

REVIEW

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Intestinal permeability – a new target for disease prevention and therapy

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Abstract

Data are accumulating that emphasize the important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In the present review, current knowledge on mucosal barrier and its role in disease prevention and therapy is summarized. First, the relevant terms 'intestinal barrier' and 'intestinal permeability' are defined. Secondly, the key element of the intestinal barrier affecting permeability are described.

The effect of diet on intestinal permeability is dependent on individual factors such as the host's genetic susceptibility, and also on the intestinal microbiota.

means vary enormously and probably assess different functional components of the barrier. The barrier assessments are further hindered by the natural variability of this functional entity depending on species and genes as well as on diet and other environmental factors. In the final part, we discuss selected diseases associated with increased intestinal permeability such as critically illness, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and – more recently recognized – obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host. In summary, intestinal permeability, which is a feature of intestinal barrier function, is increasingly recognized as being of relevance for health and disease, and therefore, this topic warrants more attention.

Keywords: Intestinal barrier, Intestinal permeability, Obesity, Inflammatory bowel disease, Irritable bowel syndrome, Prebiotics, Probiotics, Gut health

A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

- Avoid inflammatory triggers
- Include Dietary Selections That Heal Intestinal Permeability
 - Vegetables (esp for their soluble fiber = SCFA production)

Terry Wahls, MD = 12 cups vegetables/day



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Article

Apple-Derived Pectin Modulates Gut Microbiota, Improves Gut Barrier Function, and Attenuates Metabolic Endotoxemia in Rats with Diet-Induced Obesity

Tingting Jiang ^{1,†}, Xuejin Gao ^{1,†}, Chao Wu ¹, Feng Tian ¹, Qiucheng Lei ^{1,2}, Jingcheng Bi ¹, Bingxian Xie ³, Hong Yu Wang ³, Shuai Chen ^{3,*} and Xinying Wang ^{1,*}

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Another important protein for gut barrier function is intestinal alkaline phosphatase (IAP).

Abstract: This study was aimed at determining potential effects of apple-derived pectin on weight gain, gut microbiota, gut barrier and metabolic endotoxemia in rat models of diet-induced obesity. The rats received a standard diet (control; Chow group; $n = 8$) or a high-fat diet (HFD; $n = 32$) for eight weeks to induce obesity. The top 50th percentile of weight-gainers were selected as diet induced obese rats. Thereafter, the Chow group continued on chow, and the diet induced obese rats were randomly divided into two groups and received HFD (HF group; $n = 8$) or pectin-supplemented HFD (HF-P group; $n = 8$) for six weeks. Compared to the HF group, the HF-P group showed attenuated weight gain (207.38 ± 7.96 g vs. 283.63 ± 10.17 g, $p < 0.01$) and serum total cholesterol level (1.46 ± 0.13 mmol/L vs. 2.06 ± 0.26 mmol/L, $p < 0.01$). Compared to the Chow group, the HF group showed a decrease in Bacteroidetes phylum and an increase in Firmicutes phylum, as well as subordinate categories ($p < 0.01$). These changes were restored to the normal levels in the HF-P group. Furthermore, compared to the HF group, the HF-P group displayed improved intestinal alkaline phosphatase (0.57 ± 0.20 vs. 0.30 ± 0.19 , $p < 0.05$) and claudin 1 (0.76 ± 0.14 vs. 0.55 ± 0.18 , $p < 0.05$) expression, and decreased Toll-like receptor 4 expression in ileal tissue (0.76 ± 0.58 vs. 2.04 ± 0.89 , $p < 0.01$). The HF-P group also showed decreased inflammation (TNF α : 316.13 ± 7.62 EU/mL vs. 355.59 ± 8.10 EU/mL, $p < 0.01$; IL-6: 51.78 ± 2.35 EU/mL vs. 58.98 ± 2.59 EU/mL, $p < 0.01$) and metabolic endotoxemia (2.83 ± 0.42 EU/mL vs. 0.68 ± 0.14 EU/mL, $p < 0.01$). These results suggest that apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

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IAP is a type of glycoprotein anchored in the apical membrane of enterocytes.

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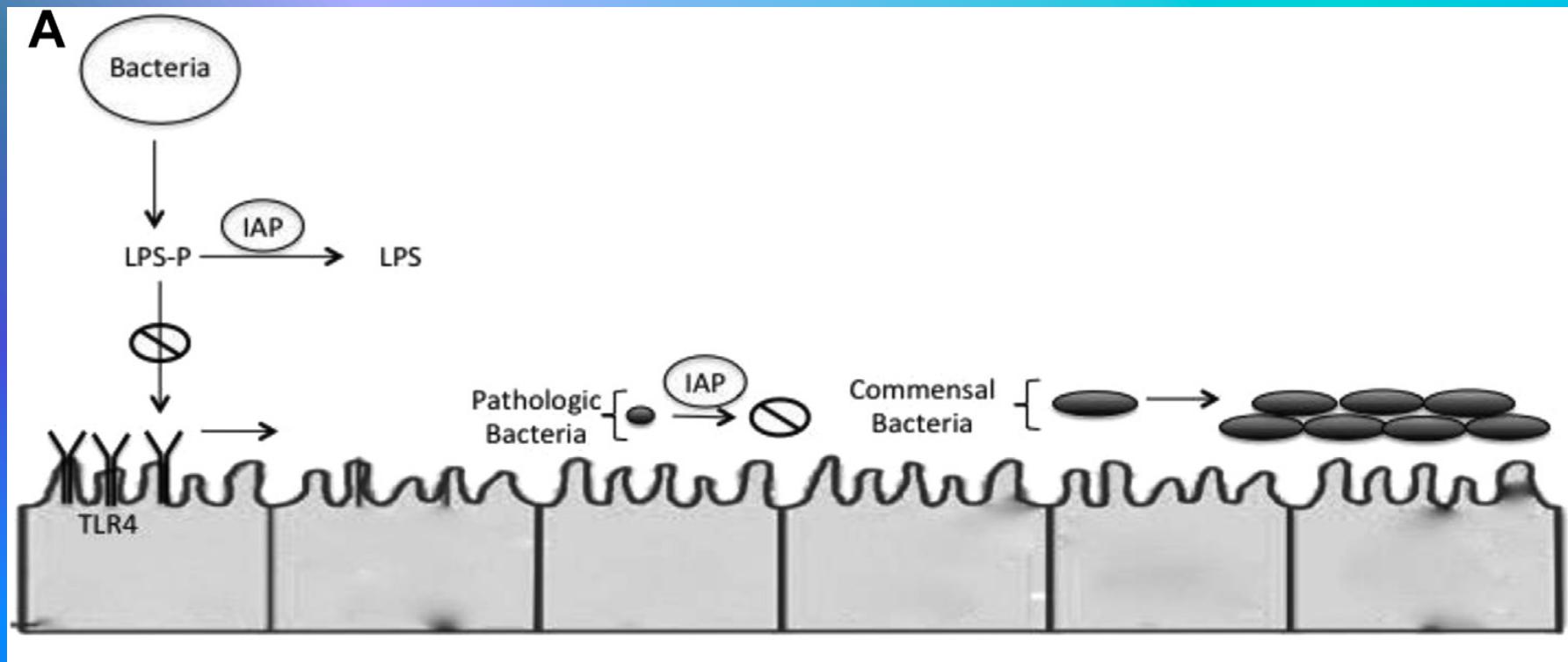
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IAP has multiple roles in maintenance of gut barrier, including:

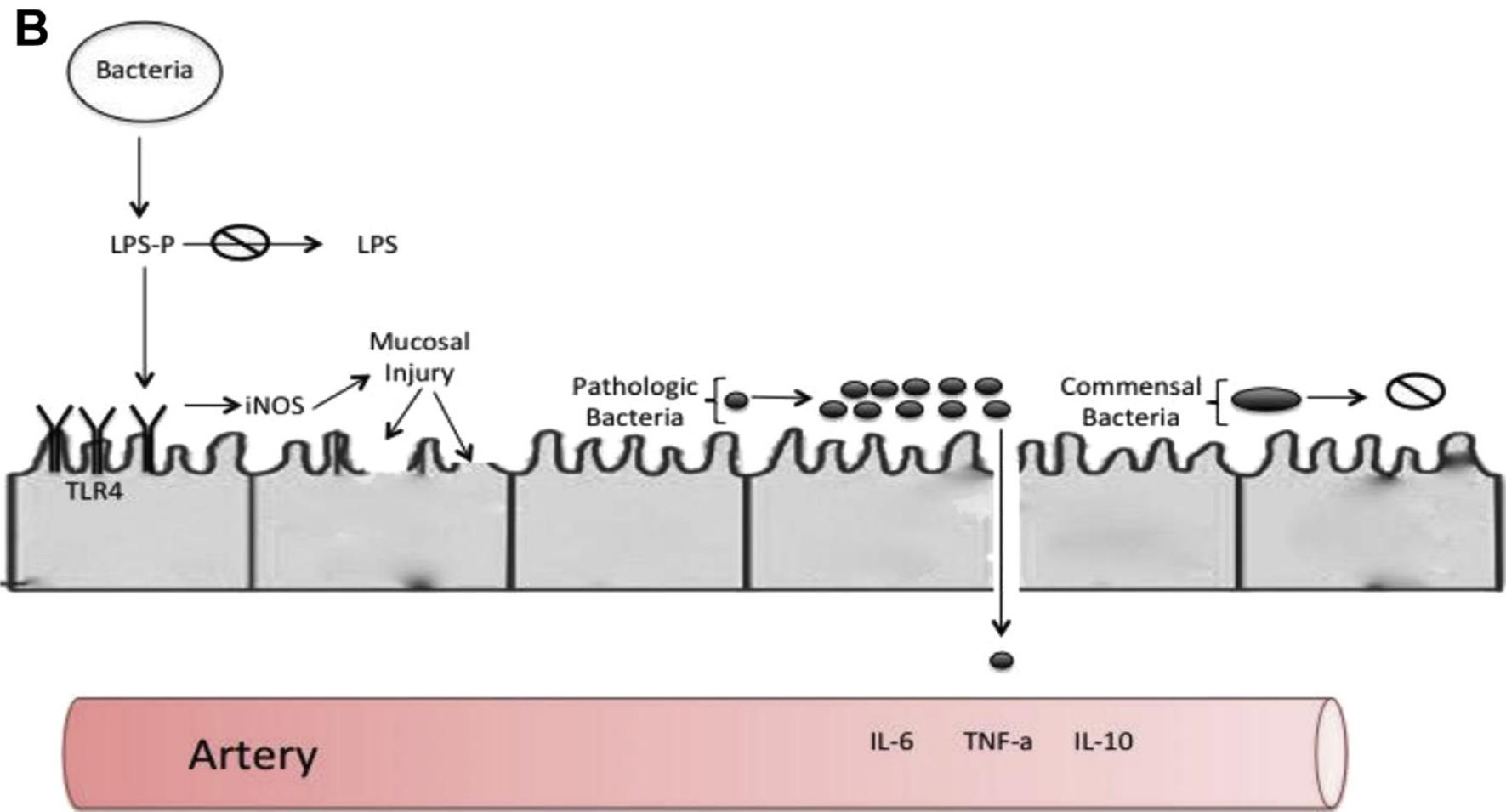
- detoxification of LPS,
- remission of systemic inflammation,
- protection of gut barrier function and
- modulation of gut microbiota

attenuated weight gain (20.50 ± 7.90 g vs. 205.65 ± 10.17 g, $p < 0.01$) and serum total cholesterol level (1.46 ± 0.13 mmol/L vs. 2.06 ± 0.26 mmol/L, $p < 0.01$). Compared to the Chow group, the HF group showed a decrease in Bacteroidetes phylum and an increase in Firmicutes phylum, as well as subordinate categories ($p < 0.01$). These changes were restored to the normal levels in the HF-P group. Furthermore, compared to the HF group, the HF-P group displayed improved intestinal alkaline phosphatase (0.57 ± 0.20 vs. 0.30 ± 0.19 , $p < 0.05$) and claudin 1 (0.76 ± 0.14 vs. 0.55 ± 0.18 , $p < 0.05$) expression, and decreased Toll-like receptor 4 expression in ileal tissue (0.76 ± 0.58 vs. 2.04 ± 0.89 , $p < 0.01$). The HF-P group also showed decreased inflammation (TNF α : 316.13 ± 7.62 EU/mL vs. 355.59 ± 8.10 EU/mL, $p < 0.01$; IL-6: 51.78 ± 2.35 EU/mL vs. 58.98 ± 2.59 EU/mL, $p < 0.01$) and metabolic endotoxemia (2.83 ± 0.42 EU/mL vs. 0.68 ± 0.14 EU/mL, $p < 0.01$). These results suggest that apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

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IAP deactivates intraluminal LPS preventing activation of the TLR4 cascade.



