New Approaches in IBD

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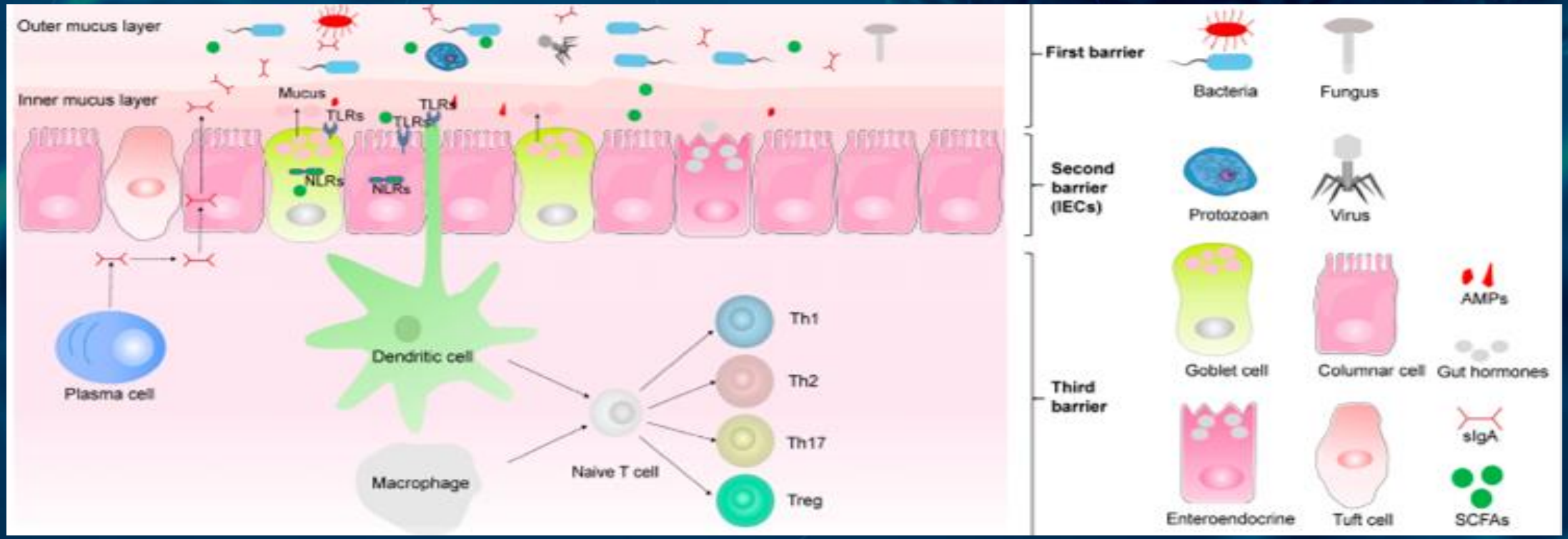
Gut Homeostasis

- Intestinal homeostasis is maintained by three immunological barriers:
  1. mucus layer (1st barrier)
  2. epithelium layer (2nd barrier)
  3. immune cell layer (3rd barrier)

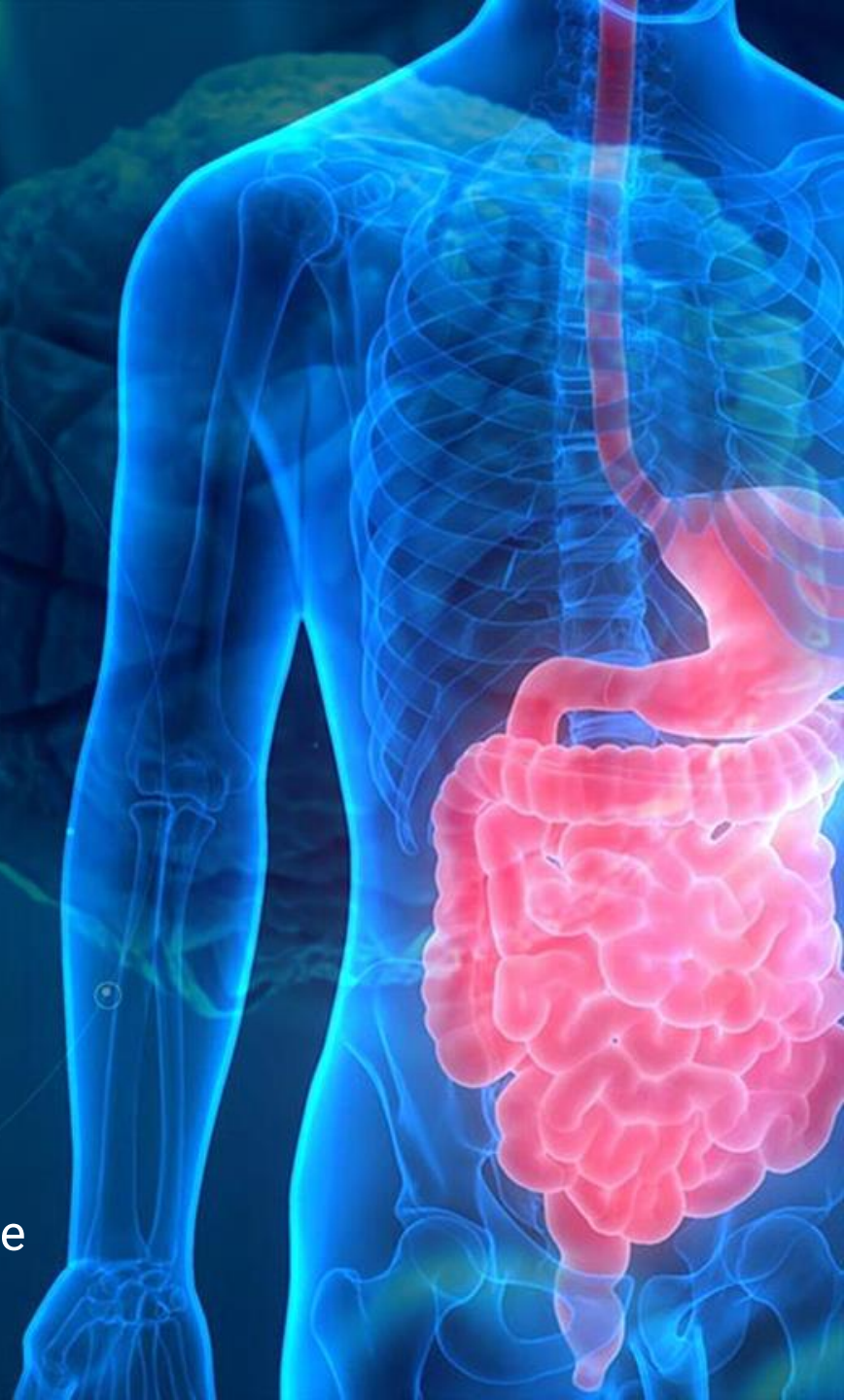


Gut Homeostasis cont.

- **The mucus layer** contains multiple immune mediators such as antimicrobial peptides (AMPs) and secretory immunoglobulin A (SIgA), which limit direct contact between the millions of microorganisms (including bacteria, fungi, viruses, and protists) and the intestinal epithelial cells (IECs).
- However, microorganisms are responsible for the degradation and digestion of dietary fiber to produce high-energy materials (e.g., short-chain fatty acids [SCFAs]) for the IECs.
- **The IEC layer**, which contains multiple pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) and nod-like receptors (NLRs), is the second immunological barrier. It rapidly detects and responds to bacteria that invade the intestinal tissue.
- **The immune cell layer** promotes the monitoring and clearance function of the IECs to limit the access of enteric microbes, thus ensuring that “unlucky” invaders are killed rapidly while also promoting intestinal homeostasis.

IBD - background

- IBDs are characterized by **chronic inflammation** of the GI tract and are comprised of two idiopathic gastrointestinal disorders known as ulcerative colitis (UC) and Crohn's disease (CD).
- Both UC and CD are chronic disorders of a remitting and relapsing kind.
- The peak age of onset is in adolescence and young adulthood. The incidence of IBDs has shown an increasing trend over the last few decades
- Despite intense research efforts, the disease etiology (ies) is (are) not fully understood.
- It appears that both genetic and environmental factors are involved in IBD causation, affecting the interaction between the intestinal mucosa and luminal bacteria, with a breakdown in the regulatory constraints of mucosal immune responses to enteric bacteria.



IBD cont.

- IBDs are complex chronic inflammatory disorders with multiple factors such as psychological distress, autonomic dysfunction, gut microbiome dysbiosis and immune modulations associated with disease activity.
- The most common symptoms of IBD include diarrhea, rectal bleeding, intermittent nausea and vomiting, and abdominal pain or tenderness.
- The symptoms are caused by the intestinal damage resulted from the exaggerated inflammatory response.
- Complications from these immune-mediated diseases include anemia, malnutrition, bowel obstruction, fistula, infection, and an increased risk of colon cancer.
- Extra-intestinal manifestations may also develop, such as joint problems (arthralgia, arthritis, and ankylosing spondylitis), rashes and skin conditions (erythema nodosum, psoriasis), chronic liver disease (primary sclerosing cholangitis) and eye conditions (such as uveitis).

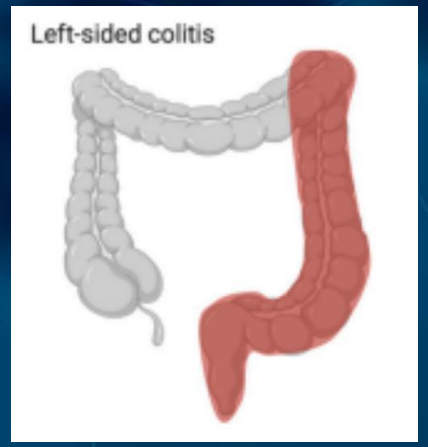
IBD cont.

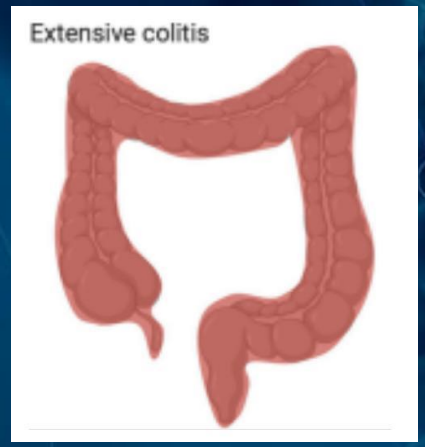
- **UC** is characterized by chronic inflammation of the large intestine with abnormal activation of the immune system. It affects the innermost layer of the colon and rectum.

- **CD** can affect any level of the intestinal tract from the mouth to the anus and across all layers of the bowel wall, but mostly affects lower small intestine (ileum) and colon.

