/dietary supplement solutions for digestive complaints- the roles of acid, bile, bitters, and enzymes
- Provide an update on the role of glutamine for overall gut function
- Review dietary supplement solutions for improving barrier function in the gut

CORE FUNCTIONS VS 4R (OR 5R)

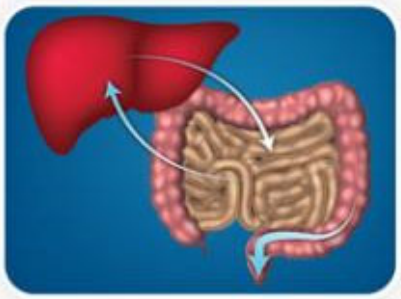


REMOVE ***(Important First Step in 4R Model)***

Promote Elimination and Detoxification

Remove Allergens and Toxins
- Elimination diet
- Detoxification protocol

Remove Harmful Organisms
- Stool testing for pathogens
- Eliminate pathogens



RATIONALE FOR DETOXIFICATION

- We ingest over 30-50 tons of food in a lifetime
  - Like air & water, most food is laden with numerous chemicals that need to be detoxified properly, otherwise deposited in various tissues
- Most of us have lifestyle habits that further encourage more toxic burden, stressing detox capability of the liver
- Detoxification is the **least expensive** and **least invasive** method that will be used as a first-line approach ("REMOVE") to treat GI illness
- Constipation is not just an inconvenience- it blocks proper detoxification and alters microbial balance.

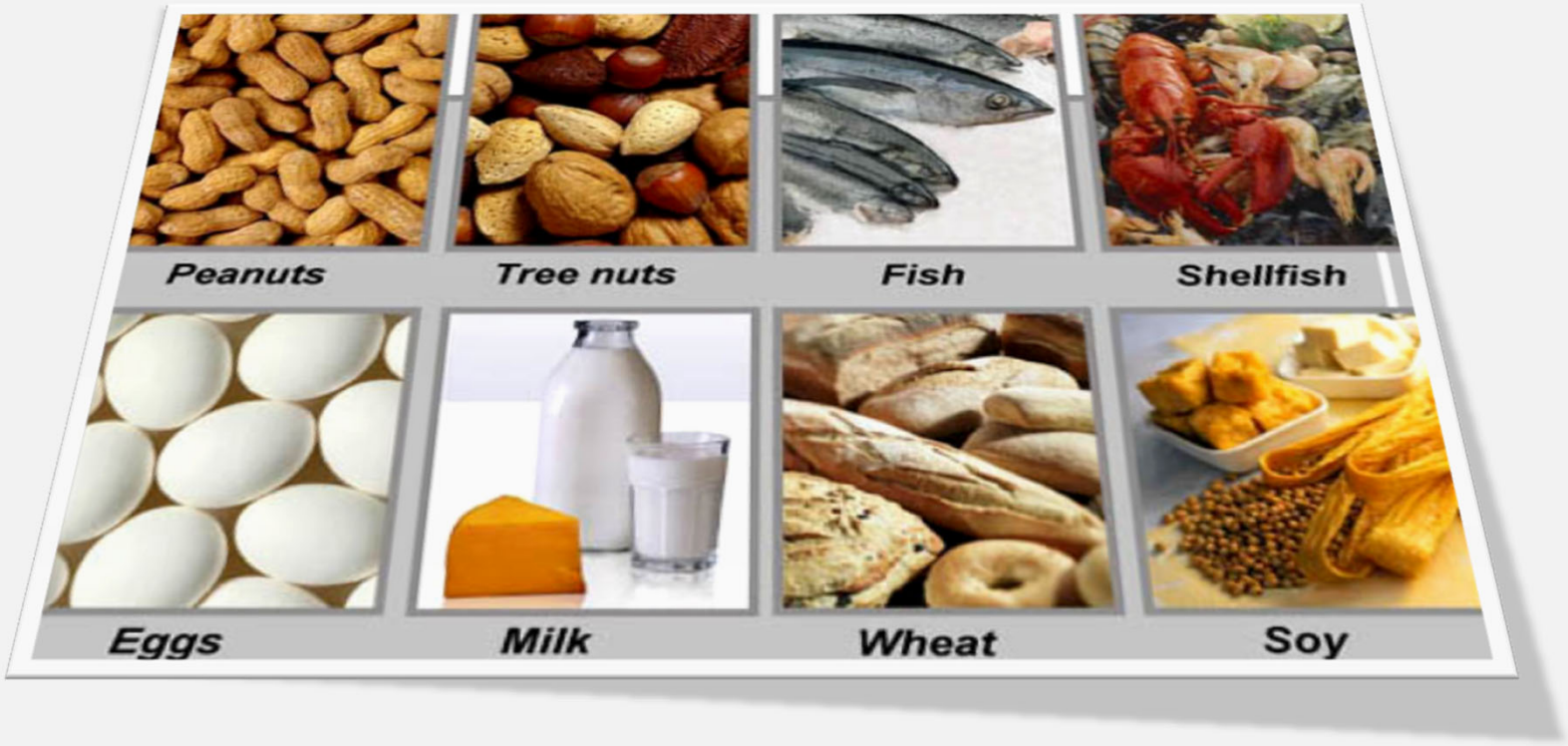
KEY POINTS TO FOLLOW BEFORE & DURING DETOXIFICATION

- Proper Hydration
  - Drink 6-8 glasses (48-64 oz) of water per day
  - Helps to flush out water-soluble toxins
- Proper Elimination
  - Establish proper BMs
- Mitochondrial function
  - The liver (other than the heart) has the most mitochondria per cell
  - Liver detoxification can be physically draining
  - Important to limit exercise & emphasize rest

ELIMINATION DIET

- 1st R: "Remove"
- Tool used to identify foods/substances causing food allergies/ intolerances/ sensitivities.
- Major food allergens eliminated for 2-3 weeks
  - If/When Symptoms disappear
  - Then, reintroduce these foods back into diet after every 3 days or so
    - If symptoms reappear when food is removed again, patient may be allergic or intolerant to the food

MOST COMMON FOODS THAT CAUSE ADVERSE REACTIONS



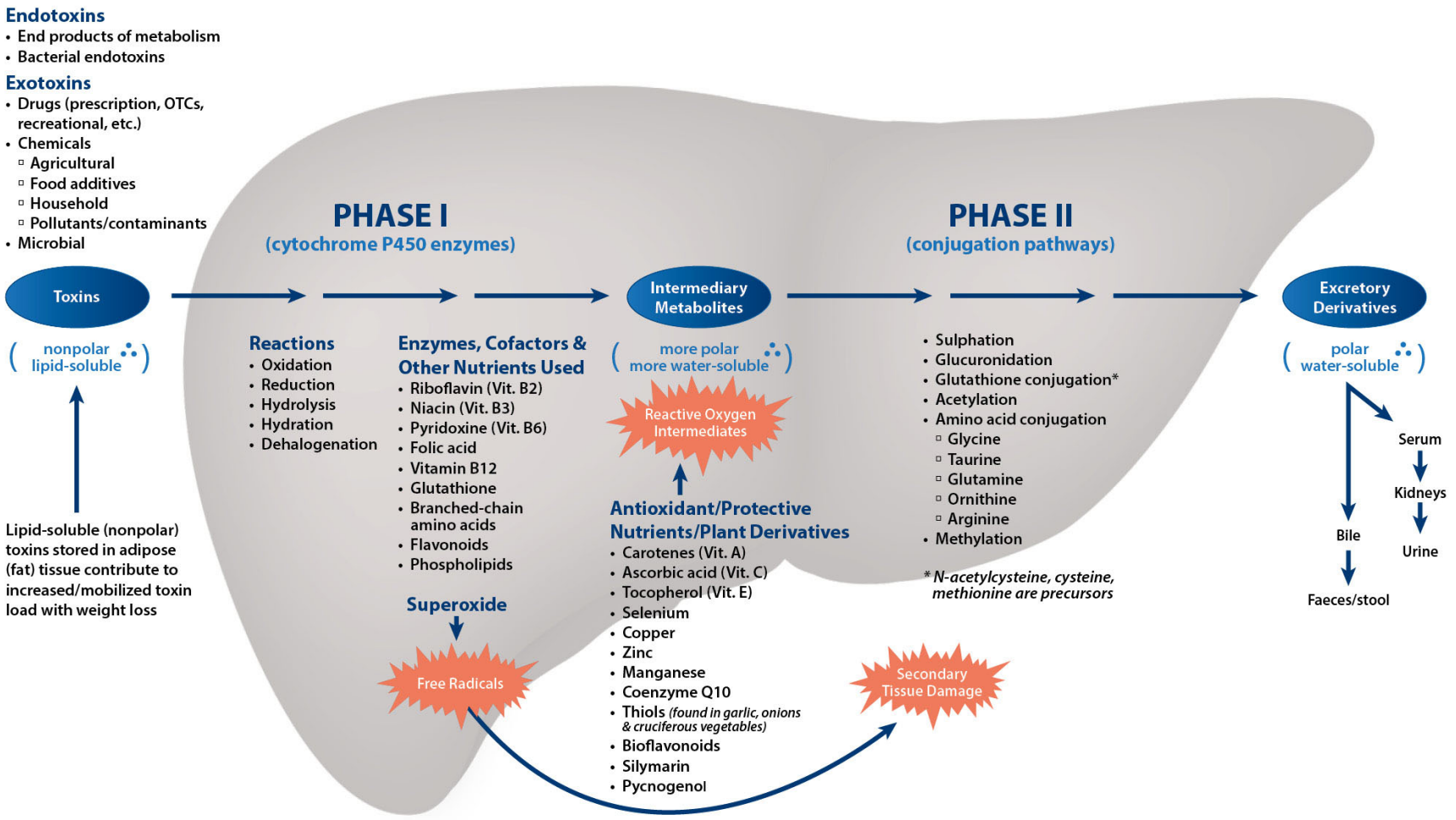
ALSO:

- Corn
- Oranges
- Artificial Colors, Flavors
- Non-wheat gluten containing grains
- Non-organic meats/ veg.

SUPPORTING DETOXIFICATION

- **Providing conjugation precursors:** This may include the increased intake of amino acids needed for conjugation (glycine, taurine, glutamine, arginine, and ornithine), sulfur groups (N-acetyl cysteine, lipoic acid, methionine, cysteine)
- **Increasing glutathione levels:** This can be accomplished quite well by the use of NAC, lipoic acid and the availability of the amino acids glycine, glutamic acid and cysteine. Since glutathione is used directly in Phase II detoxification and as a key cellular antioxidant, the importance of glutathione cannot be overemphasized.
- **Providing co-factors:** there are a number of known co-factors for both the Phase I and Phase II detoxification enzymes, most of which are familiar vitamins and minerals. It is critical to ensure subjects have a robust reserve of these nutrients to ensure no detoxification enzyme has diminished activity due to depletion in an available cofactor.

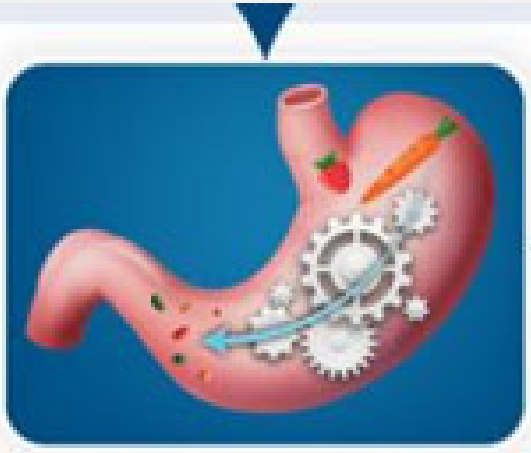
Figure 15: Liver Detoxification Pathways & Supportive Nutrients



THE BENEFITS AND CHALLENGES OF "DETOX" KITS

- Developed Kits that allow patients to "Detox" in 7, 14, 21 days etc.
- Typically developed around a ready-to-mix product (protein-based with detox ingredients).
- Helpful for patients that just want to be told how to do it and have all the products and instructions in one easy kit.
- Often well thought-out; primarily triggering elimination and phase 2 detox, prior to stimulating too much phase 1 (this is never one or the other, however).
- Differ in how much fasting is included and when the fasting is recommended.
- Some are easily modifiable for the patient, though there are limited options and often appears like a one-size fits all approach to detoxification.
- There are really only subjective outcomes to measure, rarely anything objective for patient or doc.