When IAP is not present LPS remains active, which leads to mucosal injury, increased pathogenic bacteria, and a systemic inflammatory response.



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Apple-derived pectin is the main soluble fiber in apples and can be fermented by gut microbiota in the colon to produce metabolites with local intestinal and systemic effects. Apple-derived pectin may also help to maintain the balance of gut microbiota

† These authors contributed equally to this work.

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Supplementation with apple-derived pectin significantly increased the level of Intestinal Alkaline Phosphatase (IAP)

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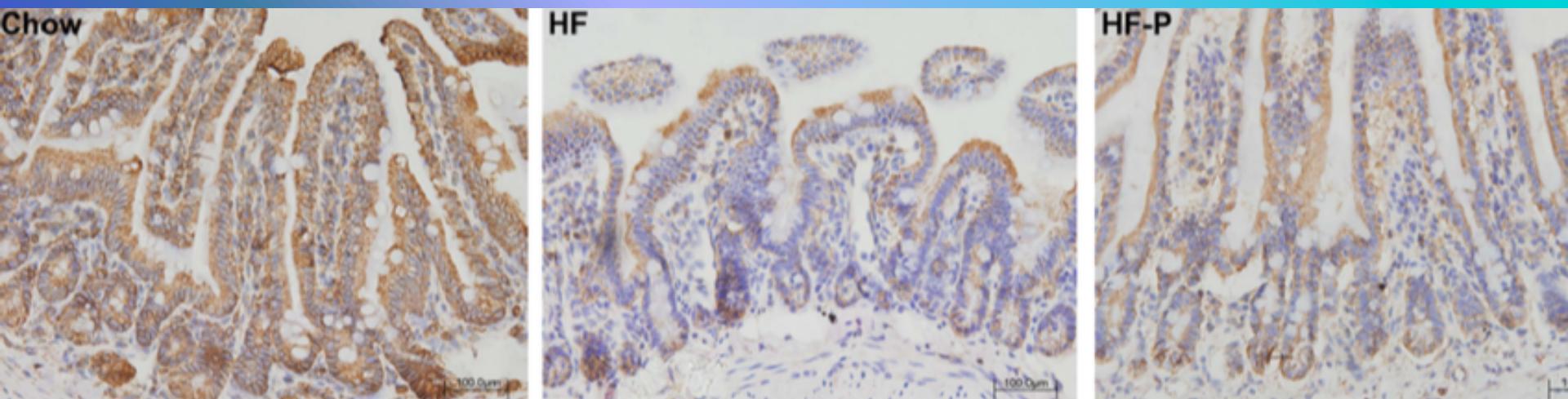


Fig. 3 immunological histological chemistry analysis of IAP in Chow, HF, and HF-P groups. Original magnification: 20[×].

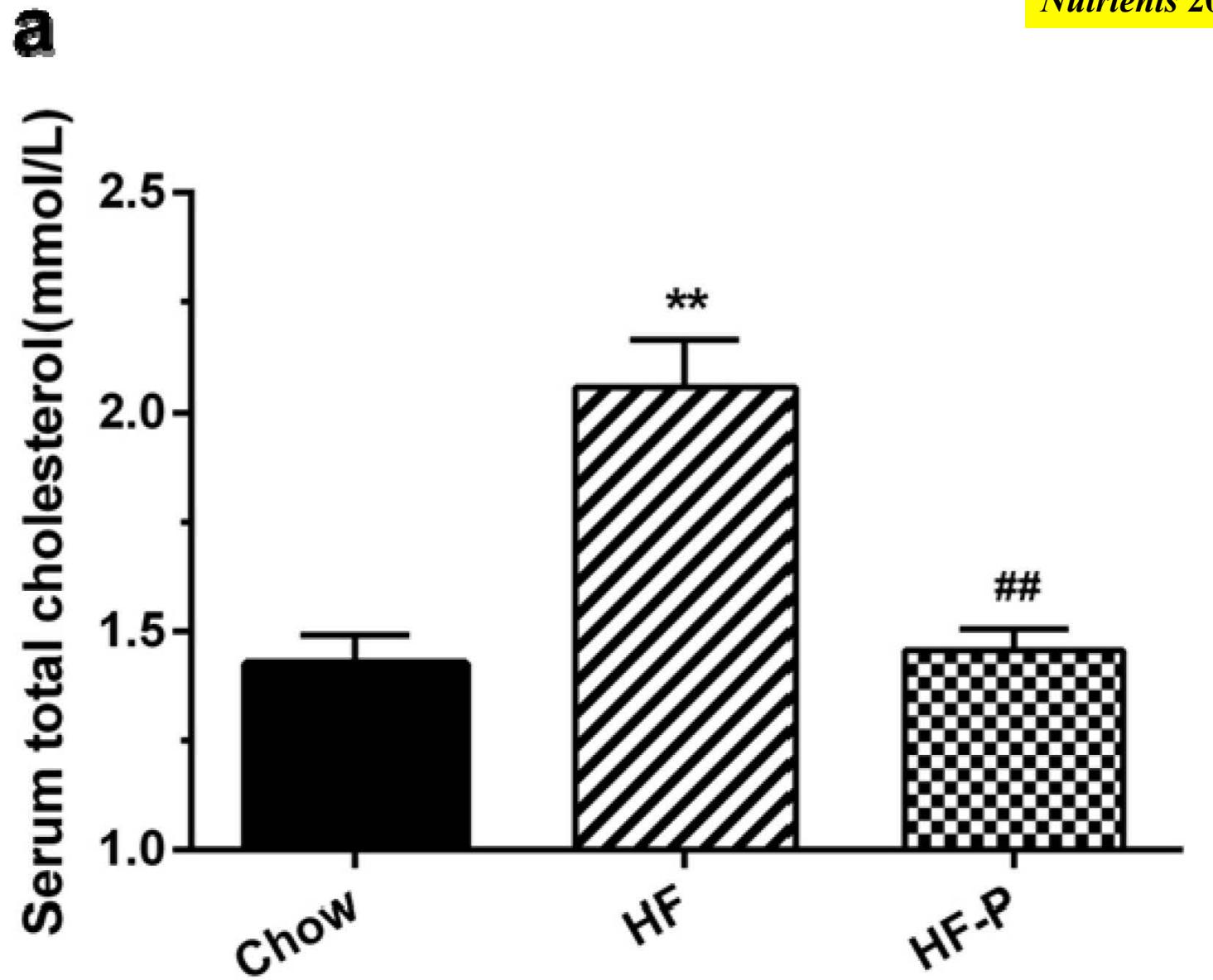


Figure 2. Effects of apple-derived pectin on HFD-induced changes in blood chemistry: (a) serum total cholesterol; (b) triglycerides; (c) glucose; and (d) insulin in Chow, HF, and HF-P groups. (** $p < 0.01$ vs. Chow, * $p < 0.05$ vs. Chow, ## $p < 0.01$ vs. HF).

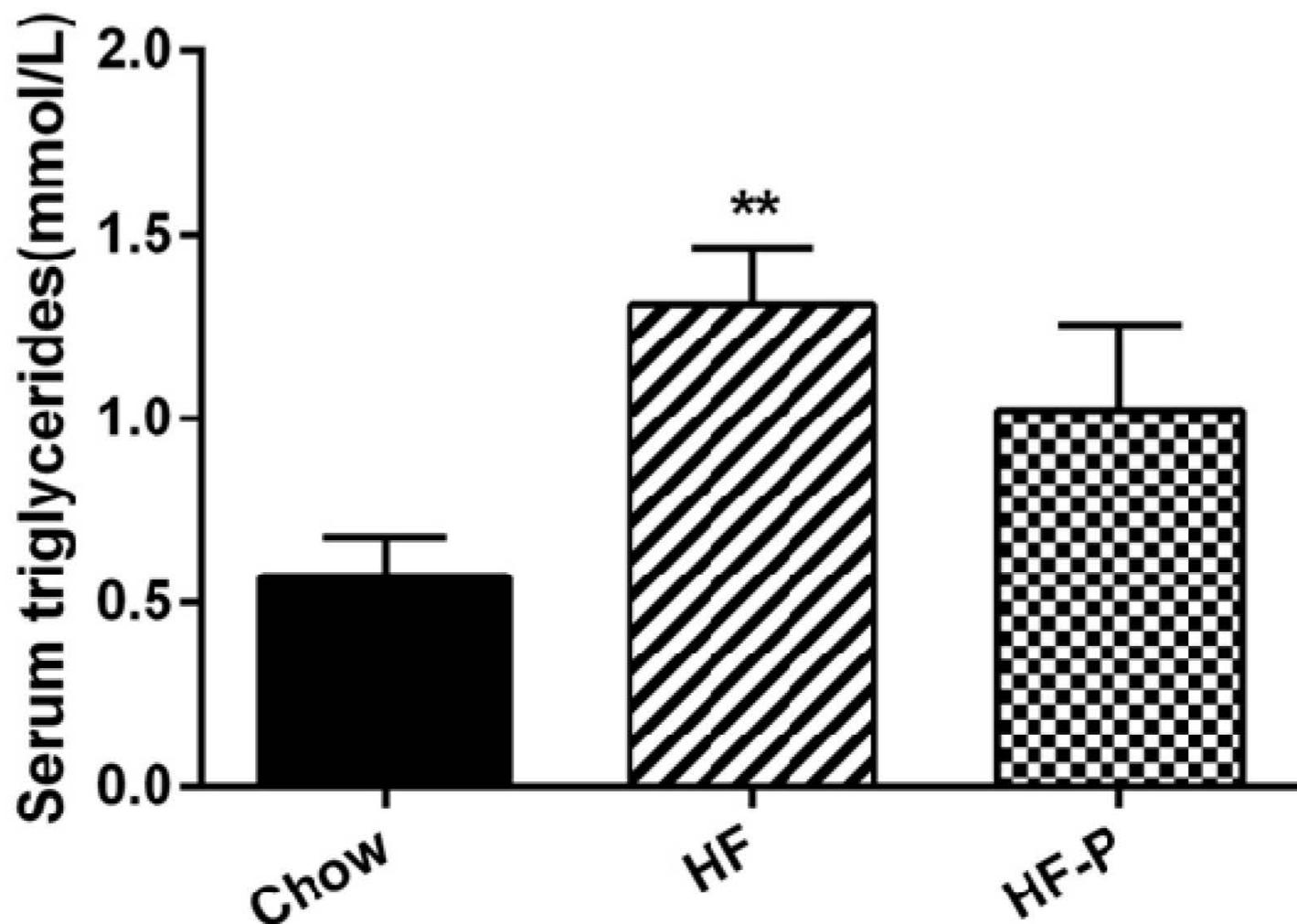
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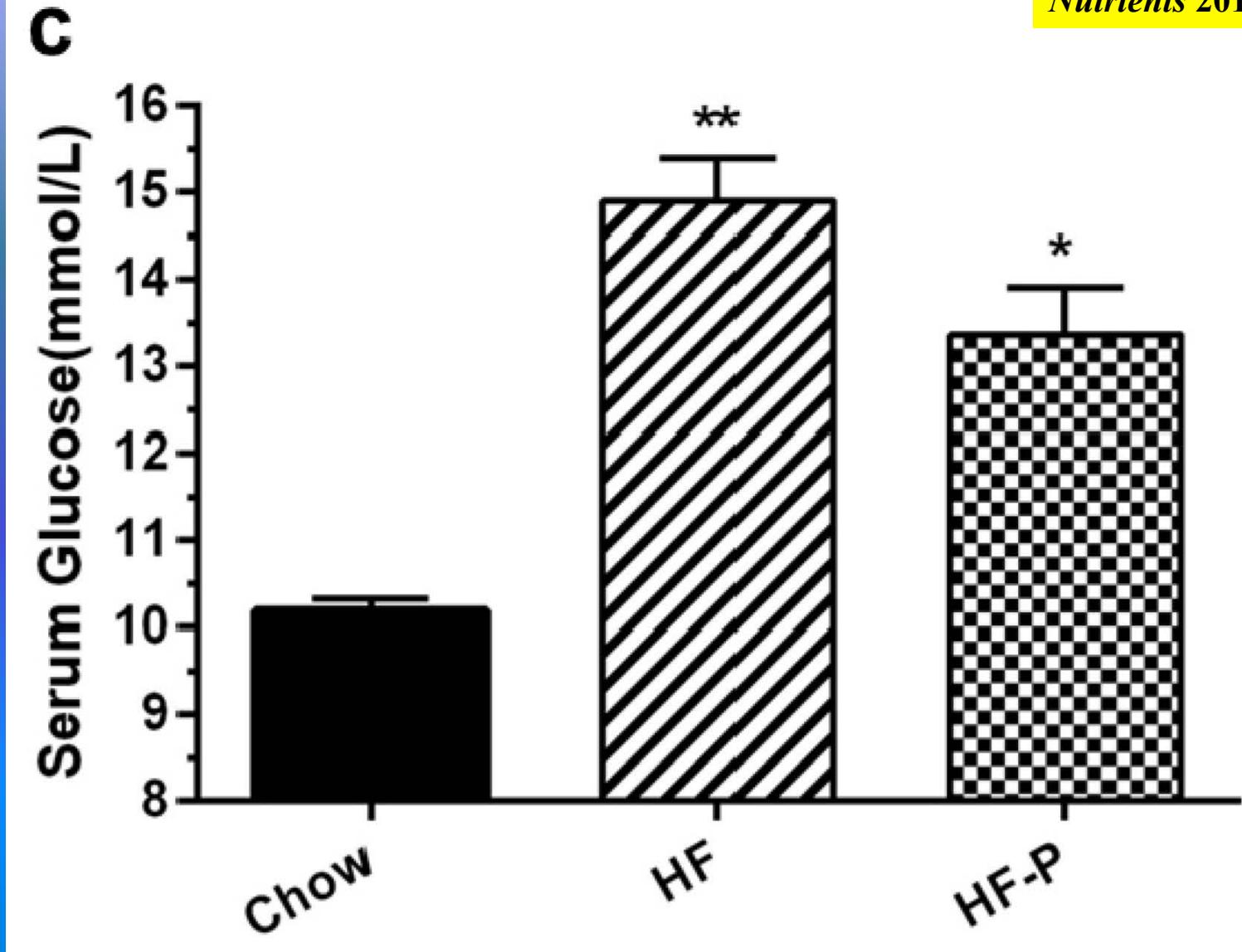