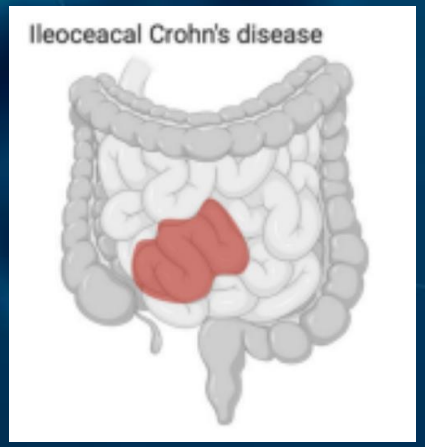
UC vs. CD

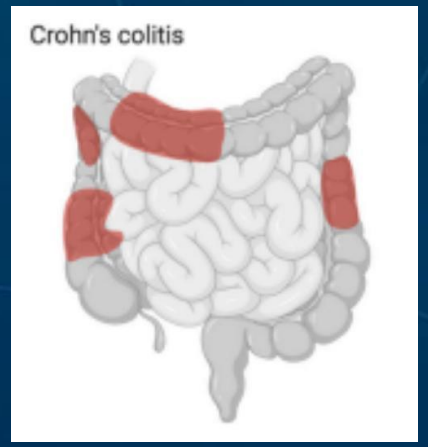
A) Ulcerative Colitis



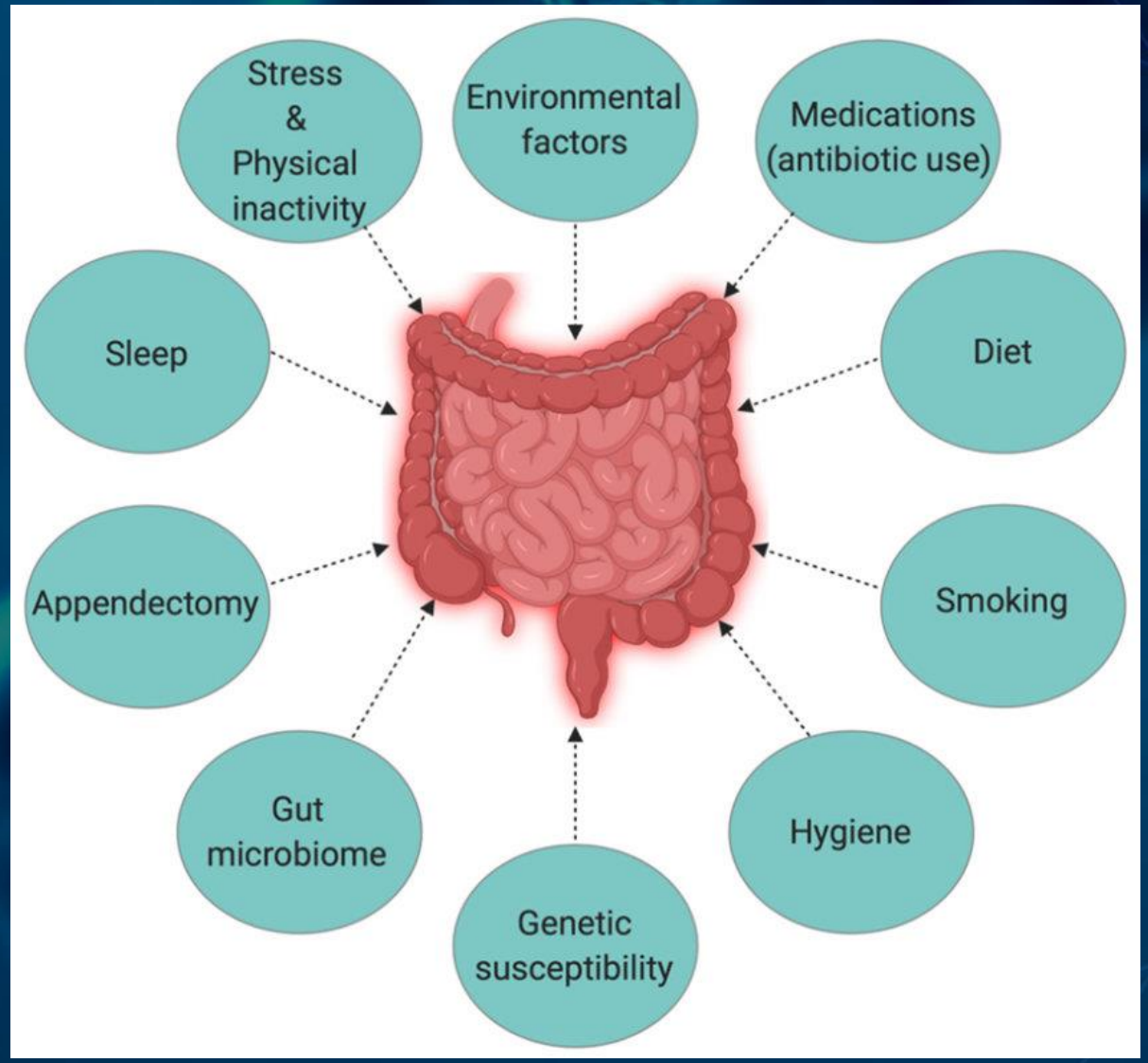


A) Crohn’s Disease

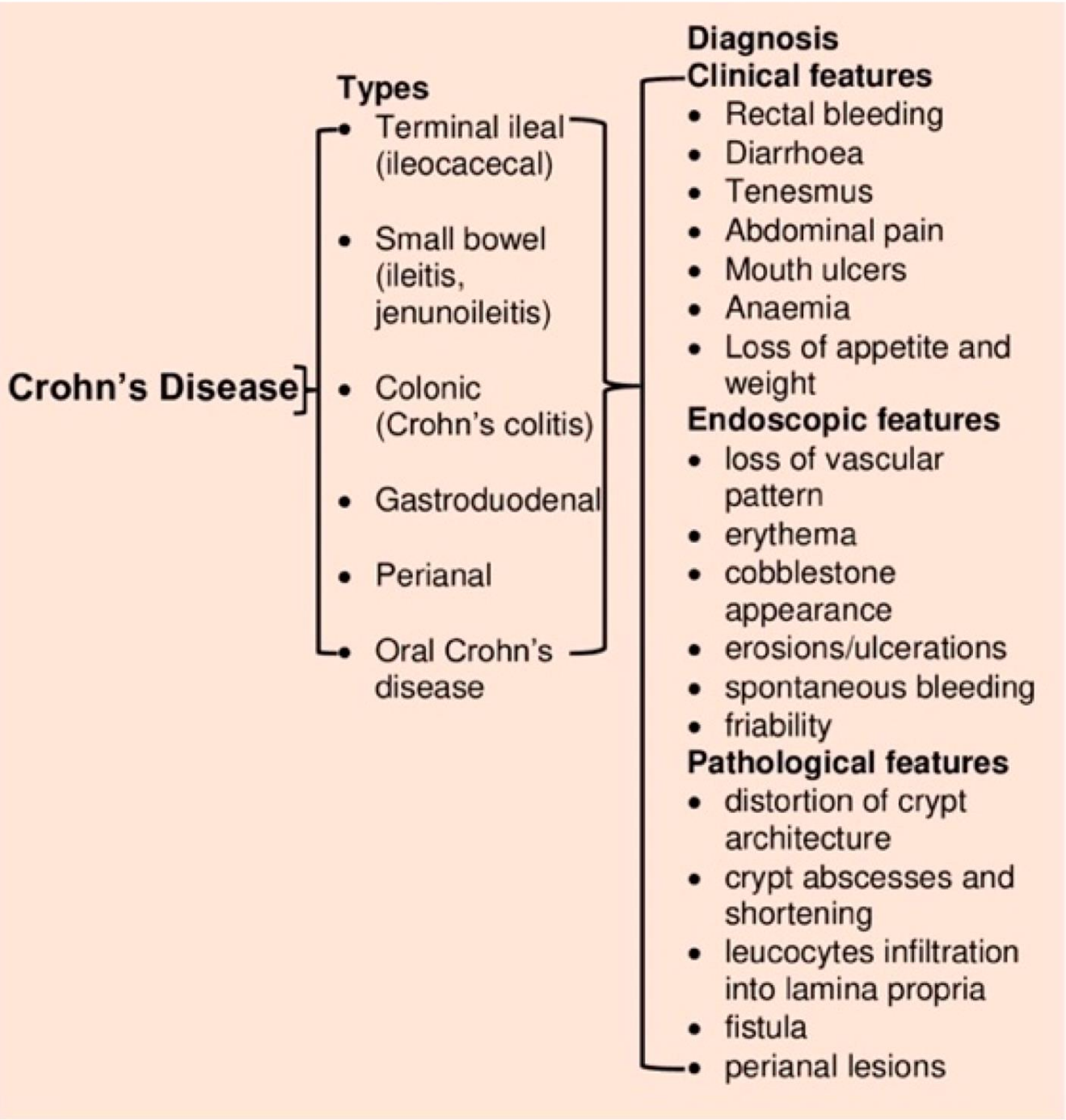




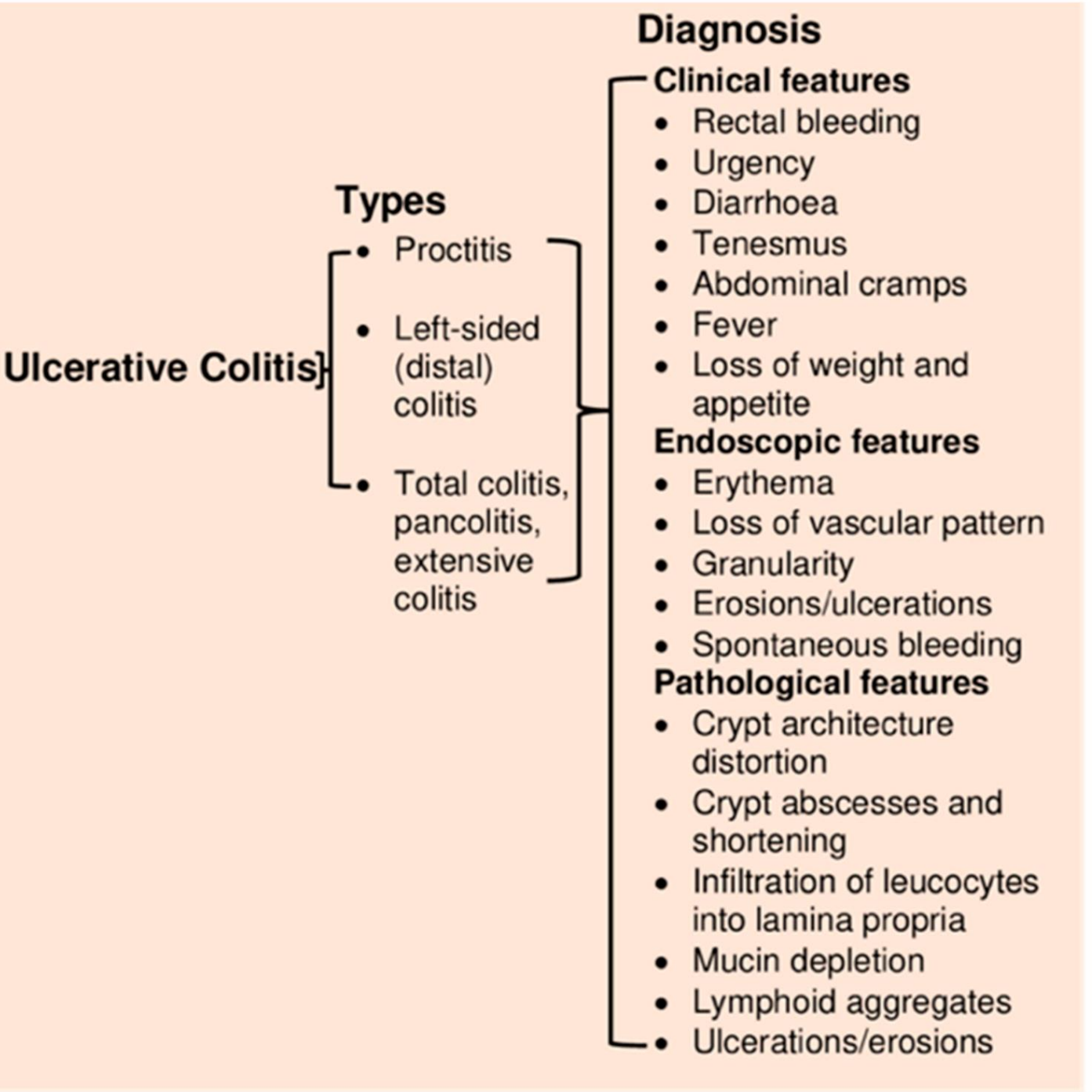
Factors contributing to IBD manifestations



