Commentary

# Candida and Long Covid

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**The pandemic has supercharged growing awareness of the gut microbiome and the gut-brain-axis as determinants of human health. Zonulin, a circulating protein that increases intestinal and endothelial permeability, has emerged as a central player. This protein can be activated by proteases secreted by Candida, opening the door to myriad autoimmune and other chronic diseases. Many of these are seen in long Covid (LC). Candida hyphal walls express proteins that are analogous to gliadin/gluten (celiac disease antibodies) and that are GPCRs, e.g., Crohn's disease antibodies present only in eukaryotes that trigger anti-gliadin and anti-GPCR autoantibodies respectively. These two autoantibody producing pathways both activate zonulin and may encompass the broad spectrum of autoimmune diseases seen in LC. The spike protein S on SARS CoV2 can attach to both ACE2 receptor and Toll-like receptor4 (TLR4) bearing cells. The latter can also activate zonulin. A hypothetical pathophysiologic model is proposed implicating Candida overgrowth, aggravated by Covid-19, in not only the genesis of LC but also that of autoimmune disease, dementia, cancer, many chronic diseases, and aging.**

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## 1. Introduction

There has been an explosion of autoimmune diseases (see Figure 1) over the last half century.

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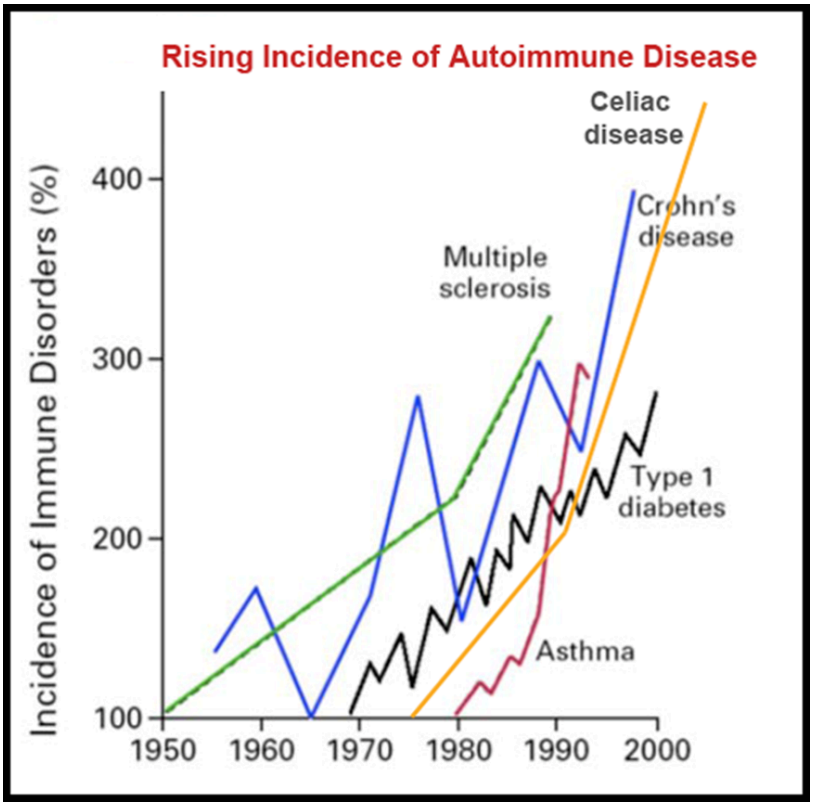


**Figure 1.** The incidence of autoimmune disease has exploded since the mid 1900s for both Crohn's disease (anti-GPCR antibody) and celiac disease (anti-gluten antibody). Source: Alessio Fasano, MD, Center for Celiac Research, Massachusetts General Hospital.

A dysbiotic gut microbiome appears to be the culprit, mediated by loss of intestinal and endothelial barrier integrity. Zonulin, discovered in 2000 by Alessio Fasano and his research team, is the primary regulator of this barrier integrity. Initially bacterial toxins in the gut microbiome were proposed as the source of the zonulin induced increase in intestinal permeability. But recently the mycobiome has come under closer scrutiny in this regard. Although a genetic predisposition to upregulation of zonulin is undeniable, focus has shifted to more controllable inputs. The zonulin hypothesis has been proposed[1]. It posits that SARS CoV2, which can bind TLR4, activates zonulin, as can IL-6 and gliadin[2]. Zonulin in turn activates complement. But does the virus act alone in the devolution of Covid-19 to LC? How are the gender disparities reconciled? Why is the range of LC symptoms so vast and why are explanatory linkages so elusive? Might LC, classified as an autoimmune disease by the Autoimmune Registry, be the consequence of an upsurge in anti-GPCR autoantibodies. Multiple international symposia have targeted


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this phenomenon[3]. Anti-CXCR3[4], anti-AT1Rs, and anti-β2 adrenergic receptors, frequently encountered in long haulers[5] are all anti-GPCRs.

