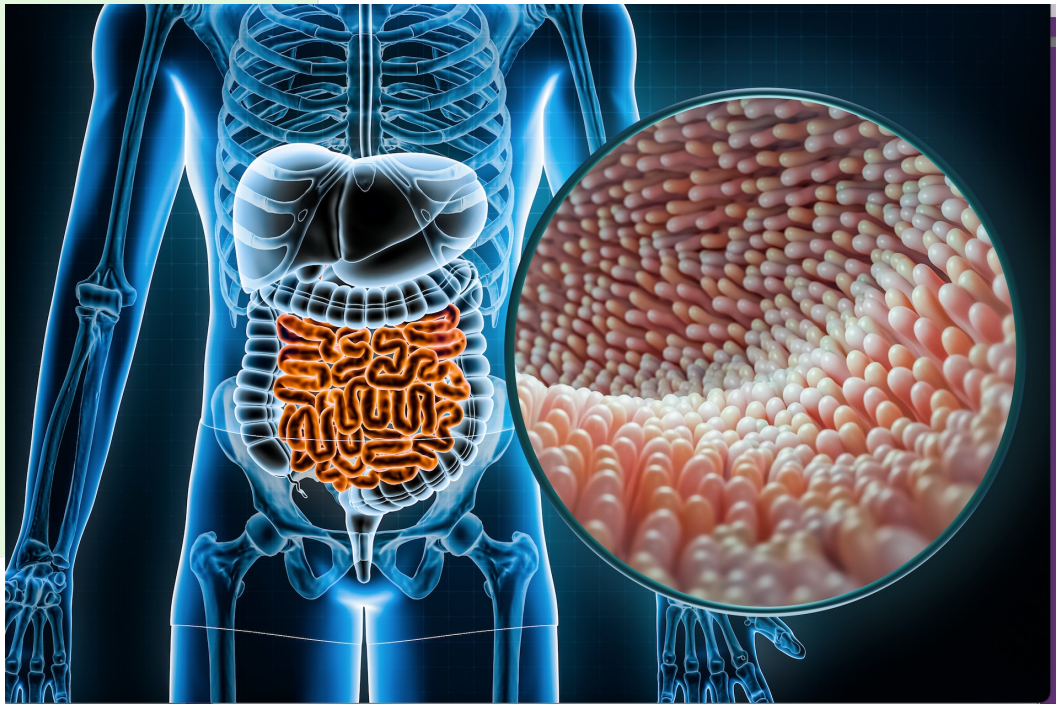
The Roadmap Series



Mapping Leaky Gut

Tanya Borowski

Head of Education

amrita education

PMID: 32340206

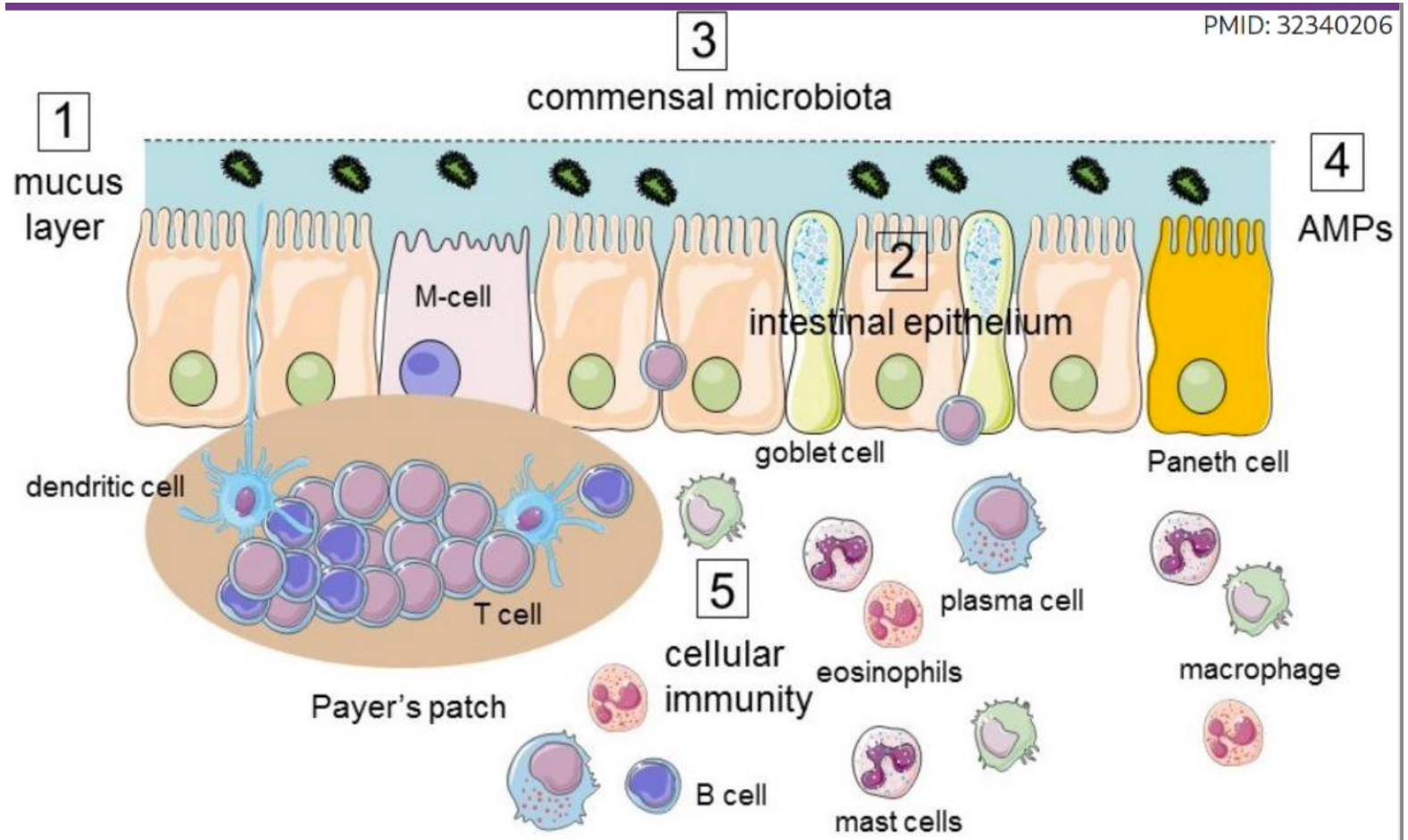


Figure 1. Summary of the different components of the mucosal barrier in the gastrointestinal tract (GI) tract. The physical elements include the (1) mucus layer, (2) intestinal epithelium, and (3) commensal microbiota. The immunological elements consist of (4) antimicrobial peptides secreted by Paneth cells and enterocytes, (5) cellular immunity. AMPs: antimicrobial peptides.

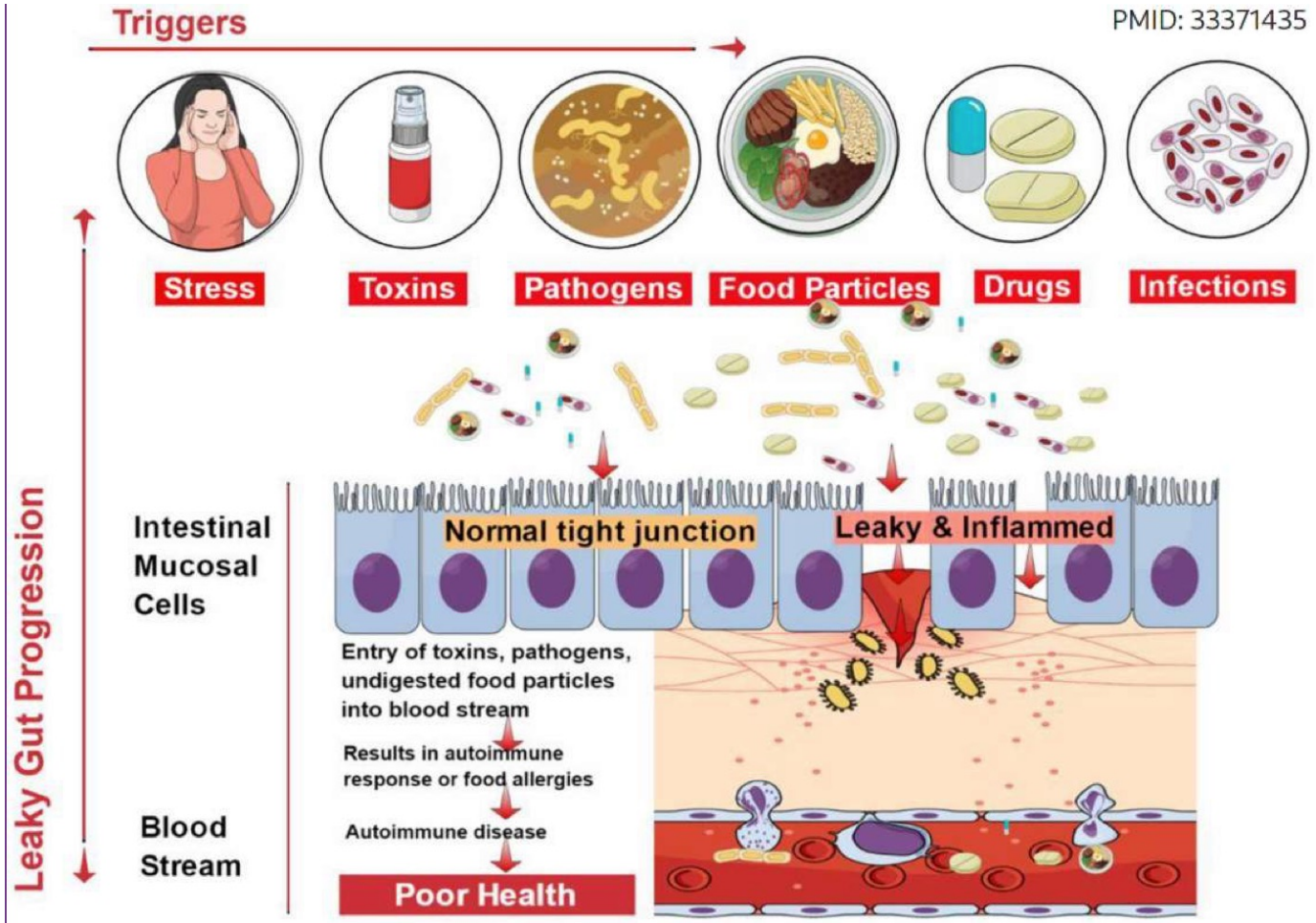


Figure 2. Factors contributing to the development of leaky gut and its relationship to autoimmune diseases. Diet, genetic susceptibility, and environmental conditions, among others, affect the intestinal epithelial barrier integrity. This imbalance leads to compromised barrier integrity and contributes to several diseases.

