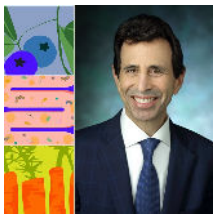
Microbiome, Gut and Systemic Health: New Frontiers in Personalised Nutrition



Keynote Speaker

Dr. Gerard Mullin, MD

Nutritional Modulation of Inflammatory Bowel Disease

9:30-10:30am

An event by: Nutritional Medicine Institute

Platinum sponsors: regenerus labs VIRIDIAN pure encapsulations

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Nutritional Modulation of Inflammatory Bowel Disease

Gerard E. Mullin, MD
Associate Professor of Medicine
Johns Hopkins University School of Medicine

NMI SUMMIT 2023
Microbiome, Gut and Systemic Health:
New Frontiers in Personalised Nutrition

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Objectives

1. To discuss the relevance of diet in the natural history, pathogenesis, and treatment of inflammatory bowel disease (IBD).
2. To understand the strategies used to effectively manage nutrition care in IBD.
3. To become familiar with the evidence-based considerations for the use of dietary supplements in IBD.

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Case Presentation

34-year-old female with ileocolonic CD. High stress levels (home and work). Long h/o antibiotic use. Diagnosed after travel to Mexico 5 years ago. **Presents with diarrhea, 25 lb. weight loss and arthritis for 12 weeks.**

ROS: fatigue **PMSHx:** lap chole

FHx: relative w/ Crohn's Disease.

Meds: Mesalamine 4 gm daily

Supplements: None **Diet:** Western

Soc: Married-2 young children, non-smoking.

Objective Data: Wt 90, ht 60", BP 104/54, skin slightly dry, slight RLQ pain (+) tenderness on exam, otherwise unremarkable exam.

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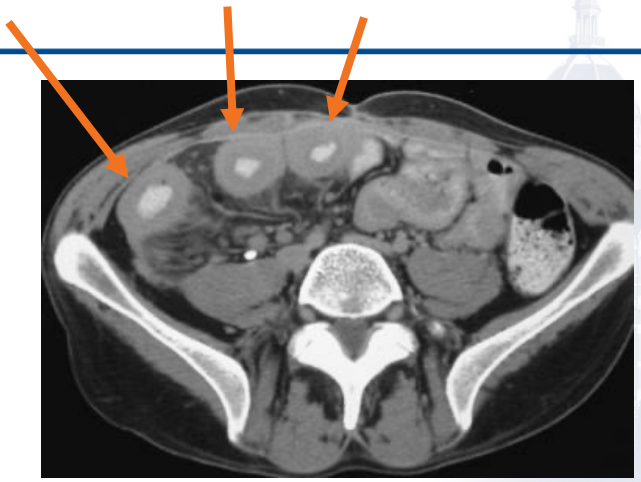

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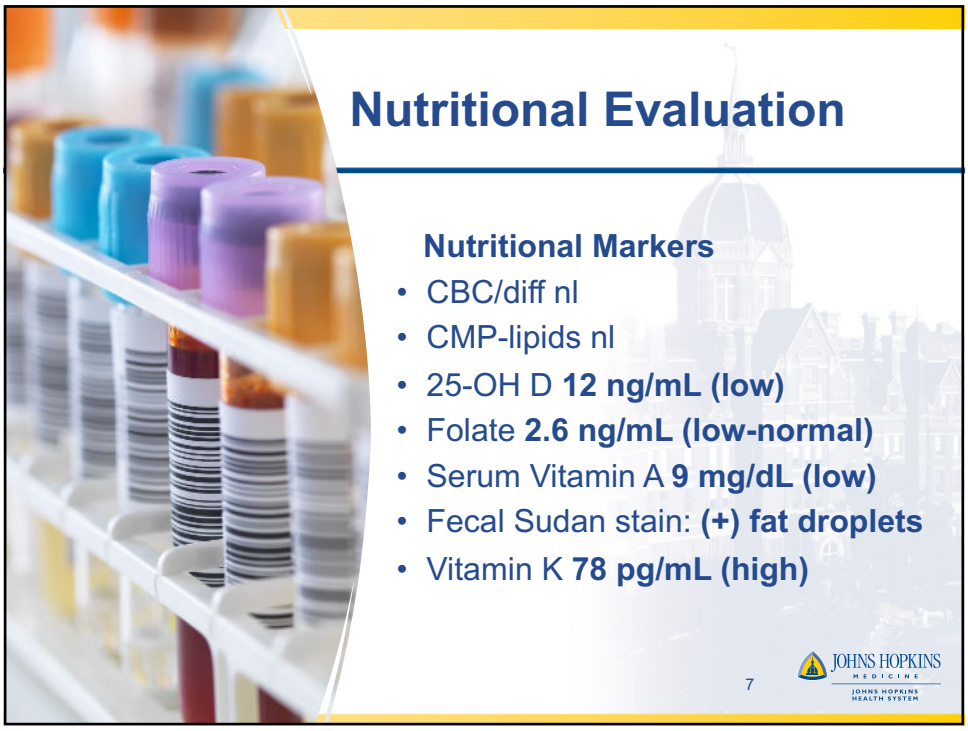
Nutritional Evaluation
Nutritional Markers
• CBC/diff nl
• CMP-lipids nl
• 25-OH D 12 ng/mL (low)
• Folate 2.6 ng/mL (low-normal)
• Serum Vitamin A 9 mg/dL (low)
• Fecal Sudan stain: (+) fat droplets
• Vitamin K 78 pg/mL (high)
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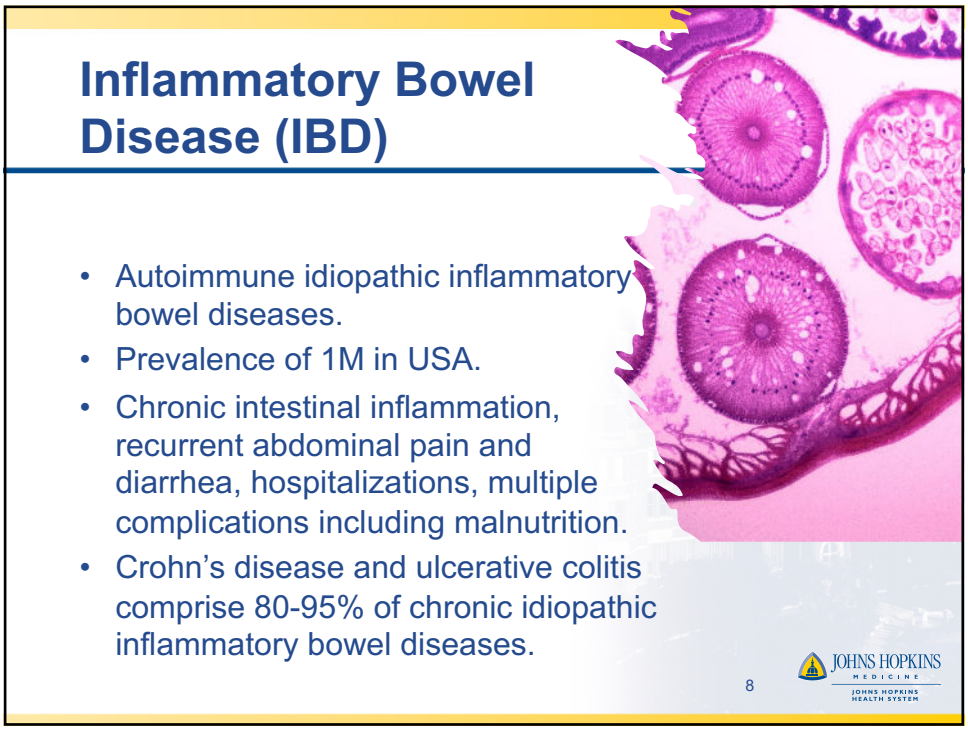
Inflammatory Bowel Disease (IBD)
• Autoimmune idiopathic inflammatory bowel diseases.
• Prevalence of 1M in USA.
• Chronic intestinal inflammation, recurrent abdominal pain and diarrhea, hospitalizations, multiple complications including malnutrition.
• Crohn's disease and ulcerative colitis comprise 80-95% of chronic idiopathic inflammatory bowel diseases.
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Characteristics of Crohn's Disease and Ulcerative Colitis

	Crohn's Disease	Ulcerative Colitis
Inflammation	Transmural	Mucosal
Distribution	Intestinal tract, patchy	Colon only, uniform
Malabsorption	Vitamins, minerals	Fluids, electrolytes
Curable	No	Surgery only
Subtypes	Inflammatory, fibrostenotic, fistulizing/perforating, reparative.	Inflammatory subtypes by location of colon.

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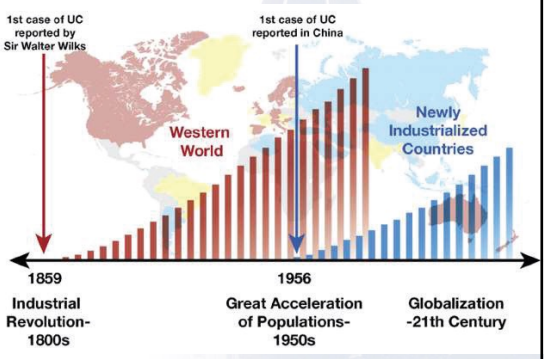
Potential Explanations for Rising IBD Prevalence Around the World

- Observational bias
- Hygiene hypothesis
- Infection
- Westernization of diet
- Microbiome hypothesis



Kaplan G, et al. Gastroenterology. 2017;152:313-321.

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Environmental Risks of Crohn's Disease and Ulcerative Colitis

Environmental Risks	Crohn's Disease	Ulcerative Colitis
Smoking	Risk in Whites and Middle East migrants	Protective in Whites and Asians
Antibiotic Use in Childhood	Risk in Whites, protective in Middle East migrants	Protective in Asians, Middle East migrants
Breastfeeding	Protective in Whites and Asians	Protective in Whites and Asians
Oral contraceptives use	Risk in Whites	Inconclusive
Appendectomy	Risk in Whites	Risk in Whites
Low vitamin D levels	Risk in Whites	Risk in Whites
Tea or coffee consumption	Protective in Asians	Protective in Asians

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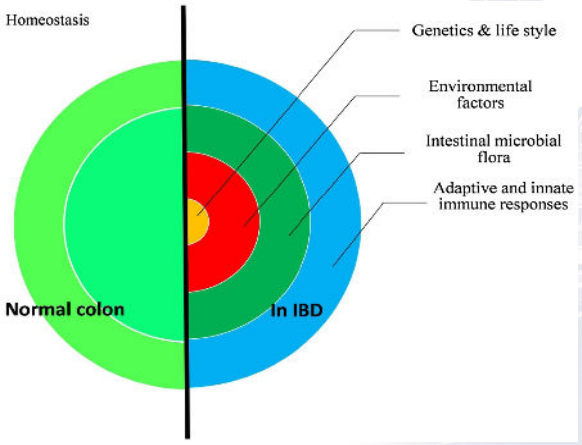
Etiopathogenesis of Inflammatory Bowel Disease



Journal of Food Biochemistry, Volume: 44, Issue: 11. First published: 04 September 2020
DOI: (10.1111/jfbc.13369).