**Hypothetical Model** (see Figure 2)

1. Commensal Candida overgrowth and transition to pathogenic hyphae can be both cause and effect of gut dysbiosis (imbalanced gut microbiome).
2. Candida hyphae secrete proteases that activate PAR2 protease activated receptors (PAR2s) and zonulin receptors on enterocytes and endothelial cells, increasing their permeability[6]
3. Zonulin and its permeability enhancing properties enable paracellular hyphal invasion into the microcirculation
4. Enhanced zonulin mediated BBB permeability facilitates neuroinflammation[7]
5. Candida hyphae contain two highly immunogenic surface epitopes, gluten-like Hwp1 (hyphal wall protein) and numerous GPCRs, present only on eukaryotes
6. These epitopes trigger either gluten/gliadin (celiac type) autoimmune disease phenotypes or GPCR (Crohn's type) autoimmune disease phenotypes
7. Persistent spike protein S binds to TLR4[8] on intestinal and endothelial cells, activating zonulin receptors[1]
8. Antibodies to host AT1Rs, β2 adrenergic receptors[5], and CXCR3[4] characterize LC. All are anti-GPCR antibodies.
9. Anti-CXCR3 antibodies (LC) compromise T-cell function, mediating autoimmunity and cancer[9]

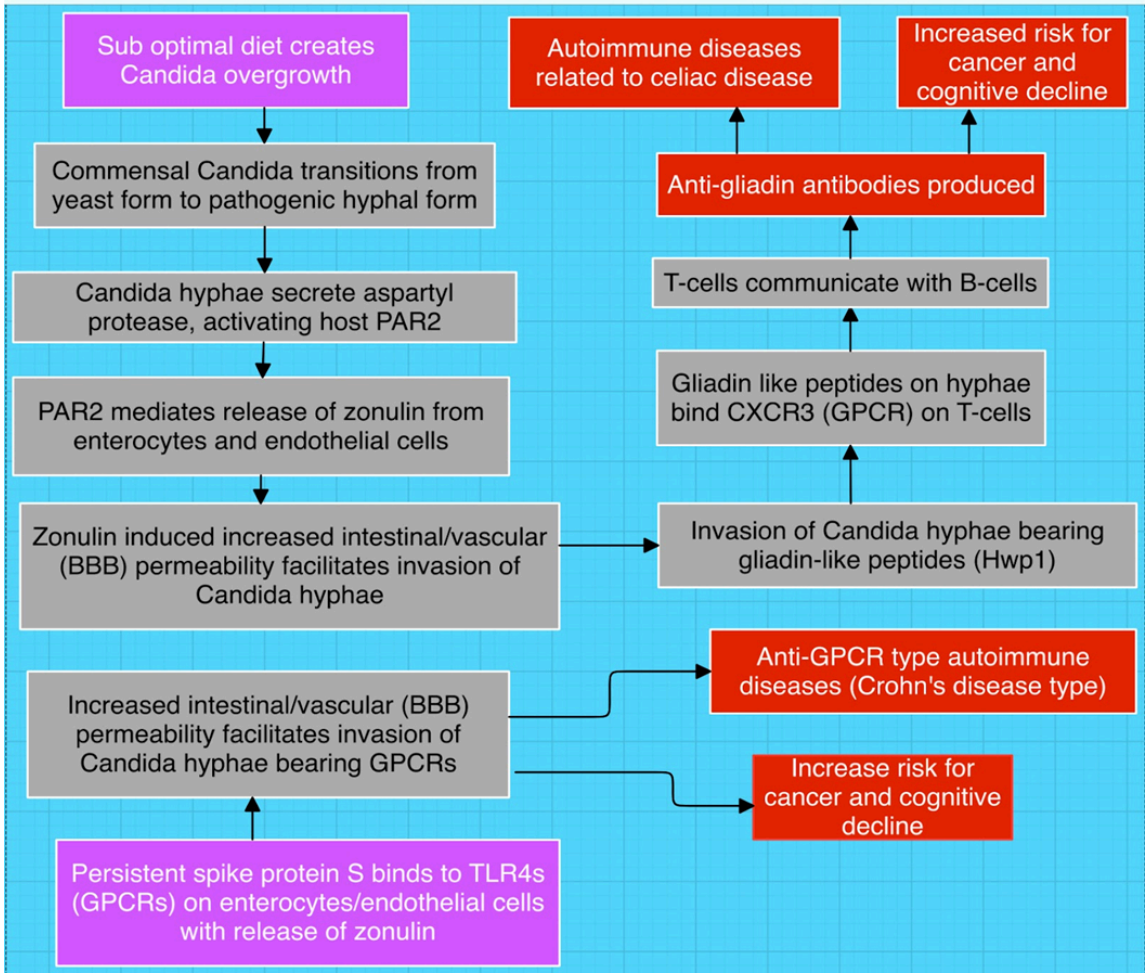


**Figure 2.** Anti-Hwp1 (gliadin-like) antibodies, similar to those seen in celiac disease, may mediate the predominant autoimmune disease phenotypes seen in females, while anti-GPCR antibodies, similar to those seen in Crohn's disease, may mediate the predominant autoimmune disease phenotypes seen in males.

## 2. Zonulin and Increased Permeability

Zonulin is the only known physiologic modulator of intercellular TJs[10]. Activated PAR2 and zonulin receptors increase intestinal and endothelial permeability[11]

### *A. Autoimmune Disease*

Zonulin release is linked to autoimmune diseases, both those associated with gluten sensitivity (anti-gliadin antibodies), e.g., celiac disease, RA, SLE, T1DM, ankylosing spondylitis[12] and those associated

with Anti-Saccharomyces cerevisiae antibodies (ASCAs)[13], e.g., Crohn's disease, autoimmune vasculitis, IgA nephropathy[11][14]. All are reported in LC.