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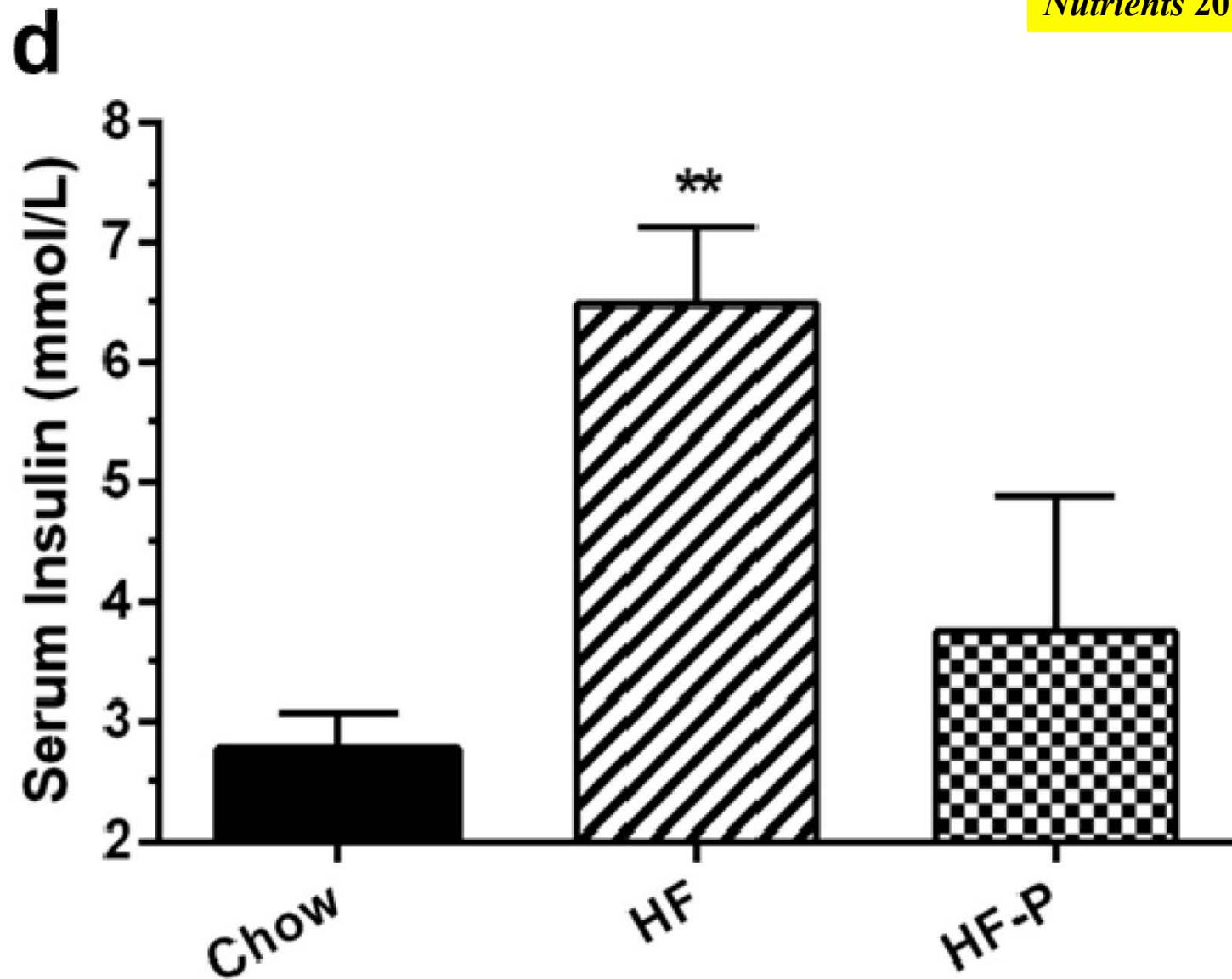


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Compared to the High Fat group, the High Fat with Pectin group showed:

- **37% reduction in weight gain ($p < 0.01$)**
- **29% reduction in serum total cholesterol level ($p < 0.01$).**

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The full-text article is available online at: <http://www.mdpi.com/2072-6643/8/1/126>

The HF-P group also showed decreased inflammation:

- **11% reduction in TNF ($p < 0.01$);**
- **12% reduction in IL-6 ($p < 0.01$)**
- **75% reduction in metabolic endotoxemia ($p < 0.01$)**
- **47% improved intestinal alkaline phosphatase, ($p < 0.05$)**

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The editors would like to thank all the authors who have contributed to this special issue.

The HF-P group also showed decreased inflammation:

- **27% reduction in claudin 1 expression ($p < 0.05$)**
- **72% reduction in Toll-like receptor 4 expression in ileal tissue ($p < 0.01$)**

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This study demonstrated that apple-derived pectin could modulate gut microbiota, as previously shown for inulin-type fructan and wheat-derived arabinoxylan oligosaccharides.

The rats received a standard diet (control; Chow group; $n = 8$) or a high-fat diet (HFD; $n = 32$) for eight weeks to induce obesity. The top 50th percentile of weight-gainers were selected as diet induced obese rats. Thereafter, the Chow group continued on chow, and the diet induced obese rats were randomly divided into two groups and received HFD (HF group; $n = 8$) or pectin-supplemented HFD (HF-P group; $n = 8$) for six weeks. Compared to the HF group, the HF-P group showed attenuated weight gain (207.38 ± 7.96 g vs. 283.63 ± 10.17 g, $p < 0.01$) and serum total cholesterol level (1.46 ± 0.13 mmol/L vs. 2.06 ± 0.26 mmol/L, $p < 0.01$). Compared to the Chow group, the HF group showed a decrease in Bacteroidetes phylum and an increase in Firmicutes phylum, as well as subordinate categories ($p < 0.01$). These changes were restored to the normal levels in the HF-P group. Furthermore, compared to the HF group, the HF-P group displayed improved intestinal alkaline phosphatase (0.57 ± 0.20 vs. 0.30 ± 0.19 , $p < 0.05$) and claudin 1 (0.76 ± 0.14 vs. 0.55 ± 0.18 , $p < 0.05$) expression, and decreased Toll-like receptor 4 expression in ileal tissue (0.76 ± 0.58 vs. 2.04 ± 0.89 , $p < 0.01$). The HF-P group also showed decreased inflammation (TNF α : 316.13 ± 7.62 EU/mL vs. 355.59 ± 8.10 EU/mL, $p < 0.01$; IL-6: 51.78 ± 2.35 EU/mL vs. 58.98 ± 2.59 EU/mL, $p < 0.01$) and metabolic endotoxemia (2.83 ± 0.42 EU/mL vs. 0.68 ± 0.14 EU/mL, $p < 0.01$). These results suggest that apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

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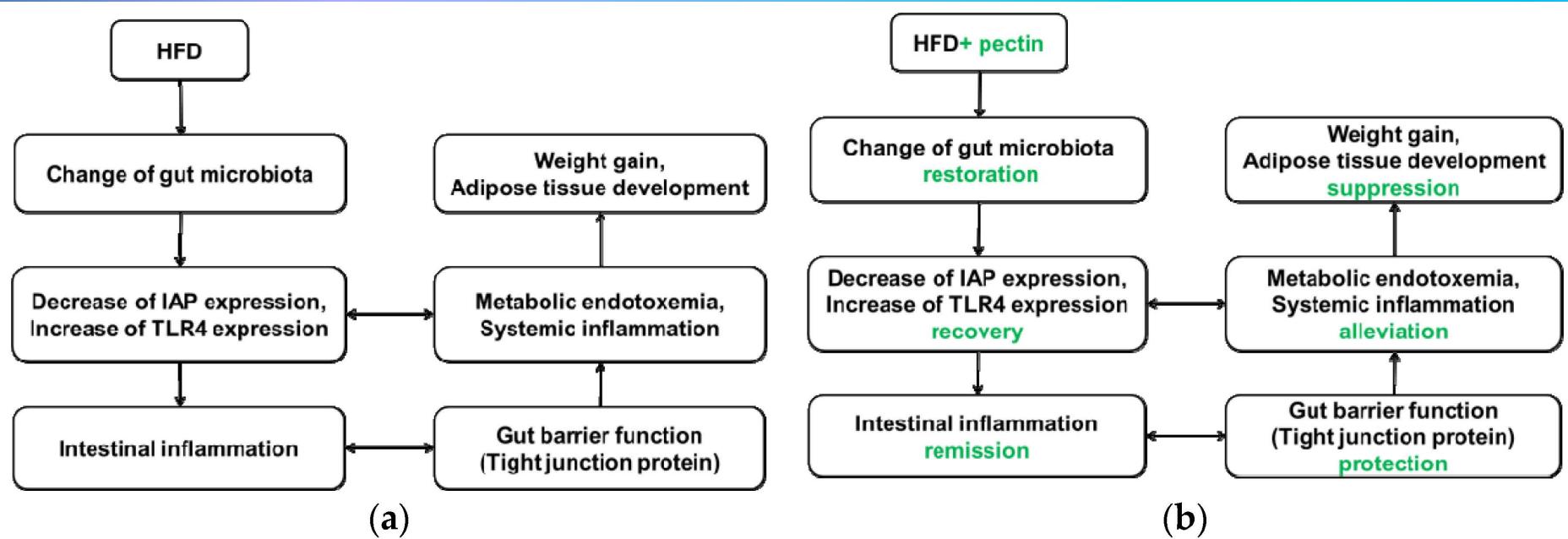
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² Department of General Surgery, South Medical University, Guangzhou 510515, China

Apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

Obese rats. The control, the Chow group contained on Chow, and the diet-induced obese rats were randomly divided into two groups and received HFD (HF group; $n = 8$) or pectin-supplemented HFD (HF-P group; $n = 8$) for six weeks. Compared to the HF group, the HF-P group showed attenuated weight gain (207.38 ± 7.96 g vs. 283.63 ± 10.17 g, $p < 0.01$) and serum total cholesterol level (1.46 ± 0.13 mmol/L vs. 2.06 ± 0.26 mmol/L, $p < 0.01$). Compared to the Chow group, the HF group showed a decrease in Bacteroidetes phylum and an increase in Firmicutes phylum, as well as subordinate categories ($p < 0.01$). These changes were restored to the normal levels in the HF-P group. Furthermore, compared to the HF group, the HF-P group displayed improved intestinal alkaline phosphatase (0.57 ± 0.20 vs. 0.30 ± 0.19 , $p < 0.05$) and claudin 1 (0.76 ± 0.14 vs. 0.55 ± 0.18 , $p < 0.05$) expression, and decreased Toll-like receptor 4 expression in ileal tissue (0.76 ± 0.58 vs. 2.04 ± 0.89 , $p < 0.01$). The HF-P group also showed decreased inflammation (TNF α : 316.13 ± 7.62 EU/mL vs. 355.59 ± 8.10 EU/mL, $p < 0.01$; IL-6: 51.78 ± 2.35 EU/mL vs. 58.98 ± 2.59 EU/mL, $p < 0.01$) and metabolic endotoxemia (2.83 ± 0.42 EU/mL vs. 0.68 ± 0.14 EU/mL, $p < 0.01$). These results suggest that apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

Keywords: obesity; apple-derived pectin; gut microbiota; gut barrier function; metabolic endotoxemia



A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

- Avoid inflammatory triggers
- Include Dietary Selections That Heal Intestinal Permeability
 - Vegetables (esp for their soluble fiber = SCFA production)

Terry Wahls, MD = 12 cups vegetables/day

-Pectin

-Bone Broth

Terry Wahls, MD 1 quart bone broth/day



Gelatin tannate reduces the proinflammatory effects of lipopolysaccharide in human intestinal epithelial cells

These results suggest that gelatin tannate exerts anti-inflammatory effects by inhibiting the specific cytokines and adhesion molecules involved in several inflammatory disorders

- strong ability to inhibit inflammatory biomarkers such as LPS-induced ICAM-1, IL-8, and TNF- α .