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Pathogenesis of IBD

Initiating Events	*Mucosal Damage*	*Abnormal Immune Response*	*Chronic Inflammation*
NSAIDs	Translocation of luminal contents	Th1/Th17 vs. Th2	Luminal antigens
Antibiotics			Food antigens
Infections			Bacteria
Viral			Bacterial products
Bacterial			FMLP
Parasitic			LPS
			PGPS

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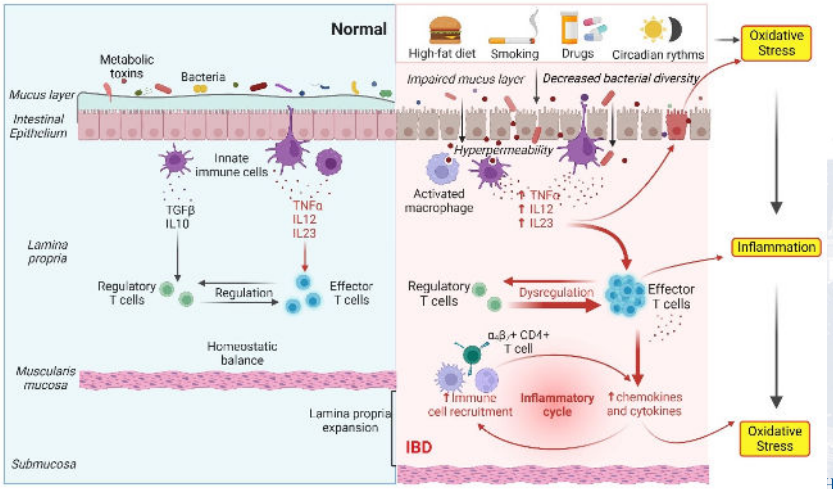
Pathogenic Mechanisms in IBD



Li L, Peng P, Ding N, Jia W, Huang C, Tang Y. *Antioxidants*. 2023; 12(4):967.

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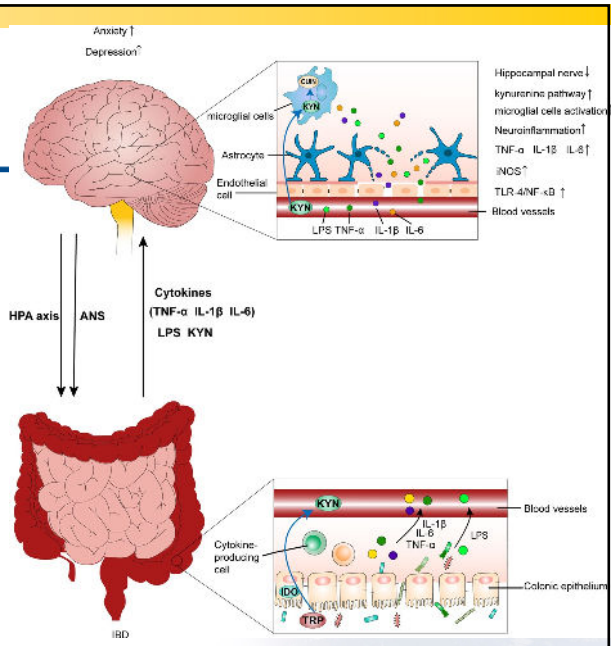
14

Role of Stress in the Pathogenesis of IBD



Ge L, Lu S, Li S. et al. Psychological stress in IBD: Psychoneuroimmunological insights. Front. Immunol. 06 October 2022. Sec Mucosal immunity.

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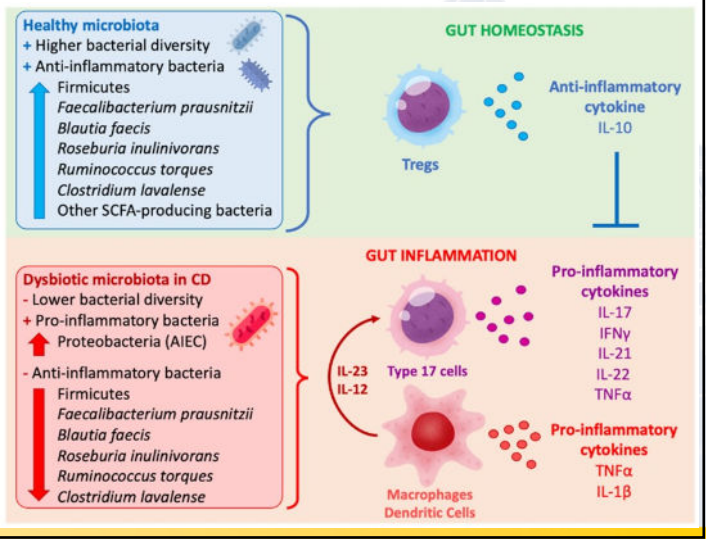
15

Overview of Gut Dysbiotic Inflammatory Mechanisms Involved in Crohn's Disease



Nunez Sanchez M, Melgar S, O'Donoghue K. et al. *Int. J. Mol. Sci.* 2022, *23*(15), 8361.

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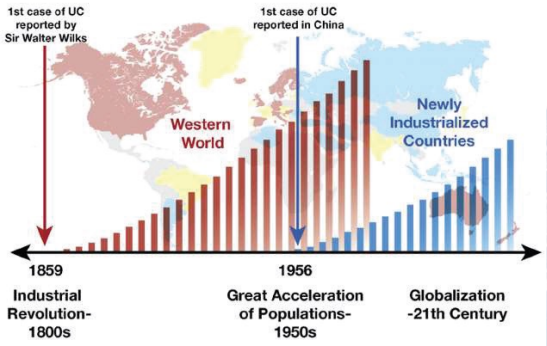
Potential Explanations for Rising IBD Prevalence Around the World

- Observational bias
- Hygiene hypothesis
- Infection
- Westernization of diet
- Microbiome hypothesis



Kaplan G, et al. Gastroenterology. 2017;152:313-321.

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Oral contraceptives use	Risk in Whites	Inconclusive
Appendectomy	Risk in Whites	Risk in Whites
Low vitamin D levels	Risk in Whites	Risk in Whites
Tea or coffee consumption	Protective in Asians	Protective in Asians

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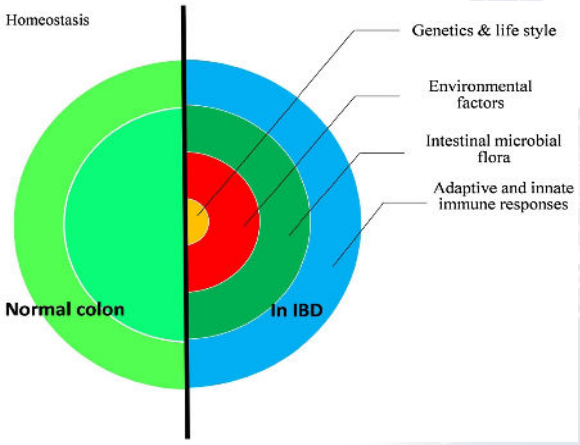
Etiopathogenesis of Inflammatory Bowel Disease



Journal of Food Biochemistry, Volume: 44, Issue: 11. First published: 04 September 2020

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Dietary Components Can Influence IBD Risk

RISK	CROHN'S DISEASE	ULCERATIVE COLITIS
Increased Risk	Animal Protein Ultraprocessed Foods	Animal Protein Refined sugars High-fat (trans)
Decreased Risk	Fiber, Fruit, Potassium, Zinc	n3-PUFA

Philipp Schreiner, Maude Martinho-Grueber, Diana Studerus, Stephan R. Vavricka, Herbert Tilg, Luc Biedermann, on behalf of Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology; Nutrition in Inflammatory Bowel Disease. *Digestion* 29 September 2020; 101 (Suppl. 1): 120–135.

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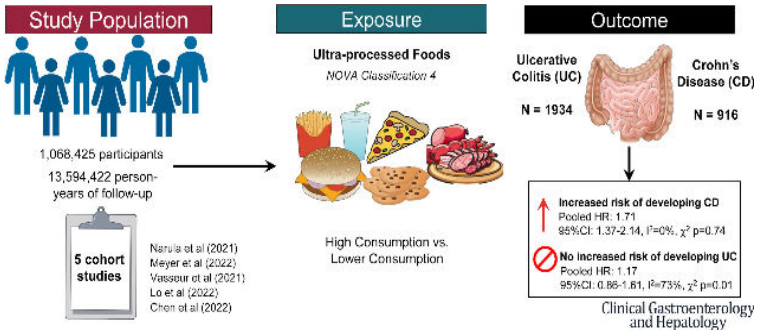
Food Processing and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Narula N, Mohamad D, Chan SM et al. *Clin Gastro Hepatol* Sept 2023;21;10: P2483-2495 E1.



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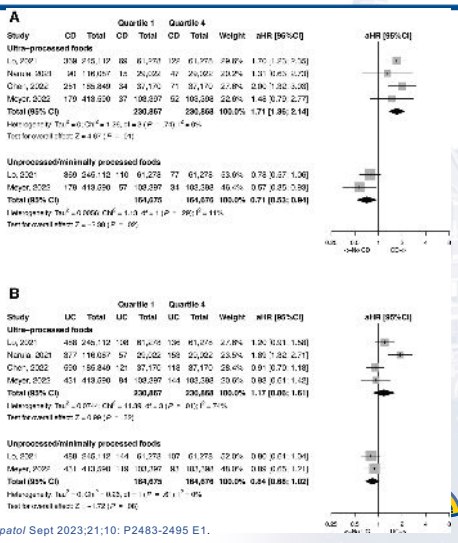
Forest Plot with Studies Reporting Association Between Food Processing and Risks of IBD

Crohn's disease

Ulcerative colitis



Narula N, Mohamad D, Chan SM et al. *Clin Gastro Hepatol* Sept 2023;21;10: P2483-2495 E1.