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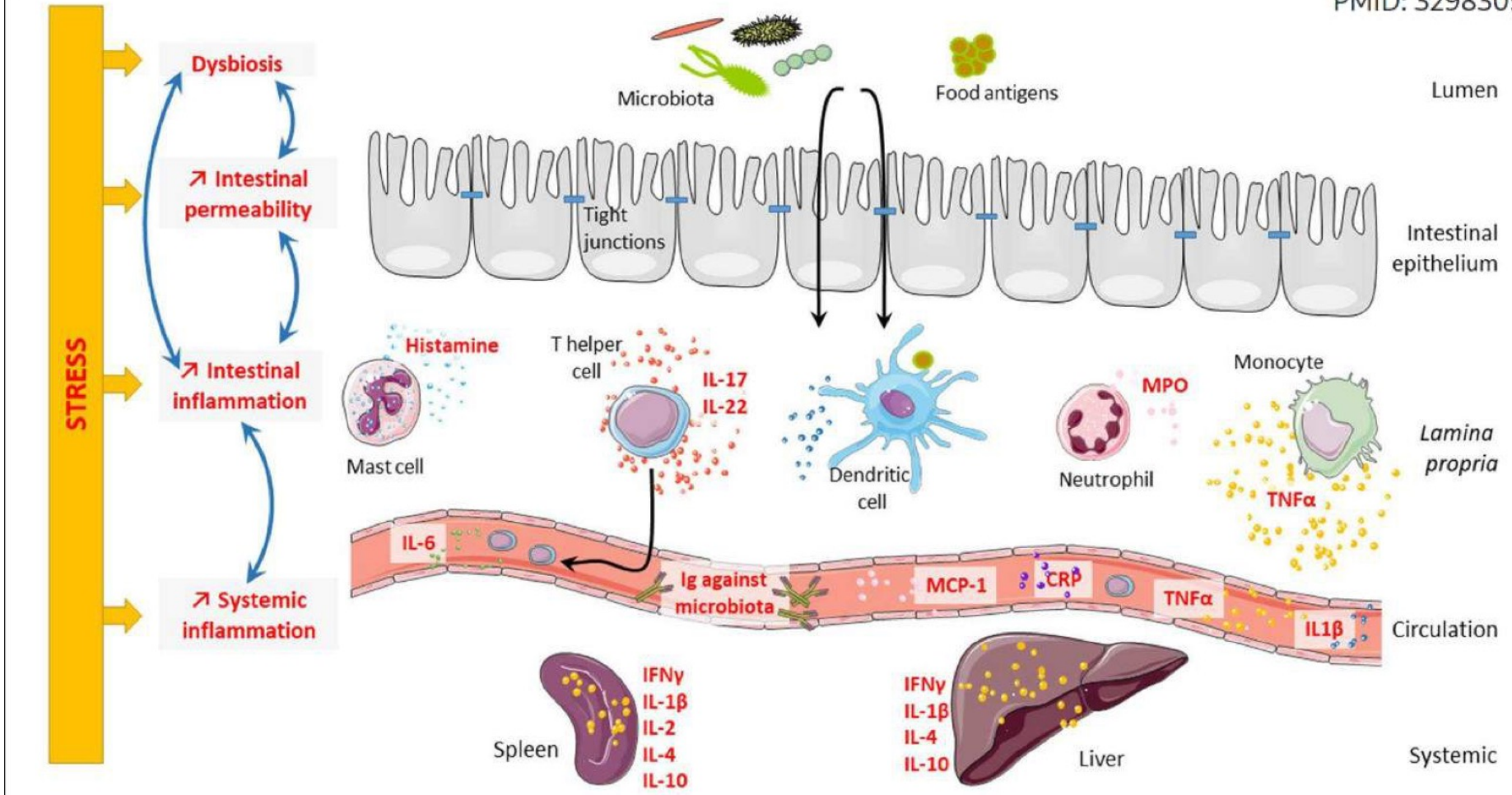


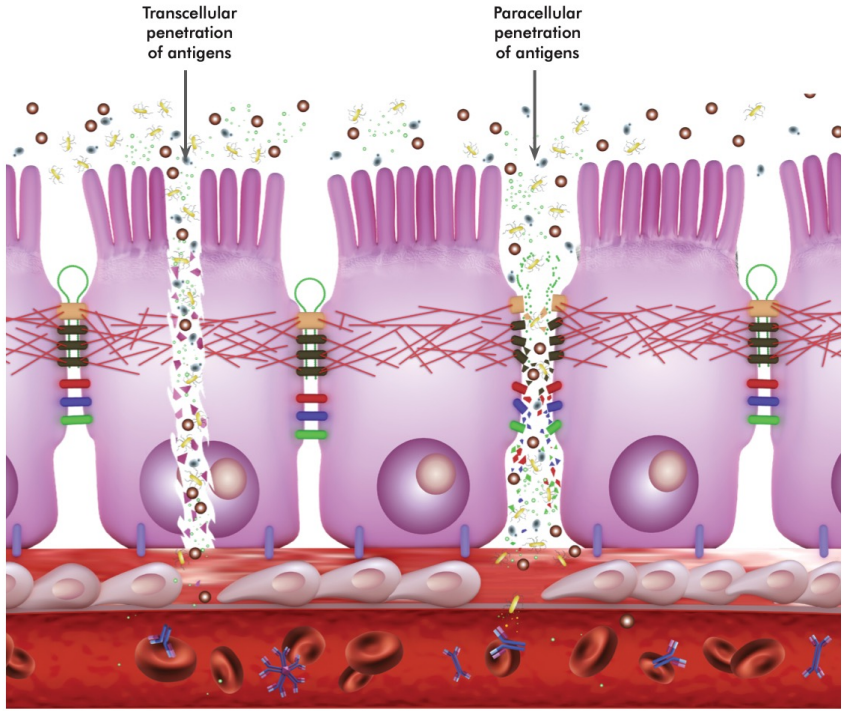
FIGURE 1 | Consequences of stress on intestinal barrier and systemic inflammation. Psychological stress can impair intestinal barrier at different levels. Indeed, stress can lead to microbiota dysbiosis, intestinal hyperpermeability, and intestinal inflammation. Interestingly, all these elements are highly connected and regulate one another. Microbiota dysbiosis can trigger intestinal hyperpermeability and intestinal inflammation; and in contrast, both intestinal hyperpermeability and intestinal inflammation can induce microbiota dysbiosis. Finally, stress can also induce systemic inflammation that might be related to intestinal inflammation.

Table 3 Pathogen interactions with epithelial tight junctions

Bacteria	*Bacterial factors*	*Mechanism of TJ disruption*	*Host targets*	*References*
H. pylori	CagA	Cdx2-mediated increase in claudin 2 expression	PAR1	[64-66]
	Urease	Phosphorylation of myosin light chain kinase and occludin internalization	MLCK, ROCK	[67]
	Unknown	Rho kinase (ROCK)-dependent loss of TJ claudin-4	IL-1R1, ROCK	[68]
EPEC	Map	Cdc42-dependent filopodia and pedestal formation	Cdc42	[69]
	EspM	Activation of RhoA and TJ disruption	RhoA	[70-72]
	NleA	Inhibition of host cell protein trafficking through COPII-dependent pathways	COPII	[73]
V. parahemo- lyticus	T3SS effectors	Alteration of actomycin ring and TJ disruption	Rho GTPase	[74,75]
Salmonella enterica serovar typhimur.	T3SS effectors SipA, SopB, SopE, SopE2	Filopodia formation and alteration of actomycin ring	Rho GTPase	[76]
Clostridium difficile	enterotoxin A and B	Inactivation of Rho family proteins causing degradation of filamentous actin	Rho and Cdc	[77]
Bacteroides fragilis	Enterotoxin or fragilysin	Toxin degradation of E- cadherin and alteration of actomycin ring	E-cadherin	[78]
Vibrio cholera	HA protease	HA induced cleavage of occludin, alteration of ZO-1 and rearrangement of actin	Occludin	[79]

Abbreviations: *TJ* tight junctions, *PAR1* phytochrome rapidly regulated 1 gene, *MLCK* myosin light chain kinase, *ROCK* Rho-associated, coiled-coil containing protein kinase 1, *IL-1R1* interleukin 1 receptor, type I, *Cdc42* cell division cycle 42, *RhoA* ras homolog family member A, *COPII* Rho GTPase, *EPEC* enteropathogenic Escherichia coli. Other explanations see text.

Assessment



Antigens Measured	
Actomyosin Proteins	
Occludin/Zonulin Proteins	
Lipopolysaccharides	Endotoxins from Gram-Negative Bacteria

- Lactulose and mannitol ratio
- Calprotectin
- sIgA
- Cyrex :_

•Actomyosin IgA
•Occludin/Zonulin IgG
•Occludin/Zonulin IgA
•Occludin/Zonulin IgM
•Lipopolysaccharides (LPS) IgG
•Lipopolysaccharides (LPS) IgA
•Lipopolysaccharides (LPS) IgM

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REVIEW

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases [version 1; peer review: 3 approved]

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Table 1. Chronic inflammatory diseases in which zonulin has been linked as a biomarker of gut permeability.

Disease	Model	References
[illegible]ng	Human	37,38
An[illegible]ic spondylitis	Human	39
Attention d[illegible]hyperactivity disorder	Huma[illegible]	
Autism	Human	41,42
Celiac disease	Human	15–20,23–27,43–48
Chronic fatigue syndrome/myalgic encephalomyelitis	Human	49
Colitis – inflammatory bowel diseases	Human	50,51
Colitis	Mouse	52
Environmental enteric dysfunction	Human	53
Gestational diabetes	Human	54,55
Glioma	Human	56
Glioma	Cell	57
Insulin resistance	Human	58
Irritable bowel syndrome	Human	59,60
Hyperlipidemia	Human	61
HIV	Human	62–66
Major depressive disorders	Human	67,68
Multiple sclerosis	Mouse	69
Multiple sclerosis	Human	70
Necrotizing enterocolitis	Rat	71
Necrotizing enterocolitis	Human	72
Non-alcoholic fatty liver disease	Human	73–77
Non-celiac gluten sensitivity	Human	53,78
Obesity	Human	79–87
Schizophrenia	Human	41,88,89
Sepsis	Human	90
Type 1 diabetes	Rat	91
Type 1 diabetes	Human	92,93
Type 2 diabetes	Human	94,95

Flameshot

Or .....

Letter

Blurring the picture in leaky gut research: how shortcomings of zonulin as a biomarker mislead the field of intestinal permeability

Table 1 Studies using zonulin ELISA and correlations with intestinal permeability

Study	Year	Zonulin kit	N	Correlation	Citation
Halasa *et al*	2019	IDK	38	R=0.11, p>0.05	8
Linsalata *et al*	2018	IDK	71	R=0.17, p>0.05	9
Kuzma *et al*	2020	IDK (distributed by ALPCO)	24	R=0.033, p=0.79	10

With great interest we read the work by Talley *et al*[1] reporting the inadequacy of zonulin as a biomarker due to its failure to identify the irritable bowel syndrome, functional dyspepsia and non-coeliac wheat sensitivity. Zonulin as a biomarker is highly disputed.[2] A recent study showed that zonulin-mediated intestinal barrier integrity is an important mechanism by which gut microbial dysbiosis affects the transition from asymptotic autoimmunity to inflammatory disease associated with increased circulating zonulin in patients with arthritis.[3] In all of these studies, zonulin measurements are based on commercial ELISA.

There is no doubt about the clinical relevance of studies addressing the relation between intestinal permeability and inflammatory diseases. Zonulin, precisely pre-haptoglobin 2 (preHP2), was identified as a human homologue to a second *Vibrio cholerae* enterotoxin regulating tight junction permeability and subsequently has gained much attention as a potential biomarker for intestinal permeability.[4] However, the commercial ELISAs very frequently used to measure zonulin were produced using the first published sequence, which later has been shown to be unrelated to the zonulin protein.[4] These developments have resulted in the following two major critical yet widely overlooked issues.

COMMERCIALLY AVAILABLE ELISAS DO NOT MEASURE ZONULIN

The shortcomings of the commercial ELISA have been demonstrated in independent work and have been discussed previously.[5 6] Measurements using these commercial ELISA do not reflect actual zonulin levels, but concentrations of unknown proteins. Consequently, this has to preclude scientists from drawing conclusions on the role and importance of zonulin in the context of intestinal permeability and related diseases based on these ELISA measurements, both positive and negative. This, also retrospectively, applies to numerous studies reporting findings relying on the commercial ELISA by, for example, lactulose mannitol test (table 1).

Importantly, this does not take away from zonulin/preHP2 as a regulator of intestinal permeability and does not rule out correlations of zonulin levels with intestinal barrier function.