Caco-2 cells. IL-8 and TNF- α are important inflammatory mediators, recruiting neutrophils and T-lymphocytes. Together with LPS, adding gelatin tannate at different concentrations induced a dose-dependent inhibition of IL-8 and TNF- α released by Caco-2 cells.

Conclusion: These results suggest that gelatin tannate exerts anti-inflammatory effects by inhibiting the specific cytokines and adhesion molecules involved in several inflammatory disorders.

Keywords: Caco-2, ICAM-1, IL-8, TNF- α

The therapeutic management of gut barrier leaking: the emerging role for mucosal barrier protectors

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Department of Internal Medicine, Gastroenterology Division, Catholic University of the Sacred Heart, Rome, School of Medicine, Polyclinic "A. Gemelli" Hospital, Rome, Italy

Abstract. – **OBJECTIVE:** Gut barrier is a functional unit organized as a multi-layer system and its multiple functions are crucial for maintaining gut homeostasis. Numerous scientific evidences showed a significant association between gut barrier leaking and gastro-intestinal/extraintestinal diseases.

Introduction

The gastrointestinal tract is the most exposed human habitat to the external environment with a surface area of 200 m². Every day, thousands of microorganisms and compounds derived from the di-

Gelatin tannate, a mucosal barrier protector, forms a layer similar to the intestinal mucus on the surface of damaged intestinal mucosa. It seems to be able to prevent gut microflora translocation, thus restoring the functionality and physiological permeability of the intestinal barrier.

a mucosal barrier protector, for an innovative approach in the management of intestinal diseases, allowing an original therapeutic orientation with the aim of enhancing mucus barrier activity and restoring gut barrier.

CONCLUSIONS: These results suggest how the mucus layer recovering, beside the gut microbiota modulation, exerted by gut barrier protectors could be a useful weapon to re-establish the physiological intestinal homeostasis after an acute and chronic injury.

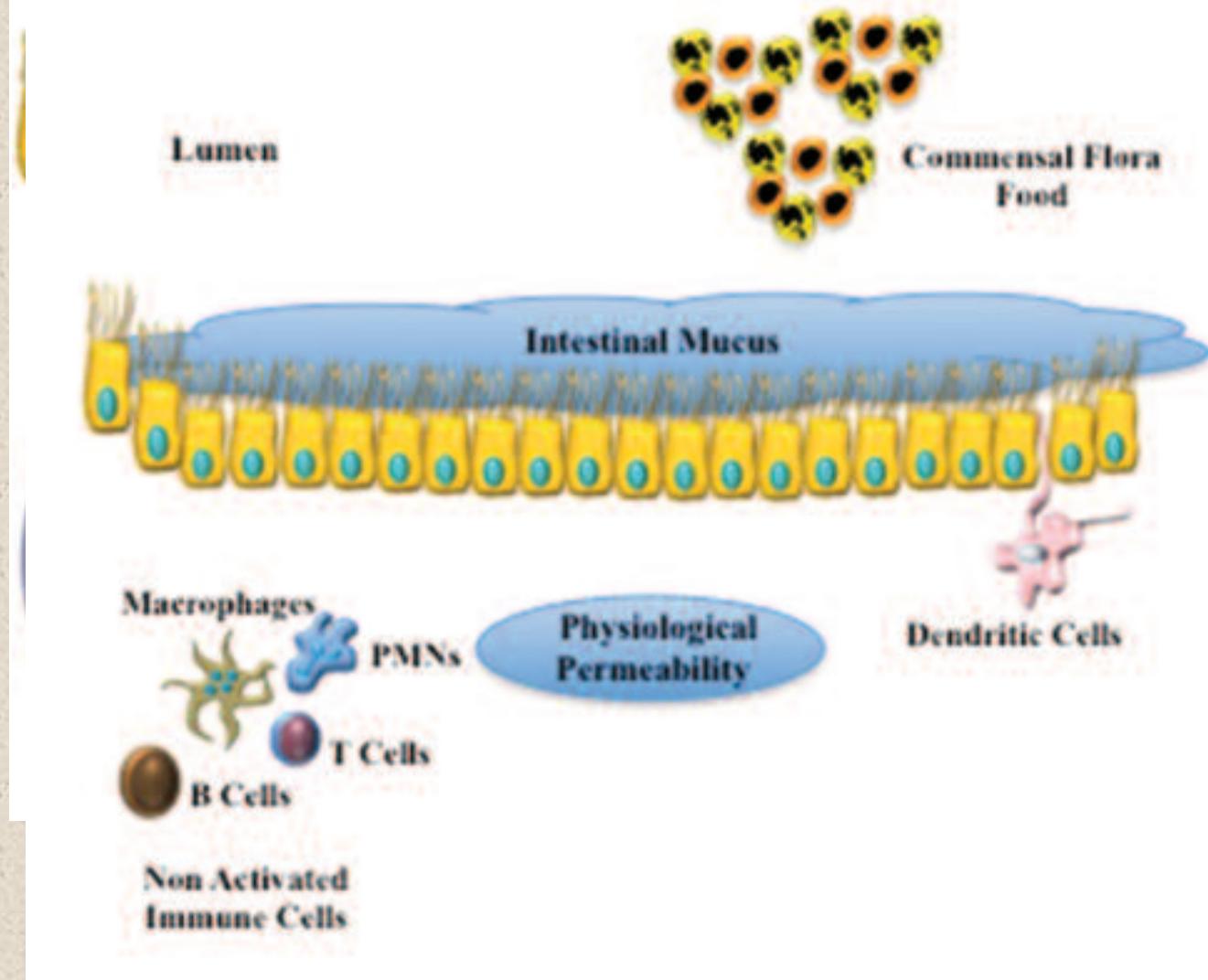
Key words:

Gut barrier, Mucus, Gut microbiota, Gelatin tannate, Mucosal protectors, Gut barrier enhancer.

gastric juice is bactericidal and therefore acts against infectious agents, while pancreatic enzymes are able to damage the bacterial cell.

The gut barrier starts from the resident microbiota. It competes with pathogens to gain space and energy resources, processes the molecules required for mucosal integrity and modulates the intestinal immunological response. The next level is represented by the mucus layer. It separates the luminal content from the deepest layers and contains antimicrobial products, and secretory IgA. Below the mucus, there is the monolayer of intestinal epithelial cells. This is able to form a physical barrier and contains the immunological cells. These cells

Restored Intestinal Barrier



A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

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- Include Dietary Selections That Heal Intestinal Permeability
 - Vegetables (esp for their soluble fiber = SCFA production)
Terry Wahls, MD = 12 cups vegetables/day
 - Pectin
 - Bone Broth
Terry Wahls, MD 1 quart bone broth/day
 - Fermented Vegetables (focus on diversity)





Health benefits of fermented foods: microbiota and beyond

Maria L Marco¹, Dustin Heeney¹, Sylvie Binda², Christopher J Cifelli³, Paul D Cotter⁴, Benoit Foligné⁵, Michael Gänzle⁶, Remco Kort⁷, Gonca Pasin⁸, Anne Pihlanto⁹, Eddy J Smid¹⁰ and Robert Hutkins¹¹



Fermented foods and beverages were among the first

Introduction

Fermented foods and beverages were among the first processed food products consumed by humans. The production of foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi, and fermented sausage were initially valued because of their improved shelf life, safety, and organoleptic properties.

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meats and fish, dairy, vegetables, soy beans and other legumes, cereals, starchy roots, and grapes and other fruits. Raw materials that contain high concentrations of monosaccharides and disaccharides, or in some cases starch, are fermented by yeasts or lactic acid bacteria. Molds and *Bacillus* are generally employed for starch saccharification or proteolysis or as secondary ripening microbiota after a primary fermentation.



Health benefits of fermented foods: microbiota and beyond

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Fermented foods and beverages were among the first

Introduction

The ingestion of fermented foods potentially increases the numbers of microbes in the diet by up to 10,000-fold

fermented foods can also have enhanced nutritional and functional properties due to transformation of substrates and formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

Addresses

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versions of major and minor food components (Figure 1). Food fermentation processes can be categorized by the primary metabolites and microorganisms involved: alcohol and carbon dioxide (yeast), acetic acid (*Acetobacter*), lactic acid (lactic acid bacteria (LAB) belonging to genera such as *Leuconostoc*, *Lactobacillus*, and *Streptococcus*), propionic acid (*Propionibacterium freudenreichii*), and ammonia and fatty acids (*Bacillus*, molds). Fermentations can also be described based on the food substrates, which include meats and fish, dairy, vegetables, soy beans and other legumes, cereals, starchy roots, and grapes and other fruits. Raw materials that contain high concentrations of monosaccharides and disaccharides, or in some cases starch, are fermented by yeasts or lactic acid bacteria. Molds and *Bacillus* are generally employed for starch saccharification or proteolysis or as secondary ripening microbiota after a primary fermentation.



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Fermented foods and beverages were among the first

Introduction

Consumption of fermented foods may provide an indirect means of counteracting the hygienic, sanitized Western diet and lifestyle.

fermented foods can also have enhanced nutritional and functional properties due to transformation of substrates and formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

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Many of the species found in fermented foods are either identical to or share physiological traits with species relevant to promoting GI tract health

formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

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A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

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- Include Pre-biotic Foods That Heal Intestinal Permeability
 - Vegetables (esp for their insoluble fiber = SCFA production)
Terry Wahls, MD = 12 cups vegetables/day
 - Pectin
 - Bone Broth
Terry Wahls, MD 1 quart bone broth/day
 - Fermented Vegetables (focus on diversity)
- Nutrient Supplementation to:
 - Address Inflammation
 - Rebuild the Microbiome
 - Healing of the Intestinal Epithelial Lining



MINIREVIEW

Exp Biol Med 229:1136–1142, 2004

Mounting Evidence for Vitamin D as an Environmental Factor Affecting Autoimmune Disease Prevalence

MARGHERITA T. CANTORNA¹ AND BRETT D. MAHON

Department of Nutritional Sciences, Pennsylvania State University,
University Park, Pennsylvania 16802

Low vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease. The optimal level of vitamin D intake required to support optimal immune function is not known but is likely to be at least that required for healthy bones. Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. The vitamin D hormone (1,25-dihydroxy vitamin D₃) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. The net

80 known autoimmune disorders exist; as a whole, they represent a leading cause of death of young to middle-aged women in the United States today (1). Despite their relatively high prevalence rate, the etiology and pathogenesis of most autoimmune disorders remain unknown, and cures remain elusive. To cure an autoimmune disorder, one would need to eradicate either the self-antigen or the immune cells responsible for the pathology. Eradication of the self-antigen is impossible; therefore, treatment options

Vitamin D plays a role in the etiology of autoimmunity.

bone fracture. *Exp Biol Med* 229:1136–1142, 2004

Key words: vitamin D; autoimmunity; multiple sclerosis; arthritis; inflammatory bowel disease; insulin-dependent diabetes mellitus

Introduction

Autoimmune diseases are characterized by the targeted destruction of self-tissue by the immune system. More than

This work was supported in part by Crohn's and Colitis Foundation of America, Senior Research Award to M.T.C., and the National Institutes of Health—National Institute of Neurological Disorders and Stroke Grant 1R01 NS38888.

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1535-3702/04/22911-1136\$15.00
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lence continues to accumulate. The data link vitamin D and insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel diseases (IBD), and rheumatoid arthritis (RA) (2). Autoimmunity is driven by T helper cells (Th1), which attack various self-tissues in the body. It is clear that both genetic and environmental factors affect disease prevalence. The fact that vitamin D has been implicated as a factor in several different autoimmune diseases suggests that vitamin D might be an environmental factor that normally participates in the control of self-tolerance. In addition, there may be a higher vitamin D requirement for patients at risk for developing and those that already have an autoimmune disease. The optimal amount of vitamin D to support the immune response may be different from the amount required to prevent vitamin D deficiency or to maintain calcium homeostasis. The current recommended intake levels for vitamin D are too low to support bone mineralization, which is already a problem in patients with autoimmunity. New evidence from human, animal, and *in vitro* mechanistic experiments suggest that vitamin D may play a role in the etiology of autoimmunity.