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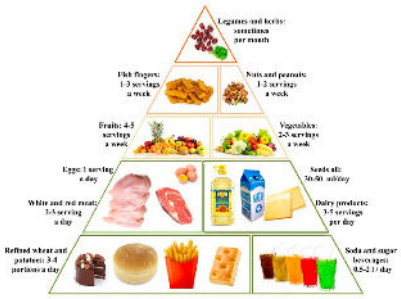
Risk of Inflammatory Bowel Disease: A Tale of Two Diets

Mediterranean food pyramid



Western-style food pyramid

Saracino, I.M.; Spisni, E.; Imbesi, V.; Ricci, C.; Dussias, N.K.; Alvisi, P.; Gionchetti, P.; Rizzello, F.; Valerii, M.C. The Bidirectional Link between Nutritional Factors and Inflammatory Bowel Diseases: Dietary Deficits, Habits, and Recommended Interventions—A Narrative Review. *Foods* **2023**, *12*, 1987.

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Potential Mechanisms Underlying Diet and Risk of IBD

Mediterranean Diet:
Fruits and vegetables
Whole grains
Seafood

Western Diet:
Red meat and processed food
Refined sugar
Saturated fat

Microbiome:
Diversity

Microbiome:
Dysbiosis

Barrier Function:
Intact permeability

Barrier Function:
Impaired permeability

Immune Function:
Tolerance vs. Inflammation

Immune Function:
Loss of tolerance

Keshteli AH, Madsen KL, Dieleman LA. Diet in the Pathogenesis and Management of Ulcerative Colitis; A Review of Randomized Controlled Dietary Interventions. *Nutrients*. 2019;11(7):1498.

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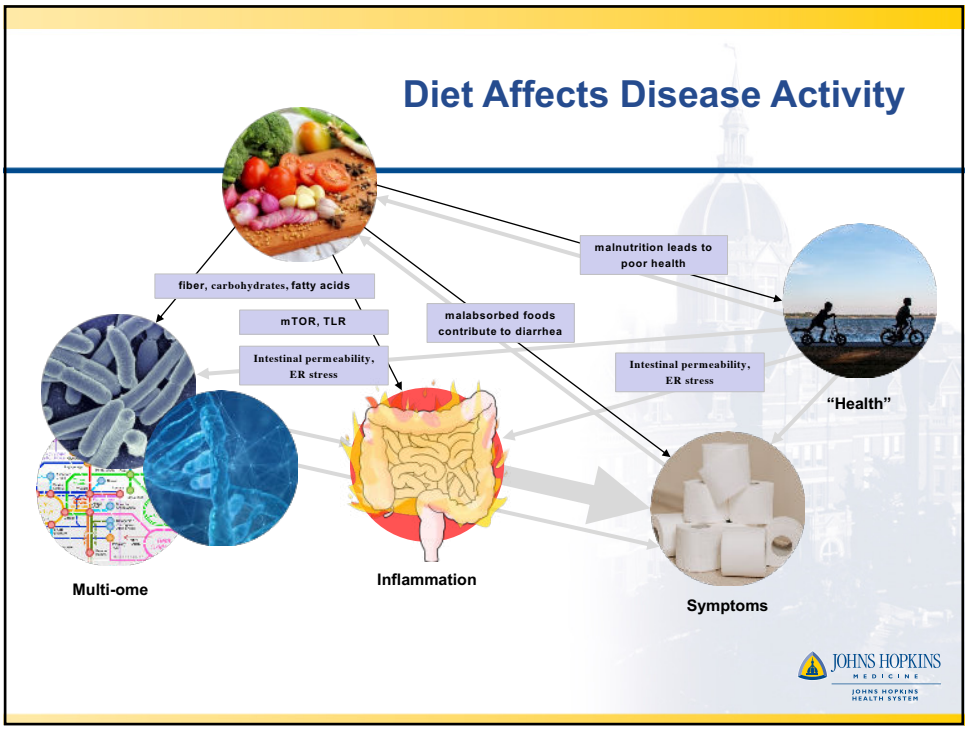
Diet Affects Disease Activity
malnutrition leads to poor health
fiber, carbohydrates, fatty acids
mTOR, TLR
malabsorbed foods contribute to diarrhea
Intestinal permeability, ER stress
Intestinal permeability, ER stress
"Health"
Multi-ome
Inflammation
Symptoms
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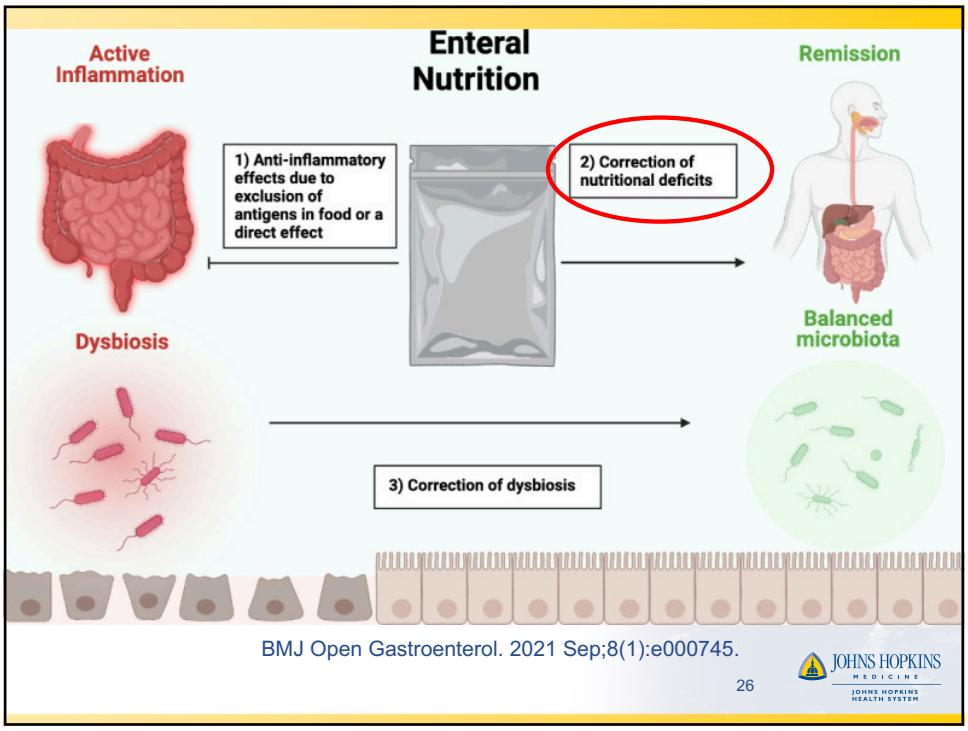
Active Inflammation
Enteral Nutrition
Remission
1) Anti-inflammatory effects due to exclusion of antigens in food or a direct effect
2) Correction of nutritional deficits
Dysbiosis
Balanced microbiota
3) Correction of dysbiosis
BMJ Open Gastroenterol. 2021 Sep;8(1):e000745.
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Prevalence (%) of Micronutrient Deficiencies in IBD

Nutrient	UC	CD
Folic acid	35	54-67
Vitamin B12	5	48
Vitamin C	16	24
Vitamin A	26-93	11-50
Vitamin D	40	70
Vitamin E	5	5
Vitamin K	44	54
Iron	81	39
Potassium	NA	6-20
Calcium	10	13
Zinc	38-45	40-50
Selenium	NA	35-40

Saracino IM, et al. The Bidirectional Link between Nutritional Factors and Inflammatory Bowel Diseases: Dietary Deficits, Habits, and Recommended Interventions—A Narrative Review. *Foods*. 2023; 12(10):1987

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Liquid Nutritional Formulas for IBD

Meal replacement liquid formulas:

- Protein/Nitrogen source: elemental, semi-elemental, or polymeric.
- Variable fat content, often including medium chain triglycerides.
- Carbohydrates: predominantly glucose, fructose and sucrose.
- No or minimal fiber content.

Uses:

- Caloric supplement: <50% of calories from formula.
- Partial enteral nutrition (PEN): ~50-60% of calories from formula.
- Exclusive enteral nutrition (EEN): ≥90% of calories from formula.

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Forest plot for the Crohn's disease activity index (CDAI), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)

Outcome	Subjects	Effect Size MD	95% CI	I^2	P value
CDAI	121	147.5	[92.7; 202.32]	97%	<0.01
CRP	173	20.5	[14.63; 23.47]	97%	<0.01
ESR	187	11.3	[2.8;19.8]	97%	<0.01

11 RCTs, 15 groups, 272 subjects

Comeche JM, et al. Enteral Nutrition in **Adult** Patients with Inflammatory Bowel Disease. Systematic Review, Meta-Analysis, and Meta-Regression. Nutrients. 2019 Nov 4;11(11):2657.

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Enteral Nutrition vs. Corticosteroids in Rx of Crohn's Disease

- 27 studies (1,011 participants) included. Meta-analysis of 8 trials EN vs. corticosteroids (223 participants).
- EN induces clinical and biochemical remission in mild-moderate pediatric Crohn's Disease (≳80%).
- Rapid: typically, within 6-10 weeks. Remission rates comparable to corticosteroids with improved mucosal healing (children).

Narula N, Dhillon A, Zhang D, et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2018; 4:CD000542.