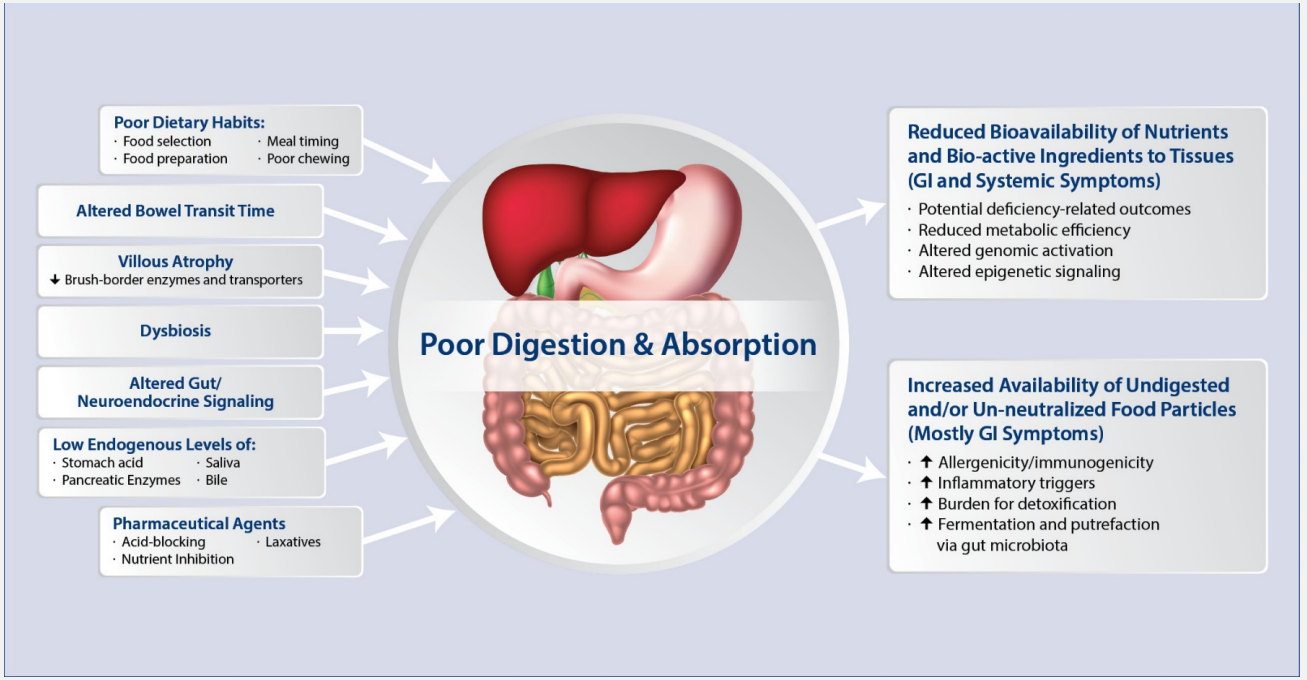
SUPPORTING DIGESTION



REPLACE

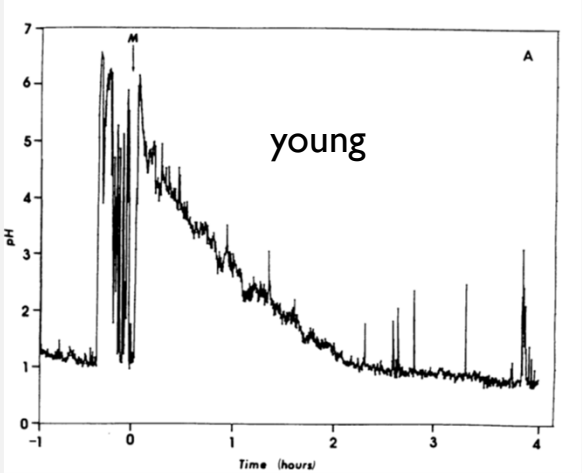
Promote Digestion and Absorption

- Supplement or stimulate
  - Stomach acid
  - Digestive anzymes
  - Bile for fat absorption
  - Easy to absorb nutrients

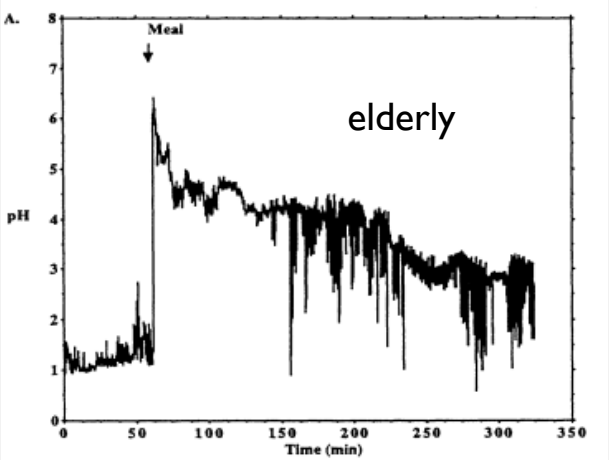


FUNCTIONAL HYPOCHLORHYDRIA

- Our body secretes acid primarily to digest food, therefore, fasting levels are not nearly as important as prandial levels (when you eat).
- If fasting gastric acid production goes down with aging, what happens to gastric pH during a meal?



Pharm Res. 1990 Jul;7(7):756-61.



Pharm Res. 1993 Feb;10(2):187-96.

INCREASING STOMACH ACID

- Consider testing for hypochlorhydria or achlorhydria
- Overhydration during meals (dilution of stomach HCl)
- Bitters
- Adding Acid: colas to Betaine HCl
- If subject is using acid suppressing drugs (OTC or Prescription), evaluate the dose and need.

BITTERS FOR INCREASING ACID PRODUCTION AND IMPROVING DIGESTION

Consuming Bitter herbals (most often delivered dissolved in alcohol) is a common remedy believed to stimulate saliva, stomach acid and enzyme production.

- Gentian root
- Wormwood (Artemisia)
- Artichoke leaf
- Dandelion leaf and root
- Endive
- Bitter greens (dandelion leaf, wild lettuce, milk thistle, chicory)
- Grapefruit rind
- Bitter chocolate

While these are extremely popular remedies, usually consumed right before a meal, there is virtually no published data evaluating the efficacy or specific mechanisms. Debate about whether bitters must be tasted (rather than merely consumed in tablets/capsules).

USING BETAINE HCL TO INCREASE STOMACH ACIDITY DURING MEALS

REVIEW ARTICLE

Meal-Time Supplementation with Betaine HCl for Functional Hypochlorhydria: What is the Evidence?

Thomas G. Guilliams, PhD; Lindsey E. Drake, MS

Abstract

It is well established that the inadequate *intake* of key nutrients can lead to nutrient deficiency-related phenomena. However, even when the intake of nutrients is sufficient, the inadequate digestion and/or absorption of macronutrients, micronutrients or other therapeutic compounds from the diet (i.e., phytonutrients) can result in similar clinical consequences. These consequences include classic GI-related symptoms related to malabsorption, as well as a broad range of clinical and subclinical signs and symptoms (though many nutrient insufficiencies are difficult to diagnose). Along with food matrix issues, the integrative and functional medicine community has long considered inadequate levels of stomach acid, pancreatic enzymes and/or bile acid secretion to greatly contribute to an individual's risk for maldigestion or malabsorption.

Thomas G. Guilliams, PhD, is a professor at the University of Wisconsin School of Pharmacy and founder of the Point Institute. Lindsey E. Drake, MS, is a Research Associate at the Point Institute.

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It is well established that the inadequate *intake* of key nutrients can lead to nutrient deficiency-related phenomena. However, even when the intake of nutrients is sufficient, the inadequate digestion and/or absorption of macronutrients, micronutrients or other therapeutic compounds from the diet (i.e., phytonutrients) can result in similar clinical consequences. These consequences include classic GI-related symptoms related to malabsorption, as well as a broad range of clinical and subclinical signs and symptoms (though many nutrient insufficiencies are difficult to diagnose). Along with food matrix issues, the integrative and functional medicine community has long considered inadequate levels of stomach acid, pancreatic enzymes and/or bile acid secretion to greatly contribute to an individual's risk for maldigestion or malabsorption. Indeed, routine mealtime "replacement" of one or more of these agents is commonly recommended by such practitioners to improve digestion and absorption. In this paper, we outline the evidence for one of these common recommendations- the supplementation of betaine HCl to support inadequate stomach acid production (hypochlorhydria)- while exploring what is known about the prevalence of this condition.

Inadequate Stomach Acid Production (Hypochlorhydria/Achlorhydria)

A variety of different methods can be used to measure gastric acid production and stomach pH (e.g., gastric intubation, catheter electrodes, radio-telemetric capsules and pH-sensitive tablets); therefore, a variety of different cut-off points have been used to define hypochlorhydria and achlorhydria in the literature. Generally, a fasting gastric pH less than 3.0 is considered "normal," while values above 3.0 are deemed to be gradually more hypochlorhydric. True achlorhydria results in a gastric pH above 7, which is characterized by very limited acid production even when stimulated by gastrin or histamine (e.g., chronic atrophic gastritis).[1] Subjects taking proton-pump inhibitors will generally have a fasting gastric pH between 5-7.

Inadequate levels of stomach acid (regardless of the root cause) can result in many nutritional and digestive issues. For instance, a reduction in gastric acid secretion prevents adequate denaturing of folded proteins resulting in poor protein digestion and increased food allergenicity.[2] Activation of pepsin (from pepsinogen) is greatest at a pH of 2 or less and its protease activity is optimal at a pH of 1.8 to 2.3.[3] A low-acid environment is linked to reduced absorption of key micronutrients such as calcium, iron, folic acid, vitamin B6 and vitamin B_{12}.[4,5] Also, since gastric acid helps to eliminate harmful ingested microorganisms and hinders bacterial overgrowth in the stomach and small bowel; low stomach acid can increase the risk for small intestinal bacterial overgrowth (SIBO) and specific microbial overgrowth from organisms like *Clostridium difficile*.[6,7,8] While most of these consequences of low stomach acid are undisputed, there is much less agreement on the prevalence of this condition in the general

- One of the most commonly recommended supplements for helping to reduce stomach pH during a meal…..
- But-Almost no published data on whether this works or exactly how to do it.
- Some confusion when using grains to define dose.
  - 1 grain=65 mg.
  - 1040 mg= 16 grains

TYPICAL PROTOCOL FOR USING BETAINE HCL

(For empiric testing of mealtime hypochlorhydria and for supplementing gastric acid)

This protocol involves giving patients increasing doses of Betaine HCl at mealtimes until such time as noticeable discomfort is reported. Patients who have exceeded the necessary dose will experience tingling, heartburn, diarrhea, *or any type of discomfort* including a feeling of unease, digestive discomfort, neck ache, backache, headache, or any new odd symptom. Upon experiencing tingling, burning, or any symptom that is uncomfortable, patients can neutralize the acid with 1 tsp baking soda in water or milk.

- Patients with suspected mealtime hypochlorhydria should begin by taking one (1) capsule containing 350–750 mg (~5-12 grains) of betaine HCl with a protein-containing meal (capsules containing betaine HCl with added pepsin are fine, and may be superior for overall benefit).
- If no discomfort or feeling of a burning sensation is noted, patient can begin taking two capsules with each protein-containing meal.
- If a burning sensation or any discomfort is noted after taking this (or any) dose, patient can neutralize the acid with 1 tsp baking soda in water or milk and discontinue the protocol.
- If there are no noticeable reactions to the betaine HCl after 2 days, patients should increase the number of capsules with each meal to three.
- Continue increasing the number of capsules every 2 days) with each meal if necessary until a dose results in tingling, burning, or any other type of discomfort. At such point, the patient should decrease the dose by one capsule per meal**.** *If the discomfort continues, they should be instructed to discontinue the betaine HCl supplementation and consult with their healthcare professional.*
- Once there is an established dose, continue this dose at subsequent meals, adjusting for meal size.
-
- Precautions: Administration of HCl/pepsin is contraindicated in peptic ulcer disease. HCl can irritate sensitive tissue and can be corrosive to teeth; therefore, capsules should not be emptied into food or dissolved in beverages.

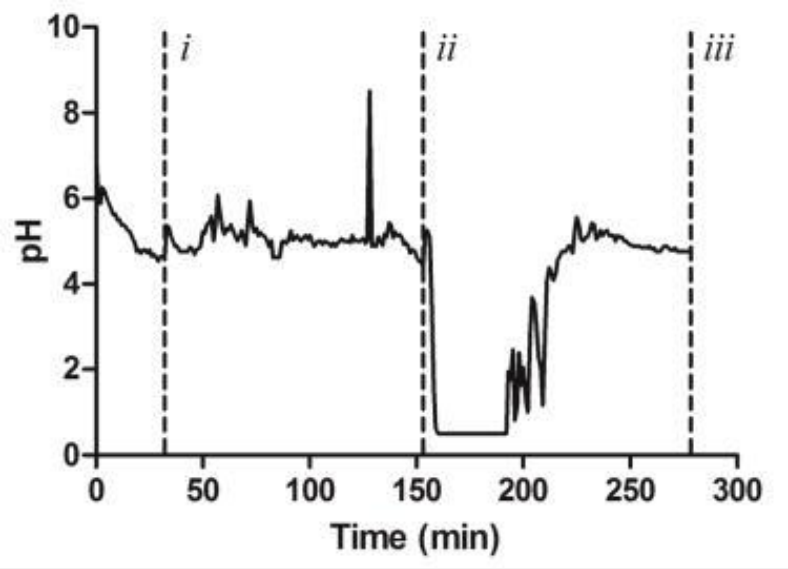
Published in final edited form as:
Mol Pharm. 2013 November 4; 10(11): 4032–4037. doi:10.1021/mp4003738.

Gastric Re-acidification with Betaine HCl in Healthy Volunteers with Rabeprazole-Induced Hypochlorhydria

(AcipHex)

Marc Anthony R. Yago[1], **Adam R. Frymoyer**[2], **Gillian S. Smelick**[3], **Lynda A. Frassetto**[4], **Nageshwar R. Budha**[3], **Mark J. Dresser**[3], **Joseph A. Ware**[3], and **Leslie Z. Benet**[1,*]

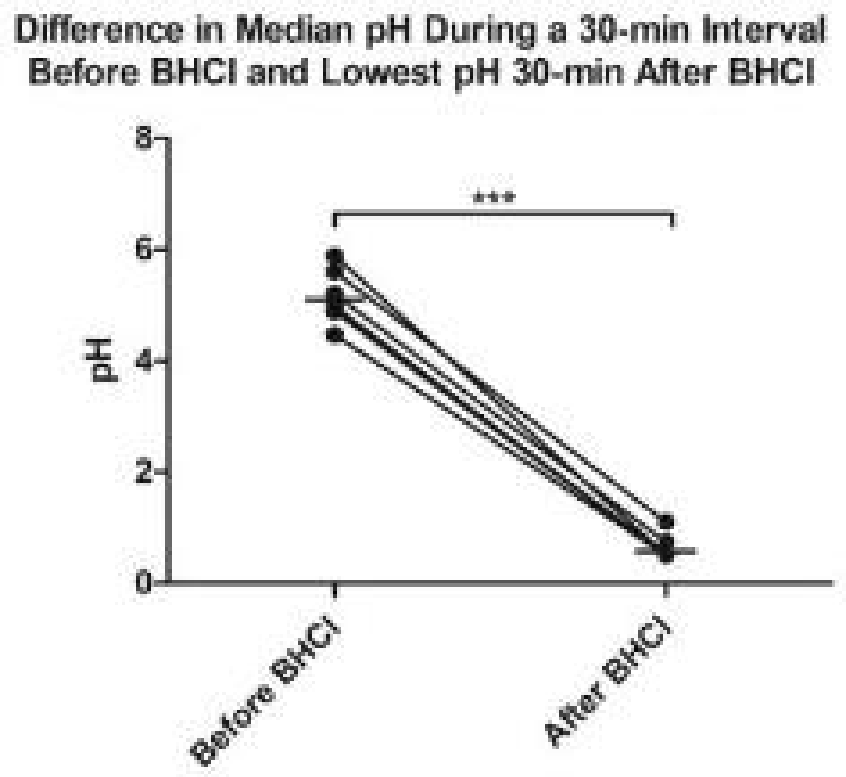
[1]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, 533 Parnassus Avenue, San Francisco, CA, 94143-0912



Sample gastric pH data of subject captured by the Heidelberg pH Capsule

Gastric pH measurements at 1-minute intervals were plotted versus time to produce the following curves. Vertical dashed lines (- - -) mark the following study events: (*i*) administration of 20 mg oral rabeprazole with 90 mL of water, (*ii*) administration of 1500 mg oral BHCl with 250 mL of water, and (*iii*) study end. The left curve represents a "best-case scenario," where a subject began the study day with a gastric pH > 4 after pre-treatment with rabeprazole for 4 days.