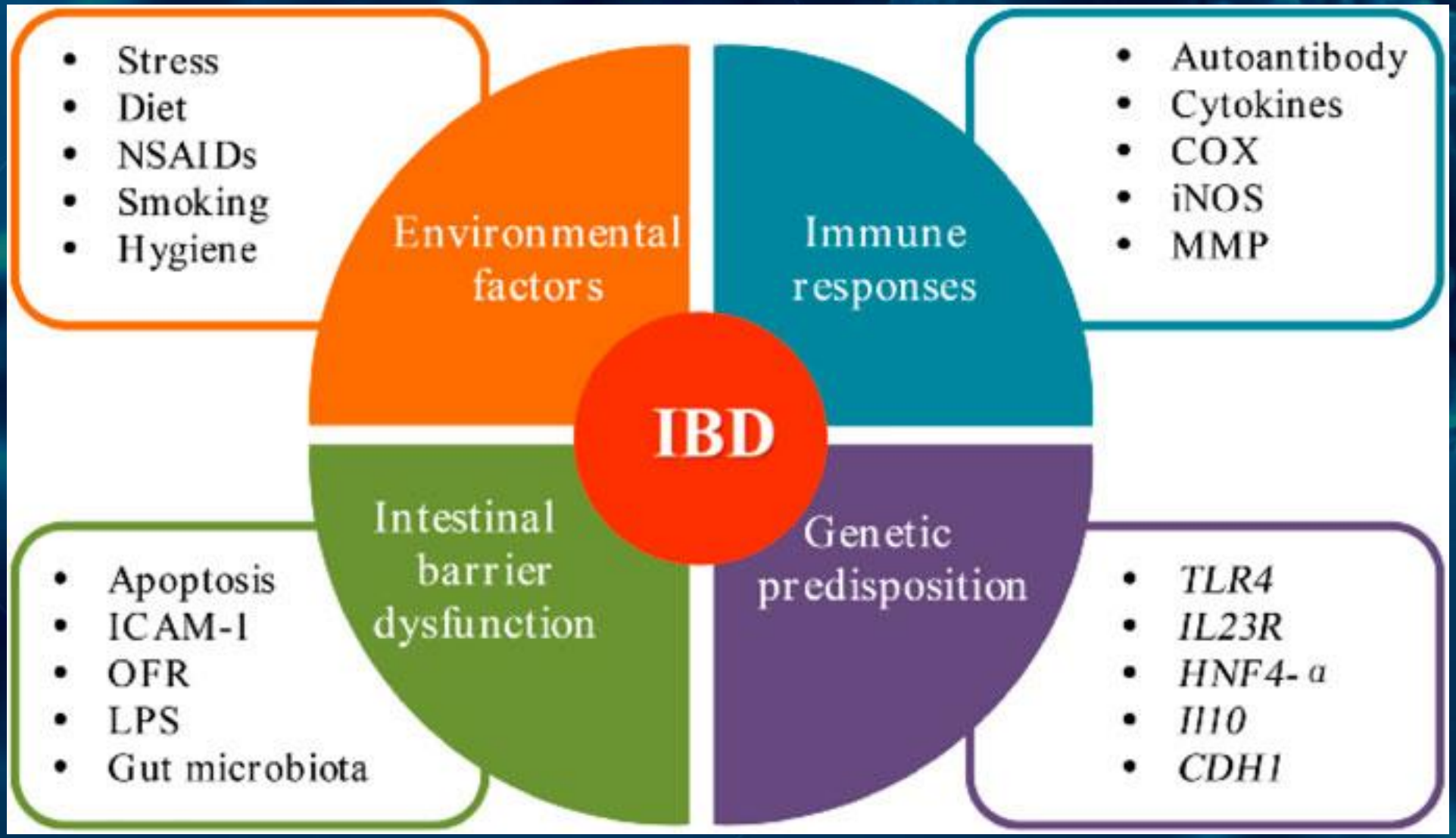
Crohn's Disease



Ulcerative Colitis



IBD Pathogenesis



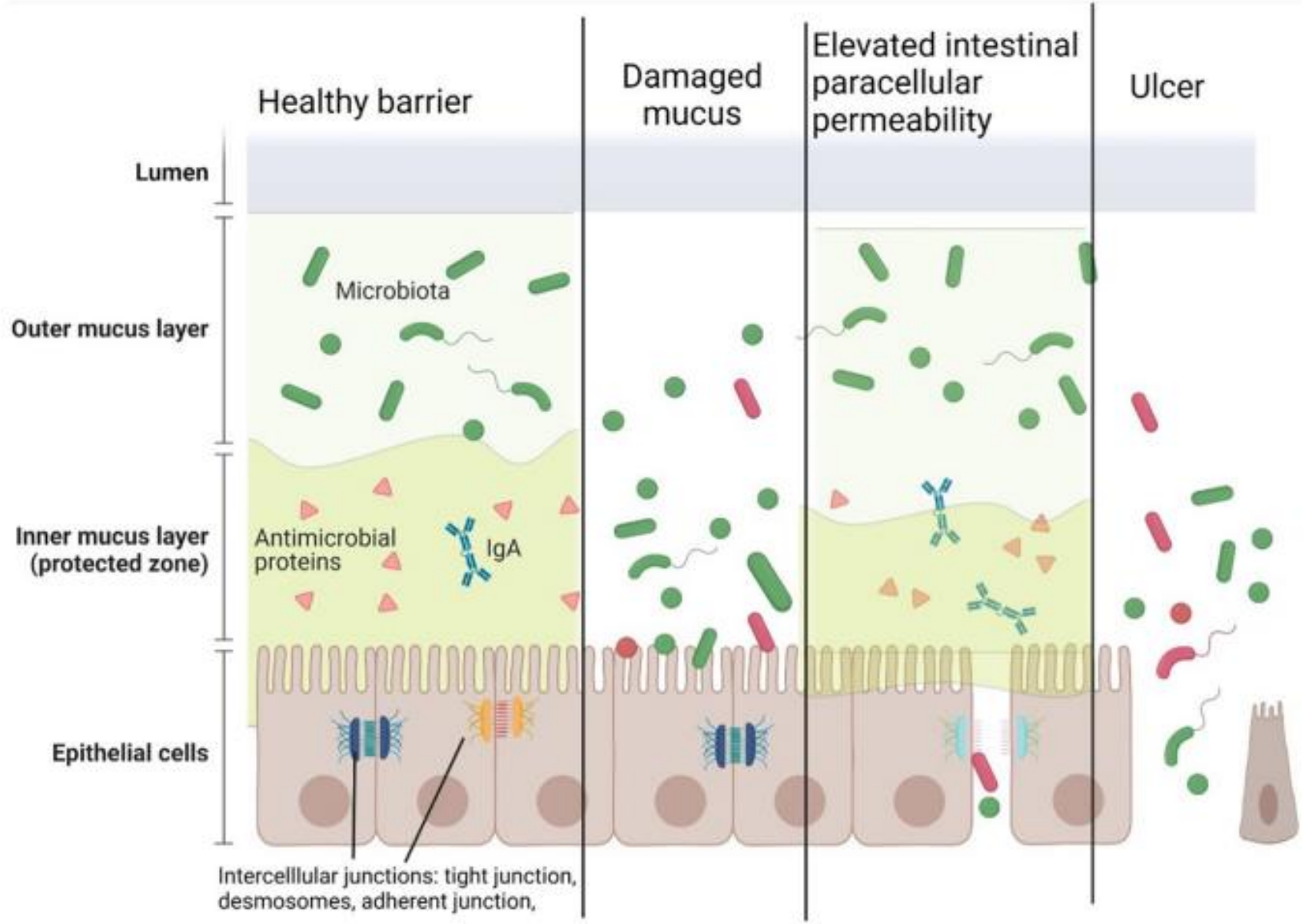


FIGURE 1 | Components of the healthy intestinal barrier and the potential mechanisms of barrier damage. The intestinal epithelial barrier consists of outer and inner layers of mucus, epithelial cells, and intercellular junctions. In a healthy stage, the outer mucous layer forms a 3-dimensional network in the gut lumen containing microbiota. The inner mucous layer containing antimicrobial peptides and secretory IgA keeps away the microbes from the epithelial cells. Intercellular junctions (tight junctions, adherent junctions, and desmosomes) connect the cells to form a barrier between the subepithelial surface and the microbiota.

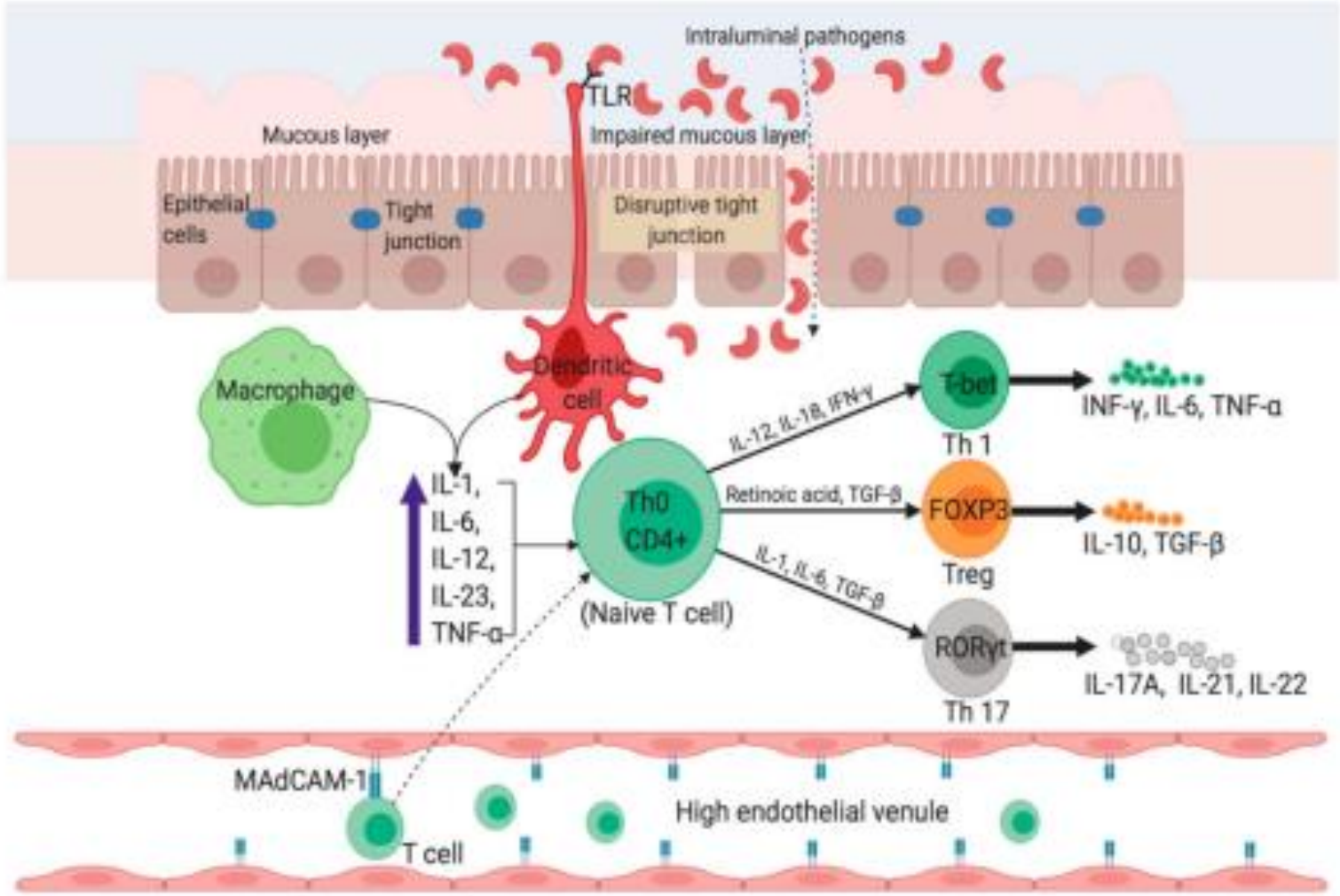


Figure 5. Pathophysiology in Crohn's disease. The uptake of luminal microflora stimulates APCs (e.g., dendritic cells and macrophages) which in turn produce proinflammatory cytokines such as TNF-α, IL-6, and IL-23. Activated APCs facilitate subsequent differentiation of naïve $CD4^+$ Th cells into Th1 and Th17 via expression of master transcription factors. Inside the high endothelial venule, binding of $\alpha_4\beta_7$-bearing lymphocytes to MAdCAM-1 causes entry of more T cells into the lamina propria. IFN-γ, interferon-gamma; FOXP3, Forkhead box protein 3; RORγt, retinoic acid receptor-related orphan nuclear receptor gamma.

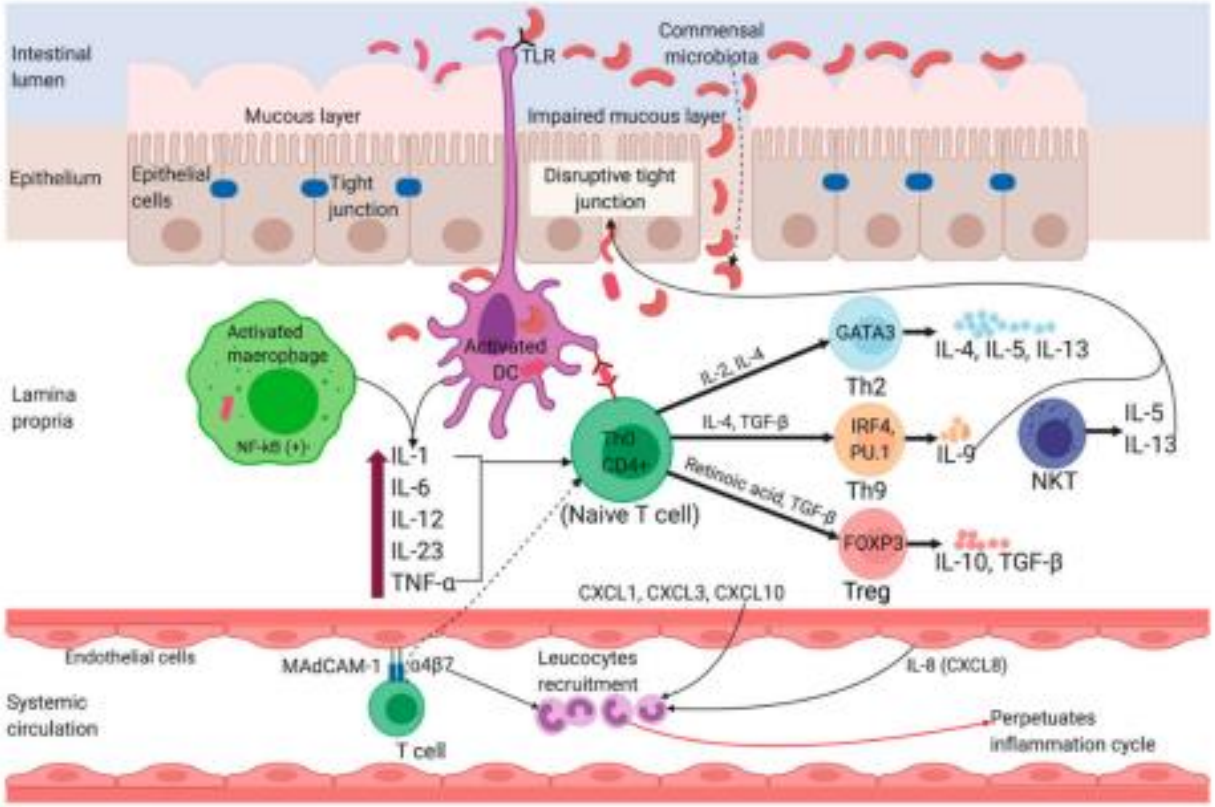


Figure 3. Pathophysiology of Ulcerative Colitis. Impairment of tight junctions and the mucous layer leads to increased permeability of the intestinal epithelium, resulting in more uptake of luminal antigens. Antigen presenting cells (APC) become activated upon recognizing non-pathogenic bacteria (commensal microbiota) through Toll-like receptors (TLRs). Activated APC initiate differentiation of naïve $CD4^+$ T-cells into Th-2 effector cells (which produce pro-inflammatory cytokines such as TNF-α, IL-5, IL-6, and IL-13). TNF-α and IL-1 activate nuclear factor κB (NF-κB) pathway, which facilitate expression of pro-inflammatory and cell survival genes. Binding of integrin-$\alpha_4\beta_7$ bearing T cells to the mucosal adhesion molecule MAdCAM-1 facilitate entry of more T cells into the lamina propria. Recruitment of circulating leucocytes due to the upregulation of inflammatory chemokines (chemokine ligands: CXCL1, CXCL3, CXCL8 and CXCL10) perpetuates the inflammatory cycle. MAdCAM-1, mucosal addressin cell adhesion molecule-1; IL, interleukin; TNF-α, tumor necrosis factor-alpha; TGF-β, transforming growth factor-beta; NKT, natural killer T; DC, dendritic cell; Th, T helper; GATA3, GATA binding protein 3; IRF4, interferon regulatory factor 4; PU.1, purine-rich PU-box binding protein; FOXP3, Forkhead box protein 3.

Current Drugs and their Disadvantages in IBD

Type	Drug	Limitation	Reference
5-amino salicylic acids	Balsalazide Sulfasalazine Mesalazine Olsalazine	There are certain adverse reactions such as diarrhea, stomachache, nausea, and emesis. The new-type 5-amino salicylic acids including mesalazine and olsalazine are expensive	Caprilli et al. (2009); Rosenberg and Peppercorn (2010)
Glucocorticoids	Hydrocortisone Prednisone BDP Budesonide	Short-term treatment has a good effect, while long-term application may lead to adverse reactions such as moon-shaped face, weakened immunity, and acne, whose efficacy and safety are difficult to be guaranteed	Ren et al. (2015); Rosenberg and Peppercorn (2010)
Immunosuppressants	Azathioprine 6-mercapopurine Cyclosporine A	The effect takes a long time. The mechanism of action will lead to the inhibition of the body's normal immune response. Long-term application may cause liver and kidney damage	Falasco et al. (2002); Mao et al. (2017)
Biologicals	Infliximab Adalimumab	These drugs also have some adverse reactions and are expensive	Danese et al. (2014); Freeman (2012)