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Polymeric Whey-based Formula Composition

	100 g	Per 100 mL (1.0 Kcal/mL)		100 g	Per 100 mL (1.0 Kcal/mL)
Energy (kcal)	493	99	**Fats (g)**	23	4.6
Carbohydrates (g)	34	11	Saturated fatty acids (g)	13	2.6
Proteins (g)	17.5	3.5	Medium chain triglycerides (g)	6	1.2
Minerals			Monounsaturated fatty acids (g)	3.9	0.78
Sodium (mg)	170	34	Polyunsaturated fatty acids (g)	2.5	0.50
Potassium (mg)	600	120	- α linolenic acid (mg)	200	40
Chloride (mg)	365	73	- Linoleic acid (mg)	2100	420
Calcium (mg)	443	89	**Vitamins**		
Phosphorus (mg)	300	60	A (µg)	410	82
Magnesium (mg)	100	20	D (µg)	4.9	0.98
Iron (mg)	5.4	1.1	E (mg)	6.5	1.3
Zinc (mg)	4.7	0.94	K (µg)	27	5.4
Copper (mg)	0.49	0.098	C (mg)	47	9.4
Manganese (mg)	0.98	0.20	Thiamin (mg)	0.59	0.12
Fluoride (mg)	<0.10		Riboflavin (mg)	0.64	0.13
Selenium (µg)	17	3.4	Niacin (mg)	5.8	1.2
Chromium (µg)	25	5	B6 (mg)	0.83	0.17
Molybdenum (µg)	37	7.4	Folic acid (µg)	120	24
Iodine (µg)	49	9.8	B12 (µg)	1.6	0.32
Other nutrients			Biotin (µg)	16	3.2
Choline (mg)	35	7	Pantothenic acid (mg)	2.4	0.48
Osmolarity (mOsm/L)	290	290			

Boumessid, K.; Barreau, F.; Mas, E. How Can a Polymeric Formula Induce Remission in Crohn's Disease Patients?. Int. J. Mol. Sci. 2021, 22, 4025.31

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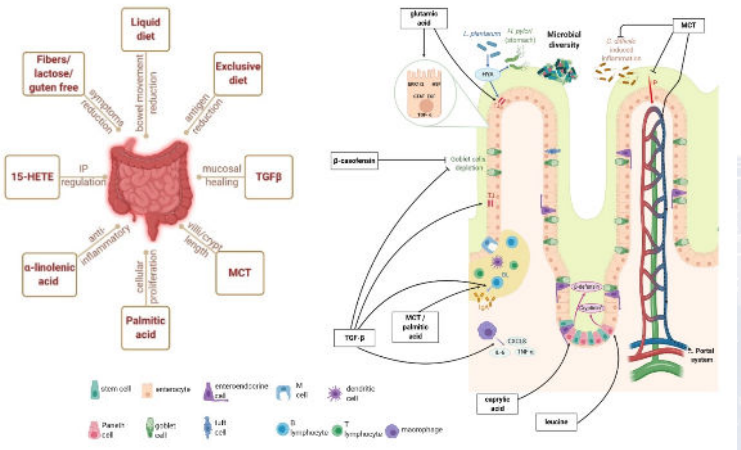
Mechanisms of Action of Polymeric Whey-based Formula on Intestinal Epithelium



Boumessid, K.; Barreau, F.; Mas, E. How Can a Polymeric Formula Induce Remission in Crohn's Disease Patients?. Int. J. Mol. Sci. 2021, 22, 4025.32

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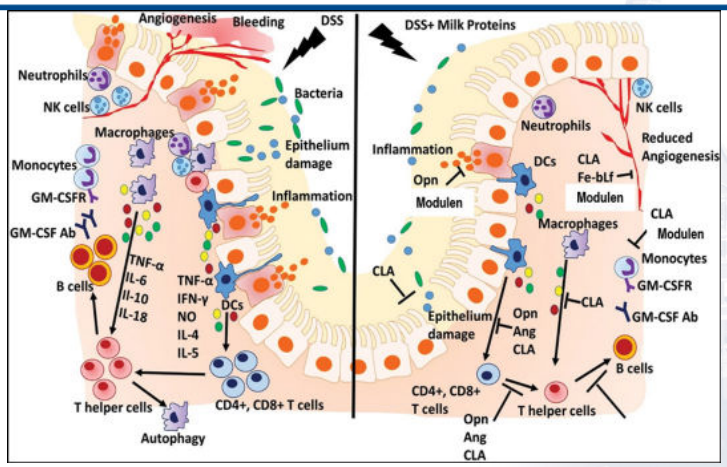
Whey Protein Mechanism of Action in Dextran Sulfate Colitis



Comparative activities of milk components in reversing chronic colitis, Journal of Dairy Science,Volume 99, Issue 4, 2016, Pages 2488-2501.

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Whey Protein-enriched Formula for Crohn's Disease

- 13 studies [6 prospective, 7 cohort] evaluated whey protein-enriched formula in patients with active Crohn's disease [12/13 children].
- Treatment duration 4-8 weeks.
- Clinical remission (PCDAI≤10) for children ranged 47-100% (≳80% within 8 weeks). Adults 38% [n=1 study].

Improvements:

- ESR and CRP levels
- Serum albumin levels
- Mucosal healing
- Clinical Disease Activity
- Serum IL-1β, IL-8, and IFN-γ.

Boumessid, K., Barreau, F., Mas, E. How Can a Polymeric Formula Induce Remission in Crohn's Disease Patients?. Int. J. Mol. Sci. 2021, 22, 4025.

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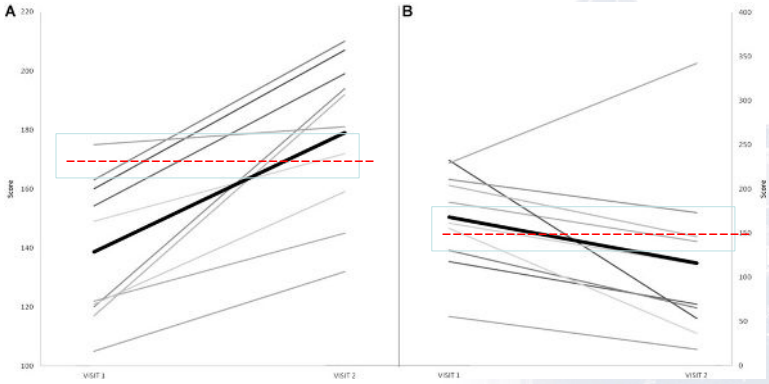
Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Patients with Final Eicosapentaenoic acid (EPA) >2%



Twenty-eight patients with active CD on stable medication were asked to consume 16 oz of IBDNF/d for 4 months.

Wiese, D.M., Lashner, B.A., Lerner, E., et al. (2011). The Effects of an Oral Supplement Enriched With Fish Oil, Prebiotics, and Antioxidants on Nutrition Status in Crohn's Disease Patients. Nutrition in Clinical Practice, 26: 463-473.

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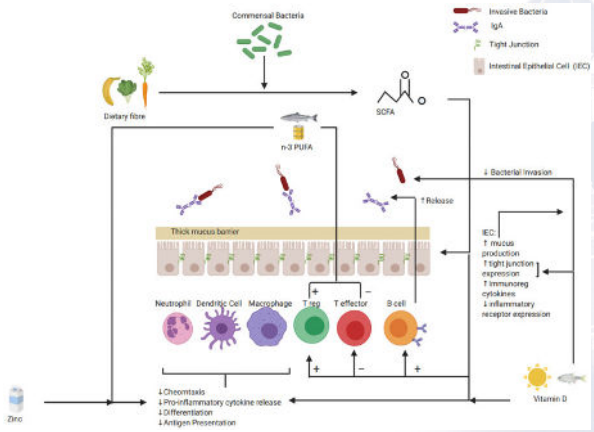
Dietary Gut-Immune Interactions Protective Against IBD



Wark G, Samocha-Bonet D, Ghaly S. et al. Nutrients. 2020 Dec 31;13(1):135.

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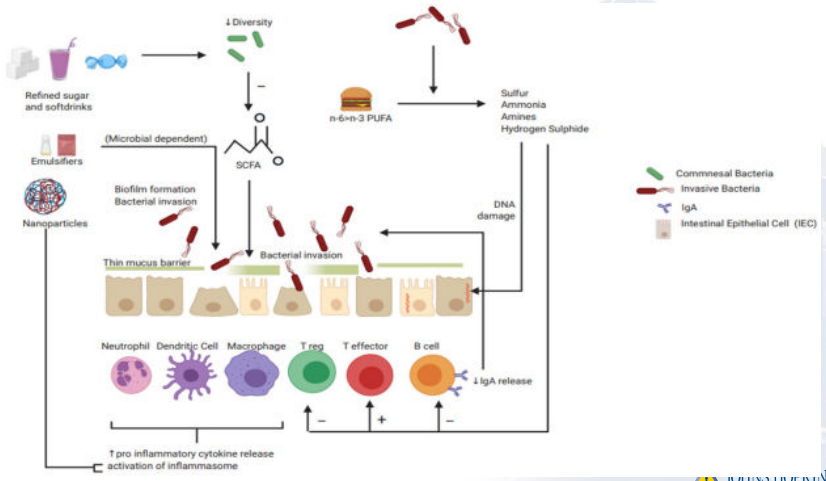
Schematic Representation of Proposed Mechanisms of Pathological Diet-immune Interactions that may Contribute to IBD Risk and Disease Activity



Wark G, Samocha-Bonet D, Ghaly S. et al. Nutrients. 2020 Dec 31;13(1):135.

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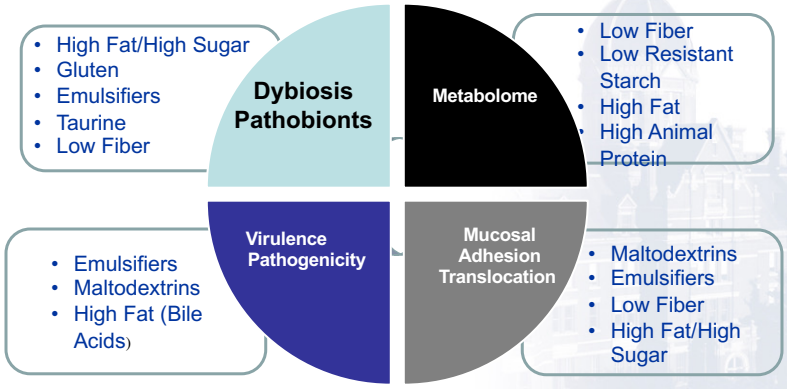
Possible Effects of Dietary Factors on Microbiota Leading to IBD (Based on Cell Lines and Animal Models)



Levine A, Sigall Boneh R, Wine E. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. Gut. 2018 Sep;67(9):1726-1738.

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Skewing the Microbiome, Diet and IBD

Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10*$^{-/-}$ mice

Suzanne Devkota[1], Yunwei Wang[2], Mark W. Musch[2], Vanessa Leone[1], Hannah Fehlner-Peach[1], Anuradha Nadimpalli[1], Dionysios A. Antonopoulos[2], Rana Jabri[3] & Eugene B. Chang[1]

The data provide a plausible mechanistic basis by which **Western-type diets** high in certain saturated fats **might increase the prevalence of immune-mediated diseases** like inflammatory bowel disease in genetically susceptible hosts.

Il10$^{-/-}$ mice. Together these data show that dietary fats, by promoting changes in host bile acid composition, can markedly alter conditions for gut microbial assemblage, resulting in dysbiosis that can perturb immune homeostasis. The data provide a plausible mechanistic basis by which Western-type diets high in certain

shown in Fig. 1a and Supplementary Table 2. With the exception of the low-fat purified mouse diet (LF), the high-fat diets were isocaloric and differed only in the type of dietary fat used, which was held constant at 37% of total calories and closely mimics Western consumption[5]. These fats also represent sources used in numerous processed

Devkota S, Wang Y, Musch M, et al. Dietary fat-induced taurocholic acid production promotes pathobiont and colitis in IL-10$^{-/-}$ mice. *Nature*. 2012;487(7405):104-108. doi:10.1038/nature11225.