1,25-Dihydroxyvitamin D₃ Stimulates the Assembly of Adherens Junctions in Keratinocytes: Involvement of Protein Kinase C

ROBERT GNIADECKI, BARBARA GAJKOWSKA, AND MICHAEL HANSEN

Department of Dermatological Research, Leo Pharmaceutical Products (R.G.), Ballerup; the Department of Dermatology, University of Copenhagen, Bispebjerg Hospital (R.G.), Copenhagen; and the Microbiology Section, Department of Ecology and Molecular Biology, The Royal Veterinary and Agricultural University (M.H.), Frederiksberg, Denmark; and the Electron Microscopy Laboratory, Polish Academy of Sciences (B.G.), Warsaw, Poland

1,25-(OH)2D3 caused assembly of adherens junctions

national proteins (E-cadherin, P-cadherin, α -catenin, and vinculin) to the cell-cell borders. The presence of α -catenin and vinculin at cell-cell bor-

and neoplastic diseases. (*Endocrinology* 138: 2241-2248, 1997)

1,25-DIHYDROXYVITAMIN D 1,25-(OH)₂D₃ PLAYS an important role in regulation of growth of epithelial cells. The effects of 1,25-(OH)₂D₃ have been particularly well investigated in keratinocytes. 1,25-(OH)₂D₃ at concentrations 10⁻⁸-10⁻⁶ M has been reproducibly shown to inhibit proliferation and induce differentiation of murine and human keratinocytes in culture (1-4). Inhibition of cell growth is also manifested *in vivo*, where 1,25-(OH)₂D₃ and its synthetic analogs inhibit excessive proliferation of keratinocytes in psoriasis (5). Recent evidence suggests that 1,25-(OH)₂D₃ may also be useful in the treatment of skin, breast, and colon cancer (6-9).

One of the aspects of epidermal cell differentiation is the formation of cell-cell junctions, which enable intercellular communication and are essential for regulation of epithelial morphogenesis, growth, and differentiation (10). In the epidermis, intercellular adhesion is mediated by two major types of junctional structures: the desmosomes and the adherens junctions (AJ) (11, 12). Ultrastructurally, desmosomes consist of two submembranous plaques separated by an electron-lucent 20- to 30-nm wide desmoglia with a distinct electron-dense midline(s) (13). The assembly of a desmosome is mediated by a homophilic interaction between the transmembrane proteins of the cadherin superfamily, desmoglein and desmocolin, the cytoplasmic tails of which bind to desmosome plaque proteins,

placoglobin and desmoplakin. AJ are ultrastructurally similar to the desmosome, but are biochemically and functionally different from the latter. Rather than mainly strengthen the epidermis, AJ are dynamic structures capable of signal transduction and facilitate the so-called juxtagrine signaling (10, 14). AJ have been implicated in the regulation of morphogenesis, tissue remodeling, cell migration and stratification, cell spreading, epithelial compactness, and apoptosis (12, 15-18). AJ are stabilized due to the homophilic binding between N-terminal domains of the classic cadherins, E- and P-cadherin. The cytoplasmic tails of the cadherins interact with the proteins of the catenin family, α -, β -, and γ -catenin, and with a number of other accessory proteins, e.g. placoglobin or vinculin. α -Catenin is required for cadherin-mediated cell adhesion and has an actin-binding activity (19). Thus, AJ are associated with actin cytoskeleton, rather than with the keratin intermediate filaments such as the desmosomes.

Here we investigated whether induction of epidermal cell differentiation by 1,25-(OH)₂D₃ was associated with assembly of cell-cell junctions. It was found that keratinocytes cultured in the presence of 1,25-(OH)₂D₃ assemble AJ, but not desmosomes. Since in epithelial cells AJ formation seems to depend on the induction of protein kinase C (PKC) (20-22), we also studied whether PKC is involved in the mechanism of action of 1,25-(OH)₂D₃.

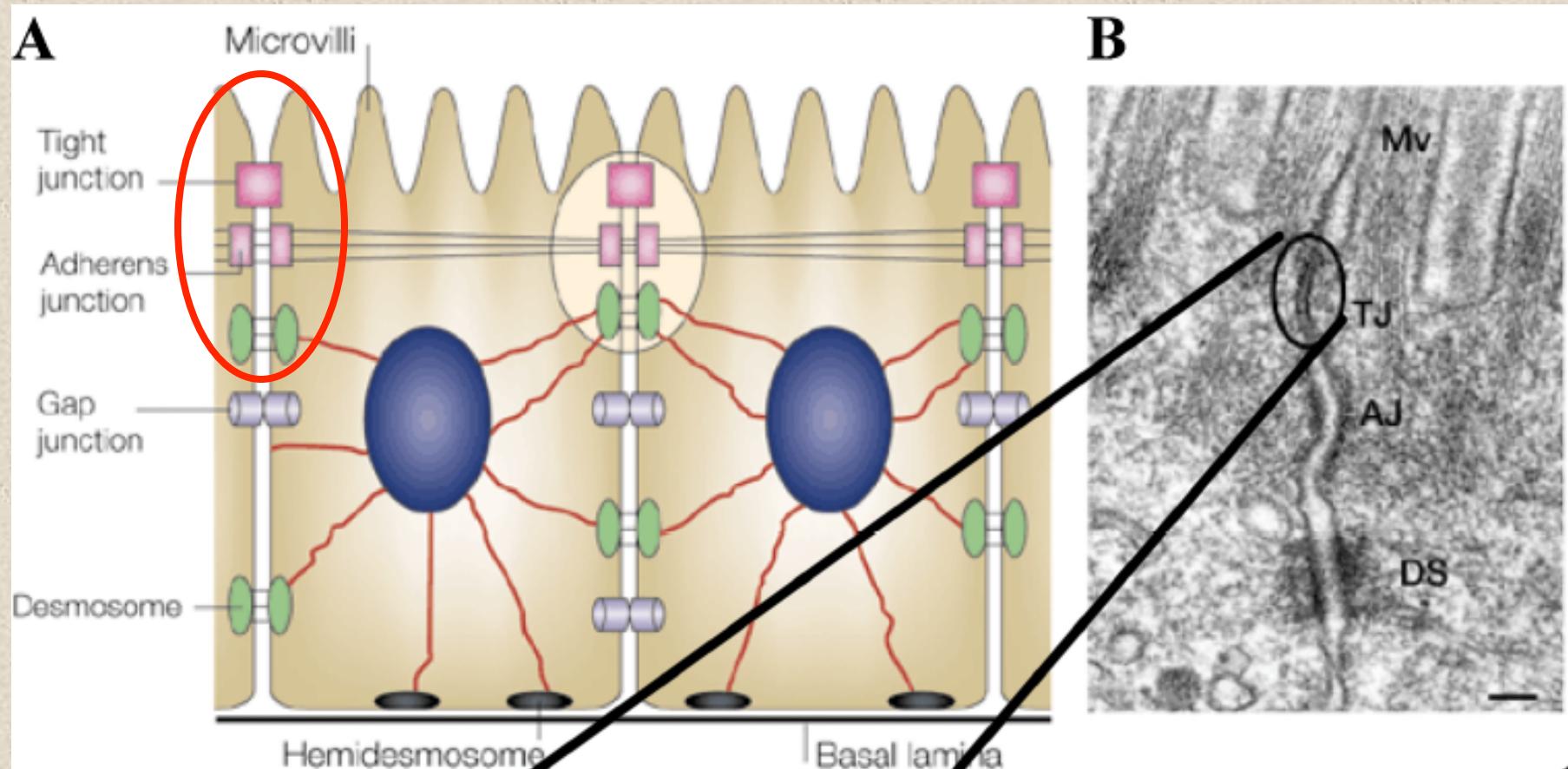
Materials and Methods

Chemicals

1,25-(OH)₂D₃ was obtained from the Chemical Research Department, Leo Pharmaceutical Products (Ballerup, Denmark), as a 4-mm solution

Received November 22, 1996.

Address all correspondence and requests for reprints to: Robert Gniadecki, M.D., Ph.D., Department of Dermatology D92, University of Copenhagen, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark.



Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

Juan Kong,¹ Zhongyi Zhang,¹ Mark W. Musch,¹ Gang Ning,² Jun Sun,³ John Hart,⁴ Marc Bissonnette,¹
and Yan Chun Li,¹

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Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G208-16

Submitted 31 August 2007; accepted in final form 23 October 2007

AQ:2 **Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC.** Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 294: G000–G000, 2008. First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.—Emerging evidence supports a pathological link between vitamin D deficiency and the risk of inflammatory bowel disease (IBD). To explore the mechanism we used the dextran sulfate sodium (DSS)-induced colitis model to investigate the role of the vitamin D receptor (VDR) in mucosal barrier homeostasis. While VDR^{+/+} mice were mostly resistant to 2.5% DSS, VDR^{-/-} mice developed severe diarrhea, rectal bleeding, and marked body weight loss, leading to death in 2 wk. Histological examination revealed extensive ulceration and impaired wound heal-

The integrity of the intestinal mucosal barrier is preserved by the enormous regenerating capacity of the mucosal epithelium. The intestinal stem cells, located at the base of the crypt, are responsible for replenishing the epithelium through cell division and differentiation. After extensive destruction, rapid resealing of the surface epithelium is accomplished by epithelial cell restitution, proliferation, and differentiation (6). Another important component of the mucosal barrier is the apical and subapical intercellular junctions between the epithelial cells, namely tight junctions and adherens junctions (18). These junction structures seal the paracellular space and regulate the permeability of the mucosal barrier.

VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of tight junction complexes and the healing capacity of the colonic epithelium.

AQ:4 These observations suggest that VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium. Therefore, vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

THE INTESTINAL EPITHELIAL barrier consists of epithelial cells and the intercellular junctions. The barrier regulates macromolecule trafficking between the lumen and the internal milieu and protects the host by preventing harmful solutes, microorganisms, toxins, and luminal antigens from entering the body (40). Compromise or disruption of the intestinal barrier function causes deleterious effects and results in exposure of the host to luminal antigens and bacteria, leading to inflammation. Impaired barrier functions have been described in a number of common gastrointestinal disorders, including inflammatory bowel disease (IBD) (7).

AQ:13 Address for reprint requests and other correspondence: Yan Chun Li, Dept. of Medicine, The Univ. of Chicago, MC 4076, 5841 S. Maryland Ave., Chicago, IL 60637 (e-mail: cyan@medicine.bsd.uchicago.edu).

vious studies have demonstrated decreased expression and differential localization of junction complex proteins in the mucosa of patients with IBD (10, 16, 29). Therefore, dysregulation of junction proteins is an important pathogenic mechanism underlying the increased permeability seen in the intestinal epithelium of IBD patients.

Previous studies have suggested a link between vitamin D deficiency and IBD risk (23). The prevalence of IBD exhibits a north-south gradient (24), paralleling sunlight exposure, an important source of vitamin D. Populations near the equator are at relatively lower risk for developing IBD. Seasonal variations in the onset and exacerbation of IBD have also been reported (27, 36) with high incidence in the winter. Early studies have reported a high prevalence of vitamin D deficiency in patients with established Crohn's disease (12, 38). Decreased vitamin D levels have also been detected in patients with newly diagnosed IBD (17, 19, 35). In the IL-10^{-/-} mouse model of intestinal inflammation, vitamin D deficiency or vitamin D receptor (VDR) deficiency exacerbates the symp-

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AQ:13

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1,25(OH)₂D₃ markedly enhanced tight junctions by increasing junction protein expression (at the kissing joints) and preserved the structural integrity of tight junctions (tight junction strands)

increased susceptibility to mucosal damage and increased risk of IBD.

AQ:4 tight junction; inflammatory bowel disease; dextran sulfate sodium

THE INTESTINAL EPITHELIAL barrier consists of epithelial cells and the intercellular junctions. The barrier regulates macromolecule trafficking between the lumen and the internal milieu and protects the host by preventing harmful solutes, microorganisms, toxins, and luminal antigens from entering the body (40). Compromise or disruption of the intestinal barrier function causes deleterious effects and results in exposure of the host to luminal antigens and bacteria, leading to inflammation. Impaired barrier functions have been described in a number of common gastrointestinal disorders, including inflammatory bowel disease (IBD) (7).