ZONULIN AS PRE-HAPTOGLOBIN2 IS NOT EXPRESSED IN MICE

Animal models of intestinal barrier dysfunction are highly useful for translational research, yet zonulin as preHP2 is not naturally expressed in mice. While haptoglobin is conserved in most mammals, the HP2 genotype is unique to humans. This renders measurements of serum zonulin in rodent models highly questionable and potentially misleading.[3] Along these lines, differential ELISA signals obtained in mouse sera further indicate detection of unspecific and unknown proteins by the ELISA.[3] For translational research, assessing zonulin levels in mouse models does only become relevant when using zonulin-specific assays in 'humanised mice' genetically modified to express human HP2, as has been previously described.[7]

CONCLUSION

Together, it has become obvious that using the commercial zonulin ELISA is neither adequate to measure intestinal permeability nor the postulated biomarker zonulin. Even more important, previously published results based on zonulin ELISA measurements have to be seen with great caution and do not establish a relation to the function of the protein zonulin/preHP2. New and specific detection methods and assays for zonulin/preHP2 are urgently needed to address the usefulness of zonulin as a biomarker for intestinal permeability. Until then, researchers are strongly encouraged to circumvent the unspecific measurement of zonulin and instead apply rigorous tests of intestinal permeability such as dual-sugar assays, and use immunohistochemistry and expression profiles of zonula occludens proteins.[3]

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Zonulin

Letter

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Effects Pro & Prebiotics

Table 1. The effects of pro-/prebiotics on intestinal integrity and immunomodulation.

	Name	Integrity	Immunomodulation	Other Effect(s)	Reference
Pro-biotics	*Lactobacillus* species	TEER↑ Intestinal permeability↓ ZO-1↑ occludin↑ E-cadherin↑ claudin-2↑	IL-10↑ IL-27↑ IL-1↓ IL-6↓ TNF-α↓ NF-κB activation↓	Integrin-p38 MAPK activation↑ HSP expression↑ Antioxidative capacity↑ Nutrient transporters↑	[77,82–84,88,89,135]
	Bifidobacterium species	claudin-3↑ Morphological damage↓ β-catenin↑	Corticosterone↓ IgA secreting cells↑ Intraepithelial lymphocytes↓	Mucin genes transcription and protein production↑	[77,88,89]
	Bacillus species				[79,80,85,88,89]
	E. coli Nissle	ZO-2 dissociation↓		-	[81,88,89]
	Streptococcus thermophiles	occludin delocalization↓		-	[84,88,89]

Defensive proteins

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Triple Probiotic Therapy

- Lactobacillus & Bifido Blend 1 X B.I.D
- Saccharmoyces boulardii 1 X B.I.D
- Spore-based 1 x QD

Probiotics & Prebiotics

Pre-biotics	HMO	ZO-1↑ occludin↑ JAM-A↑ Crypt proliferation↑ Intestinal permeability↓	IL-10↑ TLR-4↓ NF-κB translocation↓ p38 MAPK activation↓	Mucus production↑ HIF-1α↓ Cleaved caspase-3↓ EGFR activation↑	[109,123,130,136]
	GOS	TEER↑ Intestinal permeability↓ occludin↑ claudin-3↑ E-cadherin↑	IL-6 mRNA↓ IL-8 mRNA↓ TLR-4↓ IL-33↓ CXCL-8↓ CXCL-1↓ CXCL-2↓	HSP expression↓ Populations of probiotics↑ HO-1 expression↓	[99,100,102,103,119]
	MOS	Intestinal permeability↓ permeability↓ Villus height↑	-	Goblet cells↑ Populations of probiotics↑ *E. coli* load↑	[106–108]
	COS	Intestinal permeability↓ Morphological damage↓	-	-	[106,107]
	FOS	TEER↑ Intestinal permeability↓ occludin↑ ZO-1↑	-	Colonic SCFA concentration↑ Mucosal damage↓	[110,115,137]

Human oligosaccharides

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Nutrients

Table 2. The effects of α-lipoic acid and resveratrol on intestinal integrity and immunomodulation.

Compound	Integrity	Immunomodulation	Other Effect(s)	Reference
α-lipoic acid	Intestinal permeability↓ ZO-1↑ occludin↑ E-cadherin↑ Morphological damage↓	COX-2 activation↓ IL-17↓ IL-6↓ TNF-α↓ IκB activation↑	Epithelial proliferation↑ HSP70 expression↑ HO-1 activation↑	[144–148,150–154]
Resveratrol	ZO-1↑ occludin↑ TEER↑ Intestinal permeability↓ claudin-1↑ claudin-4↑ Crypt depth↓ Villus height↑	IL-6 mRNA↓ IL-1β mRNA↓ PTGS1 mRNA↓ COX-2 activation↓ NF-κB activation↓	MDA↓ SOD↑ GSH↓ ROS↓ HO-1 activation↑ HSP70↑ HSP90↑	[155,156,160–163, 165,168,169]

Upwards arrow: Increase or enhancement; downwards arrow: Decrease or inhibition. PTGS1: prostaglandin G/H synthase 1; MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathione; ROS: reactive oxygen species.

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TABLE 1 | Effect of diet-derived compounds on intestinal permeability.

PMID: 26697008

Dietary antigens	Effect on permeability	TER measurement	Mechanisms of action	Models of study	Reference
AMINO ACIDS					
Gln	Decreased	Increased	Unknown	Caco2 cell line	(66)
Gln deprivation	Increased	Not determined	Reduction of occludin, claudin-1, and ZO-1/ redistribution of claudin-1 and occludin	Caco2 cell line	(67)
Trp	Decreased	Increased	Unknown	Caco2 cell line	(70)
PEPTIDES					
β-casein	Decreased	Increased	Increase occludin expression	Caco2 cell line	(71)
β-lactoglobulin	Decreased	Increased	Modifications into the cytoskeletal structure	Caco2 cell line	(72)
VITAMINS					
Vitamin D	Decreased	Increased (in Caco2 cell line)	Enhancement of claudin-1, ZO-1 and E-cadherin proteins expression	SW480-Caco2 cell lines/$VDR^{+/+}$ and $VDR^{-/-}$ in C57BL6 background	(73)
Retinol (vitamin A)	Decreased	Increased	Neutralization *Clostridium difficile* toxin A	Caco2 cell line	(74)
POLYPHENOLS					
Quercetin	Decreased	Increased	Increase in claudin-4 expression and in ZO-2, occludin and claudin-1 assembly	Caco2 cell line	(75, 76)
Kaempferol	Decreased	Increased	Promotion of ZO-1/2, occludin and claudin-1/3/4 cytoskeletal association	Caco2 cell line	(77)
Genistein	Decreased	Increased	Inhibition of the redistribution and the dissociation of occludin/ZO-1 complex	Caco2 cell line	(78, 79)
	Decreased	Increased	Inhibition of TNFα-mediated effects	HT-29/B6 cell line	(99)
EGCG	Decreased	Increased	Inhibition of INFγ-mediated effects	T84 cell line	(98)
Curcumin	Decreased	Increased	Inhibition of TNFα- and IL-1β-mediated effects	Caco2 cell line	(100, 101)
DITERPENE GLYCOSIDE					
Capsianoside	Increased	Decreased	Changes in F/G actin ratio	Caco2 cell line	(92)
LCFAs					
EPA and DHA	Increased	Decreased	Protein kinase C regulation/unknown	Caco2 cell line	(84, 85)
	Decreased	Increased	Reduction of IL-4-mediated permeability	T84 cell line	(86)
MCFA					
Capric acid	Increased	Decreased	Redistribution of occludin and ZO-1/MLCK activation	Caco2 cell line	(87)
Lauric acid	Increased	Decreased	MLCK activation	Caco2 cell line	(88)
SCFAs					
Acetic and propionic acids	Decreased	Increased	Activation of PI3K	Caco2/T84 cell lines	(90)
MINERALS					
Zinc depletion	Increased	Decreased	Redistribution of occludin, ZO-1, E-cadherin, and β-catenin and F-actin	Caco2 cell line	(93)
ALCOHOLS					
Ethanol	Increased	Decreased	Redistribution of occludin and ZO1/MLCK activation	Caco2 cell line	(94)
Acetaldehyde	Increased	Decreased	Loss of interaction between occludin/ZO-1 and β-catenin/E-cadherin by a tyrosine phosphorylation-	Caco2 cell line/Sprague-Dawley rats and C3H/He mice	(79, 95–97)

A:-Neutralises C diff toxin 5-10,000 iu day

Lactoferrin

Lactoferrin: Antimicrobial impacts, genomic guardian, therapeutic uses and clinical significance for humans and animals

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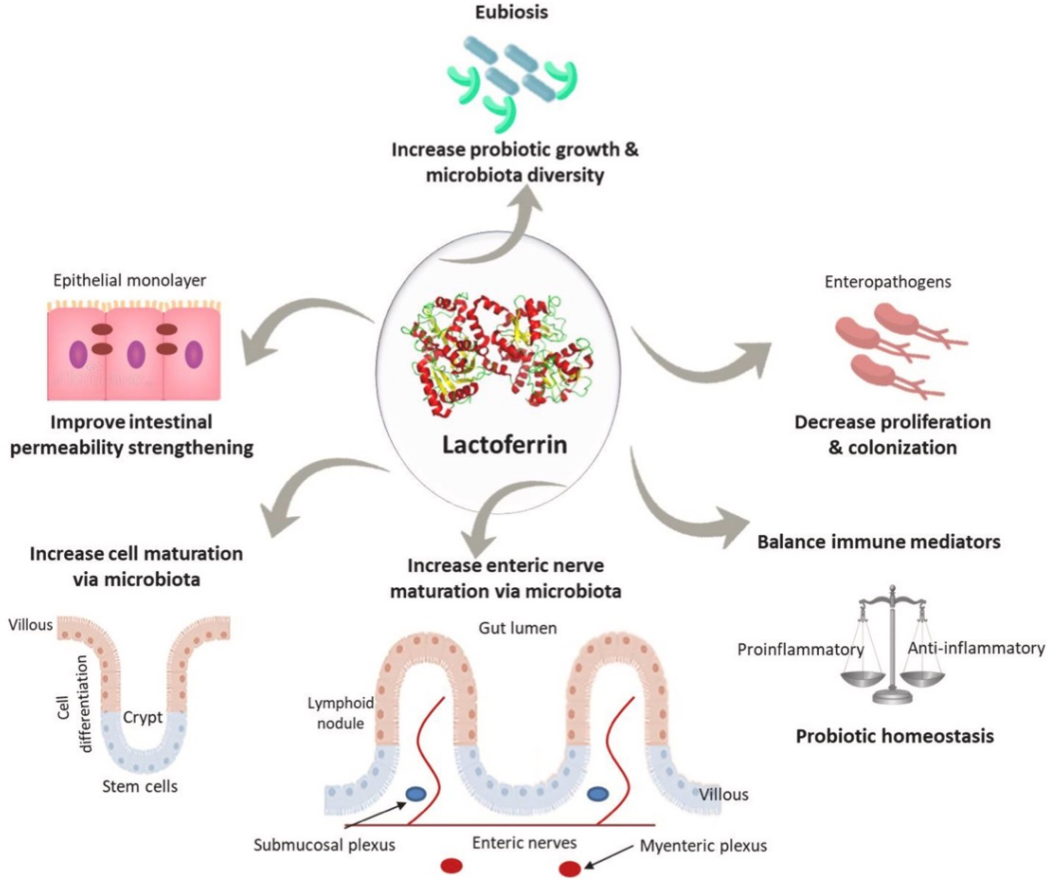

EPA & DHA

Table 3. The effects of polyunsaturated fatty acids (PUFA) on intestinal integrity and immunomodulation.