ASCAs are anti-GPCRs[15] and are elevated in inflammatory bowel disease (IBD), especially Crohn's disease, but not in celiac disease[13]. Celiac patients have higher IgA anti-gliadin antibodies than controls or IBD patients[16]. Both autoantibody types trigger an increase in zonulin

### *B. Dementia*

Brain endothelial cells express zonulin receptors and exposure of BBB to zonulin leads to increased permeability[7]. IL-17, biomarker for autoimmune disease[17] and IFN-gamma, biomarker for LC[18], also elevate zonulin.

Zonulin is elevated in AD[19] and PD[20][21]

### *C. Cancer*

Elevated zonulin has been linked to numerous cancers, including CRC[22][23] and breast, lung, ovary, pancreas, brain (gliomas)[12], and liver cancers[24].

### *D. Other Diseases*

Zonulin is directly linked to other diseases, e.g., overweight and obesity, at least in the young[25][26], MS, schizophrenia[24][27], autism[24][28] and arthritis[29]

## 3. Celiac Disease and Crohn's Disease

### *A. Celiac Disease*

Zonulin is a biomarker for celiac disease[30], a well described autoimmune disease encountered in LC and linked to antigliadin antibodies. These have high sensitivity and specificity for celiac disease[31]. Anti-gliadin antibodies are present in 5-12% of the general population and are a hallmark of celiac disease. They are also encountered in rheumatoid arthritis, Sjögren's syndrome, sarcoidosis[32], T1DM, multiple sclerosis (MS), psoriasis, Grave's disease, Hashimoto's thyroiditis[33], and rarely IBD. Rheumatoid arthritis[34], Sjögren's Syndrome[35], Sarcoidosis[36] are all associated with celiac disease. Other autoimmune diseases associated with celiac disease include T1DM[37], SLE, systemic sclerosis[38], Grave's

disease[39], Hashimoto's thyroiditis[40], and autoimmune hepatitis[41]. All are seen in LC. Many skin diseases expressing anti-gliadin antibodies are linked to celiac disease and reported in LC. These include psoriasis[42], alopecia areata[43], vitiligo[44], and dermatitis herpetiformis. Gliadin triggers T-cell mediated immunity in celiac disease[45]. There is minimal overlap with IBD, as about 4% of those with celiac disease have IBD[46].