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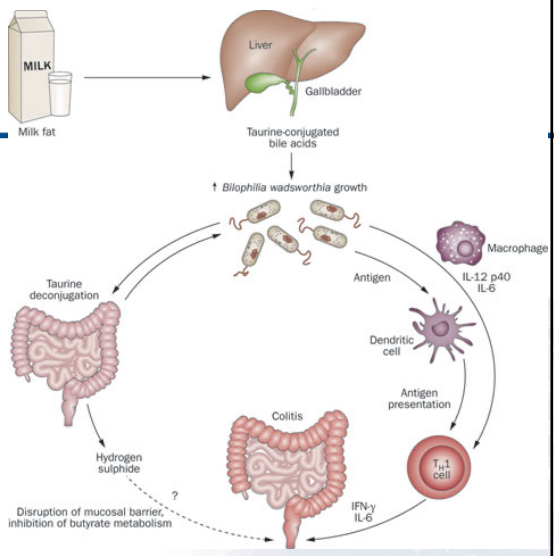
Milk Fat Induces Dysbiosis and IBD in Susceptible Hosts



Devkota S, et al. (2012). Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in IL10-/- mice. *Nature.* 2012 Jul 5;487(7405):104-8.

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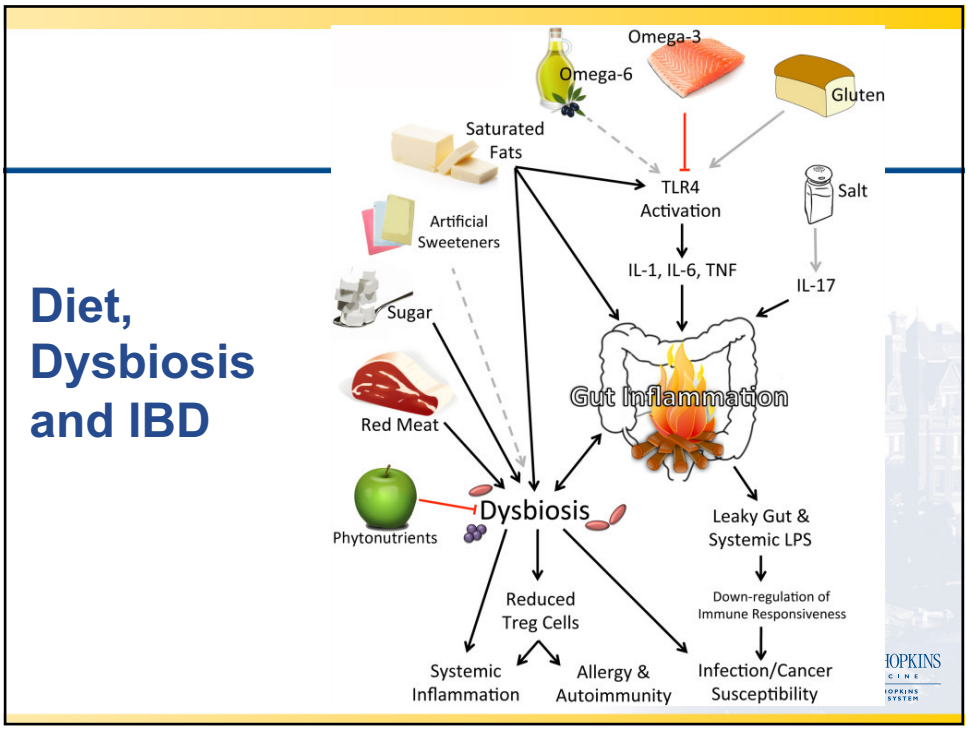

41

Popular Dietary Interventions for IBD

Diet	Include	Exclude
Exclusive Enteral Nutrition	Predigested formula: polymeric vs. elemental.	All other nutritive sources.
Partial Enteral Nutrition with Crohn's Disease Exclusion Diet	Induction: 1st 6 weeks: 50% polymeric EEN [Modulen IBD®] 50% allowed foods. Weeks 7-12: 25% polymeric EEN 75% foods. Foods: fruits, veggies, lean meat, grains, oats, rice.	Seafood other than fish, animal fat, dairy, processed foods, artificial sweeteners, emulsifiers, cocoa, coffee, alcohol, baked goods, condiments, juices, deep fried foods, ready-to-use foods.
Specific Carbohydrate Diet	Whole food diet with emphasis on fruits, most vegetables, fresh legumes, meat, seafood, hard cheeses, yogurt fermented greater than 24 hr.	Grains, starchy vegetables, most dairy, processed foods, artificial sweeteners, emulsifiers, cocoa, sugars outside of honey.
Low FODMAP	Whole food diet with certain fruits and vegetables, low lactose dairy, gluten-free grains.	Certain fruits and vegetables high in fructose, fructans, and polyols, grains, most legumes high in galacto-oligosaccharides, dairy.
Mediterranean Diet	Whole food diet with emphasis on fruits, vegetables, whole grains, legumes, seafood, nuts, olive oil.	High red meat intake, sweets, sugar, processed meat, dairy.
CD-TREAT Diet	Whole foods-based diet that recreates closely emulates EEN [Modulen IBD®] by while matching of others (macronutrients, vitamins, minerals, and fiber) and multivitamin tablet.	Excludes gluten, lactose, and alcohol.

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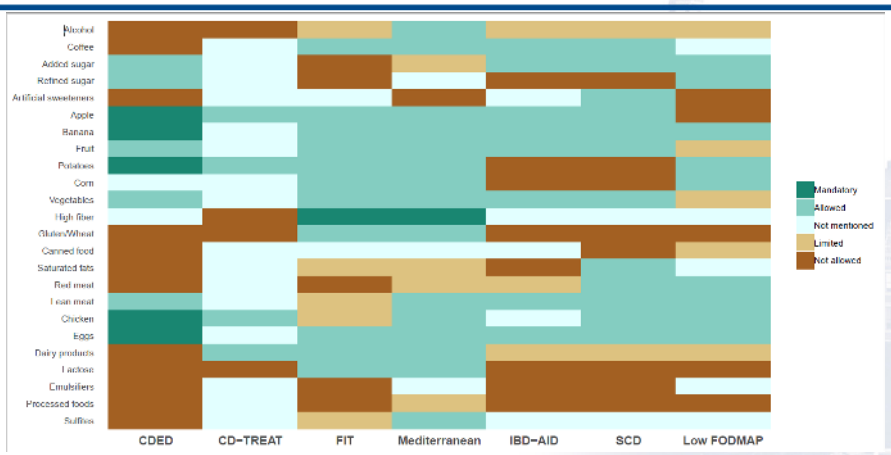
Diets Being Tested in IBD: Permitted and Prohibited Components



Sabino J, Lewis JD, Colombel JF. Treating Inflammatory Bowel Disease With Diet: A Taste Test. Gastroenterology. 2019 Aug;157(2):295-297.

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Emerging Data on Solid Food Diets

- 191 Crohn's Disease Mild/moderate, RCT, Specific Carbohydrate Diet vs. Mediterranean Diet for 12 weeks.
- The primary outcome was symptomatic remission at week 6.
- Secondary outcomes at week 6 included: Fecal calprotectin (FC) response and C-reactive protein (CRP) response.

Lewis *et al*. *Gastroenterology* 2021;161(3):837-52.

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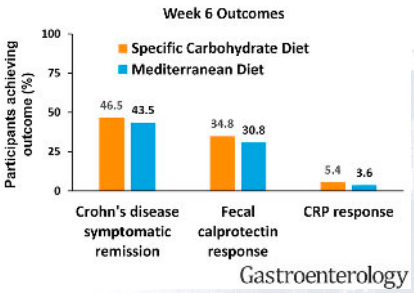
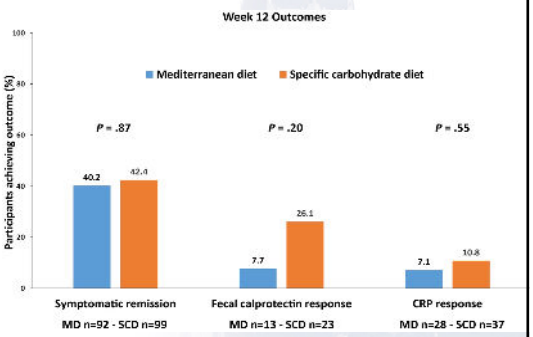
Emerging Data on Solid Food Diets



Lewis *et al. Gastroenterology* 2021;161(3):837-52.

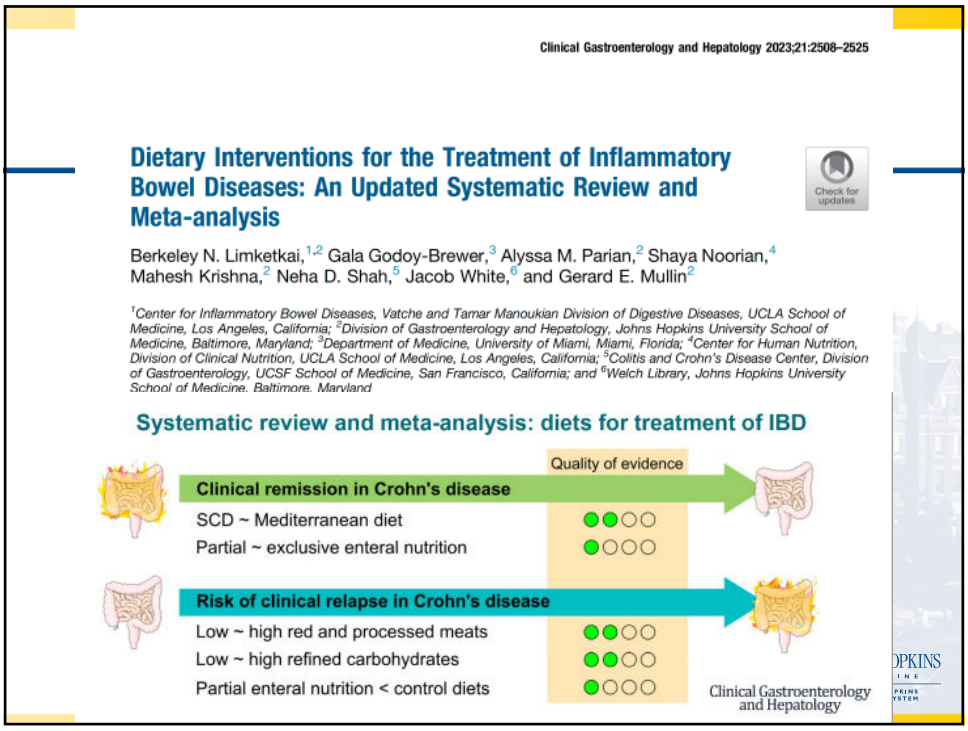
45

Emerging Data on Solid Food Diets



Lewis *et al. Gastroenterology* 2021;161(3):837-52.