The Role of Diet and Nutrition in IBD

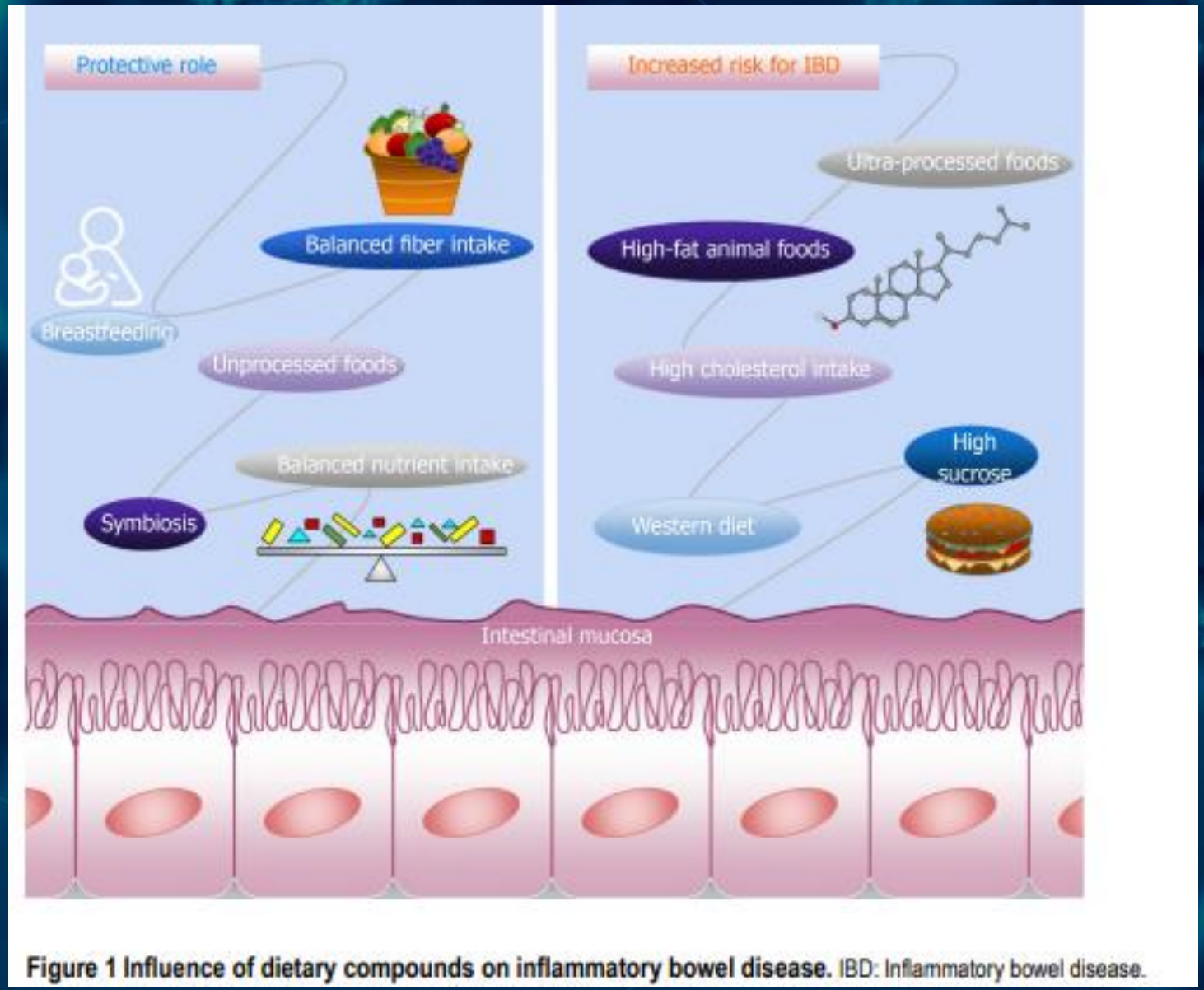
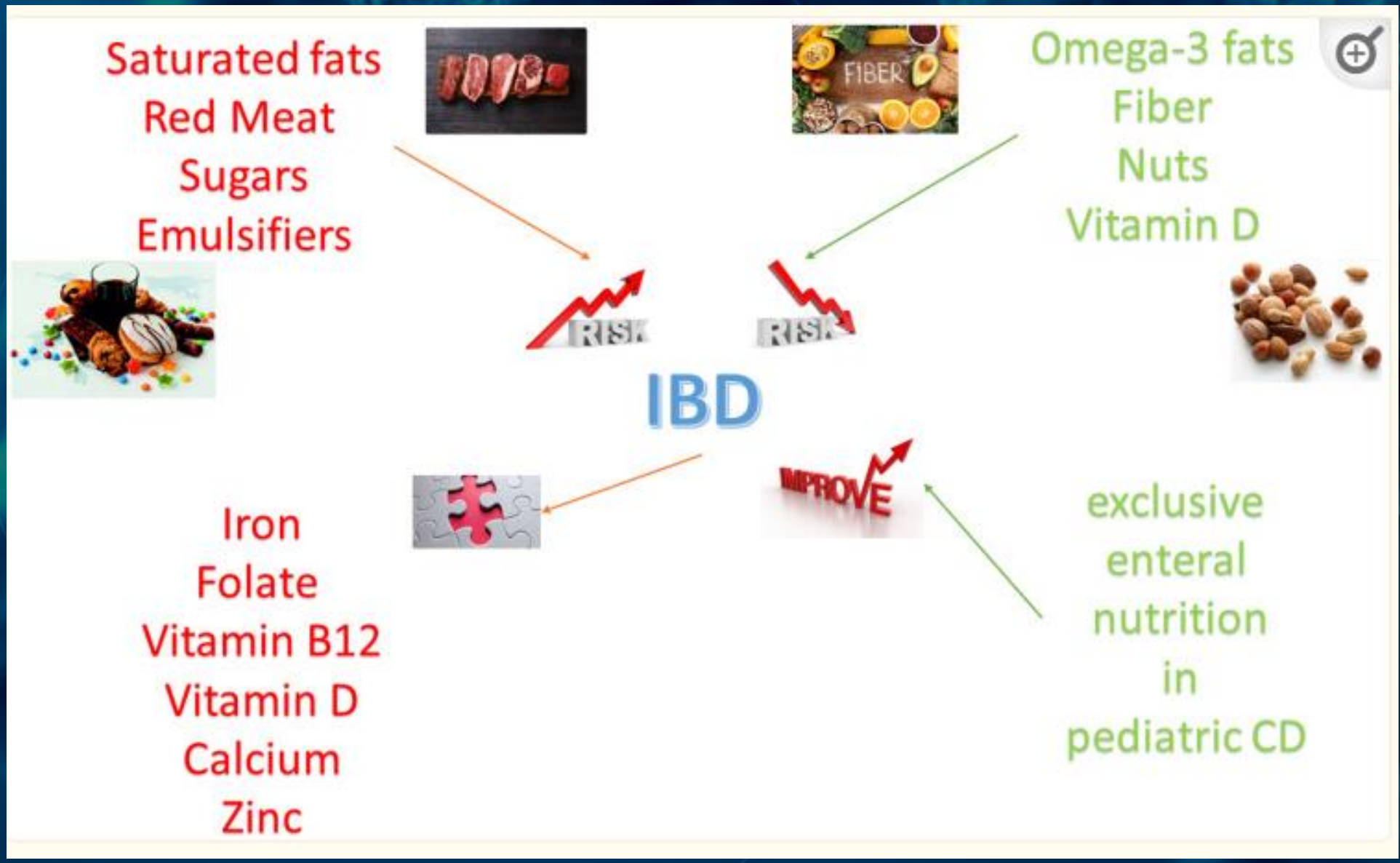


Figure 1 Influence of dietary compounds on inflammatory bowel disease. IBD: Inflammatory bowel disease.

Is there a Role for Nutritional Changes?



Effects of Specific Diet Approaches on IBD

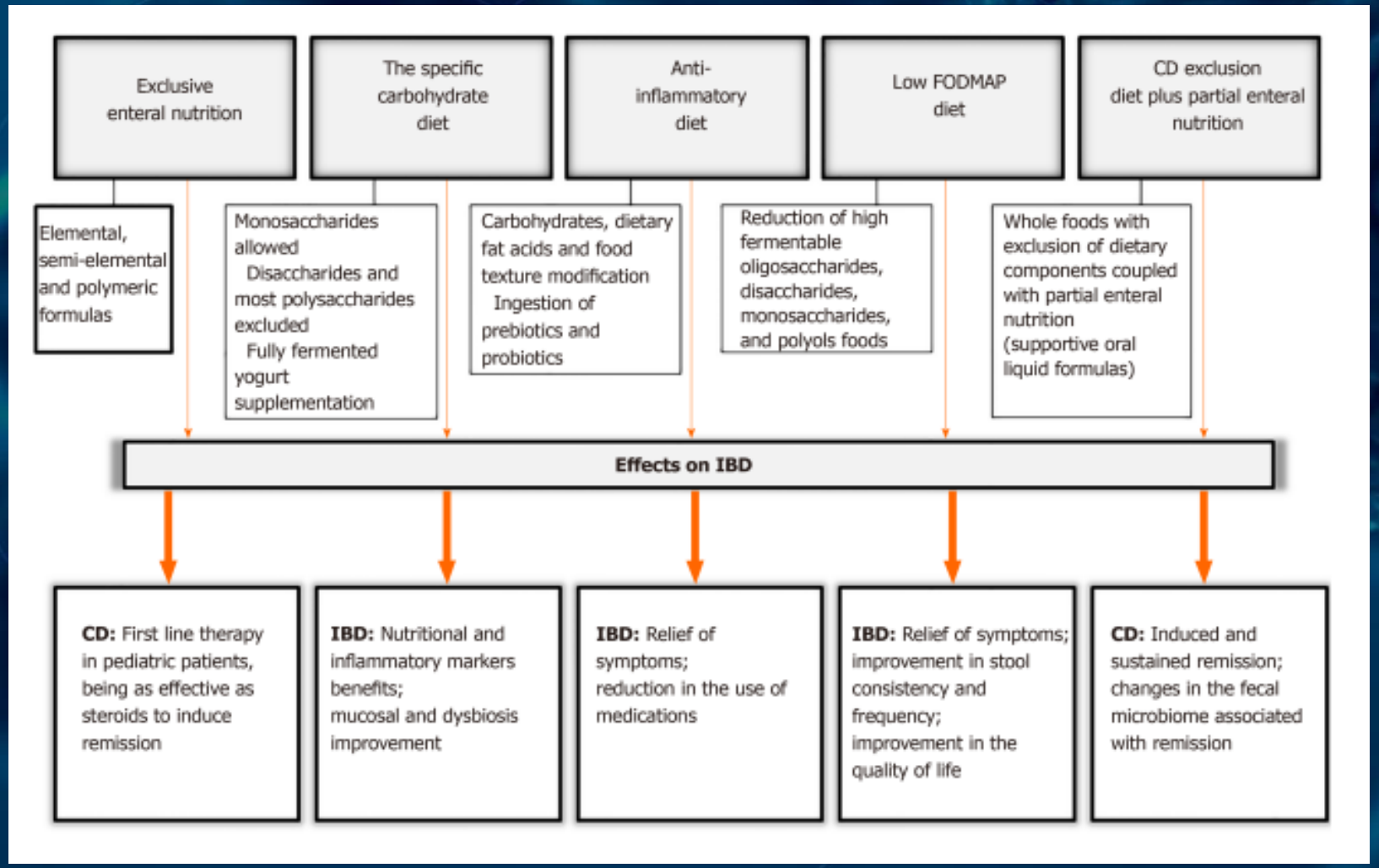


Table 1. Overview of GrAID compared to diets being tested in inflammatory bowel disease with mandatory, allowed, limited and not allowed food (groups).

Food (Groups)	GrAID	Mediterranean	IBD-AID	SCD	CDED	CD-TREAT	Low FODMAP	LEGEND:
Red meat								Mandatory
Lean meat								Allowed
Chicken								Not mentioned
Eggs								Limited
Fish								Not allowed
Dairy products								
Fruit								
Apple								
Banana								
Vegetables								
Legumes								
Corn								
Potatoes								
Wheat								
Olive oil								
Nuts								
Cacao/chocolate								
Coffee								
Green tea								
Sweetened beverages								
Alcohol								
Yeast								
Added sugar								
Refined sugar								
Honey								
Canned food								
Processed foods								

Abbreviations: GrAID, Groningen anti-inflammatory diet; IBD-AID, anti-inflammatory diet; SCD, specific carbohydrate diet; CDED, Crohn's disease exclusion diet; CD-TREAT, Crohn disease treatment-with-eating diet; Low FODMAP, low-fermentable oligosaccharide, disaccharide, monosaccharide and polyols diet.

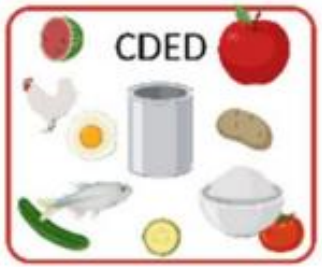
Outcome of Different Diets

EEN

80-85% remission
Restrictive, difficult to maintain long-term

↑Firmicutes
↓Proteobacteria, Actinobacteria, Bacteroidetes

CDED



70-75% remission
Restrictive, difficult to maintain long-term

↑Firmicutes
↓Proteobacteria, Actinobacteria

SCD

Small sample size
Clinical and FC improvement

↑Fusobacteria, Firmicutes
↓Proteobacteria, Actinobacteria

PEN

No efficacy for induction of remission, efficacy for maintenance of remission

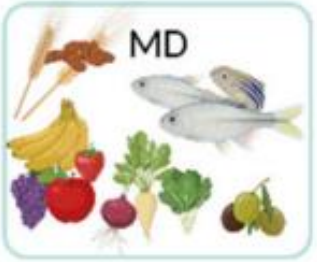
No microbiome data available

CD-TREAT

Limited data, evidence of efficacy for induction of remission, maintenance of remission, FC

No microbiome data available

MD



No efficacy for induction of remission, efficacy for maintenance of remission

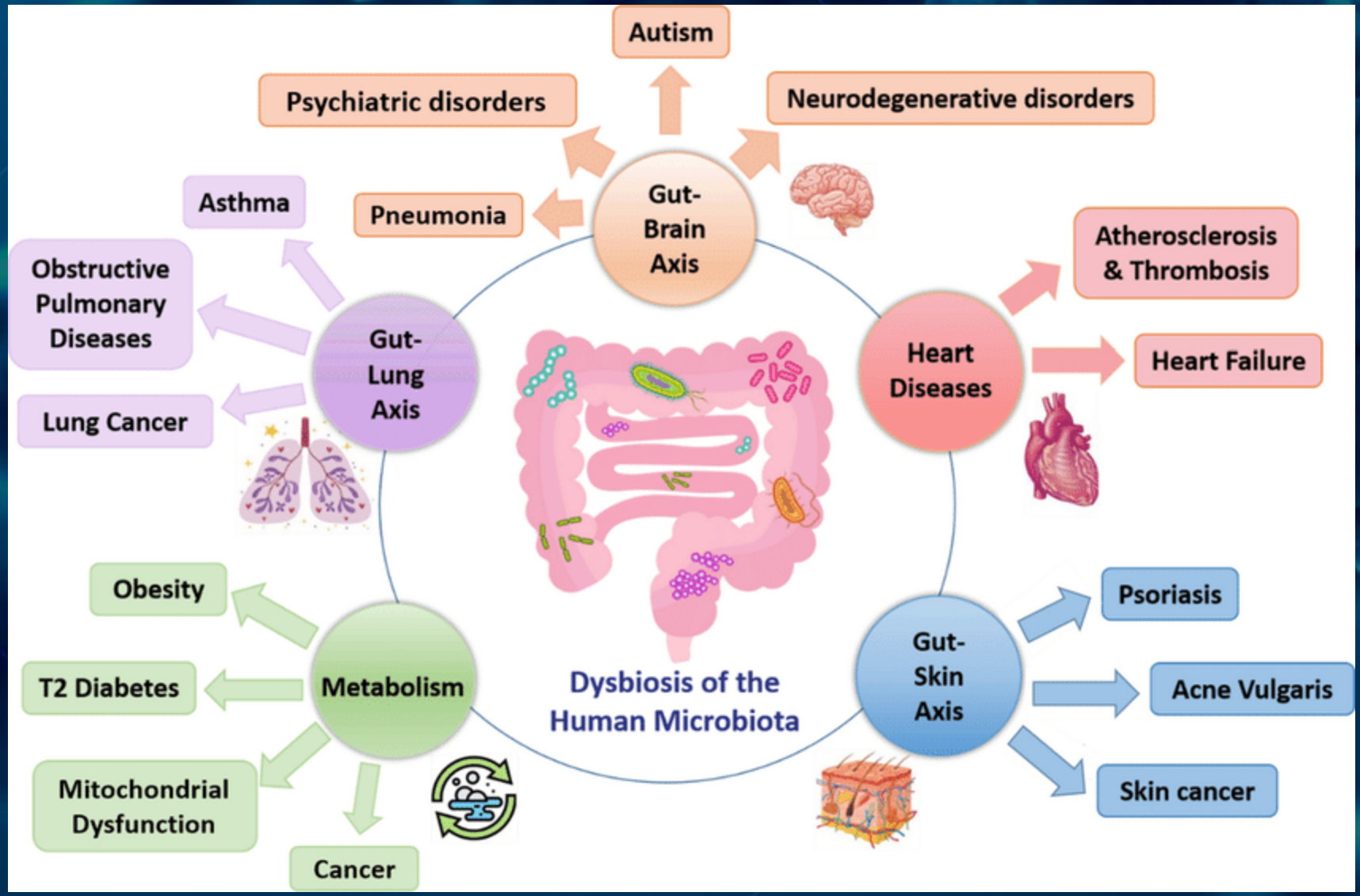
↑Firmicutes spp, Bacteroidetes
↓Proteobacteria, Firmicutes spp.