### *B. Crohn's Disease*

Anti-Saccharomyces cerevisiae antibodies (ASCAs) are biomarkers for IBD, especially Crohn's disease. They are anti-GPCR antibodies[13] and can also be generated by Candida albicans[47]. CXCR3 is another GPCR with autoantibodies seen in both Crohn's disease[48] and LC[4]. Crohn's disease, increased in LC and linked to ASCAs (anti-GPCRs), is associated with greater risks for colon cancer, liver cancer, lymphoma, melanoma, squamous cell skin cancer, and cancers of lung and bladder[49]. CXCR3 on T cells help suppress cancer[50].

## 4. Candida

### *A. Gender*

Females with autoimmune disease outnumber males (4:1). This may be due to their robust production of interferons, especially IFN-gamma, and the estrogen enabled immune evasion of Candida. One study[51] of 600,000$^{+}$ vaccine-naive, PCR-confirmed Covid-19 individuals demonstrated a significant increase in autoimmune disease within 3-15 months. But surprisingly the highest rates for recent onset were found for vasculitides, which are somewhat rare. Furthermore, although females are more susceptible to autoimmune disease, including LC, the incidence of autoimmune vasculitides in those with LC was higher in males. For example, IgA nephropathy has been reported post Covid-19 and post Covid-19 vaccine[52] and IgA vasculitis has been reported in LC[53] and possibly in Covid toes[54]. IgAN and IgA vasculitis are mediated by IgA antibodies to endothelin receptors. Endothelin receptors are GPCRs. These two autoimmune diseases predominate in males, 4:1 for IgAN[55] and 2:1 for IgA vasculitis[56]

Although the LC autoimmune response was more prominent in women following asymptomatic infection, the range and extent of expression in males correlated more with severity of Covid-19[57]. Autoantibodies targeting GPCRs and RAS-related molecules associate with Covid-19 severity, seen

primarily in males[4], is directly related to TGF-beta without an autoimmune component[58]. TGF-beta plays a critical role in the microvascular space[59]. Estrogen depresses endothelin synthesis[60], which may provide protection against autoimmune vasculitides. SARS CoV2 in females may be more autoimmune and IFN-gamma related, while in males it may be more vascular/connective tissue and TGF-beta related (thrombosis and fibrosis). This may hypothetically put female long haulers at slightly greater risk for dementia and male long haulers at slightly greater risk for cancer.

### *B. Epitopes and GPCRs*

An epitope or antigenic determinant is the locus on an antigen that is particularly immunogenic. Expression of surface amino acid sequences on Candida hyphae analogous to the gluten protein gliadin (celiac disease) was first reported in 2015[61][62]

Indeed celiac disease might serve as a partial proxy for Candida overgrowth and invasion. Candida hyphae secrete aspartyl protease that activates surface PAR2, an ubiquitous receptor on host cells. It is also known as coagulation factor II (thrombin) receptor-like 1 (F2RL1)[6]. PAR2 is a GPCR linked to zonulin receptors that, when activated, upregulates zonulin and may jointly mediate associated autoimmunity by enabling an invasive pathway for exposure to CXCR3 bearing T-cells.

Furthermore, GPCR laden hyphae may via this same zonulin enabled pathway induce a spectrum of autoimmune diseases. This interpretation is supported by the concomitant surge in both anti-GPCR mediated autoimmunity[3] (Crohn's disease) and Hwp1 linked celiac disease[63] (see Figure 1).

Candidemia can also trigger ASCAs[64], tightly linked to Crohn's disease[13]. Consequently anti-Hwp1 antibodies and ASCAs link Candida to both celiac disease[47] and Crohn's disease.

In a study of 33 patients with a variety of inflammatory and autoimmune diseases 60% of those with an elevated zonulin tested positive for yeast overgrowth[65]. Linkage between zonulin and yeast overgrowth provides additional support for an etiologic Candida-LC coupling.

However, a causative Candida connection to the autoantibodies in LC/autoimmune disease remains theoretical.