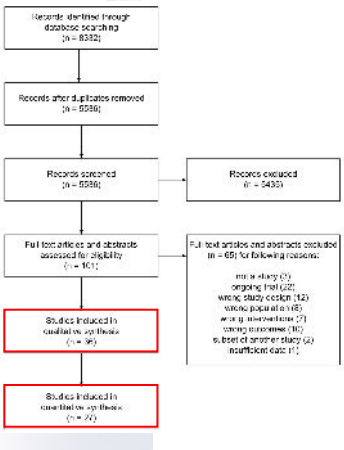
46



47

What about Solid Food Diets for IBD?

- **Prospective observational studies** and **randomized controlled trials**
- Comparison of an assigned **solid food diet** with a **control diet**
- Outcomes of interest
  - IBD-related gastrointestinal symptoms
  - Inflammatory markers (CRP, calprotectin
  - Endoscopy and histology
  - Imaging



Limketkai et al. Clinical Gastroenterology and Hepatology 2023;21:2508–2525.

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48

Induction of Remission in Crohn's Disease

Clinical remission in Crohn's disease

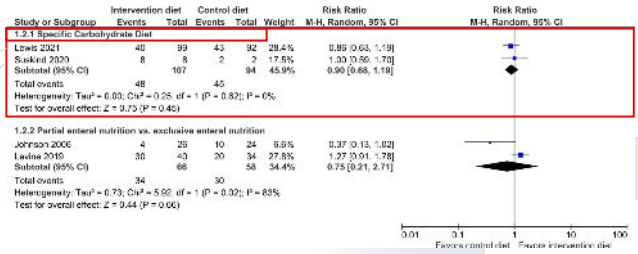
Quality of evidence

SCD ~ Mediterranean diet ●●○○

Partial ~ exclusive enteral nutrition ●○○○

Mediterranean Diet

Whole foods



Limketkai et al. Clinical Gastroenterology and Hepatology 2023;21:2508–2525.

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Crohn's Disease Exclusion Diet (CDED) and IBD

REMOVE

- Animal fat
- Wheat
- Dairy
- Red meat
- Emulsifiers
- Maltodextrin
- Carrageenan

ADD

- Fruits
- Vegetables

Levine A, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. 2019 Aug;157(2):440-450.e8.

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CDED ARTICLE

Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial

CDED Study

STUDY: Compared exclusive enteral nutrition (EEN) with the CD exclusion diet (CDED), a whole-food diet coupled with partial enteral nutrition (PEN), designed to reduce exposure to dietary components that have adverse effects on the microbiome and intestinal barrier.

METHODS: 12-week prospective RCT of children with mild to moderate CD.

INTERVENTION: Randomly received CDED plus 50% of calories from formula (Modulen®, Nestlé) for 6 weeks (stage 1) followed by CDED with 25% PEN from weeks 7 to 12 (stage 2)

OR received (Modulen®, Nestlé) for 6 weeks followed by a free diet with 25% PEN from weeks 7-12.

Levine A, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. 2019 Aug;157(2):440-450.e8. doi: 10.1053/j.gastro.2019.04.021.

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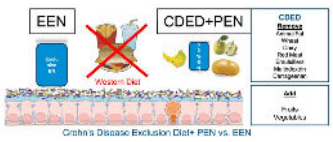
Emerging Data on Solid Food Diets



Week 1 - 6

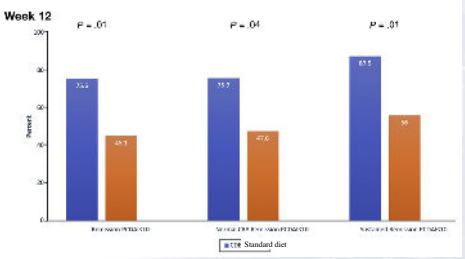
EEN (100%)
(n = 34)

PEN (50%)
CDED (50%)
(n = 40)

Week 7 - 12

EN (25%)
Standard diet (75%)

EN (25%)
CDED (75%)



Levine *et al*. Gastroenterology 2019;157:440-50

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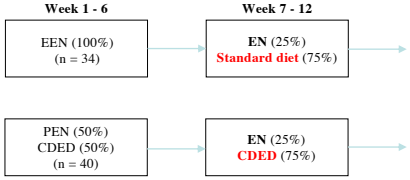
Emerging Data on Solid Food Diets



Findings

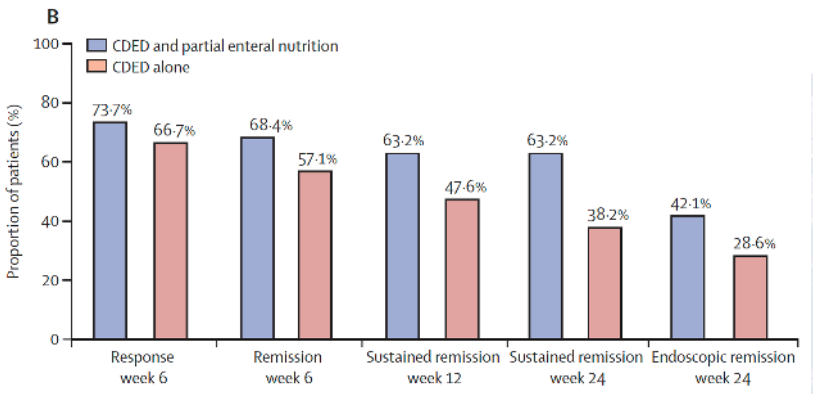
- CDED was superior to standard diet for sustained remission.

Levine *et al*. Gastroenterology 2019;157:440-50

53

Emerging Data on Solid Food Diets

Open-label pilot, RCT CDED vs. CDED/PEN in Adults



Yanai H *et al*. Lancet Gastro Hepatol 2022;7:49-59.

54

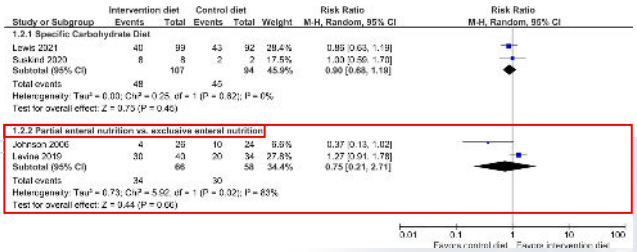
Induction of Remission in Crohn's Disease

Clinical remission in Crohn's disease

Quality of evidence

SCD ~ Mediterranean diet ●●○○

Partial ~ exclusive enteral nutrition ●○○○



EEN

Limketkai et al. Clinical Gastroenterology and Hepatology 2023;21:2508–2525.

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Maintenance of Remission in Crohn's Disease

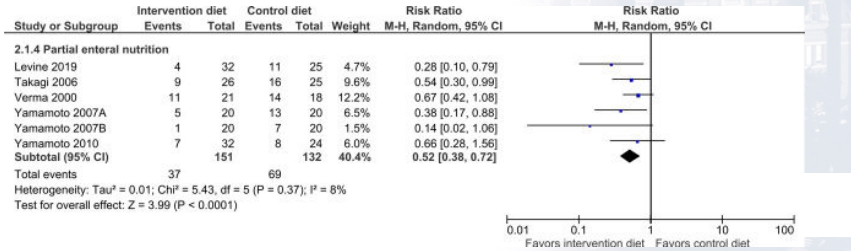
Risk of clinical relapse in Crohn's disease

Quality of evidence

Low ~ high red and processed meats ●●○○

Low ~ high refined carbohydrates ●●○○

Partial enteral nutrition < control diets ●○○○



Limketkai et al. Clinical Gastroenterology and Hepatology 2023;21:2508–2525.

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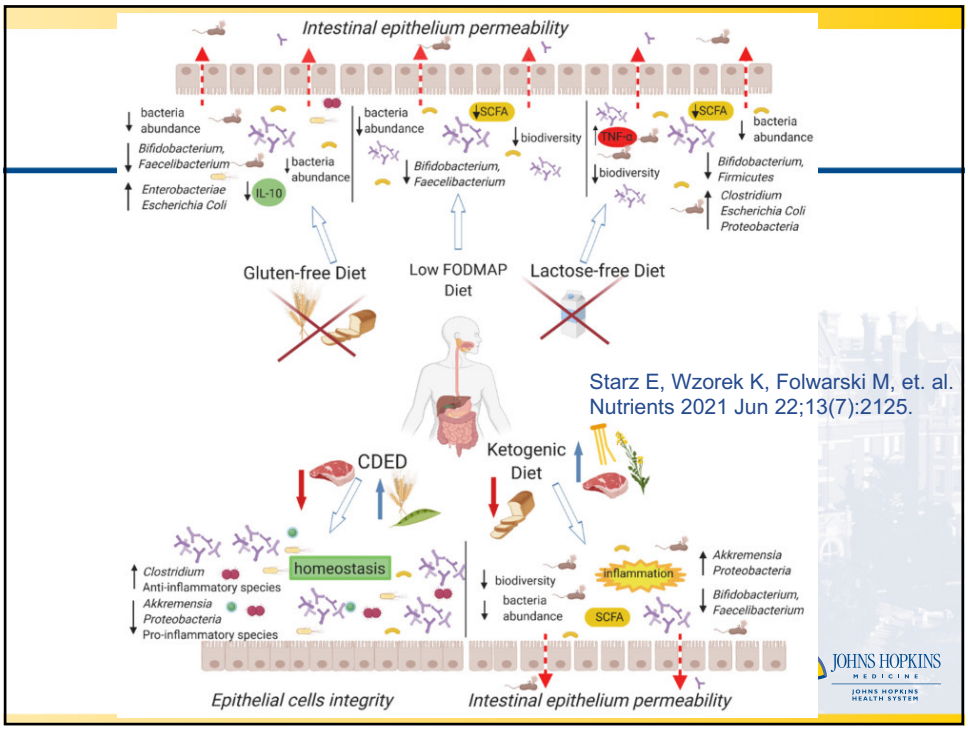

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Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases

Dietary Component	Recommendation (CD)	Recommendation (UC)
Fruits	Low evidence; reduce if stricture	?
Vegetables	Low evidence	?
Refined sugars/carbohydrates	?	?
Wheat/gluten	?	?
Red/processed meat	?	Low evidence
Poultry	?	?
Pasteurized dairy	Unable to reach consensus	Unable to reach consensus
Unpasteurized dairy	Expert opinion	Expert opinion
Dietary fats	Low evidence; saturated/trans-fat	Low evidence; myristic acid, dairy fats
Alcohol	?	?
Food additives	Low/very low evidence	Low/very low evidence

Levine A, Rhodes JM, Lindsay JO, et al. *Clin Gastroenterol Hepatol* 2020;18:1381-1392.