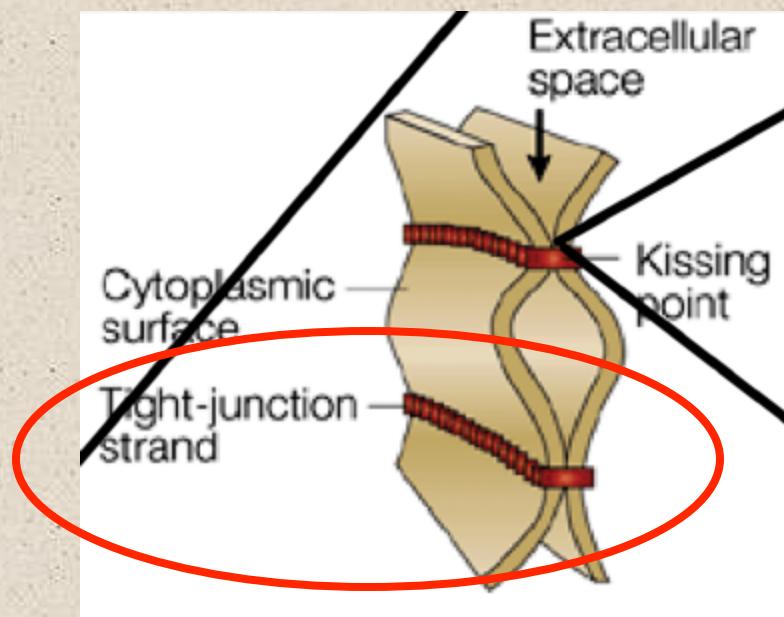
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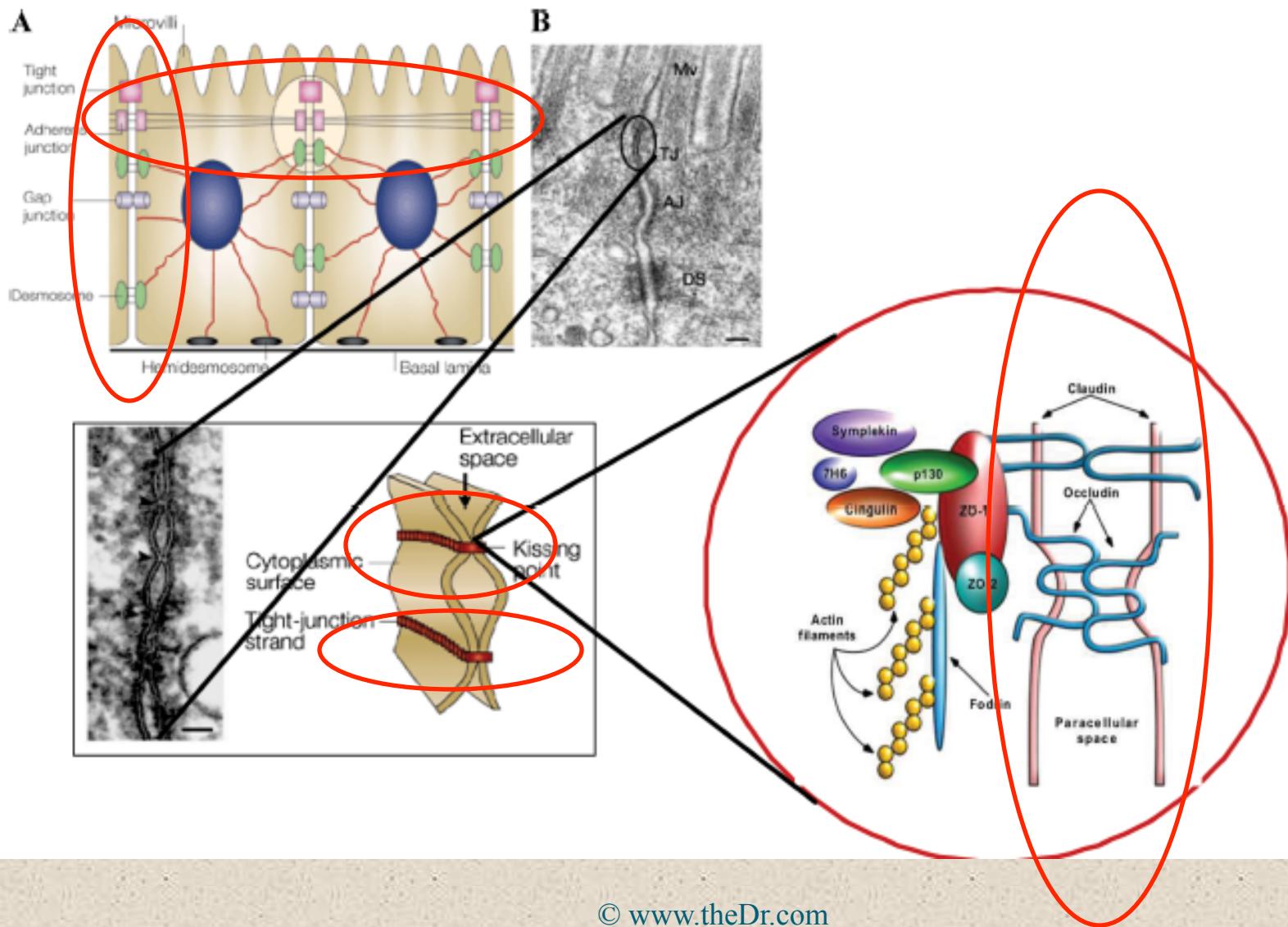
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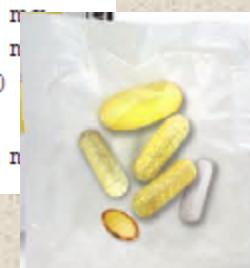
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Vitamin D-3 (as cholecalciferol) (from lanolin)	5,000 IU
Natural Marine Lipid Concentrate Containing:	1.2 g
EPA (eicosapentaenoic acid)	318-360 mg
DHA (docosahexaenoic acid)	204-240 mg
Curcumin (C3 Complex™, 95% pure curcuminoids)	250 mg
L-Lysine (as L-lysine HCl)	200 mg
Boswellia Extract (standardized to 65% boswellic acid)	200 mg
L-Glutamine	623 mg
L-Threonine	80 mg
Bromelain (2400 GDU/g)	63 mg
Bilberry Extract (standardized to 25% anthocyanosides)	50 mg
Ashwagandha Root Extract (<i>Withania somnifera</i>)	43 mg
Rosemary Leaf Extract	40 mg
Rutin	33 mg
Quercetin	33 mg
Hesperidin	33 mg
Ginger Extract (4:1; <i>Zingiber officinale</i> root)	17 mg
L-Citrulline	17 mg
N-Acetyl Cysteine (NAC)	17 mg
Broccoli Seed Extract	600 mg
Providing:	
Sulforaphane Glucosinolate	60 mg



Treatment Protocols (personal recommendations-Vitamin D)

Therapeutic dosages:

30-75 lbs = at least 2000-3000iu/day

76-125 lbs = at least 4000-5000 iu/d

> 125 lbs = 5000+ iu/d

**Note: Clinical results have been seen numerous times
with mega-dosing at 50,000 iu/d one time per week.**

Recheck Vit. D levels every 8 weeks

An excellent resource on Vitamin D is www.VitaminDCouncil.org

Review

Nutrition of the Critically Ill—A 21st-Century Perspective

Stig Bengmark

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Attempts to reconstitute a normal microbiome by supply of probiotics have often failed as they are almost always undertaken as a complement to—and not as an alternative to—existing treatment schemes, especially those based on antibiotics, but also other pharmaceuticals.

effects that can contribute to dysbiosis. About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota. The consequence is that the microbiota of modern humans is greatly reduced, both in terms of numbers and diversity when compared to the diets of our paleolithic forebears and the individuals living a rural lifestyle today. It is the artificial treatment provided in modern medical care—unfortunately often the only alternative provided—which constitute the main contributors to a poor outcome. These treatments include artificial ventilation, artificial nutrition, hygienic measures, use of skin-penetrating devices, tubes and catheters,

Nutrition of the critically ill - emphasis on liver and pancreas

Stig Bengmark

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Abstract: About 25 million individuals undergo high risk surgery each year. Of these about 3 million will never return home from hospital, and the quality of life for many of those who return is often significantly impaired. Furthermore, many of those who manage to leave hospital have undergone severe life-threatening complications, mostly infections/sepsis. The development is strongly associated with the level of systemic inflammation in the body, which again is entirely a result of malfunctioning GI microbiota, a condition called dysbiosis, with deranged composition and function of the gastrointestinal microbiota from the mouth

About 75% of the food Westerners consume does not benefit microbiota in the lower gut. Most of it, refined carbohydrates, is already absorbed in the upper part of the GI tract, and of what reaches the large intestine is of limited value containing less minerals, less vitamins and other nutrients important for maintenance of the microbiota.

a normal microbiome have often failed as they have always been undertaken as a complement to and not an alternative to existing treatment schemes, especially treatments with antibiotics. Modern nutrition formulas are clearly too artificial as they are based on mixture of a variety of chemicals, which alone or together induce inflammation. Alternative formulas, based on regular food ingredients, especially rich in raw fresh greens, vegetables and fruits and with them healthy bacteria are suggested to be developed and tried.

Key Words: Health care; surgery; stress; trauma; transplantation; liver cirrhosis; liver steatosis; obesity; osteoarthritis; pancreatitis; critical care; nutrition; enteral nutrition; parenteral nutrition; microbiota; microbiome; microbial translocation; probiotic bacteria; lactobacillus; lactobacillus plantarum; lactobacillus paracasei; microbial translocation; inflammation; infection; toll-like; neutrophils; pharmaceuticals; biological; eco-biologicals; nutraceuticals; antioxidants; curcumin; antibiotics; chemotherapeutics; barriers; leakage; gut; airways; oral cavity; skin; vagina; placenta; amnion; blood-brain barrier; growth; replication; apoptosis; mucosa; endothelium; plaques;

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The consequence is that the microbiota of modern man has a much reduced size and diversity in comparison to what our Paleolithic forefathers had, and individuals living a rural life have today.

microbiota e.g., size and diversity of microbiota, normal microbiota, eubiosis, being highly preventive.

About 75% of the food Westerners consume does not benefit microbiota in the lower gut. Most of it, refined carbohydrates, is already absorbed in the upper part of the GI tract, and of what reaches the large intestine is of limited value containing less minerals, less vitamins and other nutrients important for maintenance of the microbiota. The consequence is that the microbiota of modern man has a much reduced size and diversity in comparison to what our Paleolithic forefathers had, and individuals living a rural life have today. It is the artificial treatment provided by modern care, unfortunately often the only alternative, which belongs to the main contributor to poor outcome, among them; artificial ventilation, artificial nutrition, hygienic measures, use of skin penetrating devices, tubes and catheters, frequent use of pharmaceuticals, all known to significantly impair the total microbiome of the body and dramatically contribute to poor outcome. Attempts to reconstitute a normal microbiome have often failed as they have always been undertaken as a complement to and not an alternative to existing treatment schemes, especially treatments with antibiotics. Modern nutrition formulas are clearly too artificial as they are based on mixture of a variety of chemicals, which alone or together induce inflammation. Alternative formulas, based on regular food ingredients, especially rich in raw fresh greens, vegetables and fruits and with them healthy bacteria are suggested to be developed and tried.

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Review

Obesity and Metabolic Syndrome

Diabetes Metab J 2015;39:291-303

<http://dx.doi.org/10.4093/dmj.2015.39.4.291>

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Probiotics as Complementary Treatment for Metabolic Disorders

Mélanie Le Barz^{1,2,3}, Fernando F. Anhê^{1,2}, Thibaut V. Varin², Yves Desjardins², Emile Levy^{2,4,5}, Denis Roy², Maria C. Urdaci³, André Marette^{1,2}

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probiotic strains can not only affect the intestinal microbiota directly but also affect other organs by modulating intestinal inflammation and permeability

osis) leading to activation of pro-inflammatory mechanisms and metabolic endotoxemia, therefore promoting insulin resistance and cardiometabolic disorders. To counteract these deleterious effects, probiotic strains have been developed with the aim of reshaping the microbiome to improve gut health. In this review, we focus on benefits of widely used probiotics describing their potential mechanisms of action, especially their ability to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. We also discuss the perspective of using new bacterial strains such as butyrate-producing bacteria and the mucolytic *Akkermansia muciniphila*, as well as the use of prebiotics to enhance the functionality of probiotics. Finally, this review introduces the notion of genetically engineered bacterial strains specifically developed to deliver anti-inflammatory molecules to the gut.