## 5. LC and Autoimmune diseases

### *A. The Candida Connection*

Zonulin and β-glucan, a marker for translocation of fungal products into circulation, are elevated in individuals with long Covid[66]. Fungal but not bacterial translocation was observed during LC[67]. In mice amyloid beta is a marker for CNS Candida hyphal forms[68]. Hippocampal amyloid beta is tightly linked to Alzheimer's disease. This Candida-LC coupling is further supported by the generation of anti-GPCRs in animals infected with SARS CoV2[69]. Although Covid-19 has accelerated cognitive decline, the incidence of AD and PD in long haulers over the long term remains to be seen.

### *B. Spike S and TLR4*

The spike protein (viral or vaccine) of SARS CoV2 activates TLR4, another GPCR[8]. Activated TLR4 on enteric and endothelial cells activates zonulin, enhancing their permeability[1] (see Figure 2).

Since TLR4 is present on the spike protein S (viral or vaccine), the risk for zonulin induced autoimmune disease and cancer may be elevated regardless. Neuroinflammation in LC may be mediated by persistent spike protein that directly activates epidermal growth factor receptors (EGFRs)[70] by anti-EGFR antibodies, or by translocated Candida hyphae. The CNS is rich in EGFRs, which are GPCRs. These receptors and their ligands support a pathogenic model for LC involving Candida induced autoimmune disease. Several pathways may be involved, e.g. TLR4/GPCR related (Crohn's type) in males, especially autoimmune vasculitis, and gluten/Hwp1 related (celiac type) in females, e.g., T1DM, RA, and non-celiac gluten sensitive autoimmune diseases, e.g., SLE, autoimmune thyroiditis, 50% of which express anti-gliadin antibodies[71].

## 6. IFN-gamma and Butyrate

Females are robust producers of interferon, especially IFN-gamma. Candida elicits robust production of this cytokine, a ligand for zonulin receptors, according to a recent study[72]. Upregulated IFN-gamma can potentially increase intestinal and endothelial permeability. Butyrate immuno-modulates IFN-γ[73]

and TGF-beta (transforming growth factor), which are reciprocals and counterbalance each other[74][75]. TGF-β regulates tolerogenesis; too little (too much IFN-γ) and self antigens targeted, too much and tumor antigens are not targeted. This may be why autoimmune disease/dementia are slightly more common in

females (asymptomatic Covid-19) and cancer is slightly more common in males (severe Covid-19, elevated TGF-beta). Butyrate, a postbiotic, also stimulates the release of glucagon-like peptide (GLP-1). Ozempic, the popular weight loss drug, is a GLP-1 agonist, and obesity is directly linked to zonulin. D-mannose, a prebiotic and fiber substitute, opposes zonulin[29] (see Figure 3).