Compound	Integrity	Immunomodulation	Other Effect(s)	Reference
EPA and DHA	TEER↑ Intestinal permeability↓ occludin↑ ZO-1↑ E-cadherin↑ TJ proteins redistribution and distortion↓	Acute inflammation↓ IL-1β↓ IL-6↓ IL-17↓ TNF-α↓ INF-γ↓ COX-2 activation↓ iNOS↓ cGMP↓	Mucosal damage↓ ROS production↓ SOD↑ CAT↑ Total nitrate/nitrite ratio↓ Microbiota composition restore↑ MUC-2 gene↑ Cytokeratin gene↑	[172,174–177, 179–182]

Upwards arrow: Increase or enhancement; downwards arrow: Decrease or inhibition. EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; CAT: catalase; cGMP: cyclic guanosine monophosphate.

Daily dose
4g EPA+DHA

PMID: 29215589

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Glutamine

Glutamine	Intestinal permeability↓ Villus atrophy↓ occludin↑ claudin-1↑ claudin-4↑ JAM-A↑ ZO-1, ZO-2 and ZO-3↑ E-cadherin↑ β-catenin↑	NF-κB activation↑ CD2+ and CD4+ lymphocytes↑ CD4+/CD8+↑ Serum IgA and IgG↑ Intestinal mucosal s-IgA↑ TNF-α↓ D-lactate↓ DAO activity↓ sICAM-1↓ IL-6↓ IL-8↓ IL-10↑	Mucus production↑ HSP70 expression↑ HSF-1 expression↑ HO-1 expression↑ Cell viability and antioxidant capacity↑ Hyperthermia↓ Diarrhea occurrence↓	[188,235–243,245, 246,249–254]

Upwards arrow: Increase or enhancement; downwards arrow: Decrease or inhibition. IgG: immunoglobulin G; DAO: diamine oxidase; sICAM: soluble intercellular adhesion molecule.

5-20g day day
divided doses
With or without food
*food sensitivities**
Reactive types

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Amino Acids & Immunoglobulins

- Inflammation / Leaky gut = catabolic, stripping amino acids

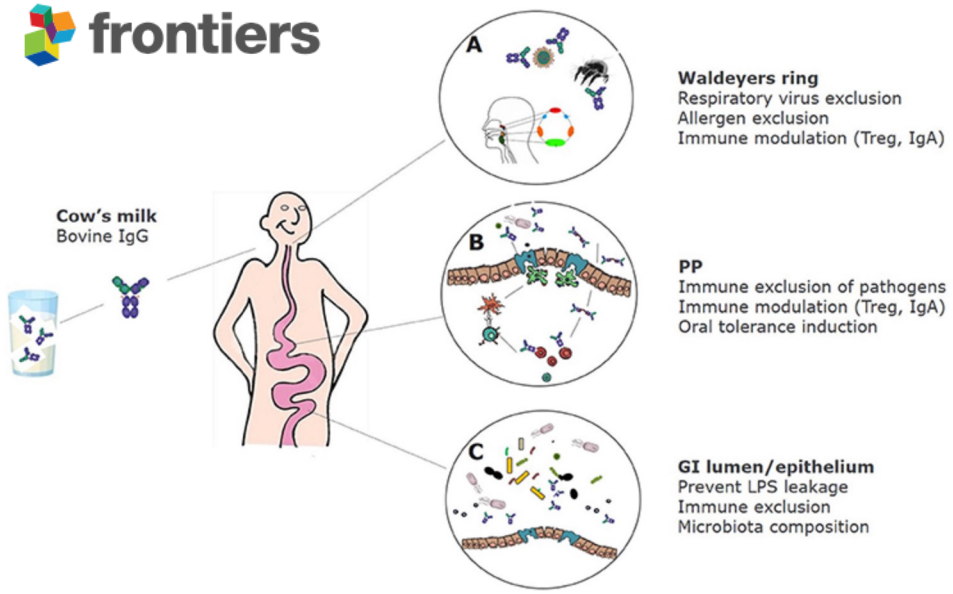
- Use an **amino acid** blend – build lean muscle

Immunoglobulins ; e.g IgYMax

- immune modulatory
-helps to prevent the attachment of unfavourable microbes and reduce mucosal inflammation in the human GI tract.
-support healthy intestinal barrier function

- IBD
- High calprotectin
- High pathogen burden

Effects of Bovine Immunoglobulins on Immune Function, Allergy, and Infection



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Diet Impact: Prebiotics

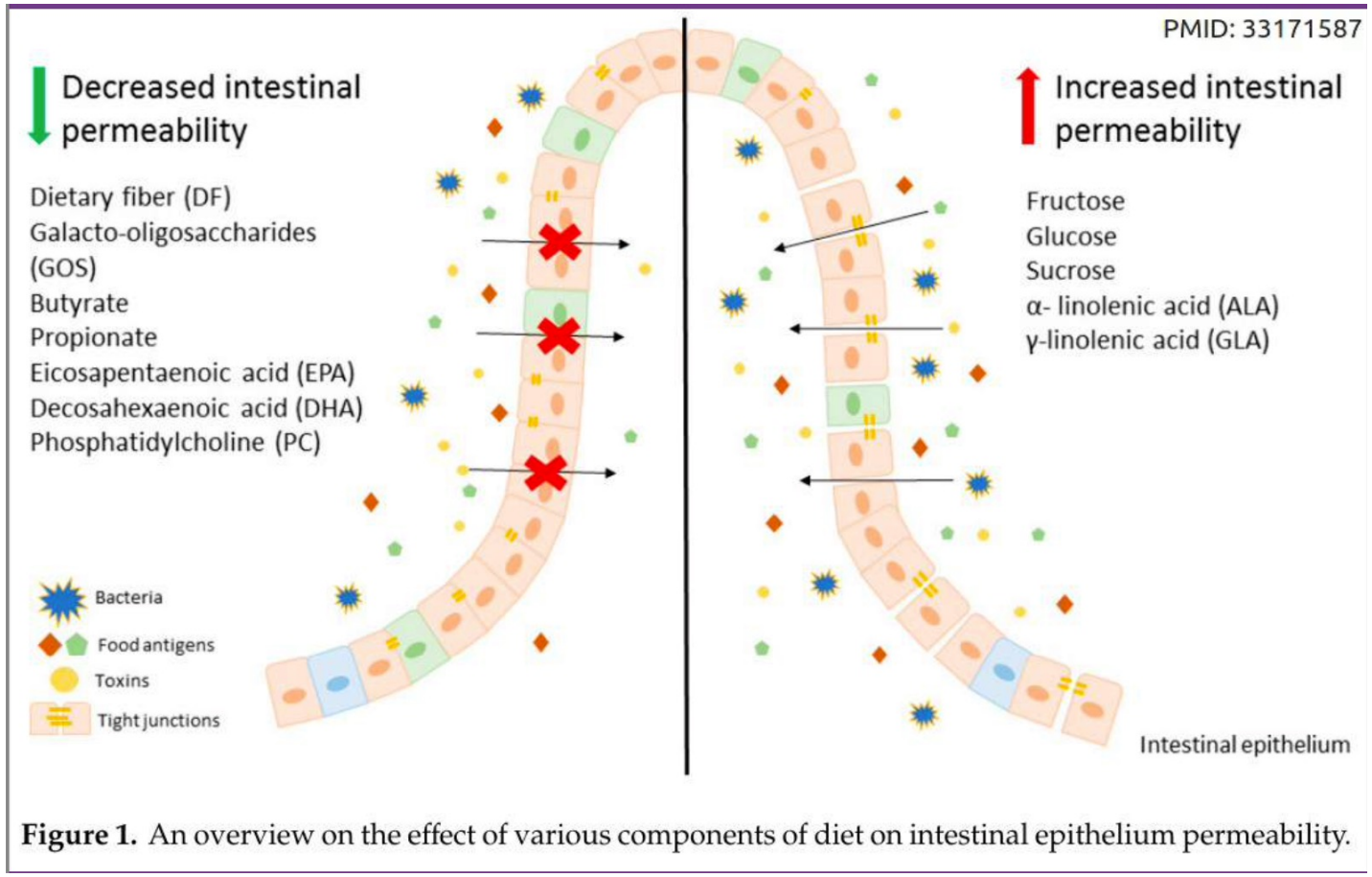

Figure 1. An overview on the effect of various components of diet on intestinal epithelium permeability.

Table 2. The effect of fatty acids on intestinal permeability markers in in vitro and in vivo studies.

Component	Fluorescein Sulfonic Acid Permeability In Vitro	Transepithelial Electrical Resistance In Vitro	Measurements In In Vivo Studies	Effect	PMID: 33171587 References
Short Chain Fatty Acids					
acetate	NS	↑	↓ blood-to lumen clearance of ^{51}Cr-EDTA	tightening	Elamin et al. [80] Wan Saudi et al. [94]
butyrate	↓	↑	increased colonic mucin secretion	tightening	Peng et al. [79] Elamin et al. [80] Nielsen et al. [81] Peng et al. [82] Barcelo et al. [83]
propionate	↓	↑	↓ blood-to lumen clearance of ^{51}Cr-EDTA	tightening	Elamin et al. [78] Wan Saudi et al. [95]
Long Chain Fatty Acids					
oleic acid (OA)	NS	NS	-	-	Usami et al. [90]
linolenic acid (LA)	NS	↓	-	slightly untightening	Usami et al. [90]
α-linolenic acid (ALA)	↑	↓	-	untightening	Usami et al. [90]
arachidonic acid (AA)	NS	↓/↑	-	slightly untightening/tightening	Usami et al. [90] Willemsen et al. [92]
eicosapentaenoic acid (EPA)	↑	↓/↑	-	untightening/tightening	Usami et al. [90] Xiao et al. [93] Willemsen et al. [92]
γ-linolenic acid (GLA)	↑	↓	-	untightening	Usami et al. [91]
decosahexaenoic acid (DHA)	↑	↓/↑	strong insulin permeability enhancement effect	untightening/tightening	Usami et al. [91] Willemsen et al. [92] Xiao et al. [93] Onuki et al. [96]

Abbreviations: AA—arachidonic acid, ALA—α-linolenic acid, DHA—decosahexaenoic acid, EPA—eicosapentaenoic acid, ^{51}Cr-EDTA—^{51}chromium-labeled ethylenediamine tetraacetic acid, GLA—γ-linolenic acid, LA—linolenic acid, NS—not significant/no change, OA—oleic acid, ↑—increased, ↓—decreased.