PH CHANGES USING 1500 MG B-HCL



Onset and duration measures of gastric re-acidification using BHCl after rabeprazole-induced hypochlorhydria. Onset of effect is characterized by the time to pH < 3, while the duration of effect is characterized by the rebound times to pH > 3 and pH > 4.

Subject	Time to pH < 3 (Post-BHCl, min)	Rebound Time to pH > 3 (min)	Rebound Time to pH > 4 (min)
P-001	2.13	29	42
P-002	12.6	83	83
P-003	4.05	46	53
P-004	1.83	90	90
P-005	8.83	121	127
P-006	8.23	66	66
Mean (±SD)	6.27 (±4.29)	73 (±33)	77 (±30)

MEALS DECREASE RE-ACIDIFICATION WITH BETAINE HCL (AFTER PPI USE)

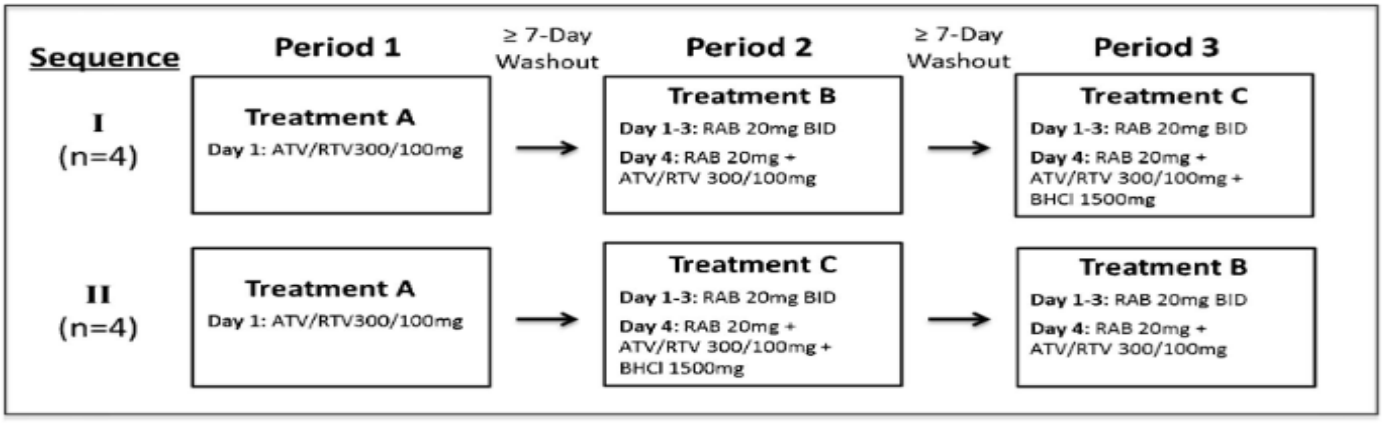
Pharm Res (2017) 34:619–628
DOI 10.1007/s11095-016-2090-2

RESEARCH PAPER

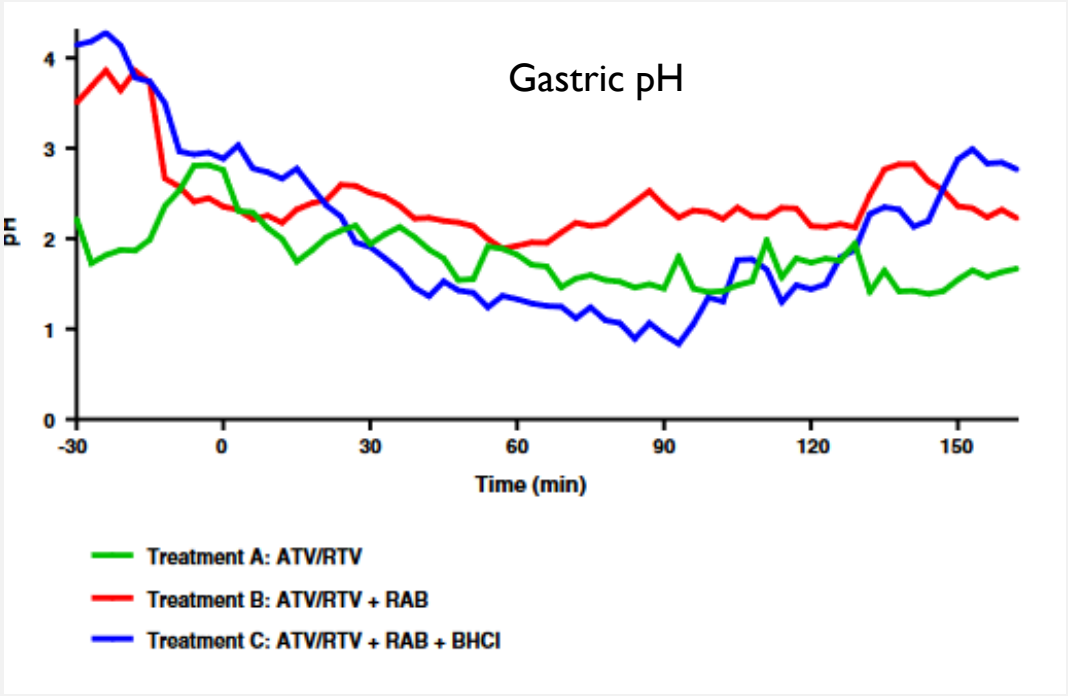
Meal Effects Confound Attempts to Counteract Rabeprazole-Induced Hypochlorhydria Decreases in Atazanavir Absorption

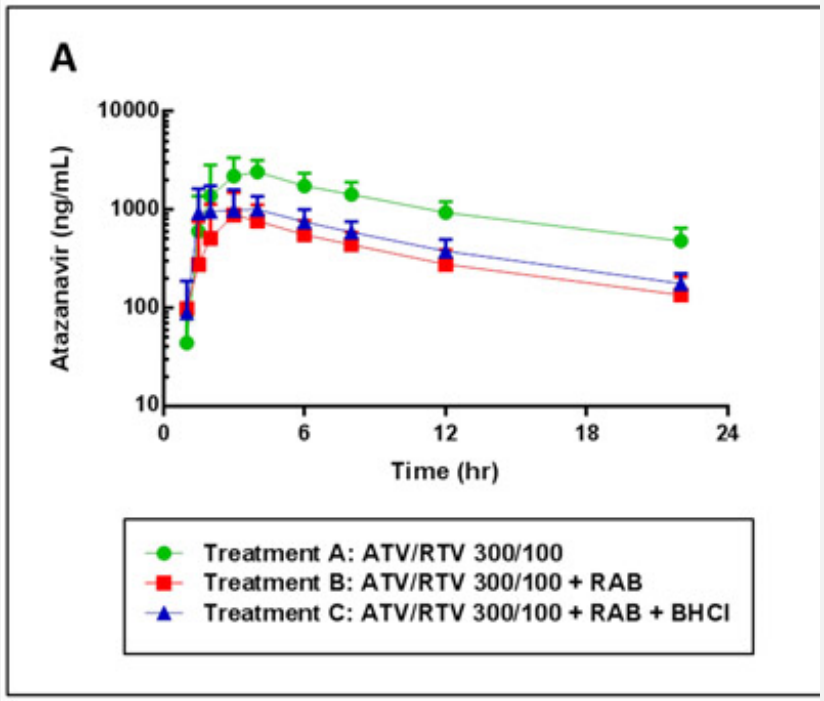
Kathleen Panter Faber[1] • Hsin-Fang Wu[1] • Marc R. Yago[1] • Xiaohui Xu[2] • Pathanjali Kadiyala[2] • Lynda A. Frassetto[3,4] • Leslie Z. Benet[1]

Standardized "Low Fat" breakfast meal, no details given.



Betaine HCl Re-acidified, but could not improve absorption of Atazanavir at 1500 mg/meal during PPI use





Faber KP, Wu HF, Yago MR, et al. Meal Effects Confound Attempts to Counteract Rabeprazole-Induced Hypochlorhydria Decreases in Atazanavir Absorption. *Pharm Res.* 2017;34(3):619-628. doi:10.1007/s11095-016-2090-2

HOW MUCH BETAINE HCL IS NEEDED TO REACIDIFY AFTER A SMALL MEAL?

Pharm Res (2019) 36: 155
https://doi.org/10.1007/s11095-019-2693-5

Check for updates

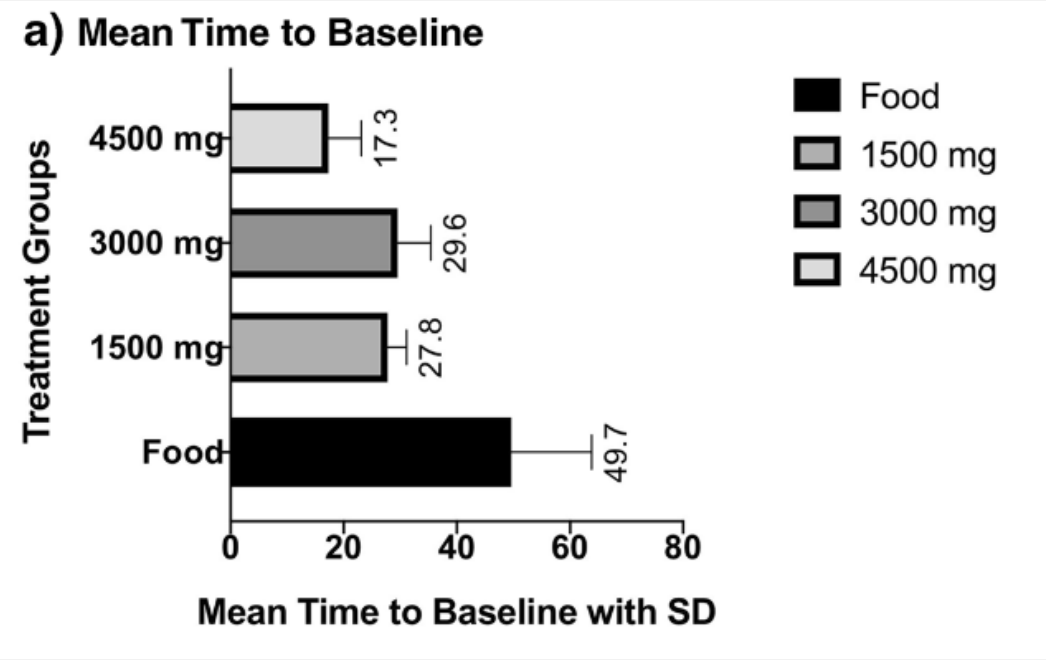
RESEARCH PAPER

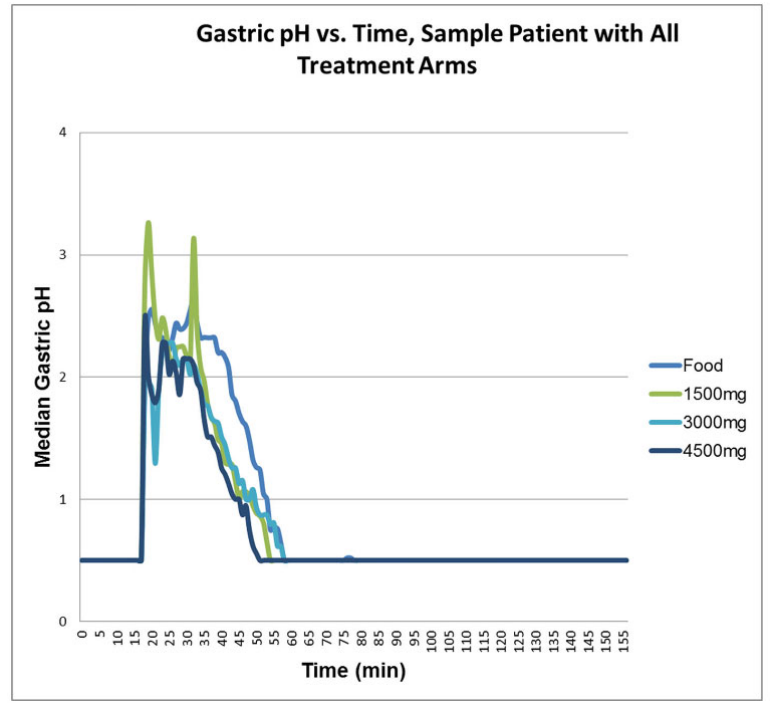
Food, Acid Supplementation and Drug Absorption – a Complicated Gastric Mix: a Randomized Control Trial

Dalga D. Surofchy[1] • Lynda A. Frassetto[2] • Leslie Z. Benet[3]