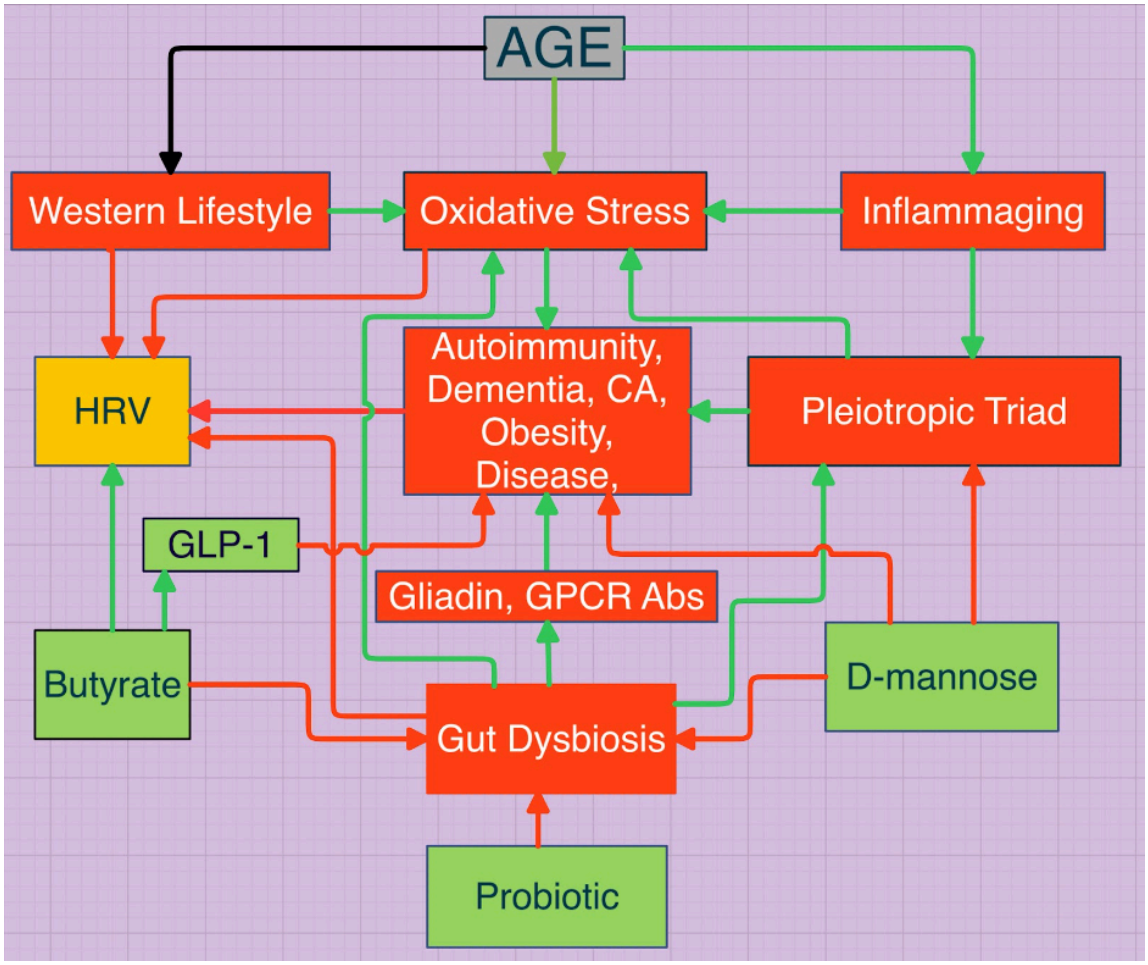


**Figure 3.** A prebiotic, probiotic, postbiotic approach may slow the inevitable age related decline in lifespan and healthspan, directly to heart rate variability (HRV). The pleiotropic triad is IL1-beta, TNF-alpha, and IL-6.

## 7. Conclusion

The commensal Candida has been a quiet member of the human microbial community for many millennia. But a potential Jekyll and Hyde pathogenic hyphal transformation has always lurked in the shadows, arising when opportunity presents. Deterioration of the modern diet must be at the top of that list, first recognized by Hippocrates over 2400 years ago.

LC is responsible for untold pain and suffering. But a micronutrient approach may alleviate much of this.

1. Vitamin D, so frequently deficient, provides many benefits, especially for Crohn's type autoimmune disease[40]. For example, D3[76] (and tryptophan[77]) inhibit hyphal transition.
2. Ca:Mg is too high in the typical Western diet and too low in the typical Asian diet; $Ca^{[2]+}$ may upregulate zonulin[78]. $Mg^{[2]+}$ is a calcium antagonist, glutamate NMDA receptor blocker, vasodilator, antioxidant, and anti-inflammatory agent. It also opposes Candida immune evasion[79]. Elevated $Ca^{[2]+}$ compromises mitochondrial function[80]. Magnesium impairs Candida albicans immune evasion[79]. Candida subsists on refined sugar and alcohol. Accordingly Candida overgrowth can elevate acetaldehyde (brain fog), which is degraded in mitochondria by an enzyme that requires magnesium as cofactor. Oxidative stress consumes antioxidants and compromises mitochondrial function. $Mg^{[2]+}$ deficiency mimics symptoms of aging[81], as do GPCR antibodies[82] and TLR4 activation[83]
3. Alpha lipoic acid is a strong anti-oxidant, immuno-modulates autoimmune disease[84] and can arrest the growth of Candida albicans[85]
4. A triple play of prebiotic, probiotic, and probiotic regimen addresses many modern maladies[86] (see Figure 3). Butyrate (postbiotic) inhibits yeast growth[87]. D-mannose, a prebiotic and fiber substitute, supports intestinal barrier integrity (see Figure 3). Our food should be our medicine and our medicine should be our food (Hippocrates). The "good bacteria" Bifidobacterium and Lactobacillus (butyrate producers) suppress intestinal release of zonulin levels, whereas other primarily Gram-negative bacteria induce zonulin release[72].
5. Exercise reversibly improves the gut microbiome[88]. Walking is a man's best medicine (Hippocrates).

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