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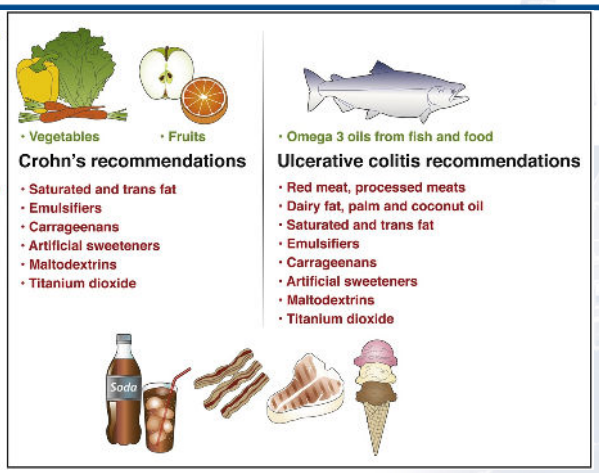
Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases.



Levine A, Rhodes JM, Lindsay JO, et al. *Clin Gastroenterol Hepatol* 2020;18:1381-1392

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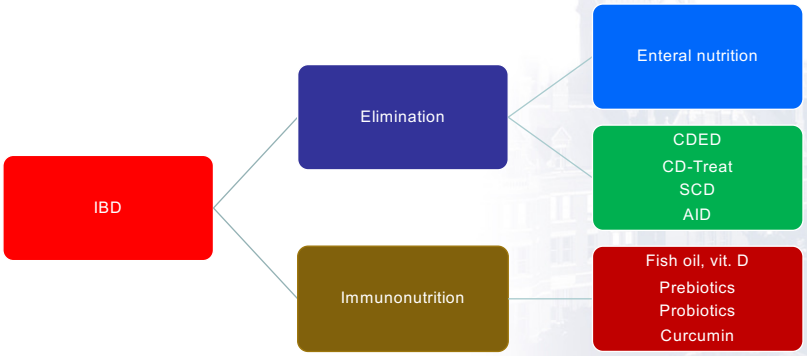
Modifying Diet to Treat Inflammatory Bowel Disease



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Dietary Supplements for IBD

Interventions:

- Omega 3 Fatty Acids
- Vitamin D
- Curcuminoids
- Boswellia
- Prebiotics
- Probiotics

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Omega 3 Fatty Acids (Fish Oil) for Maintenance of Remission in Crohn's Disease

Analysis 1.1. Comparison 1 Omega-3 versus placebo, Outcome 1 Relapse rate at one year (all studies).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Belluzzi 1996	11/39	27/39		11.98%	0.41[0.24,0.7]
Lorenz-Meyer 1996	40/70	36/65		21.4%	1.03[0.77,1.39]
Belluzzi 1997	2/26	5/24		2.19%	0.37[0.08,1.73]
Romano 2005	11/18	19/20		17.56%	0.64[0.44,0.94]
Feagan 2008a	54/183	62/180		21.24%	0.86[0.63,1.16]
Feagan 2008b	84/187	94/188		25.62%	0.9[0.73,1.11]
Total (95% CI)	**523**	**516**		**100%**	**0.77[0.61,0.98]**

Total events: 202 (Treatment), 243 (Control)
Heterogeneity: Tau^2=0.05; Chi^2=12.01, df=5(P=0.03); I^2=58.36%
Test for overall effect: Z=2.16(P=0.03)

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Lev-Tzion R, Griffiths AM, Leder O, Turner D.
Cochrane Database Syst Rev. 2014 Feb 28;2014(2):CD006320.

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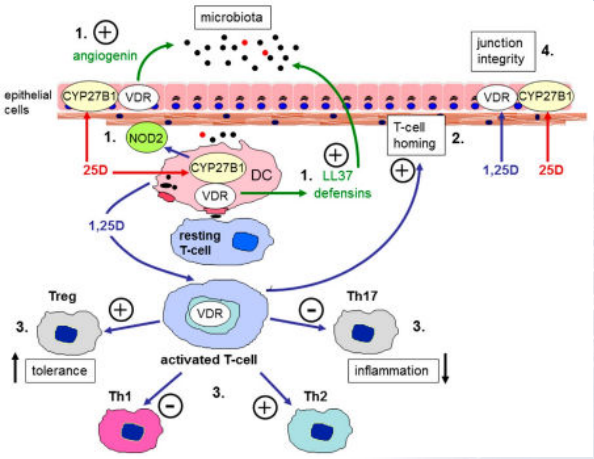
Mechanisms of Vitamin D in IBD Pathogenesis



The American Journal of Pathology
Volume 193, Issue 6, June 2023, Pages 656-668.

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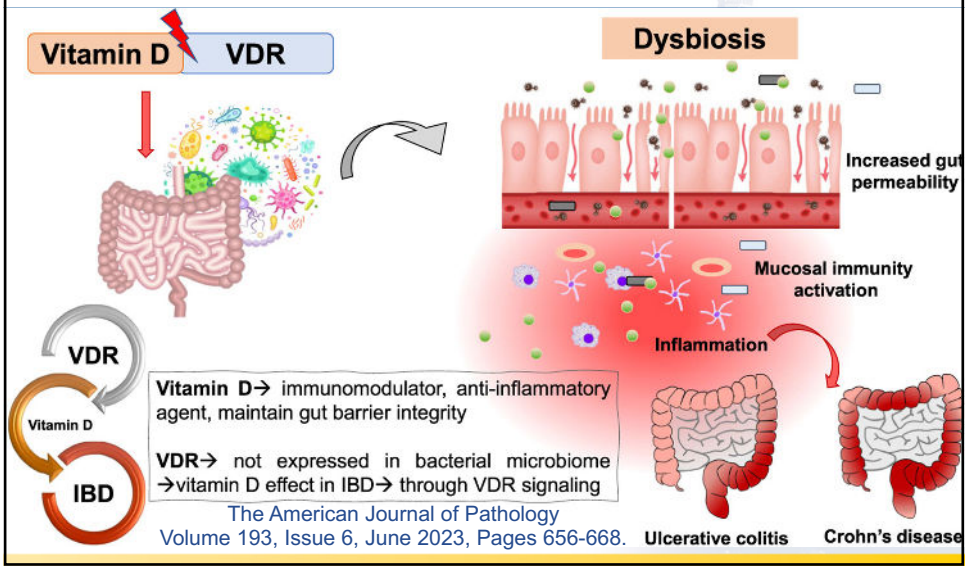
Vitamin D and Microbiome: Molecular Interaction in Inflammatory Bowel Disease Pathogenesis



The American Journal of Pathology
Volume 193, Issue 6, June 2023, Pages 656-668.

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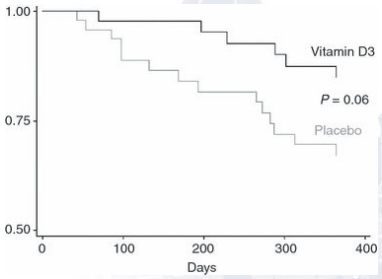
Clinical trial: Vitamin D3 Treatment in Crohn's Disease: A Randomized Double-blind Placebo-controlled Study

Percentage of patients reaching primary endpoint (clinical relapse) in the vitamin D3 vs. placebo group.



Participants: 108 patients with Crohn's disease in remission, of which fourteen were excluded later. **Patients were randomized to receive either 1200 IUs of vitamin D3 (n = 46) or placebo** (n = 48) once daily during 12 months. **The primary endpoint was clinical relapse.**

Jørgensen SP, Agnholt J, Glerup H, et al. Clinical trial: Vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics*. 2010;32(3):377–383. doi:10.1111/j.1365-2036.2010.04355.x.

65

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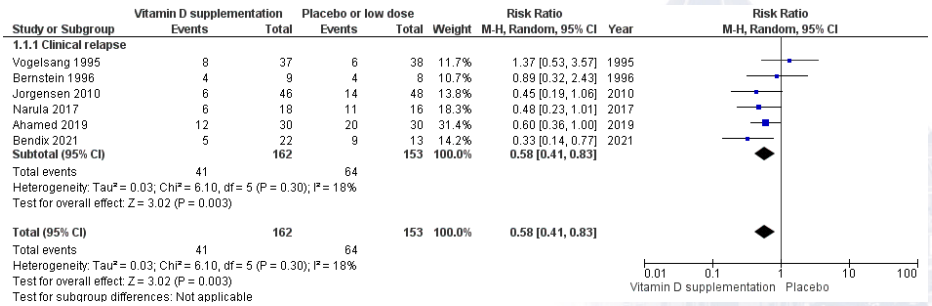
Risk of Clinical Relapse or Increase of Disease Activity in Crohn's Disease Patients and Vitamin D



Sensitivity analysis after the exclusion of post-surgery study in CD

Valvano M, Magistroni M, Cesaro N, et al. *Inflamm Bowel Dis*, Dec 29, 2022 izac253:1-11. Ahead of print.

66

Boswellia serrata in the Treatment of IBD

Aspect	Subjects	Duration	Comparator	Outcomes
Safety efficacy BS extract H15 3.6 g/D	102 active CD DBRCT	8 weeks	Mesalazine	Reduced CDAI vs. mesalamine (p=0.06)
Safety efficacy BS extract H15 1.2 g BID	108 CD in remission; DBCRT	52 weeks	Placebo	No superiority vs. placebo for MOR (p=0.85)
Safety efficacy BS extract H15 250 mg/D novel lecithin-based (Casperome®)	43 UC active Open-label	4 weeks	No supplement	Improved pain, bloody stools, reduced calprotectin (p<0.05)
Safety efficacy BS gum resin 900 mg/D	30 UC active	6 weeks	Mesalazine	Remission rates 82% BS vs 75% mesalazine ND
Safety efficacy BS extract H15 350 mg TID	30 UC active [20 H15, 10 sulfasalazine]	6 weeks	Sulfasalazine	Remission rates 70% H15 vs 40% mesalazine ND

Davila MM, Papada E. The Role of Plant-Derived Natural Products in the Management of Inflammatory Bowel Disease—What Is the Clinical Evidence So Far?Life. 2023 Aug 8;13(8):1703.