- After baseline measurements, each subject was given a standard breakfast meal, containing a total of 310 cal. The meal consisted of one 160-cal standard peach flavored yogurt (1.5 g of fat, 32 g carbohydrates, and 6 g of protein) and a 150-cal breakfast egg and cheese sandwich (8 g of fat, 12 g carbohydrates, and 8 g of protein).
- They were given 1,500 – 3,000 or 4,500 mg of Betaine HCl with 250 ml of water

BETAINE HCL- DOSE DEPENDENT REACIDIFICATION

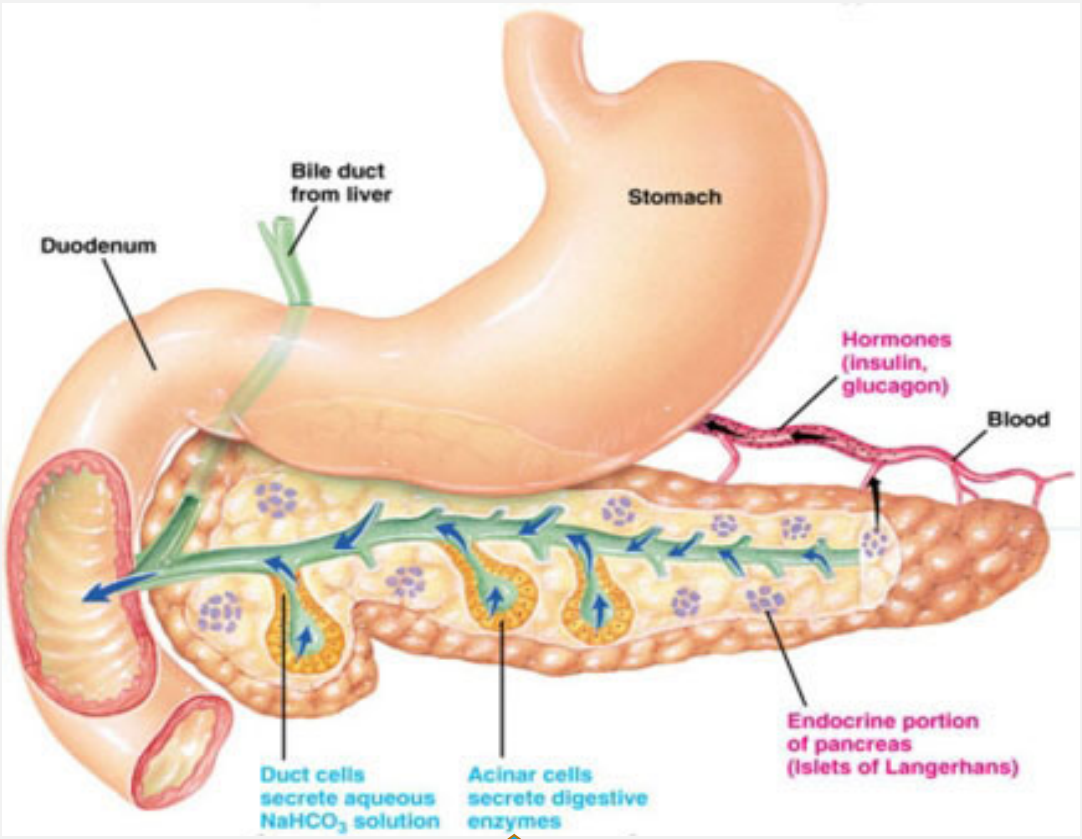




TAKE-AWAY FROM BETAINE HCL STUDIES

- 1500 mg of Betaine HCl quickly acidifies gastric pH in subjects take PPIs (on empty stomach)
- For improving the absorption of certain pH sensitive drugs, this is helpful, but limited when also consuming a meal
- Higher doses of Betaine HCl (i.e., 4,500 mg) are more potent at reacidifying pH in healthy subjects (normal fasting pH) during mealtime
- Betaine HCl- during meals- is likely safe for most individuals and may need to be higher dose than one would expect. It can (should) be used during each meal in subjects taking PPIs.
- Betaine HCl should not be taken more than 15 minutes before a meal!
- Betaine (i.e., TMG is not a substitute- it must deliver HCl!)

THE PANCREAS: MULTIPURPOSE GLAND



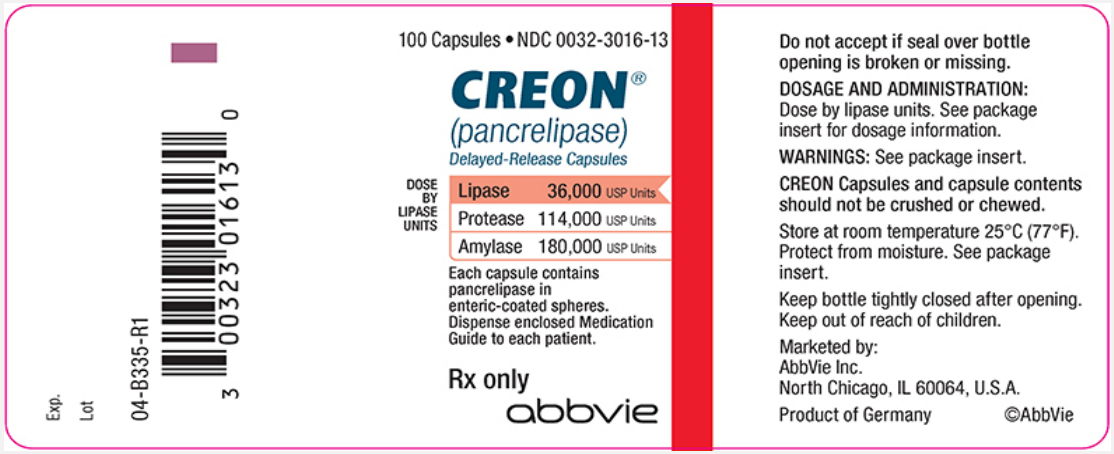
trypsin, chymotrypsin, elastase, pancreatic lipase, pancreatic amylase

INGESTING ENZYMES WITH MEALS

- The use of enzymes during meals to improve digestion is also very common, often in connection with supplementing acid, and bile
  - Pancreatin (Concentrated Pancreatic "juice")
    - Porcine (primarily)
    - Bovine
  - Bromelain (Pineapple stem)
  - Papain (Papaya)
  - Fungal Analogs (sometimes referred to as vegetable enzymes)
  - Pepsin (concentrate of porcine stomach lining)
  - Diamine Oxidase (DAO- from pork kidney extract)- Histamine intolerance
  - Dipeptidyl-peptidase IV (DPPIV): can digest gluten

PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

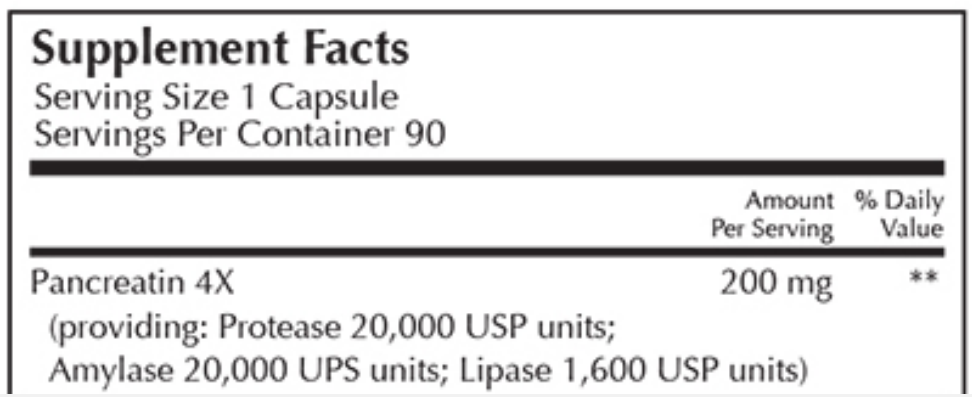
- "Drug" products exist and are all "pancrelipase"products



- Pancrelipase is a special (and expensive) concentration of pancreatin (porcine only) that has higher proportion of lipase activity, but still has more protease and amylase activity than lipase activity.
- Clinically, Pancreatic Exocrine Insufficiency focuses almost exclusively on lipase activity, as it is assumed that protease and amylase activities will still be adequate.

PANCREATIN PREPARATIONS (USP)

- The United States Pharmacopeia (USP) has set standards for each enzyme activity in pancreatin products as follows: each 1 mg of pancreatin (1X) contains not less than 25 units each of protease and amylase activity and not less than 2 units of lipase activity. (2X-10X multiply by 1X numbers)
- Product label should specify mg amount and concentrate level (sometimes also gives total units)



Supplement Facts

Serving Size 1 Capsule
Servings Per Container 90

	Amount Per Serving	% Daily Value
Pancreatin 4X	200 mg	**
(providing: Protease 20,000 USP units; Amylase 20,000 UPS units; Lipase 1,600 USP units)		

WHAT ABOUT NON-ANIMAL ENZYME SUPPLEMENTS?

- Plant Proteases: Bromelain (Pineapple), Papain (Papaya)
- Fungal Analogs:
  - Limited lipase activity, moderate protease activity, and wide-range of enzymes to break down complex carbohydrates.

Contains the enzyme alpha-galactosidase, which is derived from the fungus *Aspergillus niger*.

COMPREHENSIVE NON-ANIMAL DIGESTIVE ENZYME BLEND

Supplement Facts

Serving Size: 1 Capsule
Servings Per Container: 90

1 capsule contains	Amount Per Serving	% Daily Value
Enzyme Blend	233 mg	
Providing:		
Amylase	7,650 DU	*
Protease 4.5	20,400 HUT	*
Protease 6.0	2,550 HUT	*
Protease 3.0	10 SAPU	*
Neutral Protease	3,825 PC	*
Acid Maltase	10.7 MaltU	*
Bromelain (from pineapple) (equivalent to 25.5 GDU)	382,500 FCC PU	*
Papain	357,000 USP Units	*
Glucoamylase	12.75 AGU	*
Peptidase	2,550 HUT	*
Lactase	816 ALU	*
Alpha-galactosidase	102 GalU	*
Lipase	1,070 FIP	*
Pectinase	7.65 endo-PGU	*
Invertase	433 SU	*
Cellulase	178 CU	*
Xylanase	255 XU	*
CereCalase® (Hemicellulase, Beta-Glucanase, and Phytase)	150 MU	*
Artichoke Leaf Extract (Standardized to contain 5% Cynarin) (from Asteracea Family)	150 mg	*
Gentian Root Extract 4:1	100 mg	*

* % Daily Value not established V2

- Fungal Analogs are mostly derived through the fermentation of various Aspergillus species, sometimes other yeast/fungi are also used.
- Note the unusual and specific activity units, most enzymes have at least two different units that can report the activity of the enzyme- there is no consensus or regulation of this.
- Note the combination of plant/fruit enzyme- Bromelain/Papaya
- And the addition of plant bitters for overall digestive improvement
- These products are very helpful for digesting plant-based diets and are considered Vegan if delivered in a vegetable capsule (i.e., cellulose).

WHAT ABOUT BILE?

- Stimulating bile secretion:
  - Choleretics/Cholagogues
    - Artichoke leaf
    - Dandelion root
    - "Bitters"
- Supplementing bile: ox bile extracts
  - This is common and often added to digestive enzyme products.
  - Published data is lacking to help determine appropriate dose and what patient types may respond better than others (safety/side effects?)

GETTING THE TIMING RIGHT WHEN SUPPLEMENTING DIGESTIVE AIDS.

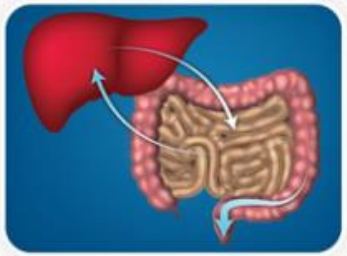
- Supplementing enzymes should be taken at the beginning of the meal.
- Many patients will need to take smaller doses throughout the entire meal for best overall results
- Should you take acid with enzymes?
- What about enteric coating?

REMOVE *(Important First Step in 4R Model)*

Promote Elimination and Detoxification

Remove Allergens and Toxins
- Elimination diet
- Detoxification protocol

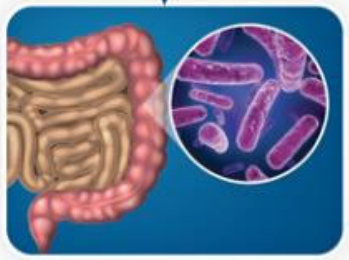
Remove Harmful Organisms
- Stool testing for pathogens
- Eliminate pathogens



REPLACE

Promote Digestion and Absorption

- Supplement or stimulate
  - Stomach acid
  - Digestive anzymes
  - Bile for fat absorption
  - Easy to absorb nutrients



RE-ESTABLISH

(Re-inoculate)

Ecosystem for Microbiome

- Microbiome-friendly diet
- Avoiding certain drugs/antibiotics
- Probiotics
- Prebiotics

REPAIR

Barrier Function/ Immune Interface

- Reduce gut inflammation
- Provide nutrients for GI cells
- Improve tight junctions
- Increase signals for immune modulation

DIETARY INTERVENTIONS FOR GUT PERMEABILITY

- It is generally assumed that common dietary patterns that induce poor microbiome balance, inflammation and chronic disease (excessive fat, refined carbohydrates, phytonutrient poor) are linked with increased intestinal permeability.
- However, there is an absence of studies using dietary interventions looking at measurable changes in gut permeability.