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Lifestyle Impact: Amino acids

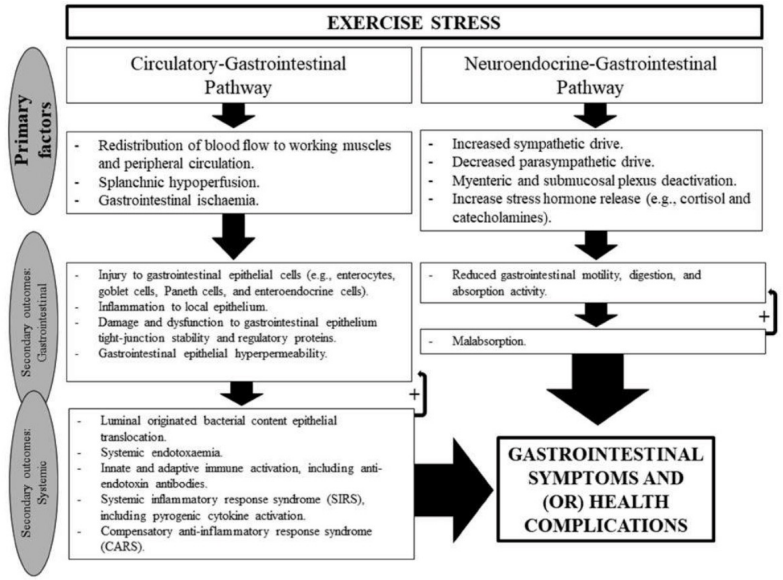
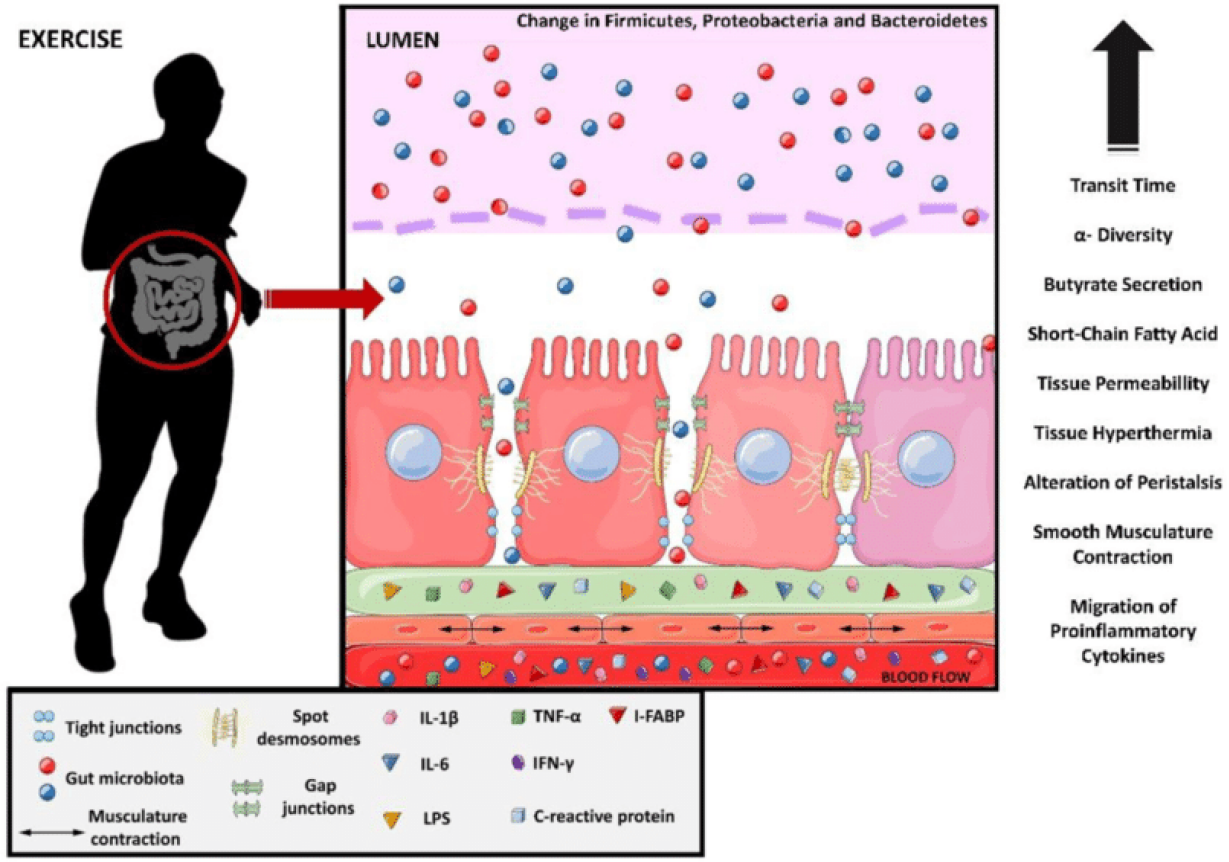


Figure 1. Schematic description of "*exercise-induced gastrointestinal syndrome*" (EIGS) including the "*circulatory-gastrointestinal*" an "*neuroendocrine-gastrointestinal*" pathways. Adopted from Costa et al. [4], with permission.



Glycine

- Glycine, the most abundant protein in body, is needed for synthesising a range of important proteins, including serine, sarcosine, purine, creatine, haemoglobin, glutathione, and **collagen**

- The vast majority of glycine synthesised in the human body comes from serine, indicating that humans can only synthesise about 2.5 g of glycine day – we require 12g for collagen synthesis

- The remainder of the glycine in the body comes from diet, being found primarily in high protein foods such as fish, meat, eggs & legumes = 3g

A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis

Enrique Meléndez-Hevia [1], Patricia De Paz-Lugo, Athel Cornish-Bowden, María Luz Cárdenas

Affiliations + expand

PMID: 20093739 DOI: 10.1007/s12038-009-0100-9

Shortfall 10g /day

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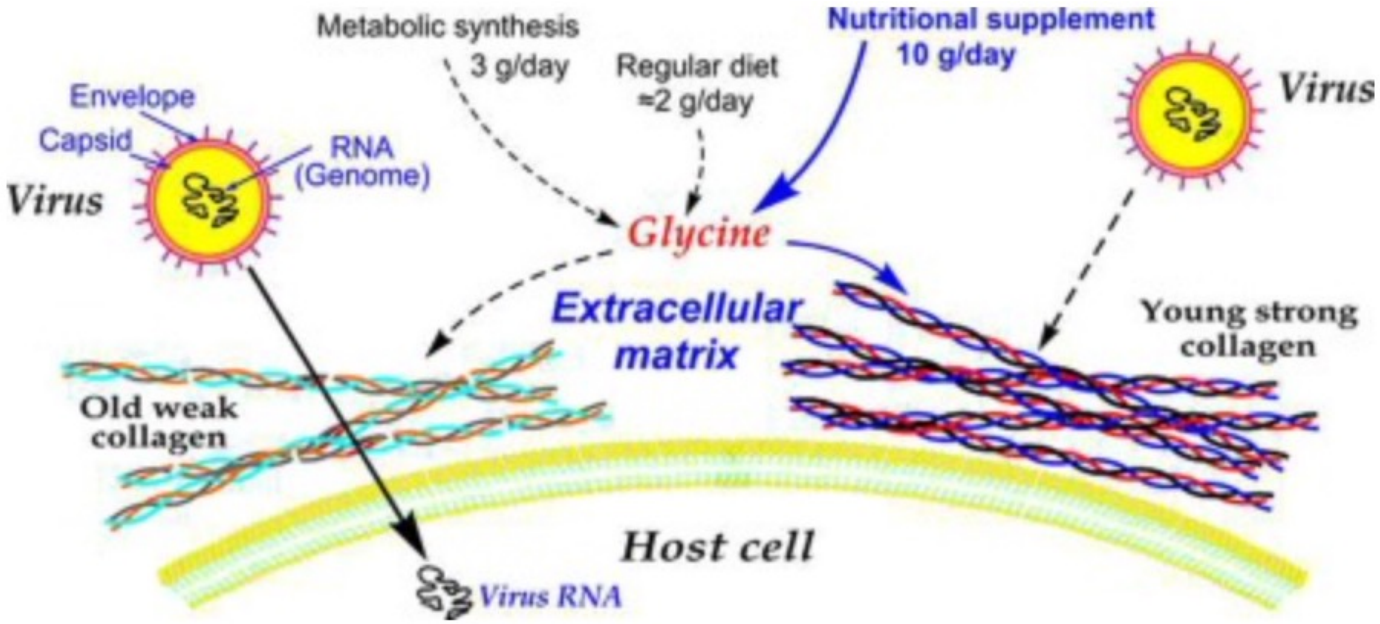
Glycine

ELSEVIER

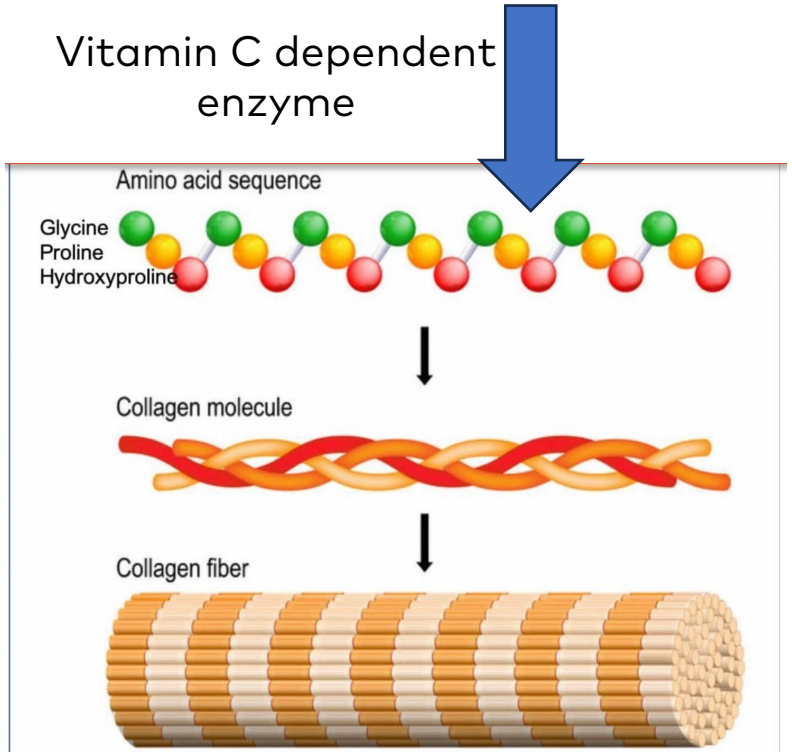
Glycine can prevent and fight virus invasiveness by reinforcing the extracellular matrix

Enrique Meléndez-Hevia [a,*], Patricia de Paz-Lugo [a,1], Guillermo Sánchez [b,2]

[a] Instituto del Metabolismo Celular, La Laguna (Tenerife), Canary Islands, Spain
[b] Clínica Tara, Carretera General del Norte s/n, El Torreón, 38350 Tenerife, Spain



Vitamin C dependent enzyme



10g/ in divided doses

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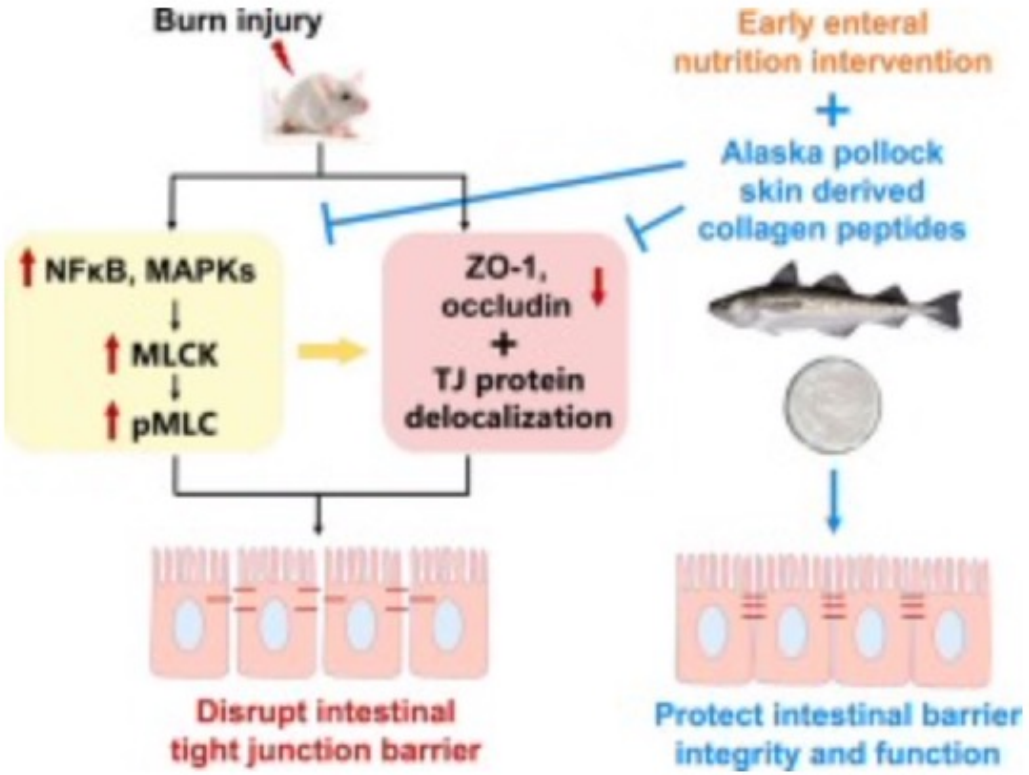
Collagen