Keywords: Gut permeability; Insulin resistance; Metabolic disorders; Mucosal barrier; Obesity; Probiotics

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(Dysbiotic) changes in gut microbiota modulate endotoxemia by a mechanism that affects gut barrier function and increases intestinal permeability

Metabolic disorders such as obesity and type 2 diabetes, indeed, obesogenic diet can drastically alter bacterial populations (i.e., dysbiosis) leading to activation of pro-inflammatory mechanisms and metabolic endotoxemia, therefore promoting insulin resistance and cardiometabolic disorders. To counteract these deleterious effects, probiotic strains have been developed with the aim of reshaping the microbiome to improve gut health. In this review, we focus on benefits of widely used probiotics describing their potential mechanisms of action, especially their ability to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. We also discuss the perspective of using new bacterial strains such as butyrate-producing bacteria and the mucolytic *Akkermansia muciniphila*, as well as the use of prebiotics to enhance the functionality of probiotics. Finally, this review introduces the notion of genetically engineered bacterial strains specifically developed to deliver anti-inflammatory molecules to the gut.

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LETTER

doi:10.1038/nature12820

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David^{1,2†}, Corinne F. Maurice¹, Rachel N. Carmody¹, David B. Gootenberg¹, Julie E. Button¹, Benjamin E. Wolfe¹, Alisha V. Ling³, A. Sloan Devlin⁴, Yug Varma⁴, Michael A. Fischbach⁴, Sudha B. Biddinger³, Rachel J. Dutton¹ & Peter J. Turnbaugh¹

Our findings that the human gut microbiome can rapidly switch between herbivorous and carnivorous functional profiles may reflect past selective pressures during human evolution. Consumption of animal foods by our ancestors was probably volatile, depending on season and stochastic foraging success, with readily available plant foods offering a fall-back source of calories and nutrient

LETTER

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We found that microbiota changes on the animal-based diet could be linked to altered faecal bile acid profiles and the potential for human enteric disease.

overwhelms inter-individual differences in microbial gene expression. The animal-based diet increased the abundance of bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*). Microbial activity mirrored differences between herbivorous and

lysis of his diet and gut microbiota).

Each diet arm significantly shifted subjects' macronutrient intake (Fig. 1a–c). On the animal-based diet, dietary fat increased from $32.5 \pm 2.2\%$ to $69.5 \pm 0.4\%$ kcal and dietary protein increased from $16.2 \pm 1.3\%$ to $30.1 \pm 0.5\%$ kcal ($P < 0.01$ for both comparisons, Wilcoxon signed rank test, Supplementary Table 5). Fibre intake was nearly

Effect of Probiotics, *Bifidobacterium breve* and *Lactobacillus casei*, on Bisphenol A Exposure in Rats

Kenji OISHI,^{1,†} Tadashi SATO,² Wakae YOKOI,² Yasuto YOSHIDA,²
Masahiko ITO,² and Haruji SAWADA²

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Received October 18, 2007; Accepted February 8, 2008; Online Publication, June 7, 2008

[doi:10.1271/bbb.70672]

Bisphenol A (BPA), a putative endocrine disruptor, may be taken up by humans via the diet and have adverse effects on human health.

geous effects compared to the control group; (i) the area under the blood concentration-time curve of BPA after its oral administration was significantly decreased, (ii) the amount of BPA excreted in the feces was significantly greater (2.4 times), and (iii) the percentage of BPA bound to the sediment fraction of the feces was significantly higher. These results suggest that BbY and LcS reduced the intestinal absorption by facilitating the excretion of BPA, and that these probiotics may suppress the adverse effects of BPA on human health.

Key words: bisphenol A; probiotic; bifidobacteria; lactic acid bacteria; rat

Bifidobacteria and lactic acid bacteria are used in the production of dairy products. These bacteria are also becoming popular with consumers due to their beneficial effects on human health. It has been reported that bifidobacteria and lactic acid bacteria have many beneficial functions such as anti-microbial effects against pathogenic microorganisms,^{10,11)} modulation of the immune system,¹²⁻¹⁴⁾ anti-tumor activity,^{15,16)} and anti-oxidative effects.^{17,18)} Bifidobacteria and lactic acid bacteria also have the ability to bind food carcinogens such as heterocyclic amines,^{19,20)} benz[a]pyrene and aflatoxin B1.¹⁹⁾ Furthermore, the administration of freeze-dried viable *Lactobacillus casei* has suppressed the increase in the level of fecal lactose in fed

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Gluten induces coeliac-like disease in sensitised mice involving IgA, CD71 and transglutaminase 2 interactions that are prevented by probiotics

Christina Papista^{1,2,3}, Vassilis Gerakopoulos¹, Andreas Kourvelis¹, Maria Sounidakis¹, Anastasia Kontana¹, Laureline Berthelot^{2,3}, Ivan C Moura^{2,3}, Renato C Monteiro^{2,3,4} and Minas Yiannou¹

Oral delivery of the *S. boulardii* KK1 strain reduced epithelial cell inflammatory immune responses and ameliorated the histopathological features of gluten-induced enteropathy, potentially indicating a new therapeutic approach for CD.

enterocytes and an increase of plasma cells producing IgA, which colocalised with the CD71. Moreover, IgA colocalised with the transglutaminase 2 (TG2), the production of which was increased in the lamina propria of G+ mice. These mice displayed increased production of cyclooxygenase-2 (COX-2), pro-inflammatory cytokines and IL-15, as well as anti-gliadin and anti-TG2 autoantibodies. The commensal flora-isolated presumptive probiotic *Saccharomyces boulardii* KK1 strain hydrolysed the 28-kDa α -gliadin fraction, and its oral delivery in G+ mice improved enteropathy development in association with decrease of epithelial cell CD71 expression and local cytokine production. In conclusion, the G+ BALB/c mouse represents a new mouse model for human CD based on histopathological features and expression of common biomarkers. The selected probiotic treatment reversing disease development will allow the study of the role of probiotics as a new therapeutic approach of CD.

Laboratory Investigation (2012) **92**, 625–635; doi:10.1038/labinvest.2012.13; published online 13 February 2012

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KEYWORDS: coeliac disease; gluten; IgA; IgA receptors; inflammatory mediators; probiotic yeast; transglutaminase

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

Moorthy Krishnan, PhD,* Harrison M. Penrose, MS,[†] Nilay N. Shah, MS,[†] Ronald R. Marchelletta, PhD,[†] and Declan F. McCole, PhD*

VSL#3 reduces IFN- γ signaling and IFN- γ -induced epithelial barrier defects in a dose-dependent manner. These data point to a key role as a therapeutic target for restoration of barrier function using probiotics.

resistance and fluorescein isothiocyanate–dextran permeability. A novel TCPTP-deficient HT-29 intestinal epithelial cell line was generated to study the role of TCPTP in mediating the effects of VSL#3. Tight junction protein distribution was assessed with confocal microscopy.

Results: VSL#3 increased TCPTP protein levels and enzymatic activity, correlating with a VSL#3-induced decrease in IFN- γ signaling. VSL#3 corrected the decrease in transepithelial electrical resistance and the increase in epithelial permeability induced by IFN- γ . Moreover, the restorative effect of VSL#3 against IFN- γ signaling, epithelial permeability defects, altered expression and localization of the tight junction proteins claudin-2, occludin, and zonula occludens-1, were not realized in stable TCPTP/(PTPN2)-deficient HT-29 intestinal epithelial cells.

Conclusions: VSL#3 reduces IFN- γ signaling and IFN- γ -induced epithelial barrier defects in a TCPTP-dependent manner. These data point to a key role for TCPTP as a therapeutic target for restoration of barrier function using probiotics.

(*Inflamm Bowel Dis* 2016;0:1–13)

Key Words: claudin-2, inflammation, IFN- γ , PTPN2, STAT-1

Probiotics (treatment time – indefinitely)

- *Lactobacillus* (various species): 10–100 billion live organisms daily or higher
- *Saccharomyces boulardii*: 500 mg–3 g daily
- *Bifidobacterium* (various species): 10–100 billion live organisms daily
- *Probiotic mixtures*: 10 billion-3.6 trillion live organisms daily

Prebiotics (treatment time – indefinitely)

- FOS: 500–5,000 mg QD-TID
- Inulin: 500–5,000 mg QD-TID
- Fiber (high soluble)
- Larch (arabinogalactans): 500–5,000 mg QD-TID

Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression

Alex Vasquez, D.C., N.D.

Abstract: Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most comprehensive information on fatty acid metabolism that has ever been published in a single article.

INTRODUCTION

Chiropractic and naturopathic physicians are the only doctorate-level healthcare providers with graduate-level training in therapeutic nutrition and are emerging as the leaders in the treatment and prevention of long-term health disorders, including nearly all of the chronic diseases seen in clinical practice such as obesity, hypertension, adult-onset diabetes, hypercholesterolemia, allergies, asthma, arthritis, depression and a long list of other musculoskeletal and non-musculoskeletal conditions.^{1,2} With the increasing substantiation of the effectiveness and cost-effectiveness of the nutritional management of these problems, and the doc-

Nutritional Perspectives, Vol. 28, no. 1, 1-16

newer selective cyclooxygenase inhibitors carry an unjustifiable cost^{16, 17} and fail to deliver improved efficacy¹⁸ despite significantly increasing the risk for kidney damage, hypertension, myocardial infarction, stroke, and sudden death.^{19, 20, 21} On the other hand, natural treatments such as dietary improvements and fatty acid supplementation have been shown to safely reduce the need for medical treatments, to improve health, to alleviate many common diseases, and to prolong life at lower cost, negligible risk, and with improved overall outcomes.^{22, 23} In order to reduce costs, promote health, and reduce iatrogenic dis-

EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-κB activation and thus reducing elaboration of proinflammatory mediators.

ing errors', hospital injuries, and what is described as 'substandard care'.¹⁴ A recent article in the *New England Journal of Medicine*⁵ concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians⁶ stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than \$136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children⁷ and adults^{8,9} and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.¹⁰ Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.^{11, 12} Many anti-inflammatory drugs for the treatment of joint

the first article in this series²⁴ and in greater detail elsewhere²⁵ is the single most powerful approach for the effective treatment of a wide range of conditions. Following closely behind general dietary modification, fatty acid supplementation offers clinicians the opportunity to improve the health of their patients in ways that no other single treatment can.

FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

An accurate and detailed understanding of fatty acid metabolism is important for the complete and effective management of many clinical conditions including mental depression, coronary artery disease, hypertension, diabetes, other inflammatory/autoimmune disorders, and many of the musculoskeletal conditions encountered in clinical practice. The practical application of this information is

Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling

Robert Caesar,^{1,*} Valentina Tremaroli,¹ Petia Kovatcheva-Datchary,¹ Patrice D. Cani,² and Fredrik Bäckhed^{1,3,*}

We showed that the type of dietary fat is a major driver of community structure, affecting both the composition and diversity of the gut microbiota.

SUMMARY

Dietary lipids may influence the abundance of circulating inflammatory microbial factors. Hence, inflammation in white adipose tissue (WAT) induced by dietary lipids may be partly dependent on their interaction with the gut microbiota. Here, we show that mice fed lard for 11 weeks have increased Toll-like receptor (TLR) activation and WAT inflammation and reduced insulin sensitivity compared with mice fed fish oil and that phenotypic differences between the dietary groups can be partly attributed to differences in microbiota composition. *Trif*^{-/-} and *Myd88*^{-/-} mice are protected against lard-induced WAT inflammation and impaired insulin sensitivity. Experiments in germ-free mice show that an interaction between gut microbiota and saturated lipids promotes WAT inflammation independent of adiposity. Finally, we demonstrate that the chemokine CCL2 contributes to microbiota-induced WAT inflammation in lard-fed mice. These results indicate that gut microbiota exacerbates metabolic inflammation through TLR signaling upon challenge with a diet rich in saturated lipids.

obesity and exhibit reduced WAT inflammation and insulin resistance (Bäckhed et al., 2007; Caesar et al., 2012; Ding et al., 2010; Rabot et al., 2010) have led to the suggestion that microbial factors may directly contribute to WAT inflammation and adverse metabolic consequences. Circulating microbial factors have, indeed, been identified in healthy humans and mice (Caesar et al., 2010). Furthermore, an increased influx of microbial factors has been linked to inflammation and impaired glucose metabolism through activation of Toll-like receptor (TLR)-dependent signaling (Cani et al., 2007; Henao-Mejia et al., 2012). Several genetic mouse models have shown that deletion of components of the TLR signaling pathway is associated with protection against WAT inflammation and/or rescue of metabolically perturbed phenotypes (Jin and Flavell, 2013). However, although TLR ligands may be of bacterial origin, they may also come from the diet or the host (Yu et al., 2010), and, thus, gnotobiotic models are required to determine how the gut microbiota contributes to WAT inflammation upon diet change.