NUTRITION RESEARCH 32 (2012) 940–946

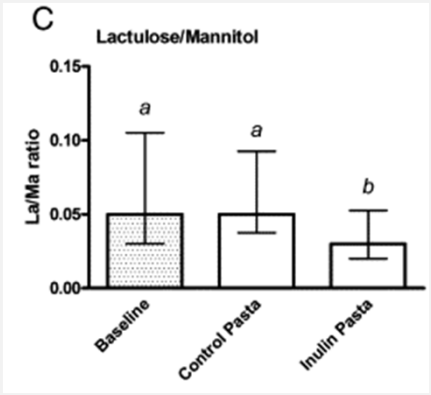
Available online at www.sciencedirect.com

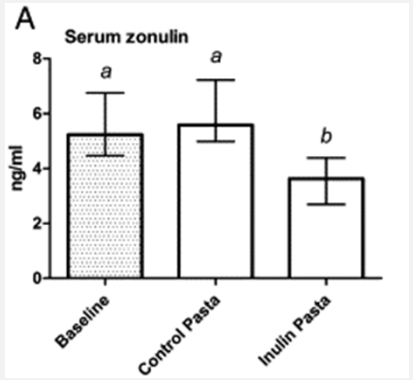
SciVerse ScienceDirect

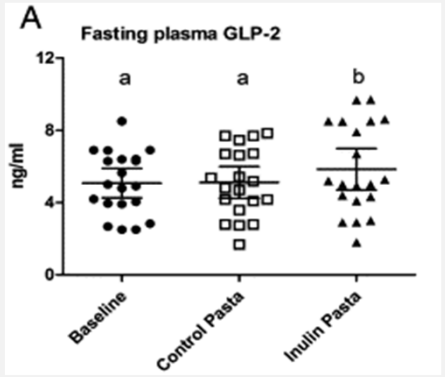
www.nrjournal.com

Inulin-enriched pasta improves intestinal permeability and modifies the circulating levels of zonulin and glucagon-like peptide 2 in healthy young volunteers

- 5 week crossover design with 8-week washout
- Healthy young (mean 18.8 y)
- 100 grams pasta/day
- Wheat Pasta with or without 11% inulin (prebiotic from Chicory)







MICRONUTRIENTS AND BARRIER FUNCTION

- Compromised barrier function is related to deficiencies in:
  - Vitamin A/ beta carotene
  - Vitamin D
  - Zinc
  - Iron
- Intervention studies are limited to vitamin A +zinc supplementation in malnourished children (improved barrier function) and zinc in IBD and exercise induced permeability.

Chen P, Soares AM, Lima AA, et al. Association of vitamin A and zinc status with altered intestinal permeability: analyses of cohort data from northeastern Brazil. *J Health Popul Nutr*. 2003 Dec;21(4):309-15.

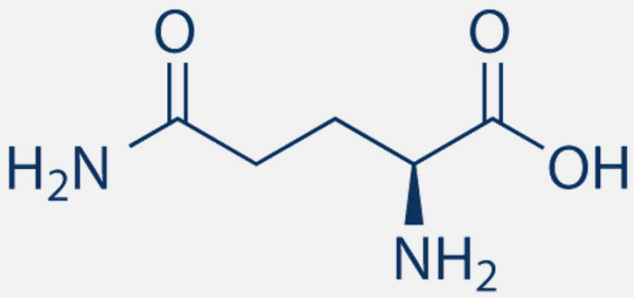
Goto K, Chew F, Torún B, Peerson JM, Brown KH. Epidemiology of altered intestinal permeability to lactulose and mannitol in Guatemalan infants. *J Pediatr Gastroenterol Nutr*. 1999 Mar;28(3):282-90.

Roy SK, Behrens RH, Haider R, et al. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *J Pediatr Gastroenterol Nutr*. 1992 Oct;15(3):289-96.

Santucci NR, Alkhouri RH, Baker RD, Baker SS. Vitamin and zinc status pretreatment and posttreatment in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2014 Oct;59(4):455-7.

Davison G, Marchbank T, March DS, et al. Zinc carnosine works with bovine colostrum in truncating heavy exercise-induced increase in gut permeability in healthy volunteers. *Am J Clin Nutr*. 2016 Aug;104(2):526-36.

L-GLUTAMINE AND BARRIER FUNCTION



- Long List of Mechanisms
- Numerous animal models to show GI barrier Benfits
- Most human Data related to severe injury/burn victims
- Frequent use within integrative/Functional Med. Community (anecdotal success)
- Recent limited research in traditional Gut Barrier human Clinical Research

GLUTAMINE

Some mechanisms linking glutamine with intestinal barrier functions:

- needed for the development of the gut epithelium during early life (supplementation used in neonates improve gut barrier function)
- critical substrate for metabolites within enterocytes including ATP, glutathione and DNA/RNA.
- important secondary signaling molecule within enterocytes, affecting critical metabolic and proliferative pathways in the cell.
- GLN has been shown to modulate TJ proteins, phosphorylation and assembly, using both GLN deprivation and supplementation studies.,
- GLN contributes to favorable alterations in the gut microbiota.
- GLN maintains intestinal structure and function during aging.
- GLN promotes sIgA secretion via direct (immunomodulatory) and indirect (microbiota) signals.
- GLN modulates the gI permeability effects of HPA axis stress (i.e., CRF).
- GLN modulates the gastrointestinal permeability effects of intensive exercise.

References: Guilliams TG: Functional Strategies for Supporting Gastrointestinal Disorders- Point Institute 2016

Amino Acids (2015) 47:2143–2154
DOI 10.1007/s00726-014-1773-4

REVIEW ARTICLE

Glutamine and intestinal barrier function

Bin Wang · Guoyao Wu · Zhigang Zhou · Zhaolai Dai · Yuli Sun · Yun Ji · Wei Li · Weiwei Wang · Chuang Liu · Feng Han · Zhenlong Wu

Received: 19 December 2013 / Accepted: 27 May 2014 / Published online: 26 June 2014

Abstract The intestinal barrier integrity is essential for the absorption of nutrients and health in humans and animals. Dysfunction of the mucosal barrier is associated with increased gut permeability and development of multiple gastrointestinal diseases. Recent studies highlighted a critical role for glutamine, which had been traditionally considered as a nutritionally non-essential amino acid, in activating the mammalian target of rapamycin cell signaling in enterocytes. In addition, glutamine has been reported to enhance intestinal and whole-body growth, to promote enterocyte proliferation and survival, and to regulate intestinal barrier function in injury, infection, weaning stress, and other catabolic conditions. Mechanistically, these effects were mediated by maintaining the intracellular redox status and regulating expression of genes associated with various signaling pathways. Furthermore, glutamine stimulates growth of the small intestinal mucosa in young animals and also enhances ion transport by the gut in neonates and adults. Growing evidence supports the notion that glutamine is a nutritionally essential amino acid for neonates and a conditionally essential amino acid for adults. Thus, as a functional amino acid with multiple key physiological roles, glutamine holds great promise in protecting the gut from atrophy and injury under various stress conditions in mammals and other animals.

Keywords Glutamine · Intestinal barrier function · Nutrition

Abbreviations

ASCT2	Neutral amino acid transporter type 2
ATP	Adenosine triphosphate
BSO	Buthionine sulfoximine
DP	Dipeptidase
EAA	Essential amino acids
4EBP1	Eukaryotic translation initiation factor 4E-binding protein-1
eIF4E	Eukaryotic translation initiation factor 4E
FOXO	Forkhead box O transcription factor
GA	GlutaminaseGALT gut-associated lymphatic tissue
GCL	Glutamate cysteine ligase
GS	Glutamine synthetase
GSH	Glutathione
GSS	Glutathione synthetase
GSSG	Glutathione disulfide
γ-GT	γ-Glutamyl transpeptidase
Ig	Immunoglobulin
IκB	Inhibitor of NF-κB
α-KG	α-Ketoglutarate
IUGR	Intrauterine growth restriction

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Springer

Amino Acids. 2015 Oct;47(10):2143-54.

REVIEW

Glutamine and the regulation of intestinal permeability: from bench to bedside

Najate Achamrah[a,b,c], Pierre Déchelotte[a,b,c], and Moïse Coëffier[a,b,c]

Purpose of review
Glutamine is the most abundant amino acid in plasma and plays a key role in maintaining the integrity of intestinal barrier.

Recent findings
Experimental studies showed that glutamine is able to modulate intestinal permeability and tight junction protein expression in several conditions. Recent articles underlined its putative beneficial role in gastrointestinal disorders such as irritable bowel syndrome.

Summary
Glutamine is a major nutrient to maintain intestinal barrier function in animals and humans. Depletion of glutamine results in villus atrophy, decreased expression of tight junction proteins and increased intestinal permeability. Moreover, glutamine supplementation can improve gut barrier function in several experimental conditions of injury and in some clinical situations. Furthermore, preventive effects of glutamine in experimental models of intestinal injuries have been recently reported. Despite promising data in experimental models, further studies are needed to evaluate glutamine supplementation in clinical practice.

Keywords
glutamine, gut, intestinal permeability, tight junction

INTRODUCTION

The digestive tract represents a large surface of exchanges in the human body and is constantly exposed to a diversity of food components, antigens, commensal microbes and pathogens. The gut provides an essential barrier that consists of an epithelial monolayer seated on the basal membrane. The intestinal epithelium plays a central role in the barrier function and in maintaining homeostasis. Intestinal epithelial cells (IECs) interact with both the luminal microbes as well as submucosal immune cells. In addition, IEC have a high turnover, and barrier integ-
rity is dependent on continuous renewal of epithelial
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lation of intestinal permeability that is affected by environmental factors (diet, stress, toxins, etc.) and altered in different pathophysiological conditions (intestinal disorders and inflammation, acute injuries, obesity, etc.).

The paracellular permeability of the intestinal barrier is regulated by a complex protein system called tight junctions [1]. The tight junction is composed of multiple proteins including transmembrane proteins, and in particular, occludin and claudin's family. These transmembrane proteins interact with cytosolic proteins, including zonula occludens family, that also interact with F-actin cytoskeleton. The association of these proteins is highly dynamic and contributes to the regulation of epithelial barrier.

Glutamine is the most abundant amino acid in
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Nutrition
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Curr Opin Clin Nutr Metab Care 2017, 20:86–91
DOI:10.1097/MCO.0000000000000339

Curr Opin Clin Nutr Metab Care. 2017 Jan;20(1):86-91.

REVIEW

Glutamine and the regulation of intestinal permeability: from bench to bedside

Najate Achamrah[A,B,C], Pierre Déchelotte[A,B,C], and Moïse Coëffier[A,B,C]

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INTRODUCTION

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The paracellular permeability of the intestinal barrier is regulated by a complex protein system called tight junctions [1]. The tight junction is composed of multiple proteins including transmembrane proteins, and in particular, occludin and claudin's family. These transmembrane proteins interact with cytosolic proteins, including zonula occludens family, that also interact with F-actin cytoskeleton. The association of these proteins is highly dynamic and contributes to the regulation of epithelial barrier.

Glutamine is the most abundant amino acid in plasma and is involved in a wide variety of metabolic

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Curr Opin Clin Nutr Metab Care 2017, 20:86–91
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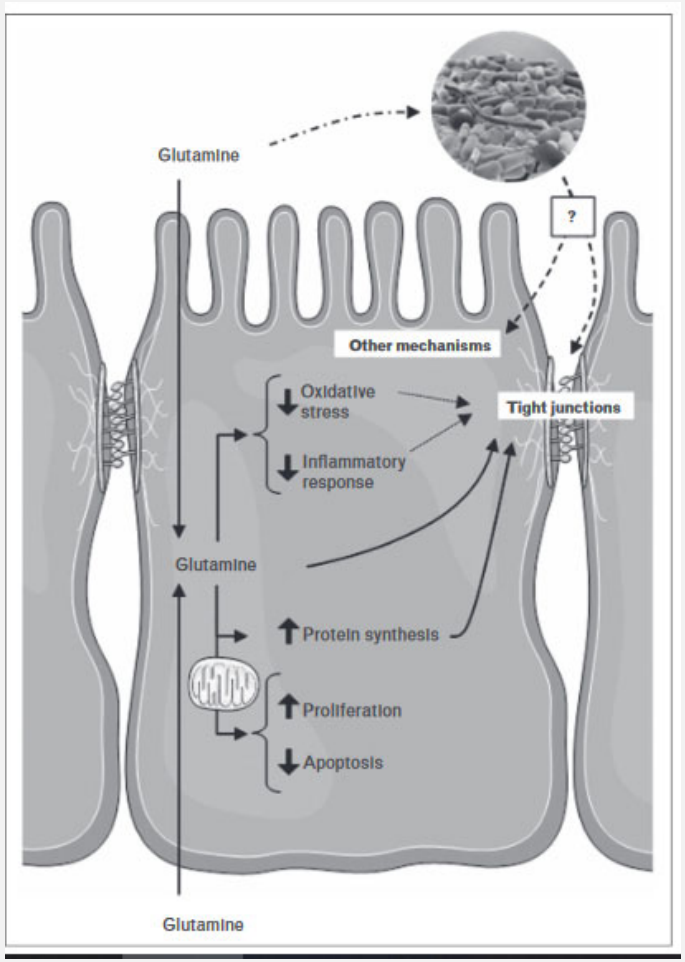


Glutamine and the regulation of intestinal permeability: from bench to bedside. *Curr Opin Clin Nutr Metab Care*. 2017;20(1):86-91. doi:10.1097/MCO.0000000000000339

GLN STUDIES IN UNDERNOURISHED CHILDREN OR SEVERE ILLNESS

LIMITED DATA ON "FUNCTIONAL" GI SITUATION

CLINICS

CLINICAL SCIENCE

Effects of glutamine alone or in combination with zinc and vitamin A on growth, intestinal barrier function, stress and satiety-related hormones in Brazilian shantytown children

Aldo A. M. Lima,[I] Gregory M. Anstead,[III] Qiong Zhang,[II] Ítalo L. Figueiredo,[I] Alberto M. Soares,[I] Rosa M. S. Mota,[I] Noélia L. Lima,[I] Richard L. Guerrant,[I,II] Reinaldo B. Oriá[I*]

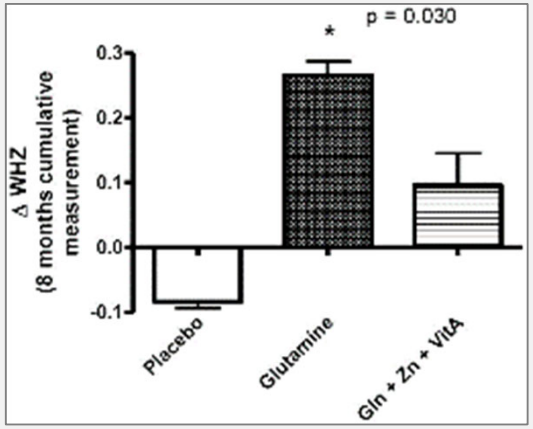
[I]Federal University of Ceará, School of Medicine, Clinical Research Unit & Institute of Biomedicine, Center for Global Health, Department of Physiology and Pharmacology, Fortaleza/CE, Brazil. [II]University of Virginia, School of Medicine, Division of Infectious Diseases, Center for Global Health, Charlottesville, VA, USA. [III]South Texas Veterans Hospital, San Antonio, TX, USA.