ScienceDirect

Collagen peptides administration in early enteral nutrition intervention attenuates burn-induced intestinal barrier disruption: Effects on tight junction structure

Qianru Chen [a], Xiang Gao [b], Hongwei Zhang [c], Bafang Li [a], Guangli Yu [a], Bo Li [d]



Berberine

Berberine induces ZIP14 expression and modulates zinc redistribution to protect intestinal mucosal barrier during polymicrobial sepsis

Yan He[a], Xiaoming Yuan[b], Hao Zuo[b], Xiangwei Li[b], Ying Sun[b], Aiwen Feng[b,*]

[a] Department of Oncological Radiotherapy, Affiliated Huai'an First Hospital, Nanjing Medical University, Huaian City, Jiangsu Province, PR China
[b] Department of Gastrointestinal Surgery, Affiliated Huai'an First Hospital, Nanjing Medical University, Huaian City, Jiangsu Province, PR China

ARTICLE INFO

Keywords:
Berberine
ZIP14
Zinc redistribution
Intestinal mucosal barrier
Sepsis
IGF-I
Tight junction

ABSTRACT

Aims: The present study investigated if berberine might induce Zrt-Irt-like protein 14 (ZIP14) and affect zinc redistribution to protect intestinal barrier in sepsis.
Main methods: Rodent model of sepsis was induced by cecal ligation and puncture (CLP). Plasma endotoxin was assayed by LAL test and plasma zinc was measured by flame atomic spectrophotometer. Gut mucosal permeability was determined by plasma FITC-dextran. Zinc content and ZIP14 mRNA in gut mucosa were assayed by spectrophotometer and qRT-PCR, respectively. Tight junction integrity of Caco-2 was evaluated by transepithelial electrical resistance (TEER). Tight junction (TJ) protein expression was detected by Western blotting.
Key findings: Berberine and zinc gluconate pretreatment to CLP rats improved survival rate, reduced plasma endotoxin level, alleviated hypozincemia, increased zinc accumulation and ZIP14 mRNA expression in the intestinal mucosa. Berberine and zinc gluconate pretreatment decreased CLP-elicited intestinal hyperpermeability to FITC-dextran. These effects of berberine in vivo were abolished by AG1024. In vitro, lipopolysaccharide (LPS) repressed zinc transfer into Caco-2 cells exposed to zinc gluconate. Berberine and IGF-I treatment increased ZIP14 protein expression and promoted zinc transfer into Caco-2 cells exposed to zinc gluconate plus LPS. Berberine treatment induced TJ protein (claudin-1 and occludin) and raised TEER in LPS-treated Caco-2 cells. These effects of berberine in vitro were partially inhibited by ZIP14 siRNA.
Significance: The present study reveals that berberine induces ZIP14 expression and affects zinc re- distribution to protect intestinal barrier in sepsis, which is partially linked with the activation of IGF-I signaling.

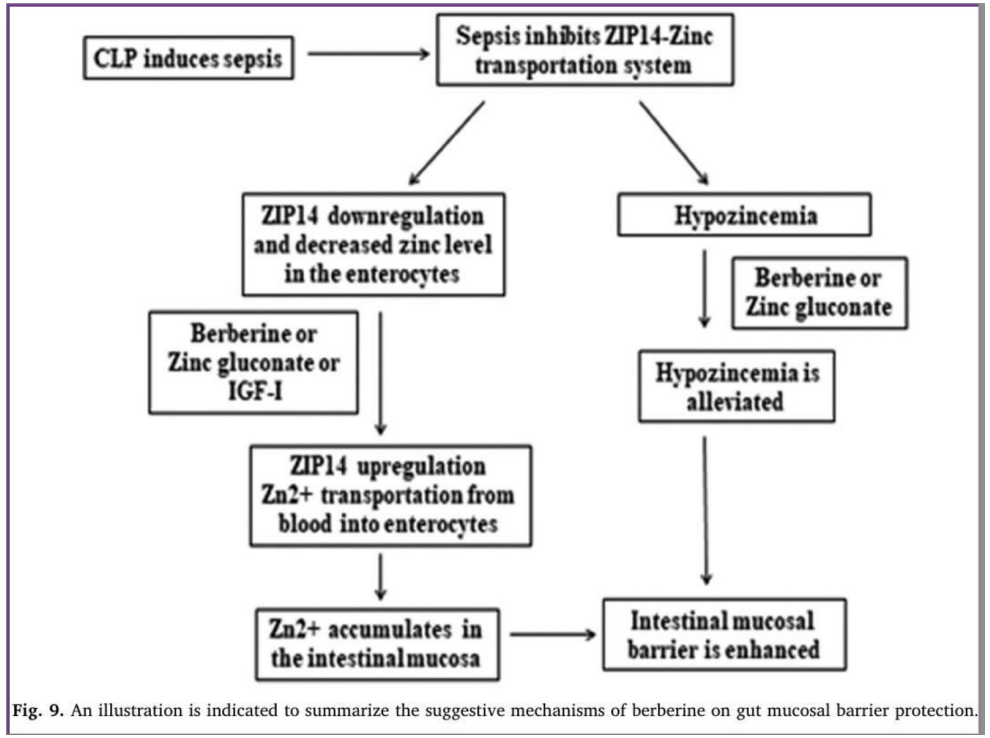


Fig. 9. An illustration is indicated to summarize the suggestive mechanisms of berberine on gut mucosal barrier protection.

Supports

- Insulin Resistance
- Antimicrobial
- Anti-inflammatory - Gut health
- Lipid metabolism

250-500mg B.I.D

Curcumin

TISSUE BARRIERS
2018, VOL. 6, NO. 1, e1425085 (13 pages)
https://doi.org/10.1080/21688370.2018.1425085

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REVIEW

Check for update

Curcumin-mediated regulation of intestinal barrier function: The mechanism underlying its beneficial effects

Siddhartha S. Ghosh, Hongliang He, Jing Wang, Todd W. Gehr, and Shobha Ghosh

Department of Internal Medicine, Virginia Commonwealth University Medical Center, Richmond, VA

ABSTRACT

Curcumin has anti-inflammatory, anti-oxidant and anti-proliferative properties established largely by in vitro studies. Accordingly, oral administration of curcumin beneficially modulates many diseases including diabetes, fatty-liver disease, atherosclerosis, arthritis, cancer and neurological disorders such as depression, Alzheimer's or Parkinson's disease. However, limited bioavailability and inability to detect curcumin in circulation or target tissues has hindered the validation of a causal role. We established curcumin-mediated decrease in the release of gut bacteria-derived lipopolysaccharide (LPS) into circulation by maintaining the integrity of the intestinal barrier function as the mechanism underlying the attenuation of metabolic diseases (diabetes, atherosclerosis, kidney disease) by curcumin supplementation precluding the need for curcumin absorption. In view of the causative role of circulating LPS and resulting chronic inflammation in the development of diseases listed above, this review summarizes the mechanism by which curcumin affects the several layers of the intestinal barrier and, despite negligible absorption, can beneficially modulate these diseases.

ARTICLE HISTORY
Received 28 November 201
Revised 15 December 2017
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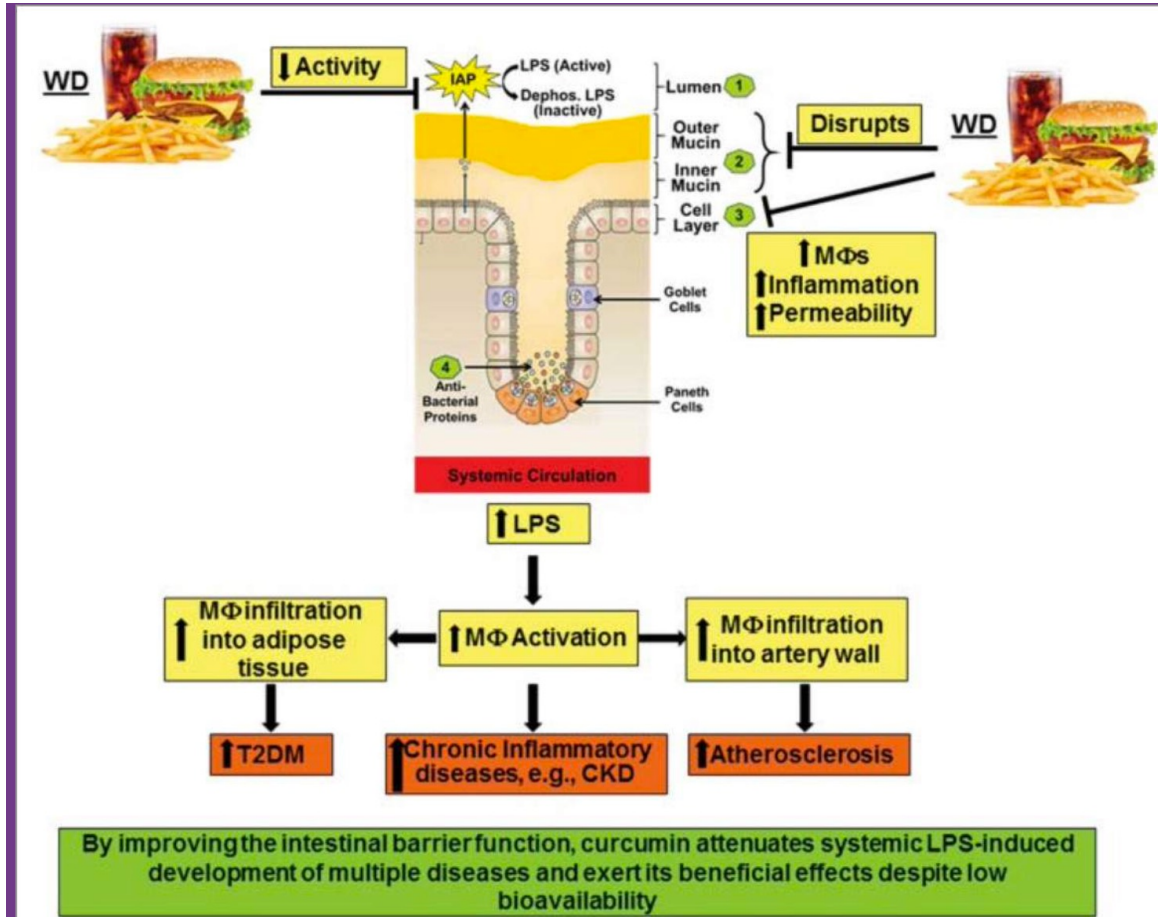
KEYWORDS
Chronic inflammation; Curcumin; Endotoxemia; Intestinal Barrier; Lipopolysaccharide; Para-cellular Transport; Tight Junctions