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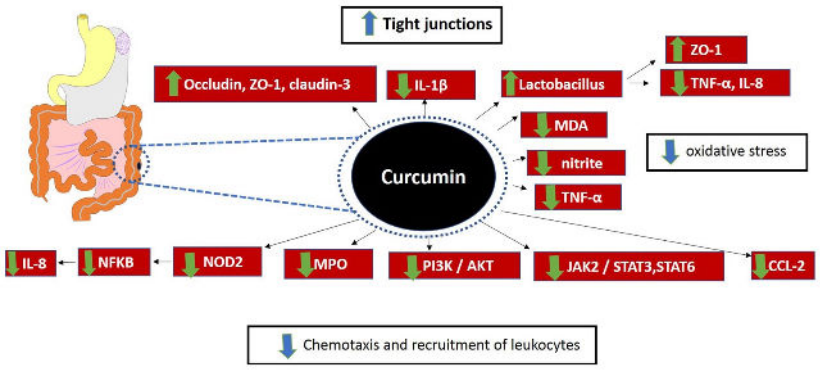
Molecular Mechanisms of Curcumin in IBD Therapy



Karthikeyan, A.; Young, K.N.; Moniruzzaman, M. et al. *Pharmaceutics* **2021**, *13*, 484.

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Curcumin for the Rx of IBD

Curcumin Dose-Duration (mo.)	N	Drugs	Findings	Markers	PI
550 mg PO BID 1 mo. TID for 1 mo.	5	5ASA, prednisone	Frequency stools↓ medication eliminated or reduced	ESR↓ CRP↓	Holt et al. 2005
1.5 g/D PO 2 mo.	70	none	Clinical remission↑ CAI↓	ESR↓ high-sensitivity CRP↓	Sadeghi et al. 2020
2 g/D PO 2 mo.	20	Selenium	DAI↓ Clinical remission↑ Endoscopic response and remission↑	ESR↓ CRP↓	Shapira et al. 2018
2 g/D PO 6 mo.	89	5ASA, sulfasalazine, mesalamine	CAI↓ EI↓ Clinical remission↑		Hanai et al. 2006
3 g/D PO 1 mo.	50	5ASA	Clinical response and remission↑ Endoscopic response and remission↑		Lang et al. 2015
100 mg/D PR 1 mo.	69	Mesalamine	Clinical response and remission↑ Endoscopic remission↑		Banjaree et al. 2021
140 mg PR/D 2 mo.	45	5ASA	Clinical response and remission↑ Mucosal healing↑		Singula et al. 2014
240 mg PR/D 1 mo.	56	5ASA	SCCAI↓		Masoodi et al. 2018

*5ASA, 5-aminosalicylic acid; 6 MP, 6-methylprednisone; CDAI, Crohn's disease activity index; CAI, Clinical Activity Index; SCCAI, Simple Clinical Colitis Activity Index; EI, endoscopic index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Lin Y, Liu H, Bu L, Chen C and Ye X (2022) Front. Pharmacol. 13:908077.[69]

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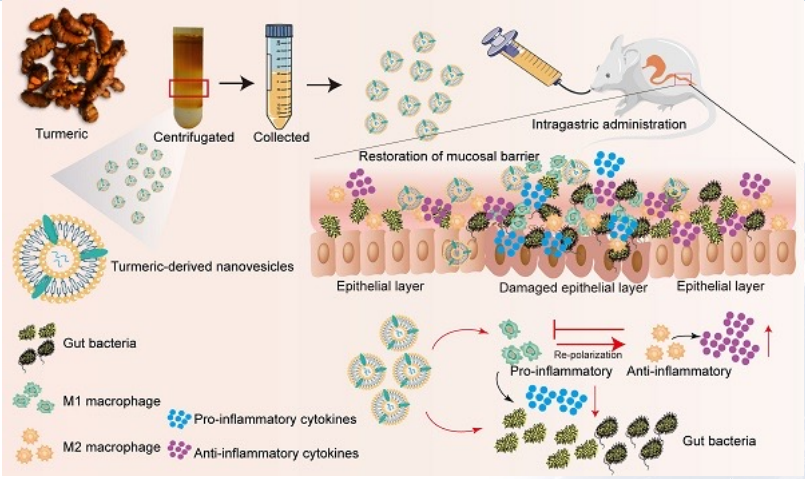
Turmeric-derived Nanovesicles as Nanobiologics for Targeted Rx of UC



Gao C, Zhou Y, Chen Z, et.al. *Theranostics* 2022; 12(12):5596-5614.

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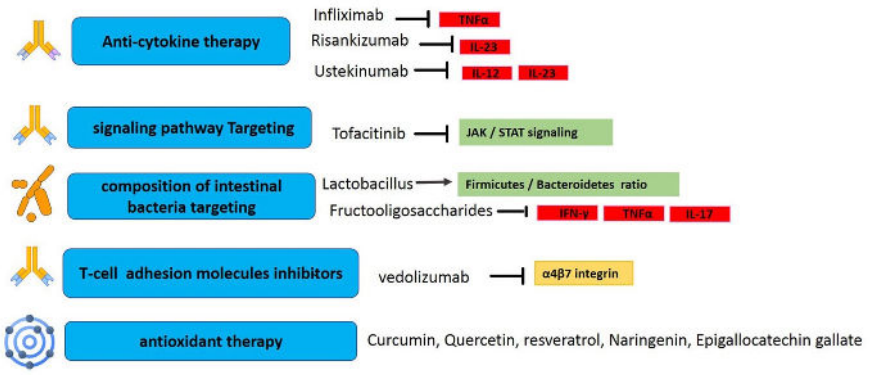
IBD Treatment Approaches



Mostafa Vaghari-Tabari, et al. Crit Rev Food Sci Nutr. 2022 Nov 8:1-24.

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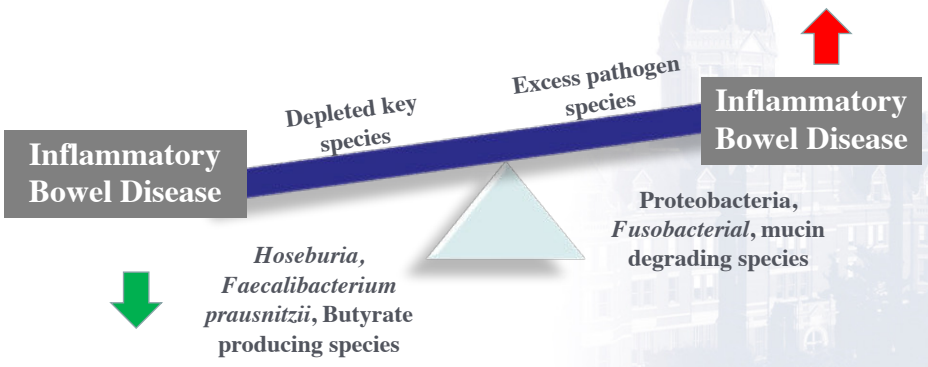
Current Microbial Therapeutic Mechanisms of Action



McIlroy J, Ianiro G, Mukhopadhya I, Hansen R, Hold GL. Review article: the gut microbiome in inflammatory bowel disease-avenues for microbial management. Aliment Pharmacol Ther. 2018 Jan;47(1):26-42. doi: 10.1111/apt.14384.

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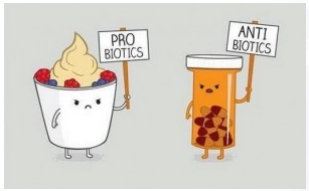
Altering the Intestinal Milieu

Diet/Fermented Foods
Soluble fiber
Prebiotics
Probiotics



Standard antibiotics
Botanical Antimicrobials

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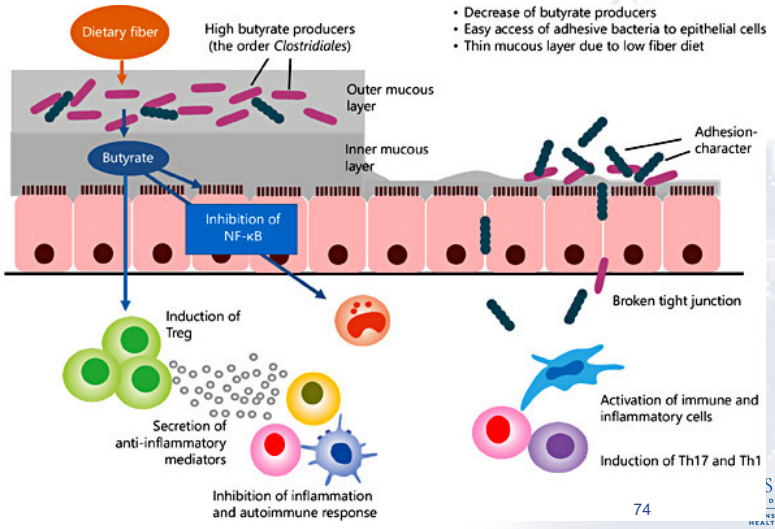
Role of Gut Microbes and SCFAs in Mucosal Immune Responses



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Microbial Manipulative Therapies for Inflammatory Bowel Disease

- Probiotics do not impact clinical recurrence rate for UC or CD.
- Probiotics and synbiotics facilitate induction of remission for active UC vs. controls.
- Desimone formulation appears to have benefit for Rx and prevention of pouchitis in UC patients.
- Sparse data on prebiotic use in IBD.
- FMT may induce remission in select IBD cases.

Cochrane Database Syst Rev. 2020 Mar 4;3(3):CD005573.
Cochrane Database Syst Rev. 2020 Jul 17;7(7):CD006634.
Cochrane Database Syst Rev. 2019 May 28;5(5):CD001176.
Nutrients. 2019 Dec 2;11(12):2913.

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Case Evaluation

D: CBC/diff nl, CMP-lipids nl, **25-OH D 12 ng/mL, Stool Analysis: fecal Sudan stain (+), high fecal fat. EFA deficient: omega 6>>>>>omega 3**

I: Leaky Gut, high lactulose/ mannitol

G: Dysbiosis

I: CRP 67, CT Scan SB thickening, mesenteric stranding, Colon biopsies-TI, ileocolonic chronic inflammation, Celiac panel (-), **Fecal calprotectin elevated, stool WBCs positive, low fecal butyrate.**

N: High Stress!

Summary Recommendations

Interventions:

- Hypoallergenic CDED diet.
- Repair program [Zn, Glutamine, DGL].
- Anti-inflammatory medical drink.
- Prebiotics, Fish oils, vitamin D, Curcumin, Boswelia.
- MBSR meditation.

→ Weight stabilized, diarrhea improved, diet advancing

*MBSR = Mindfulness-Based Stress Reduction

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Thank you!

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Microbiome, Gut
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