504 *Asia Pac J Clin Nutr 2016;25(3):504-512*

Original Article

Efficacy of glutamine-enriched enteral feeding formulae in critically ill patients: a systematic review and meta-analysis of randomized controlled trials

Azadeh Mottaghi PhD[1], Maryam Zarif Yeganeh MSc[1], Mahdieh Golzarand MSc[1], Sara Jambarsang MSc[2], Parvin Mirmiran PhD[3]



Lima AAM, Anstead GM, Zhang Q., et al. Effects of glutamine alone or in combination with zinc and vitamin A on growth, intestinal barrier function, stress and satiety-related hormones in Brazilian shantytown children. *Clinics*. 2014; 4(2), 225-233.

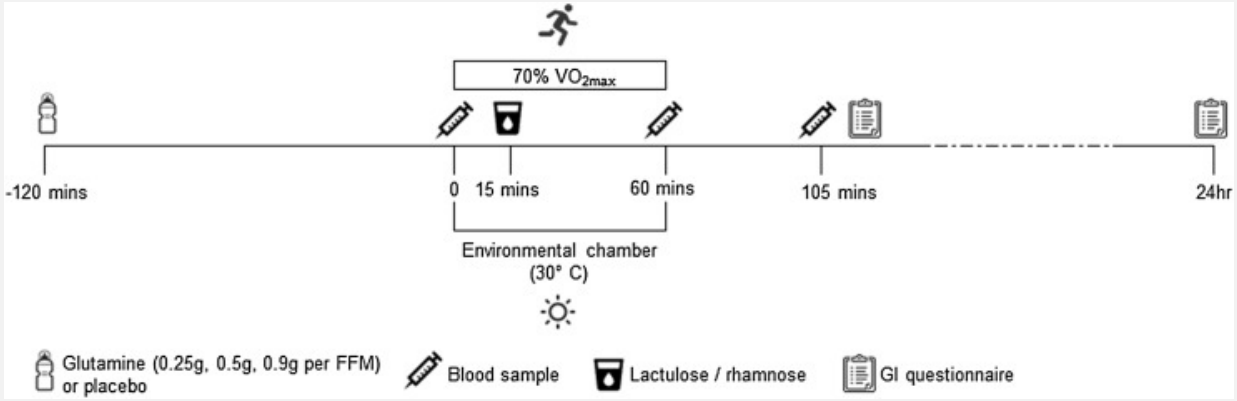
Mottaghi, A, Yeganeh MZ, golzarand M, Jambarsang S, & Mirmiran P. Efficacy of glutamine-enriched enteral feeding formulae in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. *Asia Pacific Journal of Clinical Nutrition*. 2016; 25(3), 504-512

GLUTAMINE SUPPLEMENTATION AND IMMUNE FUNCTION DURING HEAVY LOAD TRAINING

- 24 Athletes given 10 gram/day GLN or placebo for 6 weeks
- GLN was able to attenuate immunosuppression triggered by intense heavy-load training compared to placebo
- Gut permeability was not assessed in these subjects

Int J Clin Pharmacol Ther. 2015 May;53(5):372-6. doi: 10.5414/CP202227.

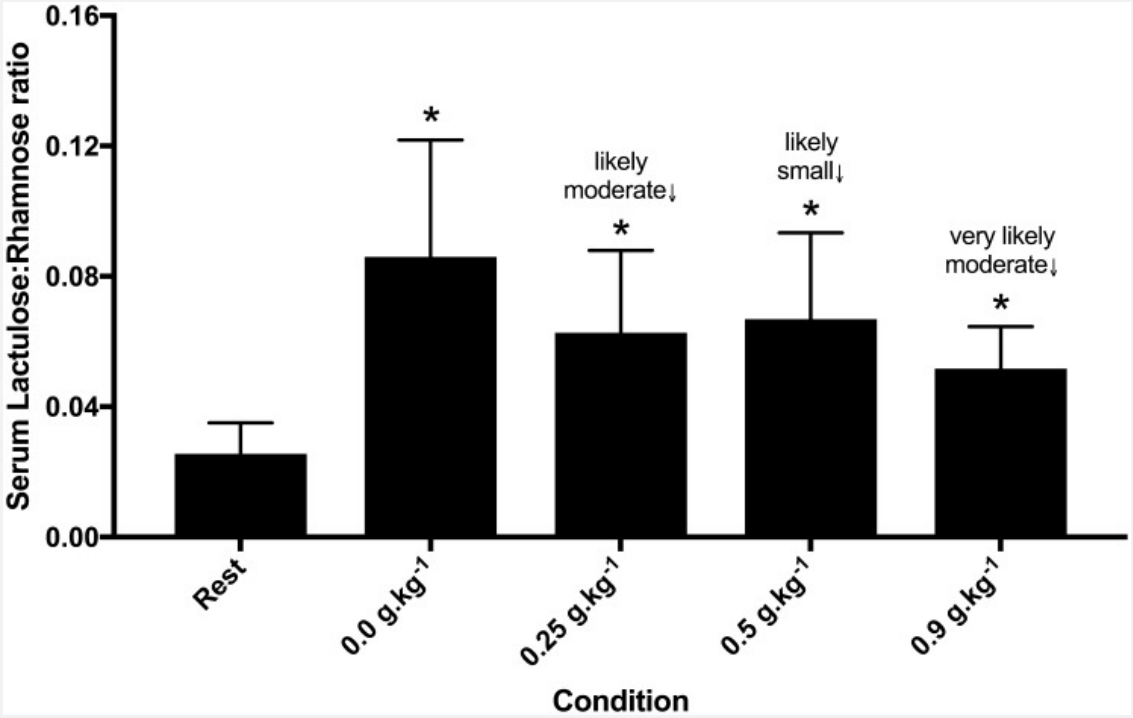
GLUTAMINE SUPPLEMENTATION REDUCES MARKERS OF INTESTINAL PERMEABILITY DURING RUNNING IN THE HEAT IN A DOSE-DEPENDENT MANNER



- 10 Healthy young male volunteers with no history of GI issues, meds or supplements
- Crossover design, for all four doses, one per week.
- Dose was 0.25-0.9 gram/kg of FFM! (54 grams for a 70 kg person with 15% body fat)

Eur J Appl Physiol. 2017; 117(12): 2569–2577.

ALL DOSES AMELIORATED INCREASED EXERCISE/HEAT-INDUCED GUT PERMEABILITY.



EXPERIMENTAL AND THERAPEUTIC MEDICINE 12: 3499-3506, 2016

Effects of glutamine on markers of intestinal inflammatory response and mucosal permeability in abdominal surgery patients: A meta-analysis

XIAO-LIANG SHU[1], TING-TING YU[2], KAI KANG[2] and JIAN ZHAO[2]

- 21 published clinical trials (most published in Chinese) were evaluated for a variety of biomarkers after surgeries (describes as: gastrectomy, GI cancer, abdominal surgery) using glutamine supplementation- variety of doses (mostly unspecified)
- Heterogeneity was very high, so random effect size was used.
- Statistically favorable results were reported for CRP, TNF-α, IL-6, lactulose/mannitol, and endotoxin.

GLUTAMINE AND IBS

Neurogastroenterology

ORIGINAL ARTICLE

Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome

QiQi Zhou,[1,2] Meghan L Verne,[3] Jeremy Z Fields,[1] John J Lefante,[4] Sarpreet Basra,[1] Habeeb Salameh,[5] G Nicholas Verne[1]

- 106 subjects with PI-IBS-D given "placebo" (whey protein) or L-glutamine 5 grams t.id. 8 weeks.
- Primary end point: >50 pt reduction in IBS-Severity Symptom score (IBS-SS)
- Secondary end points: Change in bowel frequency and morphology (BSS) and intestinal permeability (urine L/M)

Gut. 2018 Aug 14. pii: gutjnl-2017-315136.

Table 2 Trial outcomes

	Glutamine (n=54)	Placebo (n=52)
IBS-SS		
Baseline	301.39±53.61	301.63±57.97
Treatment endpoint	181.39±47.73	296.06±62.30
P value*	<0.0001	0.13
Stool frequency (no./day)		
Baseline	5.41±2.29	5.31±2.18
Treatment endpoint	2.91±0.97	5.26±2.08
P value*	<0.0001	0.17
Stool consistency†		
Baseline	6.51±0.60	6.55±0.55
Treatment endpoint	3.88±1.20	6.57±0.53
P value*	<0.0001	0.42
Intestinal permeability‡ (Lactulose/mannitol ratio)		
Baseline	0.11±0.03	0.11±0.04
Treatment endpoint	0.05±0.01	0.10±0.03
P value*	<0.0001	0.42

Values are means±SD.
*The p value was computed using the paired t-test.
†Stool consistency was measured using the Bristol stool score.
‡Intestinal permeability was measured with the urinary lactose/mannitol ratio.
IBS-SS, Irritable Bowel Syndrome Severity Scoring System.

Glutamine and Whey Protein Improve Intestinal Permeability and Morphology in Patients with Crohn's Disease: A Randomized Controlled Trial

Jaya Benjamin · Govind Makharia · Vineet Ahuja · K. D. Anand Rajan · Mani Kalaivani · Siddhartha Datta Gupta · Yogendra Kumar Joshi

Received: 2 May 2011 / Accepted: 8 October 2011 / Published online: 26 October 2011

Abstract

Background Increased intestinal permeability (IP) has been implicated in the etiopathogenesis, disease activity and relapse of Crohn's disease (CD). Glutamine, the major fuel for the enterocytes, may improve IP.

Aim We evaluated the effect of oral glutamine on IP and intestinal morphology in patients with CD.

Methods In a randomized controlled trial, consecutive patients with CD in remission phase with an abnormal IP were randomized to a glutamine group (GG) or active control group (ACG) and were given oral glutamine or whey protein, respectively, as 0.5 g/kg ideal body weight/day for 2 months. IP was assessed by the lactulose mannitol excretion ratio (LMR) in urine, and morphometry was performed by computerized image analysis system.

Results Patients (age 34.5 ± 10.5 years; 20 males) were assigned to the GG ($n = 15$) or ACG ($n = 15$). Fourteen patients in each group completed the trial. The LMR [median (range)] in GG and ACG at 2 months was 0.029 (0.006–0.090) and 0.033 (0.009–0.077), respectively, with $P = 0.6133$. IP normalized in 8 (57.1%) patients in each group ($P = 1.000$). The villous crypt ratio (VCR) [mean (SD)] in GG and ACG at 2 months was 2.68 (1.02) and 2.49 (0.67), respectively, ($P = 0.347$). At the end of 2 months LMR improved significantly in GG from 0.071 (0.041–0.254) to 0.029 (0.006–0.090) ($P = 0.0012$) and in ACG from 0.067 (0.040–0.136) to 0.033 (0.009–0.077) ($P = 0.0063$). VCR improved in the GG from 2.33 (0.77) to 2.68 (1.02) ($P = 0.001$), and in ACG from 2.26 (0.57) to 2.49 (0.67) ($P = 0.009$).

Conclusions Intestinal permeability and morphology improved significantly in both glutamine and ACG.

J. Benjamin · G. Makharia · V. Ahuja · Y. K. Joshi (✉)
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J. Benjamin
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G. Makharia

40 grams of glutamine (80kg-176 lbs)

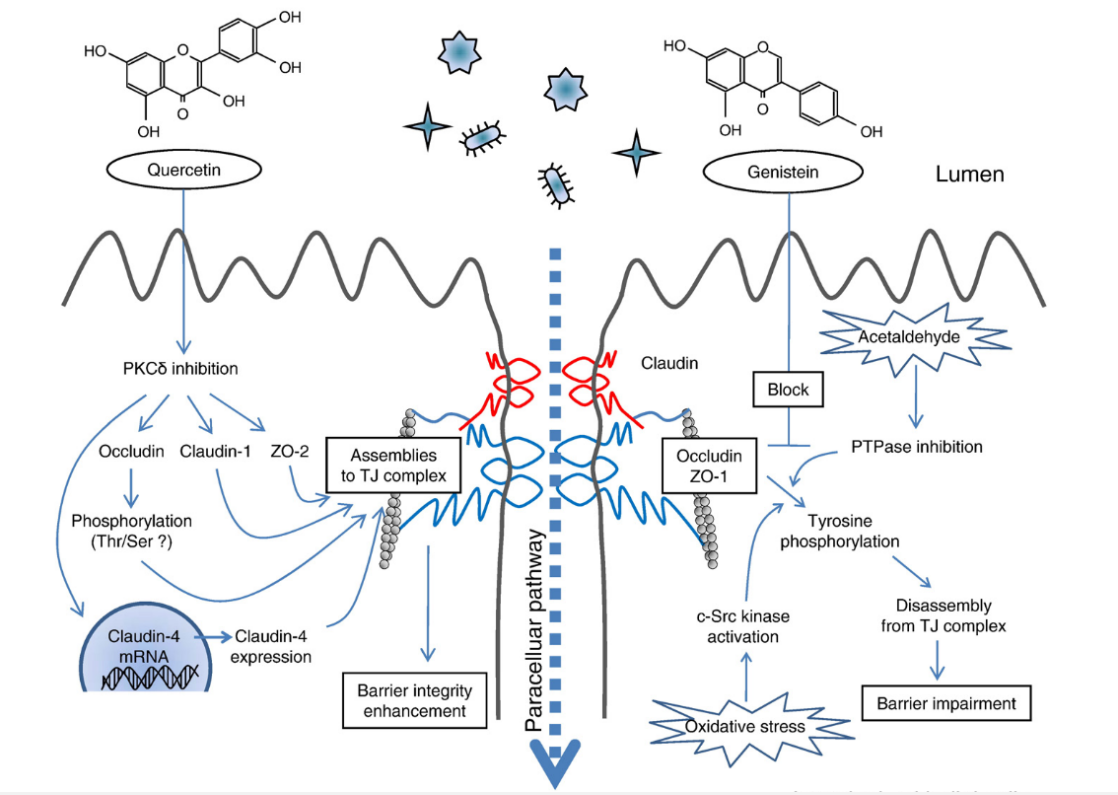
GLUTAMINE FOR GUT SUPPORT

- One of the most common recommendations for supporting Gut Barrier, though with limited published support (considered to be very safe for nearly all subjects)
- Dose recommendation starts at 4 to 8 grams/day, but may need much higher doses for desired outcome
- Often provided in powder rather than capsules to allow for higher dose therapies.