500 mg of Meriva b.i.d

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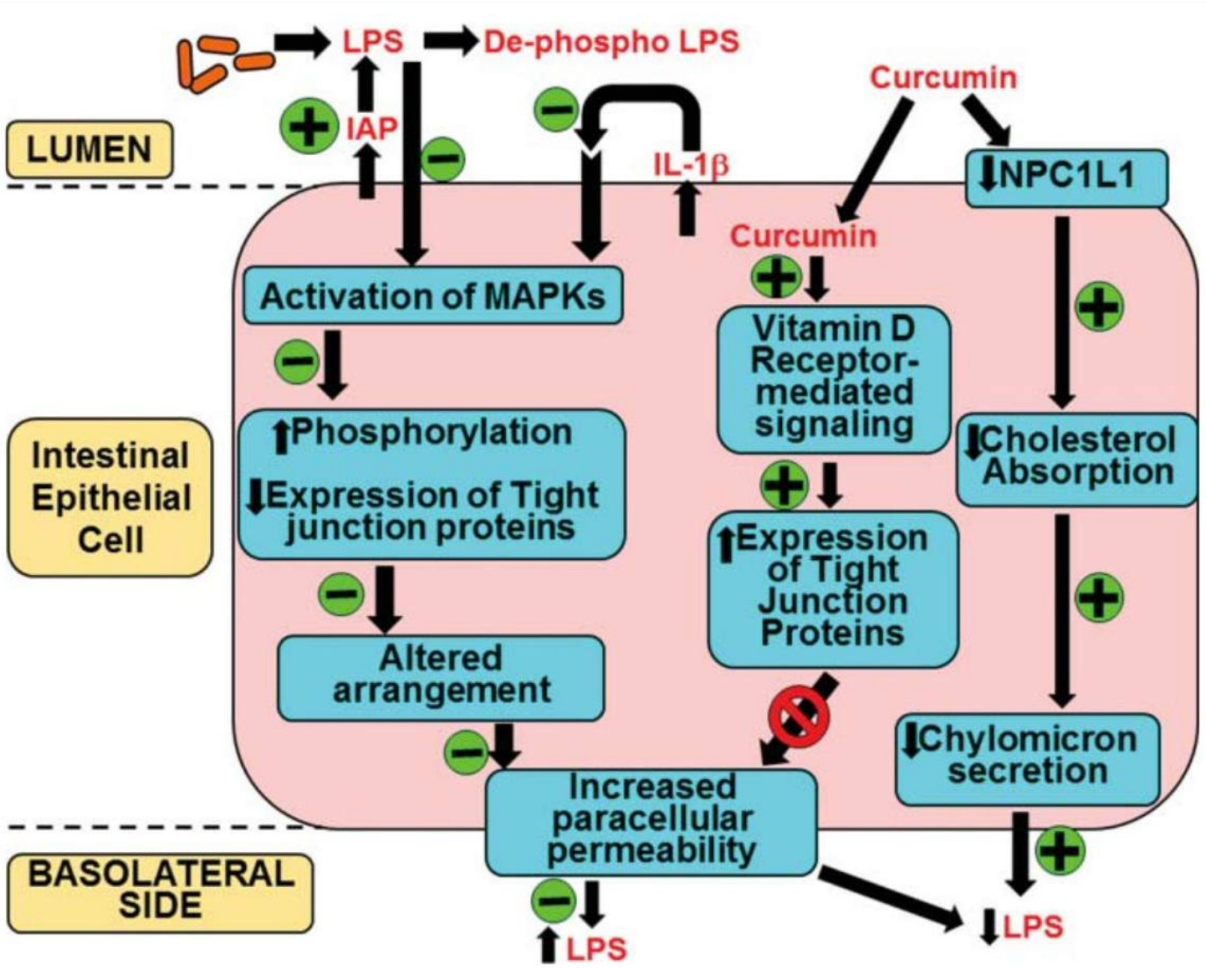
Synergistically with Vitamin D



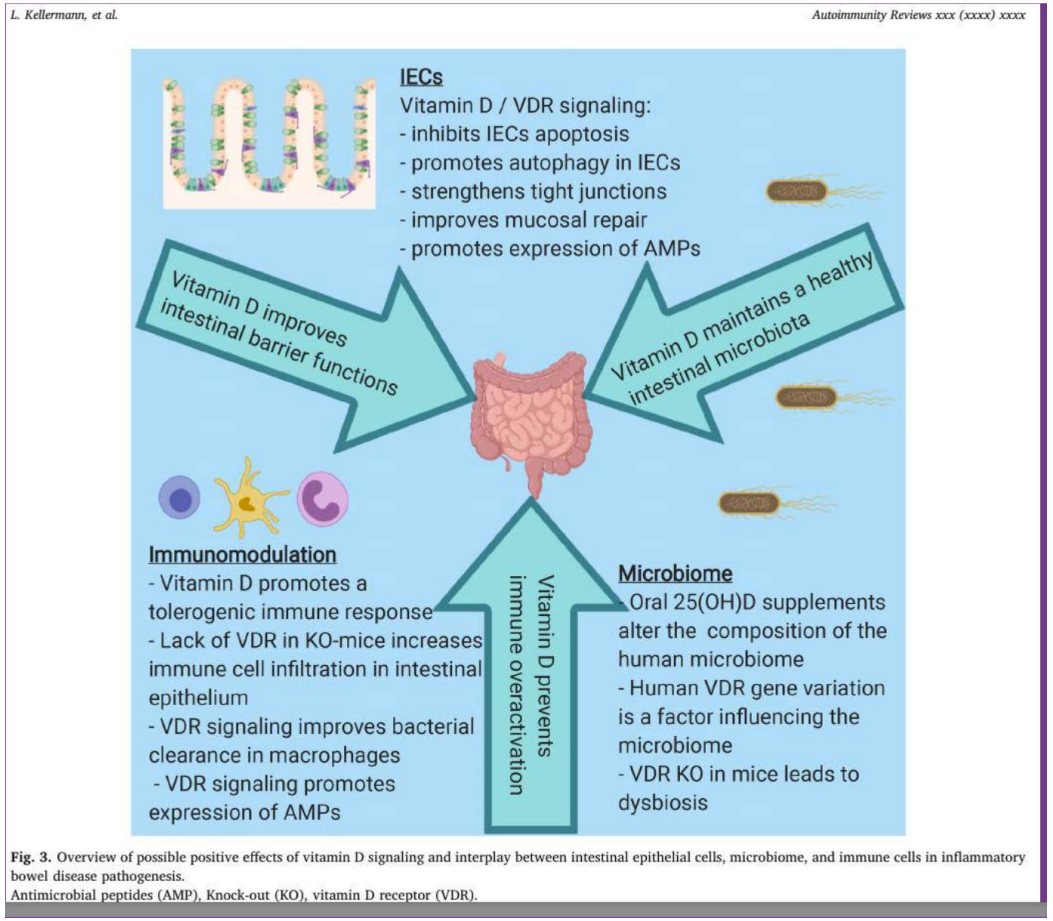


Fig. 3. Overview of possible positive effects of vitamin D signaling and interplay between intestinal epithelial cells, microbiome, and immune cells in inflammatory bowel disease pathogenesis.
Antimicrobial peptides (AMP), Knock-out (KO), vitamin D receptor (VDR).

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Summary Diseases associated

Table 3. PMID: 31076401

Summary of diseases or disorders with increased intestinal permeability and altered microbiota. In each category, it is infrequent for the altered barrier dysfunction and microbiota to be documented in the same human study.

Condition	Small Intestinal or Colonic Barrier Function		Microbiota Changes	Other Effects	Effects of Treatment
	IP probe molecules or epithelial damage	Serum biomarkers			
Aging	No difference in LMR or most TJ protein expression, but increased claudin 2 expression and decreased transepithelial resistance in ileal biopsies ex-vivo[83]	↑ zonulin[84]	↓ *Firmicutes, Bifidobacteria, Faecalibacterium prausnitzii* ↑ *Bacteroidetes, Clostridia and facultative anerobes*[85]		
Food allergy	↑ LMR 3 fold vs health[86] ↑ LMR 38% in children with food allergy[87]			Postulated mast cell and IgE-mediated increase in inflammatory cytokines[88]	Increased LMR in children with food allergy despite dietary exclusion[87]
Eosinophilic esophagitis	Increased small bowel IP based on lactulose absorption[89] but not LMR in adults[89, 90] or in children;[91] ex-vivo assessment of duodenal mucosal integrity was normal[90]		Esophageal microbiome: increased hemophilus[92] or *Neisseria* and *Corynebacterium*in in active EoE[93]	Bacterial load and TLR1, TLR2, TLR4, and TLR9 were overexpressed and mucin genes under-expressed on biopsies with active EoE[94]	No effect of elemental diet on duodenal mucosa or LMR or tight junction protein expression;[90] No effect of exclusion diets on esophageal microbiome[93]
Liver Diseases					
NAFLD/ NASH	↑ LMR or ^{51}Cr-EDTA in 39% of 139 pts with NAFLD (SRMA 5 studies)[62]	↑ LPS in 42% of NASH;[95] ↑ LPS in NAFLD associated with SIBO[96]	↑ SIBO (37.5%) in pts with NAFLD, especiallygram –ve bacteria and *E.coli*;[96] Review documents show diverse microbiota changes (variable in different studies)[97]	Increased endogenous ethanol production by gut bacteria in NAFLD[61]	
Cirrhosis			Significant microbiota change in liver cirrhosis[98]		Reduced cirrhosis severity with *Lactobacillus* and VSL#3 probiotics[64]
Sclerosing cholangitis	LRR normal [83% (19/22) with quiescent IBD][99]	Higher serum I-FABP associated with IgA antibodies against F-actin[100]	1/22 had SIBO (*Enterobacter*);[94] Enhanced mucosal immune response to various microbial antigens associated with IgA antibodies against F-actin[99]	IgA antibodies against F-actin, independent predictor of poor disease outcome [100]	
TPN or enteral deprivation	↑ FITC-Dextran I.P ex-vivo and ↓ ZO-1, E-cadherin, and claudin-4 in unfed segments in pediatric patients;[101] ↓ ZO-1 and villus height in mice[102]		Wide variability in microbial diversity in patients with small bowel resections;[103] Patients with short bowel on TPN have "lactobiota" enriched in the *Lactobacillus/ Leuconostoc* group, depleted in anaerobic micro-organisms (especially *Clostridium* and *Bacteroides*)[104]	In TPN-liver disease, microbes or LPS reaching liver and activating Kupffer cells;[105] *Lactobiota* fermentation leads to increased risk of d-encephalopathy[104]	Successful use of fecal microbial transplant for the treatment of recurrent D-lactic acidosis[106]

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Summary Diseases associated

Parkinson	Down-regulation of occludin not ZO-1 in colonic mucosa; however, flux of sulfonic acid and horseradish peroxidase not abnormal with or without Lewy bodies;[109] LMR normal, but ↑ 24h urinary sucralose (marker of total intestinal permeability)[110]	Lower plasma levels of LPS binding protein, an indirect measure of systemic endotoxin exposure[110]	Significantly more intense staining of *E. coli* in epithelium and lamina propria of sigmoid mucosa;[110] Reduced butyrate-producing bacteria from the genera *Blautia, Coprococcus* and *Roseburia*, putative "proinflammatory" *Proteobacteria* of the genus *Ralstonia* significantly more abundant in mucosa of Parkinson's patients[111]	Correlation of increased intestinal permeability in Parkinson disease with intestinal alpha–synuclein;[109] Relative abundance of *Enterobacteriaceae* positively associated with severity of postural instability and gait difficulty[112]	
ALS	↑ LPS in most severe amyotrophic lateral sclerosis[113]		Low diversity of the microbiome compared to healthy cohorts; low *Ruminococcus* spp. in 3/5 patients with low *Firmicutes/ Bacteroidetes* (F/B) ratio[114]	Decreased levels of butyrate-producing bacteria; decreased levels of micro-organisms of the genera *Oscillibacter, Anaerostipes, and Lachnospira*;[115] 3/5 patients had elevated inflammatory markers in stool[114]	
Psychiatric diseases	Plasma levels of LPS, zonulin and FABP2 were each significantly elevated in depression/anxiety patients compared to non-depressed or anxious controls.[116]		A review documents extensive literature on cross-sectional and longitudinal studies documenting association between stool microbiota and anxiety and depression.[117] A review documents studies of the microbiome and microbial translocation in patients with schizophrenia and bipolar disorder.[118]	Elevated serum IgM and IgA against LPS in depression;[119] Psychological stress increases pro-inflammatory cytokines (extensive literature reviewed in ref. 120).	Probiotics reduce depression scores in 6 randomized, placebo-controlled trials (reviewed in ref. 121).