LFD

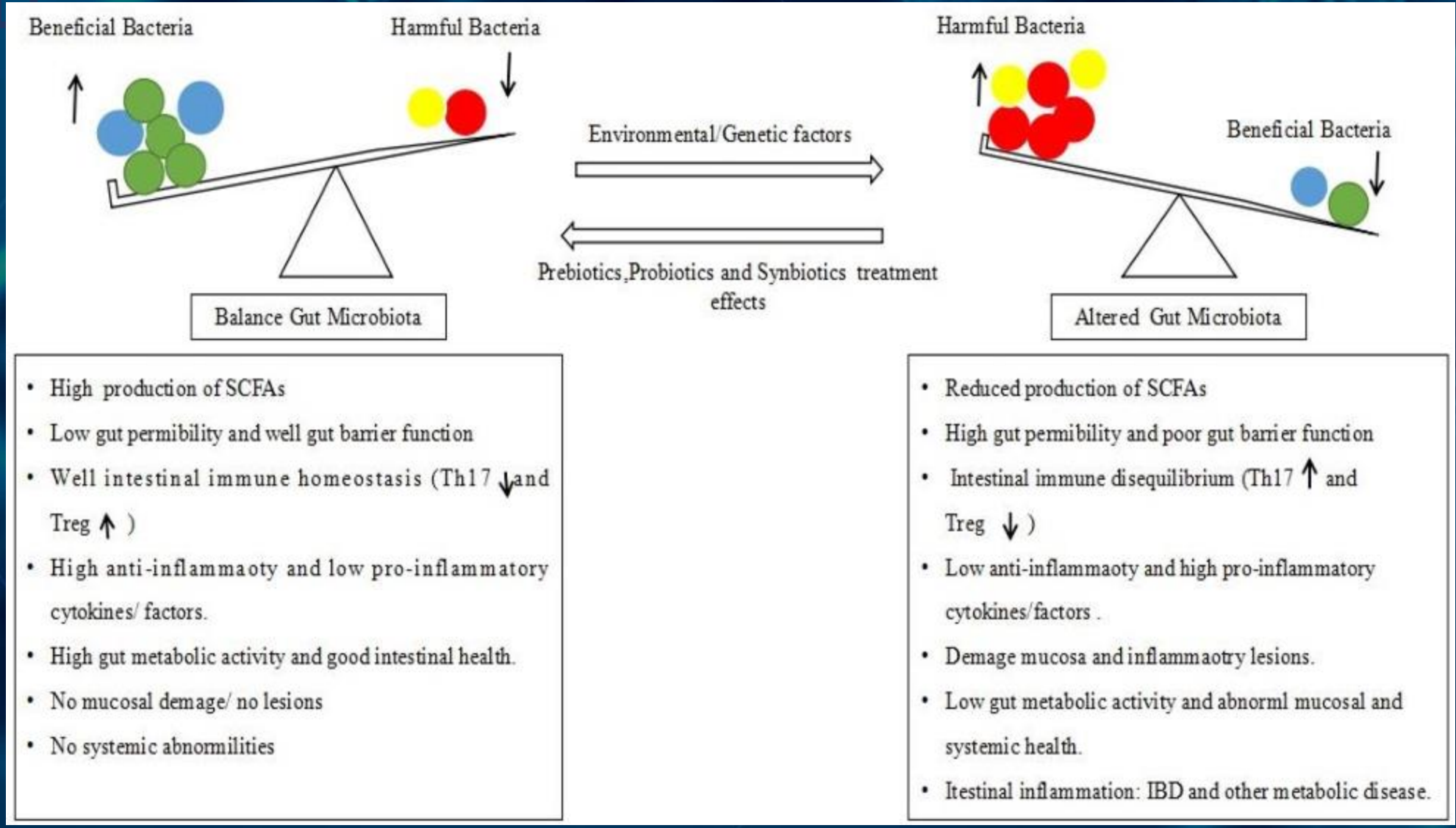
Limited data, evidence of efficacy for induction of remission, maintenance of remission, FC

↑Actinobacteria spp.
↓Actinobacteria spp.

The Gut Microbiome



The Gut Microbiome and IBD



The Gut Microbiota in IBD

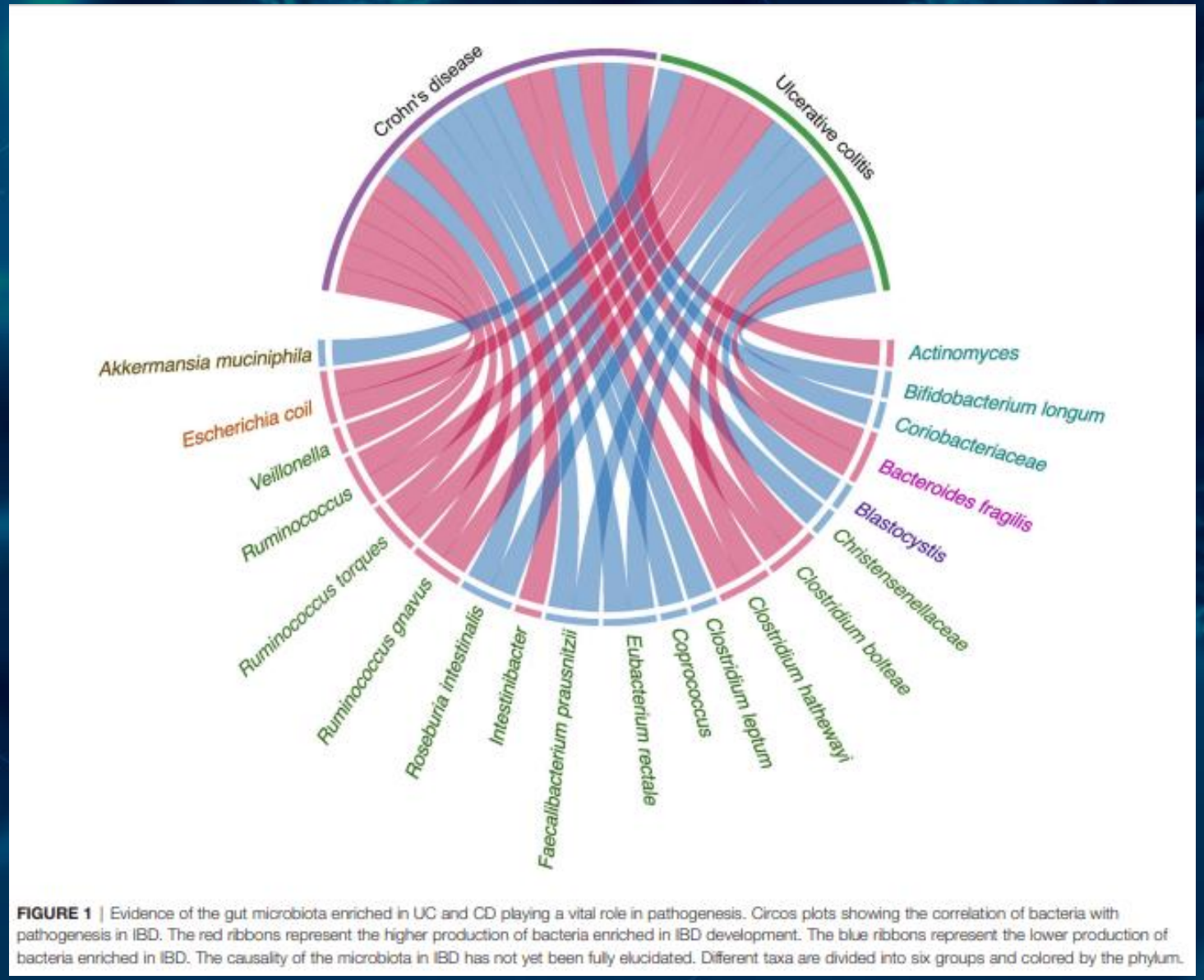
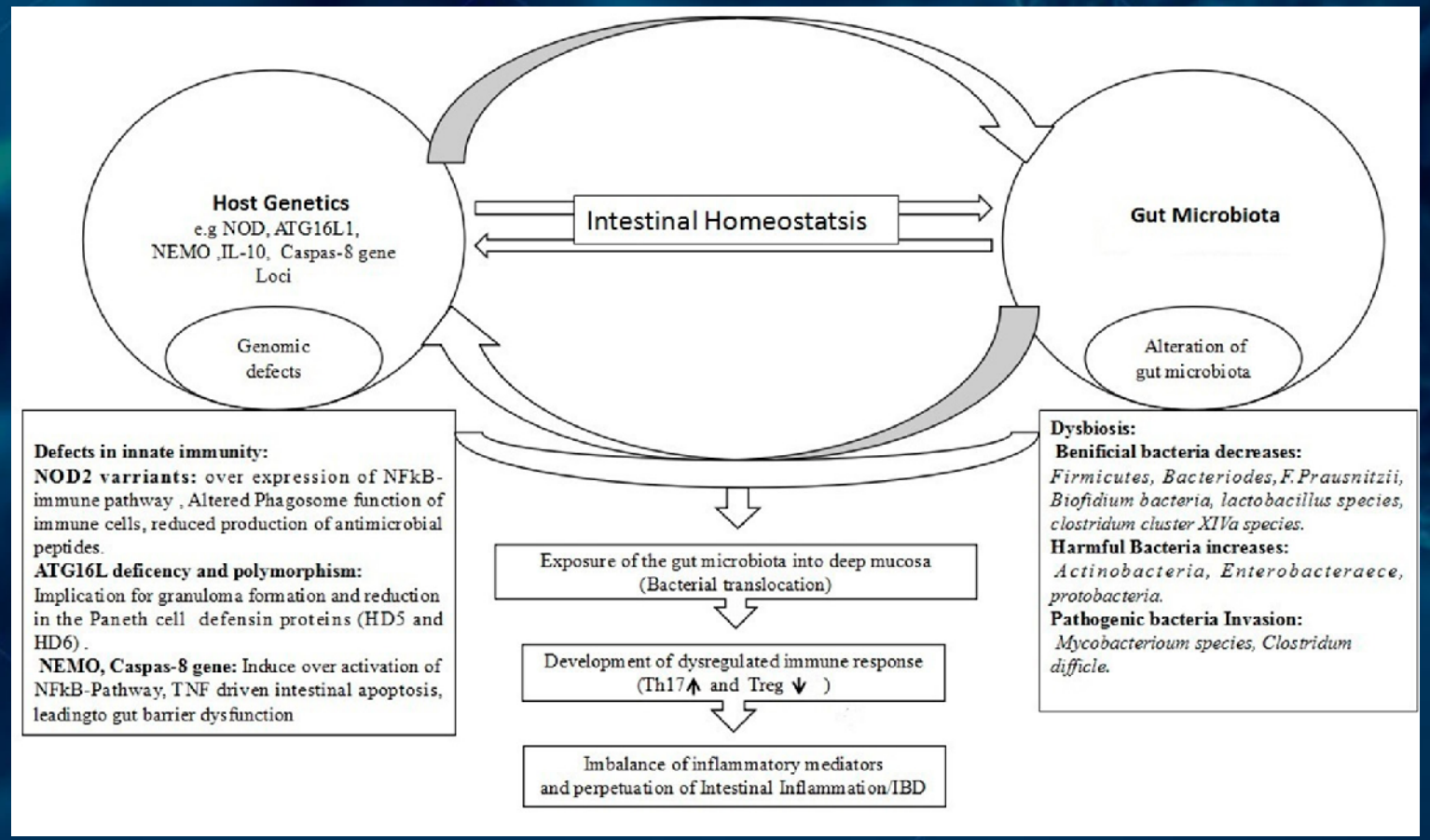
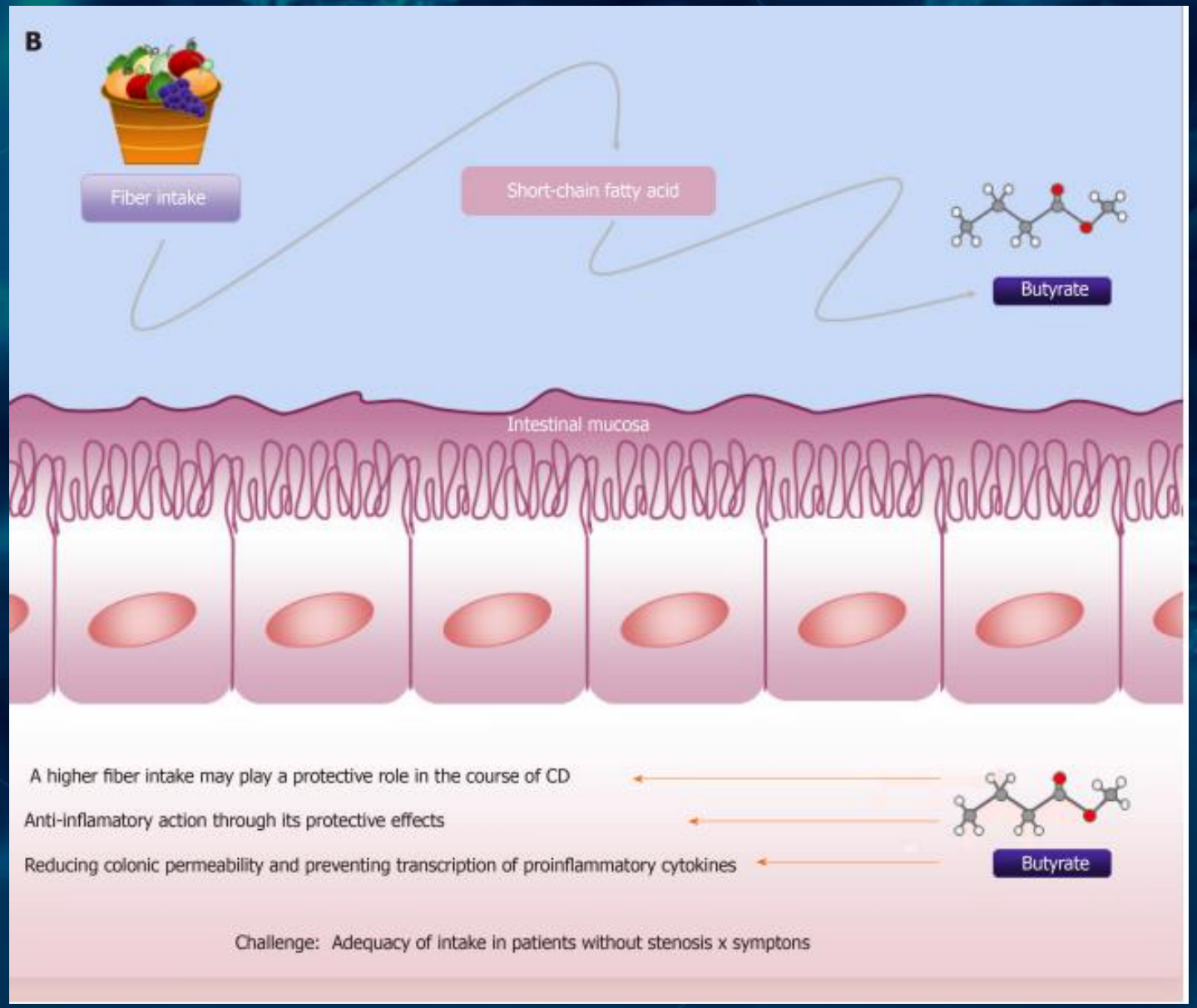