PHYTONUTRIENTS

- Flavonoids (of all kinds) have been shown to promote strong tight junction formation when tested *in vitro* (Directly signaling enterocytes)
- Flavonoids have been shown to create a diverse and healthy gut population (indirect benefit on barrier)
- Many Supplemental flavonoids are potent anti-inflammatory agents
- Diverse diet is best option, followed by range of flavonoids via supplementation (dose not as important and long-term use)

SOME MECHANISTIC (FLAVONOID) EXAMPLES

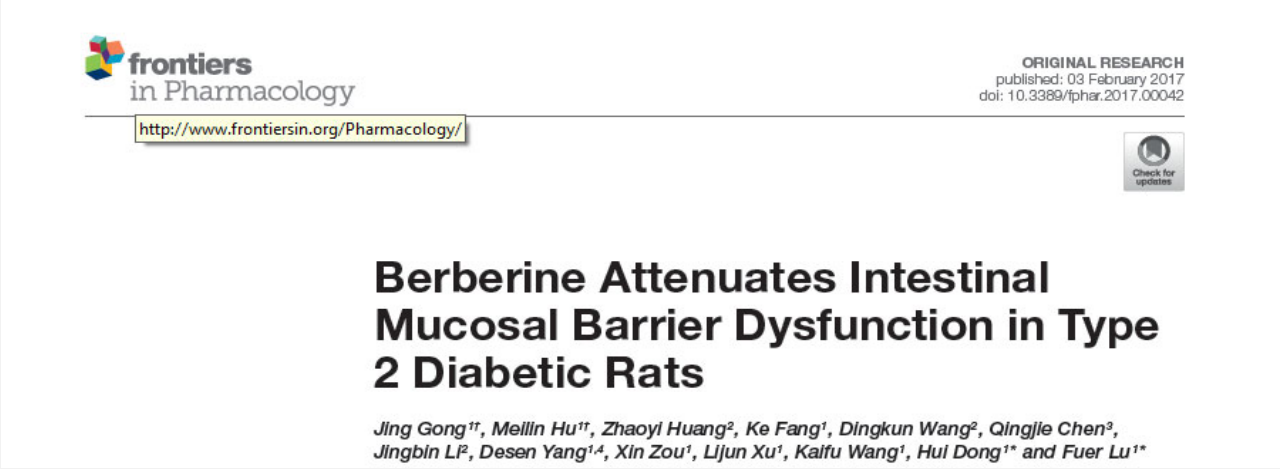


Suzuki T, Hara H. Role of flavonoids in intestinal tight junction regulation. *J Nutr Biochem*. 2011;22(5):401-408. doi:10.1016/j.jnutbio.2010.08.001

- **Quercetin** enhances intestinal barrier function through the assembly of zonula [corrected] occludens-2, occludin, and claudin-1 and the expression of claudin-4 in Caco-2 cells. *J Nutr*. 2009;139(5):965-974.
- **Kaempferol** enhances intestinal barrier function through the cytoskeletal association and expression of tight junction proteins in Caco-2 cells. *J Nutr*. 2011;141(1):87-94.
- **Naringenin** enhances intestinal barrier function through the expression and cytoskeletal association of tight junction proteins in Caco-2 cells. *Mol Nutr Food Res*. 2013;57(11):2019-2028.

BERBERINE

- Popular Alkaloid for antimicrobial and metabolic-related outcomes (LDL-C, FBG, Met-syn, BP etc.)
- Numerous in vitro and animal studies suggesting potent affects on improving TJ formation and function
- Berberine has affect on microbiome and type 2 diabetes, both known to affect or be affected by gut barrier issues
-



PHYTOTHERAPY RESEARCH
Phytother. Res. **29**: 1822–1827 (2015)
Published online 24 September 2015 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.5475

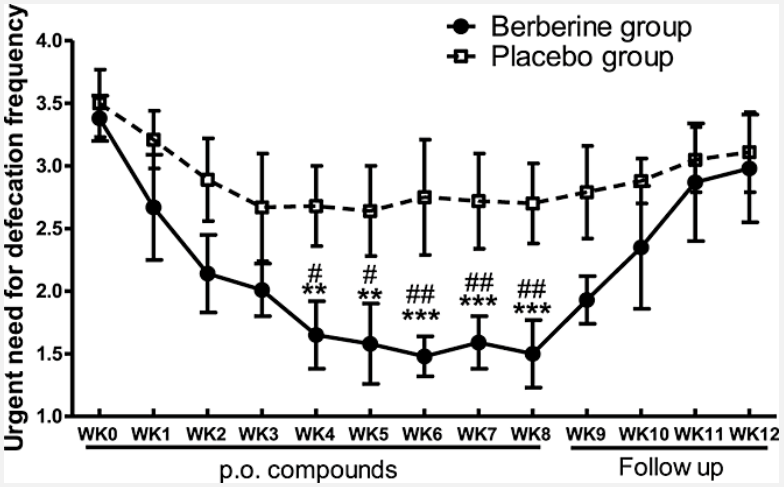
Did not measure gut permeability in IBS-D subjects

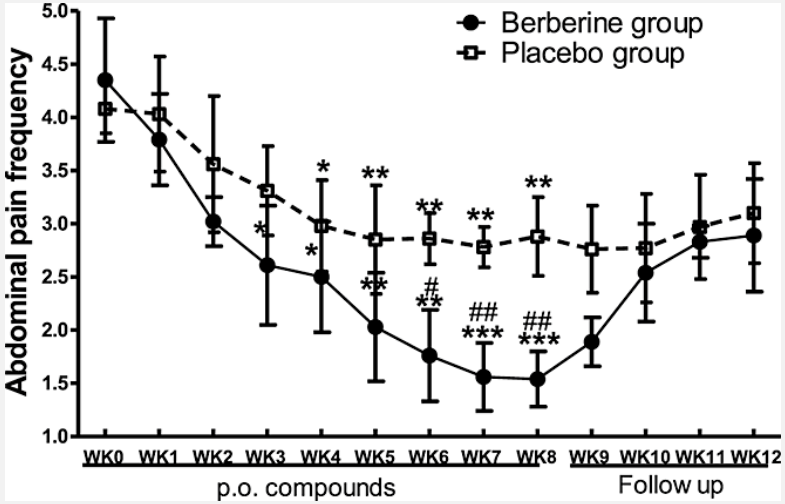
A Randomized Clinical Trial of Berberine Hydrochloride in Patients with Diarrhea-Predominant Irritable Bowel Syndrome

Chunqiu Chen,[1†] Chunhua Tao,[1†] Zhongchen Liu,[1*] Meiling Lu,[1] Qiuhui Pan,[1] Lijun Zheng,[1] Qing Li,[1] Zhenshun Song[1] and Jakub Fichna[2]

[1]Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China
[2]Department of Biochemistry, Medical University of Lodz, Lodz 92-215, Poland

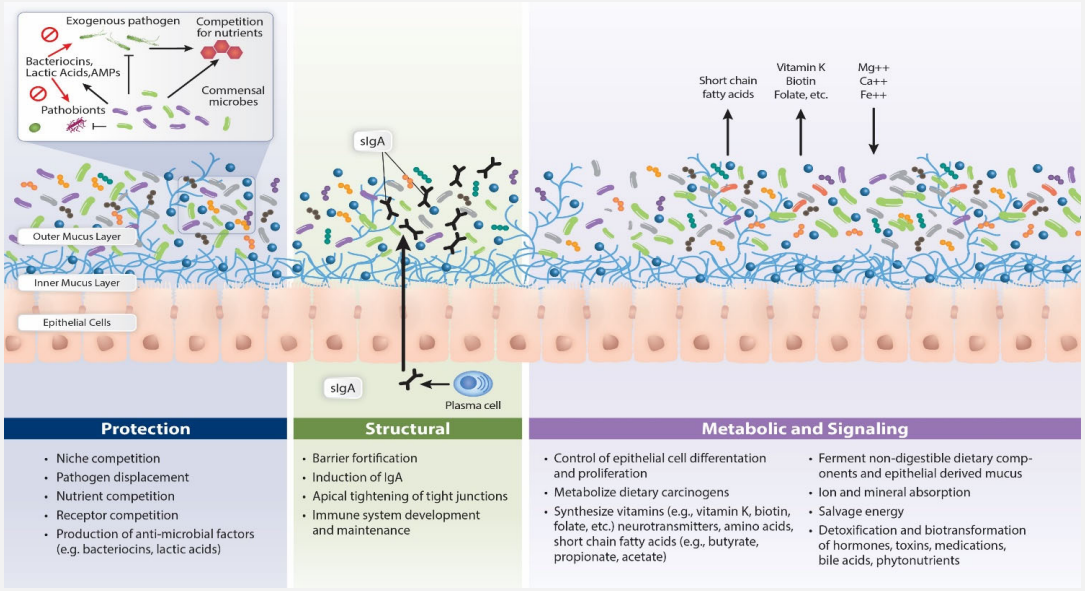
400 mg/day Berberine





PROBIOTICS

- A wide-range of probiotics are likely to help balance the microbiome, benefit immune function and improve gut barrier function……however
- Few clinical trials actually measure gut barrier function as an outcome in probiotic clinical trials



MANY IN VITRO STUDIES

Physiol Rep. 2015 Mar;3(3). pii: e12327. doi: 10.14814/phy2.12327.

Strengthening of the intestinal epithelial tight junction by Bifidobacterium bifidum.

Hsieh CY[1], Osaka T[1], Moriyama E[1], Date Y[2], Kikuchi J[3], Tsuneda S[4].

Vet Immunol Immunopathol. 2016 Apr;172:55-63. doi: 10.1016/j.vetimm.2016.03.005. Epub 2016 Mar 5.

Protective effects of Lactobacillus plantarum on epithelial barrier disruption caused by enterotoxigenic Escherichia coli in intestinal porcine epithelial cells.

Wu Y[1], Zhu C[2], Chen Z[2], Chen Z[2], Zhang W[2], Ma X[3], Wang L[3], Yang X[3], Jiang Z[4].

Inflamm Bowel Dis. 2016 Dec;22(12):2811-2823.

VSL#3 Probiotic Stimulates T-cell Protein Tyrosine Phosphatase-mediated Recovery of IFN-γ-induced Intestinal Epithelial Barrier Defects.

Krishnan M[1], Penrose HM, Shah NN, Marchelletta RR, McCole DF.

J Pediatr Gastroenterol Nutr. 2017 Mar;64(3):404-412. doi: 10.1097/MPG.0000000000001310.

Secretions of Bifidobacterium infantis and Lactobacillus acidophilus Protect Intestinal Epithelial Barrier Function.

Guo S[1], Gillingham T, Guo Y, Meng D, Zhu W, Walker WA, Ganguli K.

J Crohns Colitis. 2017 Feb 22. doi: 10.1093/ecco-jcc/jjx030. [Epub ahead of print]

Saccharomyces boulardii CNCM I-745 restores intestinal barrier integrity by regulation of E-cadherin recycling.

Terciolo C[1], Dobric A[1], Ouaissi M[2], Siret C[1], Breuzard G[1], Silvy F[1], Marchiori B[3], Germain S[1], Bonier R[1], Hama A[3], Owens R[3], Lombardo D[1], Rigot V[1], André F[1].

Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

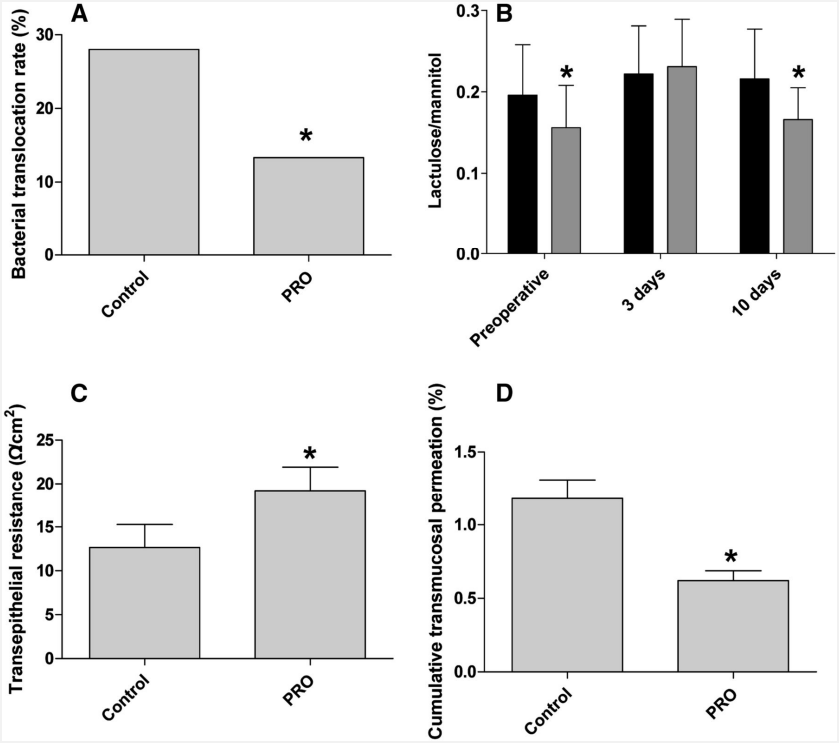
Effects of Probiotics on Intestinal Mucosa Barrier in Patients With Colorectal Cancer after Operation

Meta-Analysis of Randomized Controlled Trials

Dun Liu, Xiao-Ying Jiang, Lan-Shu Zhou, MD, PhD, Ji-Hong Song, and Xuan Zhang, MD

- Most studies published in Chinese (poor quality-low JADAD score)
- Most probiotics showed improvement in variety of TJ and inflammatory markers and L/m when measured
- Large heterogeneity of Probiotic strains and doses

The effects of perioperative probiotic treatment on serum zonulin concentration and subsequent postoperative infectious complications after colorectal cancer surgery: a double-center and double-blind randomized clinical trial. *Am J Clin Nutr*. 2013 Jan;97(1):117-26.