EoE=eosinophilic esophagitis; FABP= fatty-acid binding protein; FITC=fluorescein isothiocyanate; IBD=inflammatory bowel disease; I-FABP=intestinal fatty-acid binding protein; IgA=immunoglobulin A; IP=intestinal permeability; LMR=lactulose mannitol excretion ratio; LPS=lipopolysaccharide; LRR=lactulose-rhamnose ratio; NAFLD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; SIBO=small intestinal bacterial overgrowth; TJ=tight junction; TLR=toll-like receptor; TPN=total parenteral nutrition; ZO=zonula occludens

PMID: 3107640

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PMID: 3107640

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Probiotics

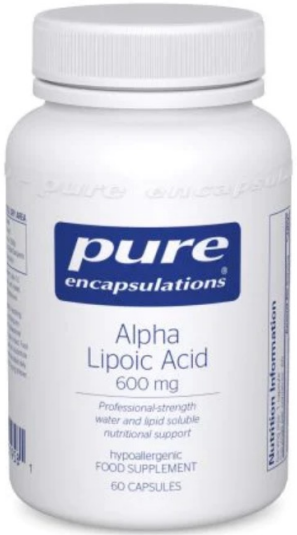

MOSS NUTRITION
Probiotic Select
25+ Billion CFUs
High Potency
Multi-Strain Formula
Dietary Supplement
120 Vegetarian Capsules
MOSS NUTRITION
Saccharomyces
boulardii
Supports Healthy Gut Flora Balance*
Dietary Supplement
120 Vegetarian Capsules
MOSS NUTRITION
BacilloSpore Select
3+ Billion CFUs
Shelf-Stable
Spore Based Probiotics
Dietary Supplement
100 Vegetarian Capsules


MICROBIOME LABS
HU58
High-Potency
Bacillus Subtilis
60
Food Supplement

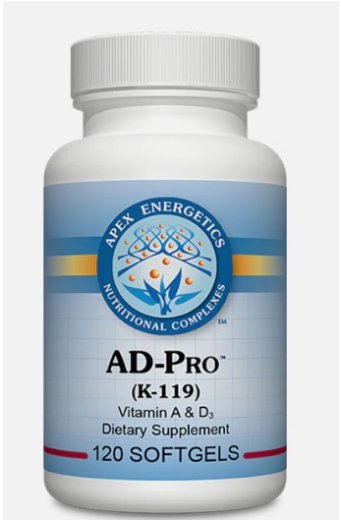

MICROBIOME LABS
RESTOR FLORA
Dual-Action
Formula For
Digestive
Support
50
Food Supplement

Nutrients

Immunomodulatory



Metabolic
Oxidative stress



Calcifediol

Antimicrobial/viral
Immunomodulatory

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Pre & Probiotic Therapy

Polyphenols
+ GOS & XOS

Polyphenols alone

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EPA & DHA

Supplement Facts
Serving Size: One teaspoon (5 ml)
Servings Per Container: 48

	Amount Per Serving	% Daily Value
Calories	40	
Calories from Fat	40	
Total Fat	4.6 g	7%*
Saturated Fat	0.8 g	5%*
Polyunsaturated Fat	1.5 g	
Monounsaturated Fat	2.3 g	
Vitamin A (as retinyl palmitate)	5000 IU	100%
Vitamin D3 (as cholecalciferol)	460 IU	115%
Omega-3 Fatty Acids	1081 mg	**
DHA (Docosahexaenoic Acid)	460 mg	**
EPA (Eicosapentaenoic Acid)	345 mg	**
Other Omega-3s	276 mg	**

* Percent Daily Values are based on a 2000 calorie diet.
** Daily Value not established.

3500 mg	
2000 mg	EPA
1000 mg	DHA
200 mg	
300 mg	
17 mg	

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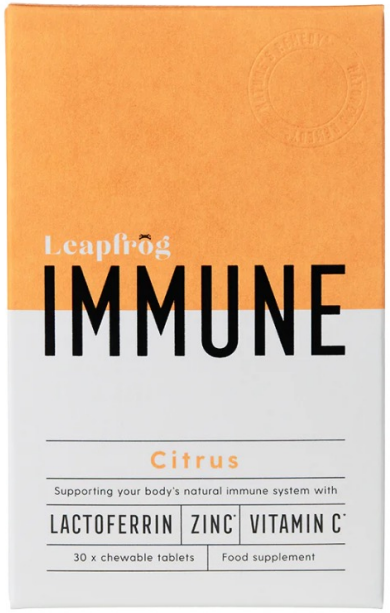
Nutrients: super sensitive folk



Zn carnosine + Glutamine

Zinc (as zinc carnosine)	15 mg	136%
L-Glutamine	2240 mg	†
Zinc Carnosine	140 mg	†
Proprietary Blend:	375 mg	†
DPP IV Peptidase Blend (protease I, II, III, IV, V), Amylase I, Amylase II, Glucoamylase, Lactase, Alpha-galactosidase, Papain, Bromelain, Lipase, Cellulase.		

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Glutamine & Herbs

Supplement Facts
Serving Size: 5.3 grams (1 heaping scoop)
Servings Per Container: 30

	Amount Per Serving	% Daily Value
L-Glutamine	1500 mg	**
N-Acetyl Glucosamine	1000 mg	**
MSM (methylsulfonylmethane)	200 mg	**
Aloe Vera Gel inner leaf (200:1) (*Aloe barbadensis*)	200 mg	**
Quercetin	125 mg	**
C3 Reduct® (*Curcuma longa* extract; 95% tetrahydrocurcuminoids)	100 mg	**
Slippery Elm bark powder (*Ulmus rubra*)	100 mg	**
Marshmallow root powder (*Althaea officinalis*)	100 mg	**
GutGard™ Deglycyrrhizinated Licorice root extract (*Glycyrrhiza glabra*)	75 mg	**

Vitamin A (palmitate)	300 mcg RAE
Vitamin E (as d-alpha tocopherol succinate)	67 mg
Folate (as [6S]-5-Methyltetrahydrofolate, calcium salt)	400 mcg
L-Glutamine	1000 mg
N-Acetyl Glucosamine	500 mg
Okra powder (*Abelmoschus esculentus*)	300 mg
Cat's Claw inner bark (*Uncaria tomentosa*)	300 mg
Aloe Vera inner leaf gel (200:1) (*Aloe barbadensis*) (5% polysaccharides)	200 mg
Quercetin Dihydrate	100 mg
Sodium Butyrate	100 mg
Gamma Oryzanol	75 mg
Zinc-L-Carnosine (providing 4.5 mg elemental zinc)	37.5 mg

IBD & inflammatory picture
& H.pylori

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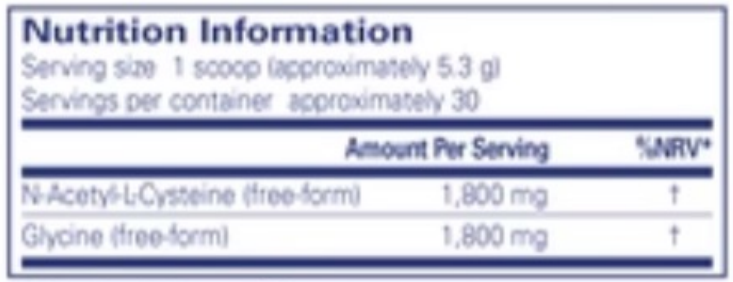
Immunoglobulins & Amino Acids

IgY Max- egg shell

Bovine immunoglobulins



Nutrition Information

Serving size 1 scoop (approximately 5.3 g)
Servings per container approximately 30

	Amount Per Serving	%NRV*
N-Acetyl-L-Cysteine (free-form)	1,800 mg	†
Glycine (free-form)	1,800 mg	†

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Collagen

Marine- type 1
+vitamin C

Bovine

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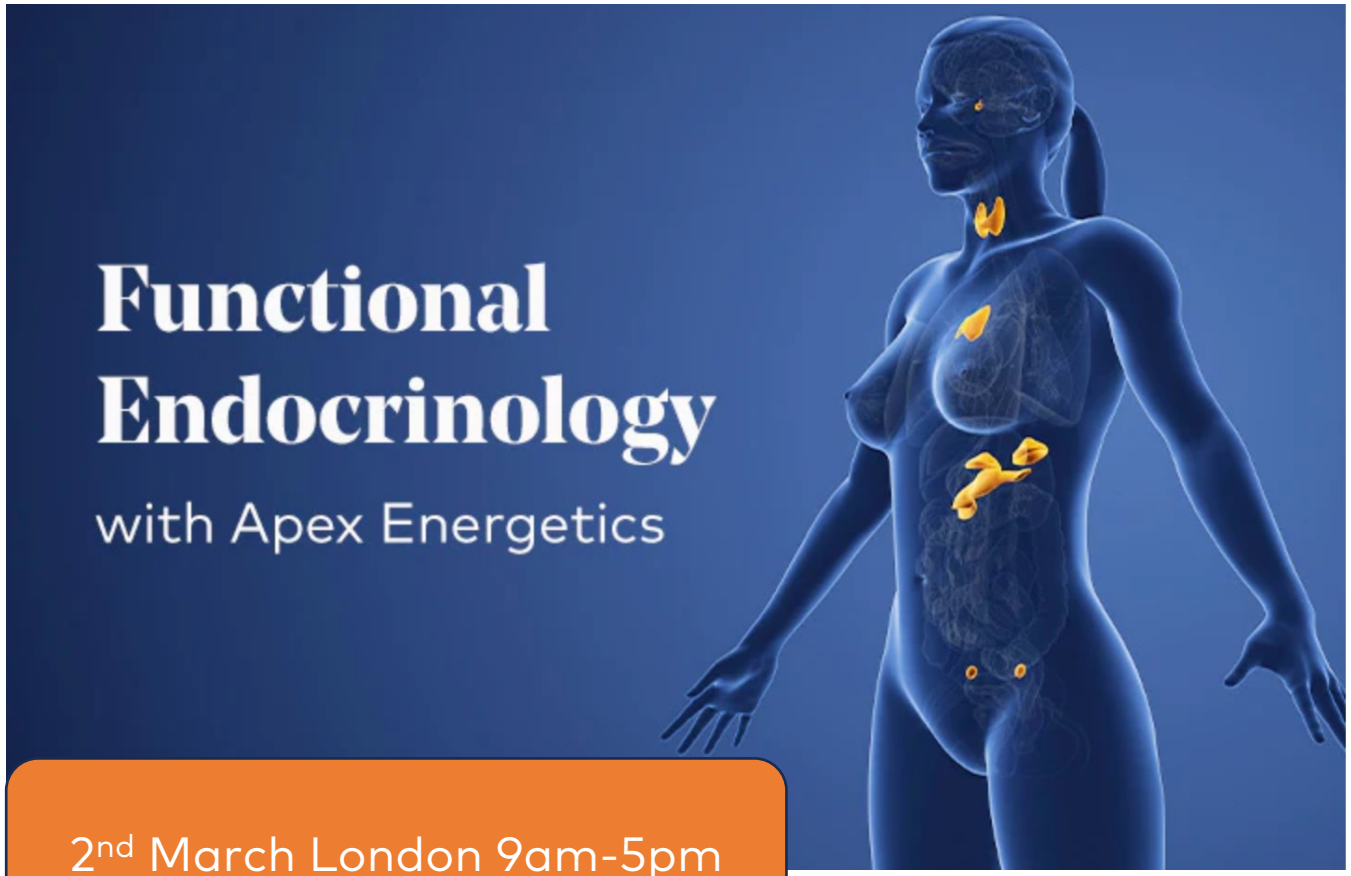
Curcumin


MOSS
NUTRITION
CurcuSelect
MERIVA
Optimum Curcumin Absorption
from Indena Phytosome™ Technology
Dietary Supplement
120 Vegetarian Capsules


TURMERO
ACTIVE
(K-75)
Liquid Herbal
Dietary Supplement
8 fl oz (236 mL)

What's coming



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