FIGURE 1 | Evidence of the gut microbiota enriched in UC and CD playing a vital role in pathogenesis. Circos plots showing the correlation of bacteria with pathogenesis in IBD. The red ribbons represent the higher production of bacteria enriched in IBD development. The blue ribbons represent the lower production of bacteria enriched in IBD. The causality of the microbiota in IBD has not yet been fully elucidated. Different taxa are divided into six groups and colored by the phylum.

The Host-Microbe Interactions in IBD Pathogenesis



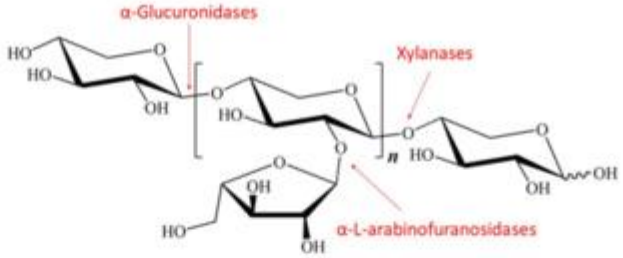
Role of Fibers in IBD



Fibers by Groups

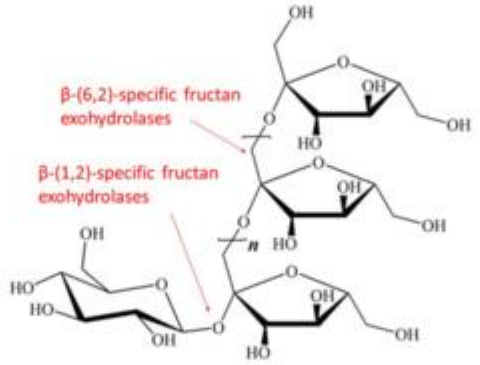
Arabinoxylan:

Cereal grains, rye, wheat, oats, barley, rice, sorghum, legumes.



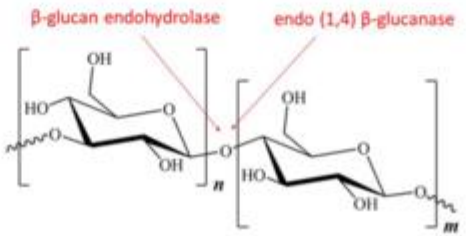
B-fructans:

Chicory root, agave, artichokes, banana, wheat, onion, garlic.



B-glucan:

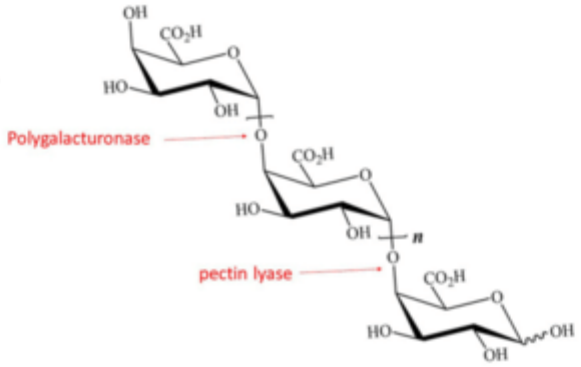
Oat, barley, rice, mushrooms.



Fibers by Groups

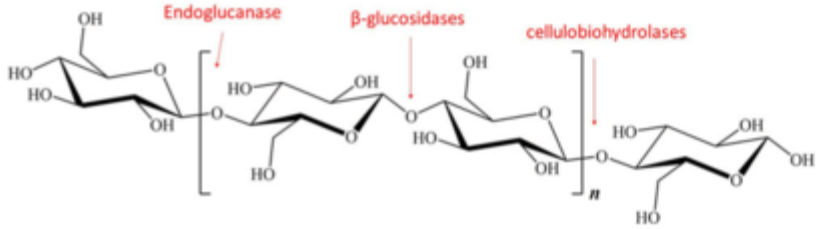
Pectin:

Fruits, vegetables, nuts.



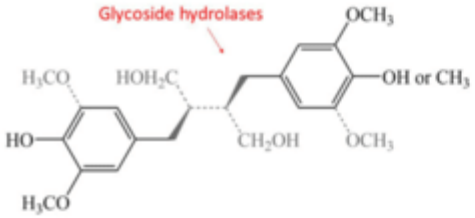
Cellulose:

Plant cell walls including fruit and vegetable skins.



Lignan:

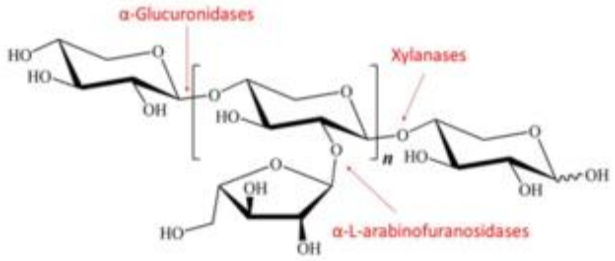
Grain, vegetables, flax seeds.



Arabinoxylan

Arabinoxylan:

Cereal grains, rye, wheat, oats, barley, rice, sorghum, legumes.



Arabinoxylan:

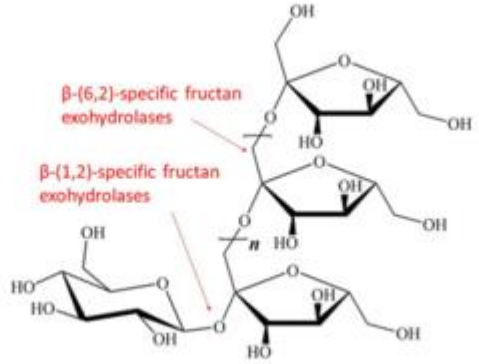
Streptococcus, Bifidobacteria ← Acetate, propionate, butyrate

Saccharomyces → Ethanol

ß Fructans

B-fructans:

Chicory root, agave, artichokes, banana, wheat, onion, garlic.



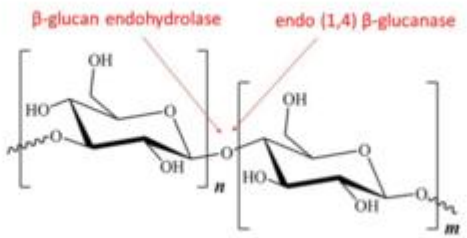
B-fructans:

SCFA butyrate ← *Bifidobacteria, Lactobacillus, Streptococcus, Flavobacterium*

Kluyveromyces marxianus, S. cerevisiae T. delbrueckii → Lactic acid, CO_2

ß Glucans

B-glucan: Oat, barley, rice, mushrooms.



B-glucan:

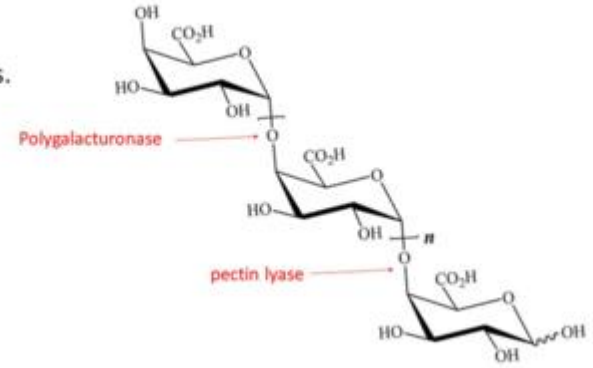
Variable SCFA ← *Lactobacilli, Enterococcus, Bifidobacteria*

Saccharomyces, maitake/shiitake mushrooms →

Pectin

Pectin:

Fruits,
vegetables, nuts.



Pectin:

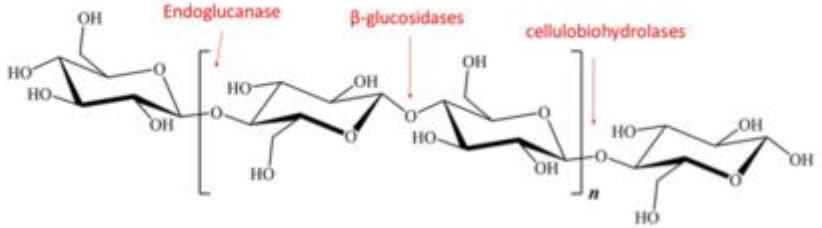
Bacteroides, Prevetella, Bacillus, Agrobacterium, Pseudomonas, Ralstonia, Dickeya ← Variety of SCFA and gases, including CO_2, H_2, H_2S, CH_4.

Rhizopus oryzae → Lactic acid, ethanol

Cellulose

Cellulose:

Plant cell walls including fruit and vegetable skins.



Cellulose:

Bacteroides, Clostridium, Fibrobacter, Ruminococcus

Succinate, a variety of SCFS, predominantly acetate.

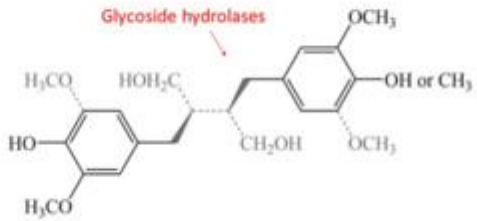
Neocallinastix, Piromyces, Caecomyces

Lactate, acetate, CO_2 and H_2

Lignan

Lignan:

Grain, vegetables, flax seeds.



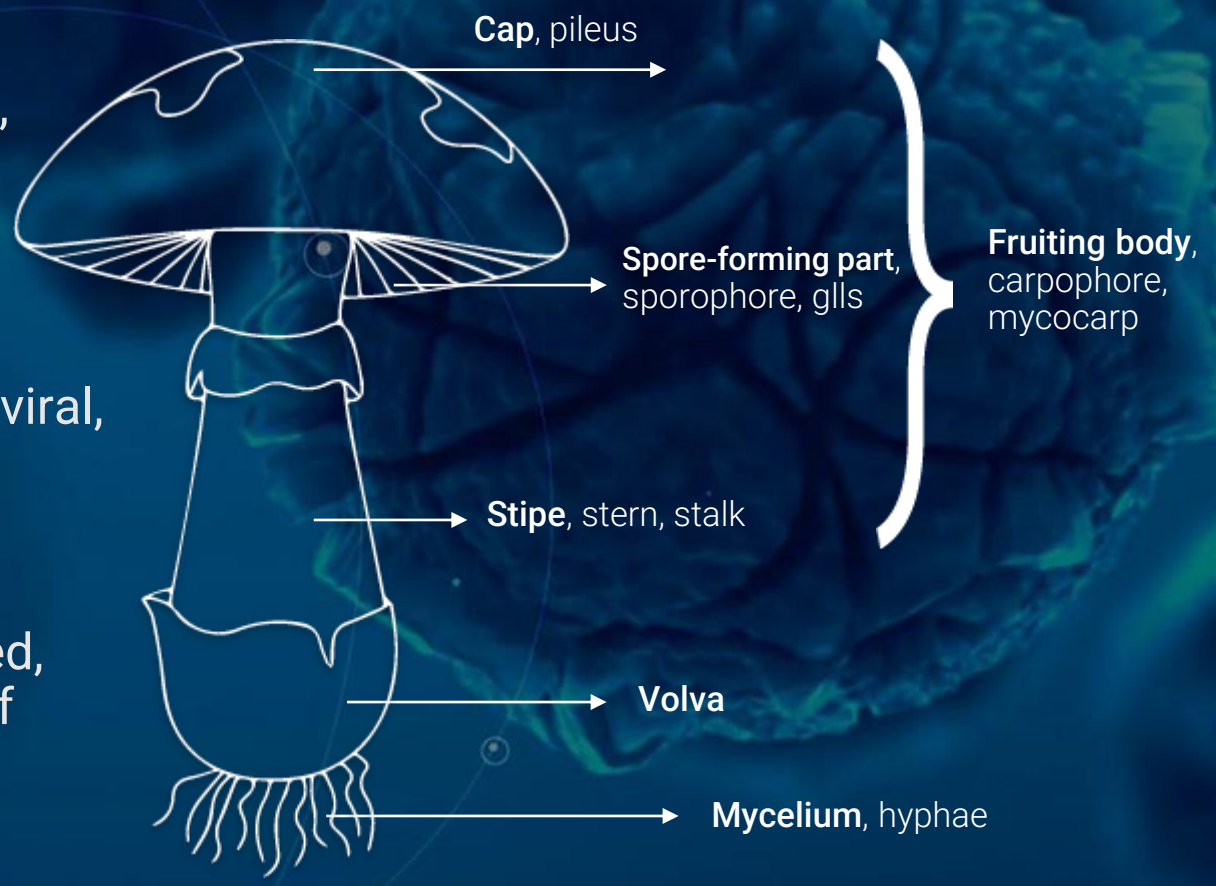
Lignan:

Lipids ← *Rhodococcus, Pseudomonas, Sphingobacterium*

Bjerkandera, Fomitopsis, Schizophyllum, → Ethanol

Medicinal Mushrooms

- Medicinal mushrooms, especially those belonging to higher basidiomycete groups, are reservoir of bioactive compounds with terapeutic properties.
- Contain compounds with a wide range of therapeutic effects such as immunomodulatory, anticarcinogenic, antiviral, antioxidant, and anti-inflammatory agents.
- The concentration and efficacy of the bioactive compounds vary and depend on the type of mushroom, substrate applied, cultivation and fruiting conditions, stage of development, age of the fresh mushroom, storage conditions, and processing and extraction procedures.