- 160 Subjects given probiotic or placebo for 6 days prior to surgery and 10 days after.
- The probiotic was delivered in acid-resistant capsules containing 2 g of a mixture of L. plantarum (>10^{11} CFU/gram), L. acidophilus (>$7x10^{10}$ CFU/gram) and B. longum (>$5x10^{10}$ CFU/gram).
- The postoperative serum zonulin concentration in the control group (1.08 ± 0.28 ng/mg protein) was significantly higher than that in the probiotics group (0.39 ± 0.26 ng/mg protein; P = 0.001

ORIGINAL ARTICLE

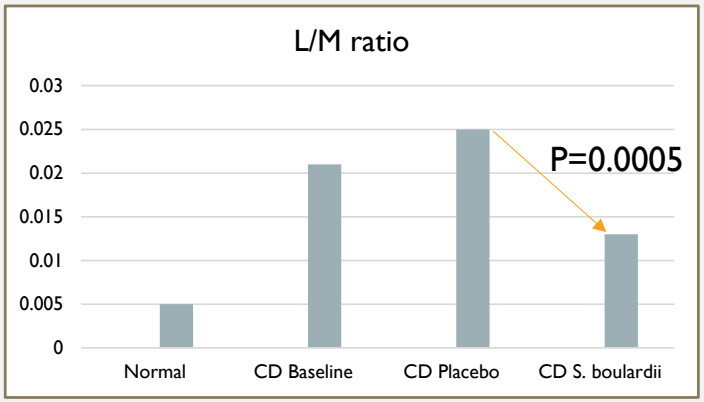
Influence of *Saccharomyces boulardii* on the intestinal permeability of patients with Crohn's disease in remission

Eduardo Garcia Vilela, PhD, Maria De Lourdes De Abreu Ferrari, Henrique Oswaldo Da Gama Torres, Ademar Guerra Pinto, Ana Carolina Carneiro Aguirre, Fabiana Paiva Martins, ...Show all

Pages 842-848 | Received 03 Nov 2007, Published online: 08 Jul 2009

Download citation http://dx.doi.org/10.1080/00365520801943354

- 34 Crohn's patients randomized for treatment with either placebo or *Saccharomyces boulardii*. Baseline medications (mesalamine, azathioprine, prednisone, metronidazole and/or thalidomide) were maintained.
- 400 million CFU of *S. boulardii* every eight hours
- Intestinal permeability (lactulose/mannitol ratio) was evaluated immediately before the beginning of treatment and at the end of the first and third treatment month. Fifteen healthy volunteers were also submitted for the intestinal permeability test.



nutrients

MDPI

Article

Oral Supplementation with Bovine Colostrum Decreases Intestinal Permeability and Stool Concentrations of Zonulin in Athletes

Maciej Hałasa [1,*], Dominika Maciejewska [1], Magdalena Baśkiewicz-Hałasa [2], Bogusław Machaliński [2], Krzysztof Safranow [3] and Ewa Stachowska [1]

1 Department of Biochemistry and Human Nutrition, Pomeranian Medical University, Szczecin 70-204, Poland; domi.maciejka@wp.pl (D.M.); ewast@pum.edu.pl (E.S.)
2 Department of General Pathology, Pomeranian Medical University, Szczecin 70-111, Poland; poziomka@pum.edu.pl (M.B.-H.); machalin@pum.edu.pl (B.M.)
3 Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin 70-111, Poland; chrissaf@mp.pl
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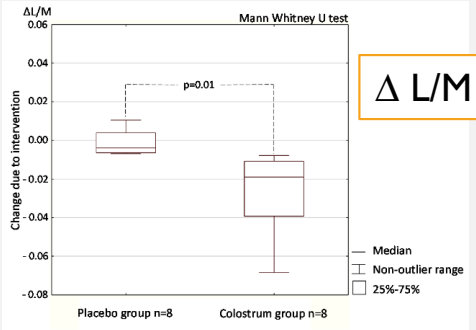
Received: 8 March 2017; Accepted: 5 April 2017; Published: 8 April 2017

Abstract: Increased intestinal permeability has been implicated in various pathologies, has various causes, and can develop during vigorous athletic training. Colostrum bovinum is a natural supplement with a wide range of supposed positive health effects, including reduction of intestine permeability. We assessed influence of colostrum supplementation on intestinal permeability related parameters in a group of 16 athletes during peak training for competition. This double-blind placebo-controlled study compared supplementation for 20 days with 500 mg of colostrum bovinum or placebo (whey). Gut permeability status was assayed by differential absorption of lactulose and mannitol (L/M test) and stool zonulin concentration. Baseline L/M tests found that six of the participants (75%) in the colostrum group had increased intestinal permeability. After supplementation, the test values were within the normal range and were significantly lower than at baseline. The colostrum group Δ values produced by comparing the post-intervention and baseline results were also significantly lower than the placebo group Δ values. The differences in stool zonulin concentration were smaller than those in the L/M test, but were significant when the Δ values due to intervention were compared between the colostrum group and the placebo group. Colostrum bovinum supplementation was safe and effective in decreasing of intestinal permeability in this series of athletes at increased risk of its elevation.

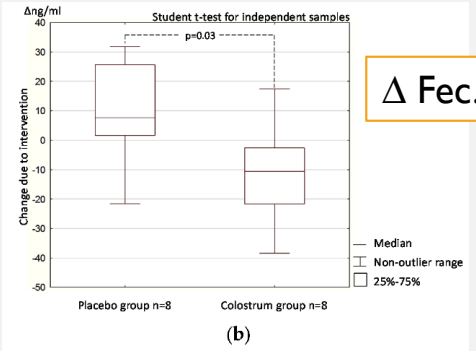
16 Athletes given either placebo (whey) or 500 mg of bovine colostrum (both with 500 mg of desiccated banana) for 20 days.

Tested during peak training when it is known that gut permeability is compromised



Δ L/M Ratio

(b)



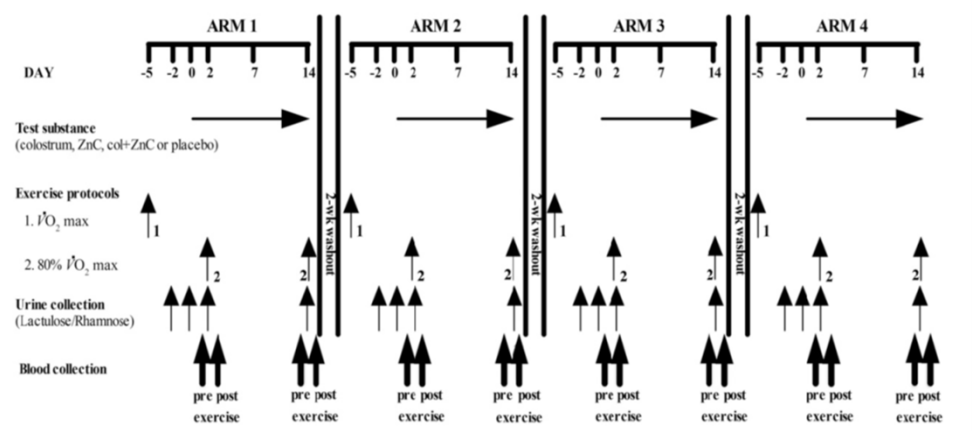
Δ Fec. Zon.

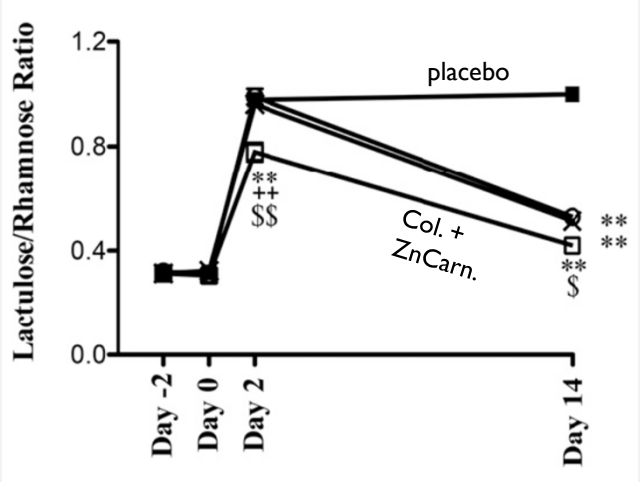
(b)

Zinc carnosine works with bovine colostrum in truncating heavy exercise–induced increase in gut permeability in healthy volunteers[1,2]

Am J Clin Nutr. 2016 Aug;104(2):526-36.

- Eight healthy volunteers- 4 arms (crossover design, 2 week washout)
- 14 days of Supplementation with the following (TWICE/DAY):
  - Placebo
  - 10 grams Colostrum
  - 37.5 mg ZnCarnosine
  - 10 grams Colostrum plus 37.5 mg ZnCarnosine





THERAPEUTIC SUMMARY

- Discover and avoid foods known to cause increased intestinal permeability.
  - May include: gluten, dairy/lactose, capsicum/spicy foods, FODMAPs, etc.
  - Test for (and avoid) food allergens (IgE/Mast cell stimulation).
- Cease NSAID use, if possible.
- Assess HPA axis stressors and treat accordingly. Stress directly influences gut permeability.
- Avoid strenuous physical activity/exercise or pay special attention to supporting gut and immune health before and after such activities. Moderate exercise is helpful.
- Avoid processed foods with artificial colors and flavors.
- Eat abundant amounts of fresh fruits and vegetables to maximize the amount and diversity of phytonutrients.

THERAPEUTIC SUMMARY CONT.

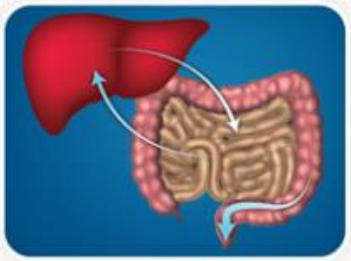
- Consider the following nutrients for supplementation:
  - Omega-3 fatty acids, ALA, EPA, DHA (through diet and supplementation)
  - Glutamine (4 to 8 grams daily)
  - Vitamin D (1,000 IU minimum daily; best to test and dose to desired serum levels)
  - Probiotics (mixed strain combination 20-40 billion CFU; consider high doses for long-standing intestinal barrier issues or when associated with IBD)
  - Prebiotics (precursor for important short-chain fatty acids [may be contraindicated if FODMAPs are to be avoided])
  - Zinc (25 mg daily with other minerals)
  - Iron (only when iron deficiency is confirmed)
  - Flavonoids (for quercetin and related compounds, dose not as important as consistent daily consumption from foods and supplementation)
  - Colostrum/Lactoferrin/IgG
  - Berberine (consider adding 1 g/day when subject is obese, insulin-resistant or has type 2 diabetes)

REMOVE *(Important First Step in 4R Model)*

Promote Elimination and Detoxification

Remove Allergens and Toxins
- Elimination diet
- Detoxification protocol

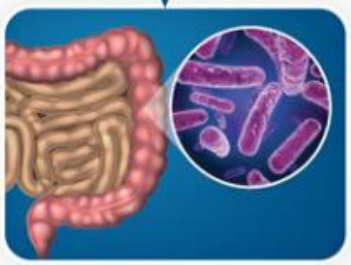
Remove Harmful Organisms
- Stool testing for pathogens
- Eliminate pathogens



REPLACE

Promote Digestion and Absorption

- Supplement or stimulate
  - Stomach acid
  - Digestive anzymes
  - Bile for fat absorption
  - Easy to absorb nutrients



RE-ESTABLISH

(Re-inoculate)

Ecosystem for Microbiome

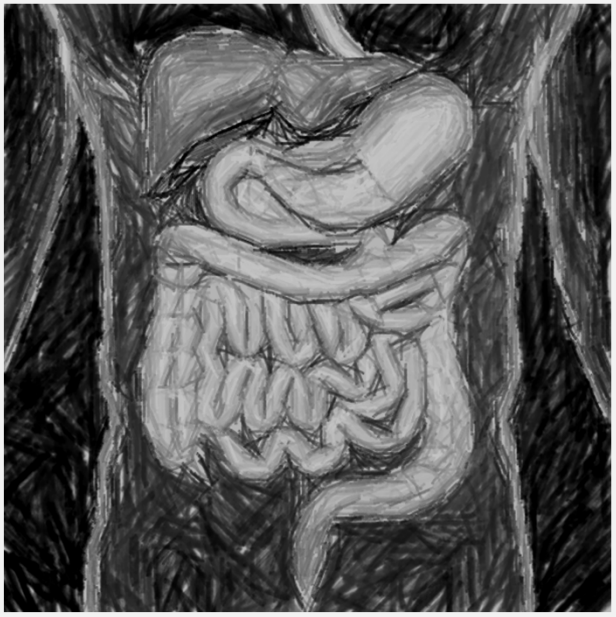
- Microbiome-friendly diet
- Avoiding certain drugs/antibiotics
- Probiotics
- Prebiotics

REPAIR

Barrier Function/ Immune Interface

- Reduce gut inflammation
- Provide nutrients for GI cells
- Improve tight junctions
- Increase signals for immune modulation

THANK YOU



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