Bioactive Compound in Mushrooms

- Polysaccharides, particularly β-d-glucans
- Lectins
- Phenols, polyphenols
- Fungal immunomodulatory proteins (FIPs) (Glycoproteins or polysaccharide–protein complexes)
- Terpenes, triterpenoids, sesquiterpenoids
- Sterols, ergosterols
- Proteins, peptides, and amino acids
- Nucleosides
- Alkaloids
- Vitamins and essential minerals

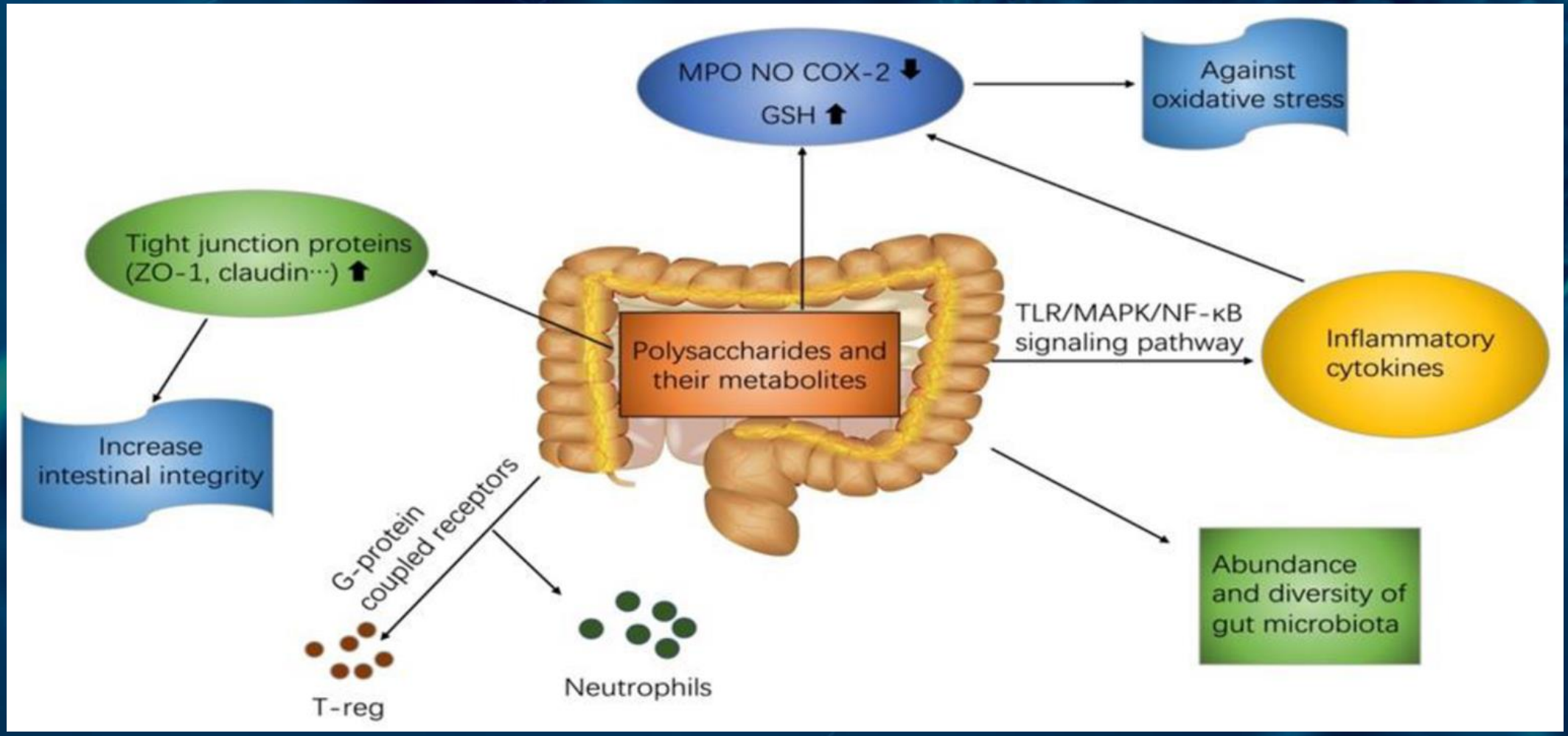
Medicinal Mushrooms Biological Activities

- Immunomodulation

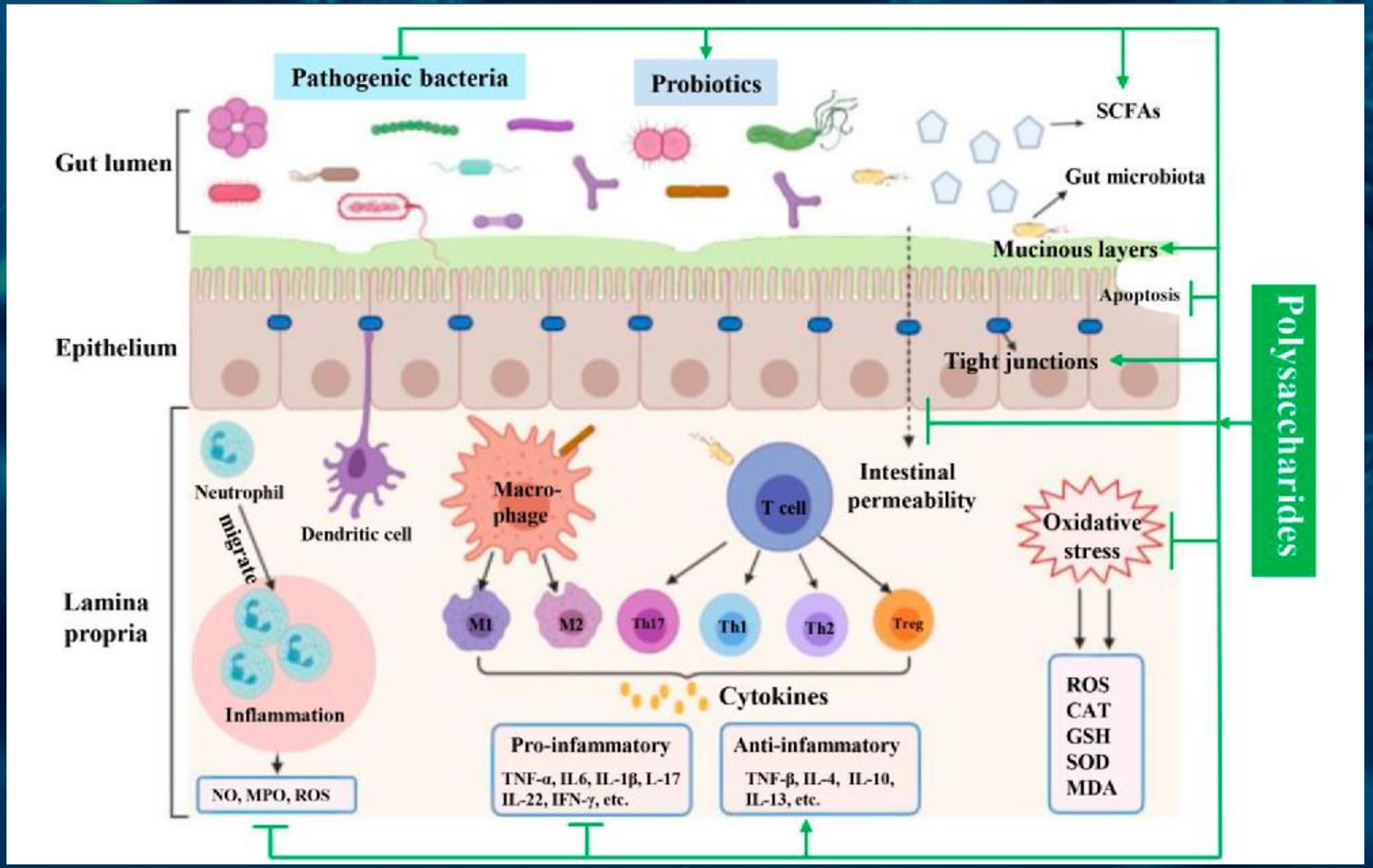
  Stimulating both innate and adaptive immune responses. They activate innate immune system components such as natural killer (NK) cells, neutrophils, and macrophages, and stimulate the expression and secretion of cytokines. These cytokines in turn activate adaptive immunity by promoting B cell proliferation and differentiation for antibody production and by stimulating T cell differentiation to T helper (Th1 and Th2 cells), which mediate cellular and humoral immunities, respectively.

- Antioxidant potentials and free radical scavenging
- Anti-inflammatory
- Antiproliferative
- Antitumor

The Effect of Natural Polysaccharides on IBD



Involved Mechanisms in IBD Treatment



Involved Mechanisms of Natural Polysaccharides in Colon Inflammation Amelioration

Table 2. The mechanisms of natural polysaccharides involved in colon inflammation amelioration.

Mechanism Involved	Source of Polysaccharides	Results	Reference
MAPK transduction signaling pathway	*Ganoderma lucidum and G. sinense/Pleurotus eryngii*	Increase the phosphorylation level of ERK, JNK, and p38 in macrophage cells	[38,84]
	Dictyophora indusiata	Decrease the phosphorylation level of ERK and pro-inflammatory cytokines in DSS-induced mice	[27]
NF-κB signaling pathway	*Blidingia minima/H. erinaceus/Arctium lappa L./Purple sweet potato*	Restore phosphorylation level of NF-κB, IκB-α, and AKT in colitis mice model	[18,46,53]
G-protein-coupled receptors	*Hericium Erinaceus*	Increase the expression of GPR41/43 in acetic acid-induced colitis mice	[85]
	Dendrobium officinaleon	Inhibit β-arrestin1and NLRP3 inflammasome signaling pathway in DSS-induced mice	[86]
Increase intestinal integrity via upregulate tight junction proteins	*Ficus carica*	Increase the expression of light junction protein claudin-1 and decrease the expression of TNF-α and IL-1β in DSS-induced mice	[82]
	Dictyophora indusiata	Increase the expression of claudin-1, occludin, and ZO-1 in DSS-induced mice	[27]
Regulation of oxidative stress	*Graciliaria lemaneiformis/Flammuliana velutipes*	Decrease the expression of MPO and NO in DSS-induced mice	[34,44]
	Hericium Erinaceus	Decrease the expression of COX-2 in acetic acid-induced mice	[14]
	Graciliaria caudata	Restoration of GSH and decrease of MDA in acetic acid-induced mice	[43]

Clinical Study

Effect of a Medicinal Agaricus blazei Murill Based Mushroom Extract, AndoSan™, on Symptoms, Fatigue and Quality of Life in Patients with Ulcerative Colitis in a Randomized Single-Blinded Placebo Controlled Study

Conclusions:

Beneficiary effects on symptoms, fatigue and HRQoL from AndoSan™ consumption were demonstrated in this per-protocol study, supporting its use as a supplement to conventional medication for patients with mild to moderate symptoms from ulcerative colitis. The patients did not report any harms or unintended effects of AndoSan™ in this study

Stig Palm Therkelsen1 *, Geir Hetland2,5, Torstein Lyberg3 , Idar Lygren4 , Egil Johnson1,5 PLOS ONE | DOI:10.1371/journal.pone.0150191 March 2, 2016

Myco Digest

Agaricus Blazei Murill

Hericium Erinaceus

Trarmetes (Coriolus) Versicolor

Does CBD have a synergistic effect with Myco Digest in a DSS colitis mice model?

- A DSS mouse model
- 5 arms
- CBD 30 mg/kg
- Myco Digest 6 gr/kg

Study Design

- Day 0-5: DSS drinking water
- Day 5-11: drinking water

1. Treatment - (Day 4-10) - given by gavage daily, according to the abovementioned
2. Check overall well-being of the mice: Daily (0-10), including body weight, presence and severity of diarrhea, and/or bleeding
3. Day 11: sacrifice
    a. Collect blood samples *
    b. Sacrifice the mice, remove the colons (from the rectum to the cecum), measure colon length using a ruler and a photo
    c. Fix with 4% formaldehyde, and embed in paraffin blocks

Study Endpoints

- Weight loss
- Colon length
- Diarrhea
- Blood in feces
- Histopathology

Histopathological Scoring

Lymphocyte infiltration:

a. 0= No lymphocyte infiltration
b. 1= Mild (< 10 cells)
c. 2= Moderate to severe (>10 cells)

Erosions:

a. 0= Intact mucosa
b. 1= Mild (up to 10% erosions)
c. 2= Moderate (10%- 50% erosions).
d. 3= Severe (>50% erosions).

Cellular inflammatory response:

a. 0= No inflammation
b. 1= Mild (< 20 cells)
c. 2= Moderate to severe (>20 cells)

Crypt loss:

a. 0= Intact colon.
b. 1= Mild crypt loss
c. 2= Moderate to severe crypt loss

Inflammatory cellular differentiation

a. Macrophages %
b. Lymphocytes %
c. Neutrophils %

Hemorrhages:

a. 0= No hemorrhages.
b. 1= Mild hemorrhages.
c. 2= Moderate to severe hemo
d. rr0hages

Fibrin deposition:

a. 0= No fibrin deposition.
b. 1= Mild fibrin deposition.
c. 2= Moderate to severe fibrin deposition

Fibrin deposition:

a. 0= No fibrin deposition.
b. 1= Mild fibrin deposition.
c. 2= Moderate to severe fibrin deposition

Study Design

Table A. Study design				
Animal NO.	Group	Number of animals	Treatment	Termination
4151-4155	1	5	Naive	
4111-4120	2	10	DSS + no treatment	
4121-4130	3	10	DSS + treatment	
4131-4140	4	10	DSS + treatment	
4141-4150	5	10	DSS + treatment	
	Total	45		

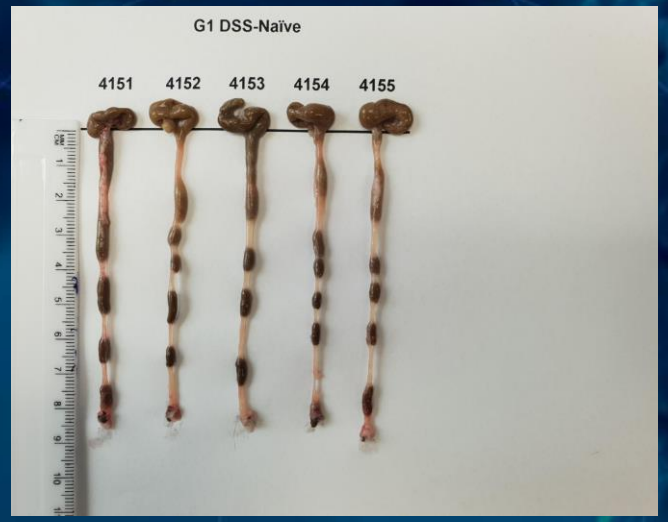
Weight Loss

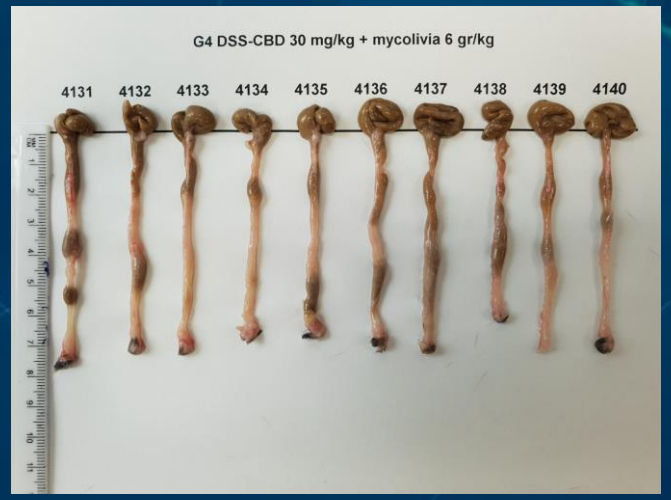
		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	ANOVA Sig.	Pairs comparisons using Bonferroni correction		Sig.
					Lower Bound	Upper Bound						
Weight Loss	Naive	5	1.1	0.6	0.3	1.9	0.4	2.0	<0.001	Naive	DSS	<0.001
	DSS	10	-3.4	0.8	-4.0	-2.8	-4.5	-1.5		Naive	DSS+CBD	<0.001
	DSS+CBD	10	-2.4	1.5	-3.5	-1.4	-4.4	0.0		Naive	DSS+CBD+Mycolivia	<0.001
	DSS+CBD+Mycolivia	10	-3.1	1.0	-3.8	-2.4	-5.3	-2.2		Naive	DSS+Mycolivia	<0.001
	DSS+Mycolivia	10	-1.8	0.8	-2.4	-1.2	-2.8	-0.4		DSS	DSS+Mycolivia	0.013
	Total	45	-2.3	1.7	-2.8	-1.8	-5.3	2.0				

Colon Lenght

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	ANOVA Sig.	Pairs comparisons using Bonferroni correction		Sig.
					Lower Bound	Upper Bound						
Colon_length	Naive	5	86.8	2.2	84.1	89.5	85.0	90.0	<0.001	Naive	DSS	<0.001
	DSS	10	57.1	5.3	53.3	60.9	48.0	66.0		Naive	DSS+CBD	<0.001
	DSS+CBD	10	65.9	4.5	62.7	69.1	58.0	74.0		Naive	DSS+CBD+Mycolivia	<0.001
	DSS+CBD+Mycolivia	10	71.3	4.9	67.8	74.8	62.0	77.0		Naive	DSS+Mycolivia	0.001
	DSS+Mycolivia	10	75.2	4.8	71.8	78.6	70.0	84.0		DSS	DSS+CBD	0.002
	Total	45	69.5	10.0	66.5	72.5	48.0	90.0		DSS	DSS+CBD+Mycolivia	<0.001
										DSS	DSS+Mycolivia	<0.001
										DSS+CBD	DSS+Mycolivia	0.001

Colon Length





Blood Scores

Table 4:

Feces score and blood score in each visit, and proportions in visits 6-11 (Method: χ^2 / Fisher exact test)

Only one comparison was statistically significant: Naïve vs. DSS+CBD+Mycolivia $p<0.001$

			0		1		2		3		4		5		6		7		8		9		10		11		
Naive	5	No visible blood	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	1.00
		Visible blood	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00
DSS	10	No visible blood	10	1	10	1	10	1	9	0.9	6	0.6	5	0.5	4	0.4	6	0.6	7	0.7	9	0.9	10	1	10	1	0.77
		Visible blood	0	0	0	0	0	0	1	0.1	4	0.4	5	0.5	6	0.6	4	0.4	3	0.3	1	0.1	0	0	0	0	0.23
DSS+CBD	10	No visible blood	10	1	10	1	10	1	10	1	8	0.8	8	0.8	4	0.4	4	0.4	7	0.7	8	0.8	10	1	10	1	0.72
		Visible blood	0	0	0	0	0	0	0	0	2	0.2	2	0.2	6	0.6	6	0.6	3	0.3	2	0.2	0	0	0	0	0.28
DSS+CBD+Mycolivia	10	No visible blood	10	1	10	1	10	1	10	1	10	1	10	1	6	0.6	2	0.2	6	0.6	8	0.8	10	1	10	1	0.70
		Visible blood	0	0	0	0	0	0	0	0	0	0	0	0	4	0.4	8	0.8	4	0.4	2	0.2	0	0	0	0	0.30
DSS+Mycolivia	10	No visible blood	10	1	10	1	10	1	10	1	10	1	10	1	9	0.9	7	0.7	7	0.7	7	0.7	10	1	10	1	0.83
		Visible blood	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1	3	0.3	3	0.3	3	0.3	0	0	0	0	0.17

Feces Scores

Table 4:

Feces score and blood score in each visit, and proportions in visits 6-11 (Method: χ^2 / Fisher exact test)

Only one comparison was statistically significant: Naïve vs. DSS+CBD+Mycolivia $p<0.001$

	n		0	Prop	1	Prop	2	Prop	3	Prop	4	Prop	5	Prop	6	Prop	7	Prop	8	Prop	9	Prop	10	Prop	11	Prop	Mean proportion 6-11
Naïve	5	Normal feces	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	1.00
		Soft feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00
		Liquid feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00
DSS	10	Normal feces	10	1	10	1	10	1	4	0.4	2	0.2	1	0.1	0	0	0	0	0	0	0	0	0	0	0	0	0.00
		Soft feces	0	0	0	0	0	0	6	0.6	8	0.8	9	0.9	7	0.7	5	0.5	1	0.1	1	0.1	2	0.2	3	0.3	0.32
		Liquid feces	0	0	0	0	0	0	0	0	0	0	0	0	3	0.3	5	0.5	9	0.9	9	0.9	8	0.8	7	0.7	0.68
DSS+CBD	10	Normal feces	10	1	10	1	10	1	7	0.7	4	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00
		Soft feces	0	0	0	0	0	0	3	0.3	6	0.6	10	1	8	0.8	6	0.6	2	0.2	1	0.1	4	0.4	6	0.6	0.45
		Liquid feces	0	0	0	0	0	0	0	0	0	0	0	0	2	0.2	4	0.4	8	0.8	9	0.9	6	0.6	4	0.4	0.55
DSS+CBD+Mycolivia	10	Normal feces	10	1	10	1	10	1	8	0.8	4	0.4	1	0.1	0	0	0	0	0	0	0	0	0	0	0	0	0.00
		Soft feces	0	0	0	0	0	0	2	0.2	6	0.6	9	0.9	6	0.6	6	0.6	1	0.1	2	0.2	7	0.7	7	0.7	0.48
		Liquid feces	0	0	0	0	0	0	0	0	0	0	0	0	4	0.4	4	0.4	9	0.9	8	0.8	3	0.3	3	0.3	0.52
DSS+Mycolivia	10	Normal feces	10	1	10	1	10	1	8	0.8	4	0.4	1	0.1	0	0	0	0	0	0	0	0	1	0.1	4	0.4	0.08
		Soft feces	0	0	0	0	0	0	2	0.2	6	0.6	9	0.9	8	0.8	6	0.6	2	0.2	4	0.4	9	0.9	6	0.6	0.58
		Liquid feces	0	0	0	0	0	0	0	0	0	0	0	0	2	0.2	4	0.4	8	0.8	6	0.6	0	0	0	0	0.33

Feces Scores

1. אנליזה עבור ביקורים 10, 11 עבור ההשוואות הבאות:
   a. Naïve vs DSS
   b. Naïve vs DSS+Mycollivia
   c. DSS vs Mycolivia

Visit10	Liquid feces	Normal feces	Uncorrected Pv	Fisher Exact (Corrected) Pv
DSS	8	0	0.003	0.111
DSS+Mycolivia	0	1		
Naïve	0	5	<0.001	<0.001
DSS	8	0		
Naïve	0	5	NA	NA
DSS+Mycolivia	0	1		

Visit11	Liquid feces	Normal feces	Uncorrected Pv	Fisher Exact (Corrected) Pv
DSS	7	0	0.001	0.003
DSS+Mycolivia	0	4		
Naïve	0	5	0.001	0.001
DSS	7	0		
Naïve	0	5	1.000	1.000
DSS+Mycolivia	0	4		

χ^2, Fisher exact test

Pathology Scores

2. הבדלים בין קבוצות 2, 5 (DSS vs DSS+Mycolivia) עבור תוצאות טבלה B ב- Draft report:

לא נמצאו כל הבדלים סטטיסטיים בין הקבוצות בשיטת T-test for independent samples ולא בשיטת Independent-Samples Kruskal-Wallis Test

T-Test

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Inflammation	2.00	10	2.0000	.00000[a]	.00000
	5.00	10	2.0000	.00000[a]	.00000
Lymphocyte_infiltration	2.00	10	2.0000	.00000[a]	.00000
	5.00	10	2.0000	.00000[a]	.00000
Erosions	2.00	10	2.6000	.51640	.16330
	5.00	10	2.2000	.63246	.20000
Crypt_loss	2.00	10	2.0000	.00000	.00000
	5.00	10	1.8000	.42164	.13333
Sum_Path_Score	2.00	10	8.6000	.51640	.16330
	5.00	10	8.0000	.94281	.29814

a. t cannot be computed because the standard deviations of both groups are 0.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
						Significance				95% Confidence Interval of the Difference	
		F	Sig.	t	df	One-Sided p	Two-Sided p	Mean Difference	Std. Error Difference	Lower	Upper
Erosions	Equal variances assumed	.000	1.000	1.549	18	.069	.139	.40000	.25820	-.14246	.94246
	Equal variances not assumed			1.549	17.308	.070	.139	.40000	.25820	-.14402	.94402
Crypt_loss	Equal variances assumed	16.000	<.001	1.500	18	.075	.151	.20000	.13333	-.08012	.48012
	Equal variances not assumed			1.500	9.000	.084	.168	.20000	.13333	-.10162	.50162
Sum_Path_Score	Equal variances assumed	.288	.598	1.765	18	.047	.095	.60000	.33993	-.11418	1.31418
	Equal variances not assumed			1.765	13.954	.050	.099	.60000	.33993	-.12931	1.32931

Clinical Trial

U.S. National Library of Medicine

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The Effect of Mycobiome Supplementation on Gastrointestinal Symptoms in IBD Patients

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04329481

Recruitment Status : Recruiting
First Posted : April 1, 2020
Last Update Posted : February 1, 2022

See Contacts and Locations

Sponsor:

Tel-Aviv Sourasky Medical Center

Clinical Trial

- Aims:
- To evaluate the impact of "Myco Digest" supplementation to inflammatory bowel disease (IBD) patients on:
  1. Clinical response and remission rates
  2. Quality of life
  3. Inflammatory markers
  4. Fecal microbiome composition and diversity

Clinical Trial

- Study design
  - A randomized, double-blind, placebo-controlled, cross-over clinical trial.
- Study population
  - 100 IBD patients, 50 Crohn’s disease (CD) and 50 ulcerative colitis (UC) patients with a mild-moderate disease activity.

Clinical Trial Conclusions

- Many studies have shown a significant improvement in Ulcerative Colitis symptoms by changing the diet.
- Medicinal mushrooms have been shown to improve symptoms in animal models and human studies as well.
- Myco Digest have shown to alleviate symptoms in a mice model, and the results of a human study are impending.
- The improvement in UC clinical course may be caused by:
  - An immunomodulation activation caused mainly by the specific composition of its beta glucans and other fibers components.
  - A change in the microbiome due to prebiotic activity of mushrooms' glucans and other polysaccharides.
  - An anti-inflammatory response.

מסקנות המחקר הקליני

- מחקרים רבים הדגימו הטבה בתסמיני קוליטיס כיבית בשינוי הדיאטה.
- גם מחקרים קליניים ומחקרים במודל חיה, שבדקו שימוש בפטריות מרפא, הדגימו הטבה בקוליטיס כיבית.
- שימוש במיקו דייג'סט במחקר במודל חיה הוביל להטבה .
- הסיבות האפשריות להטבה בתסמיני קוליטיס כיבית:
  - פעילות אימונומודולטורית של הפוליסכרידים בפטריות, בעיקר בטא גלוקנים.
  - שינויים בהרכב המיקרוביום של הנבדקים עקב פעילות פרה-ביוטית של גלוקנים ופוליסכרידים אחרים בפטריות.
  - פעילות אנטי דלקתית.

Thank You

מיקוליביה פטריות מרפא

Mycolivia Medicinal Mushrooms

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