In the present paper, we aim to determine whether WAT inflammation induced by dietary lipids is mediated through the gut microbiota and to identify molecular mechanisms through which the gut microbiota induces macrophage accumulation in WAT.

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Robert Caesar,^{1,*} Valentina Tremaroli,¹ Petia Kovatcheva-Datchary,¹ Patrice D. Cani,² and Fredrik Bäckhed^{1,3,*}

¹The Wallenberg Laboratory, Department of Molecular and Clinical Medicine, University of Gothenburg, 41345 Gothenburg, Sweden

²Université Catholique de Louvain, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, WELBIO (Walloon Excellence in Life Sciences and BIOTECHnology), 1200 Brussels, Belgium

Mice fed fish oil had increased levels of *Lactobacillus*, a known probiotic that has been linked to reduced inflammation and mucosal lesion scores in several models of inflammatory bowel diseases, and increased *Akkermansia muciniphila*, which has been shown to reduce fat mass gain and WAT macrophage infiltration and improve gut barrier function and glucose metabolism when administered to mice with diet-induced obesity

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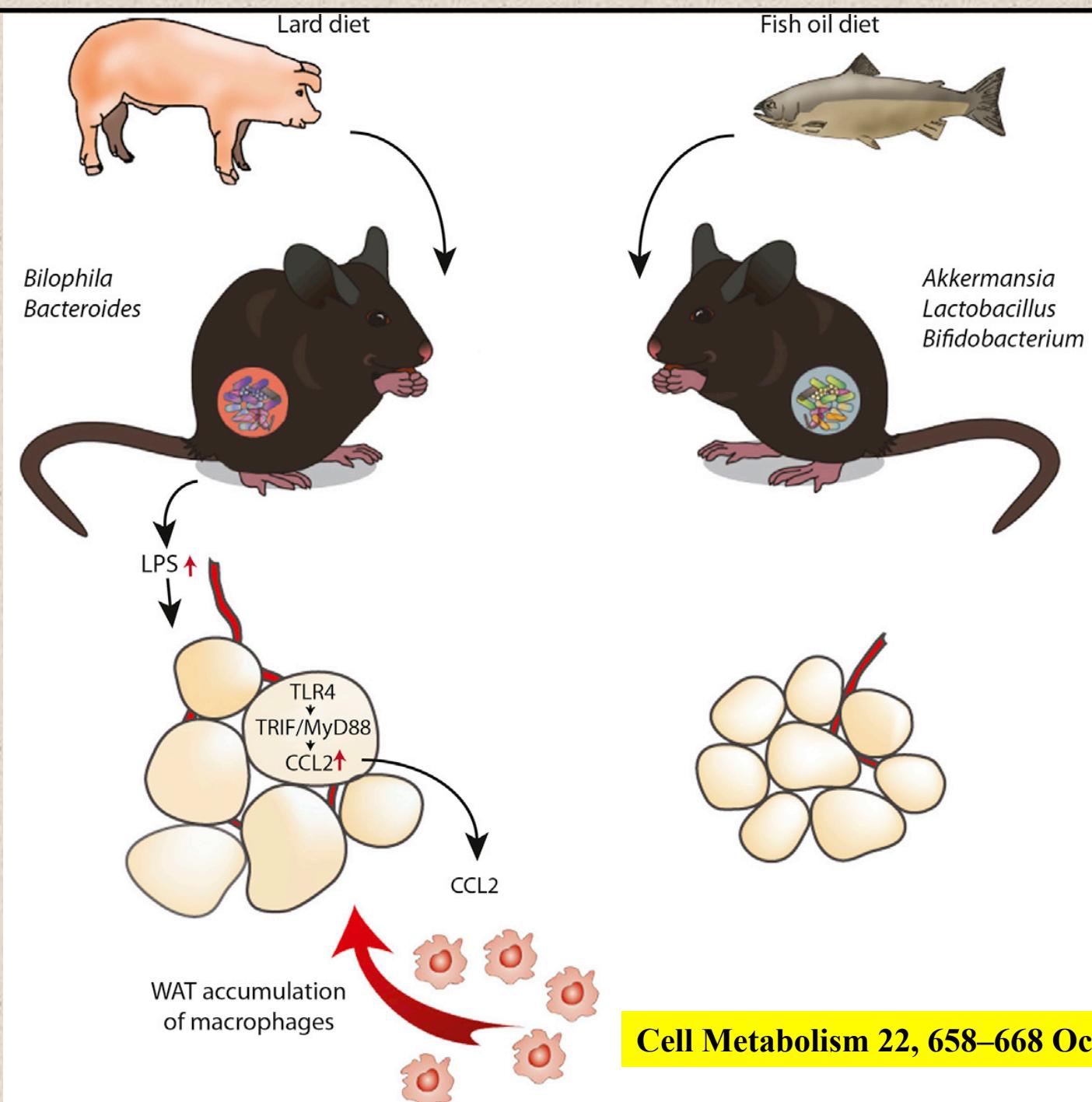
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RESULTS

Impact of Lard versus Fish-Oil Diet on Gut Microbiota

To assess how the dietary fat sources affects the microbiota, we



Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression

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Abstract: Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most comprehensive information on fatty acid metabolism that has ever been published in a single article.

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Nutritional Perspectives, Vol. 28, no. 1, 1-16

newer selective cyclooxygenase inhibitors carry an unjustifiable cost^{16, 17} and fail to deliver improved efficacy¹⁸ despite significantly increasing the risk for kidney damage, hypertension, myocardial infarction, stroke, and sudden death.^{19, 20, 21} On the other hand, natural treatments such as dietary improvements and fatty acid supplementation have been shown to safely reduce the need for medical treatments, to improve health, to alleviate many common diseases, and to prolong life at lower cost, negligible risk.

The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids.

"substandard care."⁴ A recent article in the *New England Journal of Medicine*⁵ concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians⁶ stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than \$136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children⁷ and adults^{8, 9} and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.¹⁰ Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.^{11, 12} Many anti-inflammatory drugs for the treatment of joint

inflammation are associated with greater health care where²⁵ is the single most powerful approach for the effective treatment of a wide range of conditions. Following closely behind general dietary modification, fatty acid supplementation offers clinicians the opportunity to improve the health of their patients in ways that no other single treatment can.

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A Review of Complementary and Alternative Approaches to Immunomodulation

John O. Clarke, MD; and Gerard E. Mullin, MD
Division of Gastroenterology, The Johns Hopkins Hospital, Baltimore, Maryland

Nutrition in Clinical Practice 23:49–62, Feb 2008

ABSTRACT: Current Western therapies for inflammatory diseases are suboptimal; increasingly, patients are turning to complementary and alternative medicine for symptom relief and improved quality of life. There is emerging evidence that many of these therapies have the ability to modulate the immune system and disrupt the proinflammatory cascade through a variety of mechanisms, including antioxidant effects, alterations in cell signaling (in particular the nuclear factor (NF)-κB pathway), cytokines, proinflammatory mediators, and disrupt-

fact, there were already 30,000–40,000 books regarding these practices already in existence.

With all the focus on drug development and marketing, it is easy to forget that nutrition represents the world's earliest medicinal therapy. In the words of Hippocrates (obviously translated) "He who does not know food—how can he cure the disease of man?" Many of the medicinal agents used for therapy today are directly derived from food sources. The role of functional foods in health and disease pre-

A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption.

ated, and explore the data to date for the prevention or treatment of IBD.

The majority of reimbursed care in the United States today is *via* Western medicine, a tradition that harkens back, in a primitive form, only to the Renaissance. Complementary and alternative medicine (CAM) refers to medical practices that are not currently considered to be part of conventional medicine. However, these "alternative" and "natural" approaches have significant time-proven history, just not in Western literature. Traditional Chinese medicine stretches back 5000 years, and traditional Indian (Ayurvedic) medicine can trace its history for over 2000 years. At the start of the 20th century, in

gallocatechin, curcumin, and boswella), ω-3 essential fatty acids (EFA; fish oil), vitamin D, and probiotics. Although many diseases can be examined as a model for inflammation (including inflammatory bowel disease [IBD], rheumatoid arthritis, and multiple sclerosis, to name a few), we have elected to focus on IBD exclusively because: (a) we are gastroenterologists and this is our bias, and (b) to dwell on every inflammatory condition would make this paper too unwieldy to be readable without coercion.

In the words of Hippocrates: "Let food be thy medicine."

Polyphenols

Polyphenols are phytochemicals that are found in food substances produced from plants. Polyphenols are separated from essential micronutrients in that a deficiency state has not been identified; nevertheless, these chemicals are believed to play biologically active role and have been shown to be potentially immunomodulating.² Although numerous polyphenols have been identified, 4 in particular have a preponderance of evidence in the role of immune modulation and will be addressed in this review: resveratrol, epigallocatechin, curcumin, and boswellia. The findings of polyphenols to prevent and treat animal models of IBD are summarized in Table 1.^{3–22}

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Treatment Protocols

(personal recommendations-EPA/DHA)

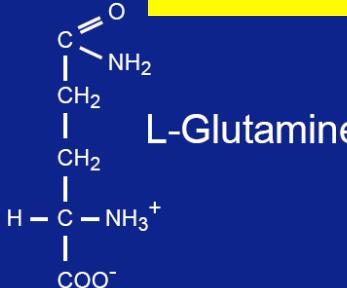
Therapeutic dosages:

30-75 lbs = at least 1 g/d (Total Omega 3's)

76-125 lbs = at least 2g/d (Total Omega 3's)

> 125 lbs = 3+ g/d (Total Omega 3's)

Note: Numerous studies regarding the impact of Omega 3's on CardioVascular and Cognitive function show beneficial results with dosages of 3 g/d up to 20 g/d. Caution is recommended regarding hypocoagubility



Monograph

L-Glutamine

Introduction

L-glutamine is the most prevalent amino acid in the bloodstream and because human cells readily synthesize it, is usually

The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel.

tients, immune enhancement in endurance athletes, and prevention of complications associated with chemotherapy, radiation, and bone marrow transplant.^{1,2}

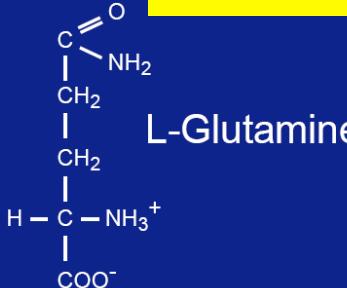
Biochemistry

L-glutamine accounts for 30-35 percent of the amino acid nitrogen in the plasma. It contains two ammonia groups, one from its precursor, glutamate, and the other from free ammonia in the bloodstream. One of glutamine's roles is to protect the body from high levels of ammonia by acting as a "nitrogen shuttle." Thus, glutamine can act as a buffer, accepting, then releasing excess ammonia when needed to form other amino acids, amino sugars, nucleotides, and urea. This capacity to accept and donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.^{1,2}

Clinical Indications

Gastrointestinal Disease

The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel. Most of the research on glutamine

**Monograph****L-Glutamine****Introduction**

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A clinical study of ulcerative colitis patients

- **30 g daily of glutamine four weeks**
- **significant clinical and endoscopic improvement,**
independent of disease state.
- **Disease exacerbation returned when treatment was discontinued.**

donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.^{1,2}

Clinical Indications**Gastrointestinal Disease**

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CME

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Patrick Hanaway, MD

Patrick Hanaway, MD, is a board-certified family physician who holds dual appointments as medical director for the Family to Family Clinic and chief medical officer for Genova Diagnostics, both in Asheville, NC.

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needs that require support for the whole being to regain balance and optimal function.

TARGET AUDIENCE

This activity is designed to meet the educational needs of physicians and other healthcare professionals who diagnose, treat, and manage patients who have or are at risk for gastrointestinal disorders.

L-glutamine is a very useful clinical tool, but it is also a substrate for lymphocytes and macrophages, in addition to being a precursor of nitric oxide. Thus, it is necessary to ensure that inflammation is resolved before treating with this powerful trophic factor. Glutamine has also been noted to be a substrate for *Candida synthesis*, so this should be evaluated before initiating therapy.

the textbook's Chapter 28, "Clinical Approaches to Gastrointestinal Imbalance." For more information or to purchase the textbook, contact The Institute for Functional Medicine, PO Box 1697, Gig Harbor, WA 98335; (800) 228-0622; or visit its website, www.functionalmedicine.org.



will ingest many tons of macronutrients,

Release date: Sept 1, 2006
Expiration date: Sept 30, 2007
Reprint requests: Ph: (760) 613-3910 or (866) 828-2962; e-mail, alternative.therapies@innovisionway.com. Or visit our online CME website at <http://www.alternative-therapies.com> and select the Continuing Education option.

Treatment Protocols (personal recommendations-Glutamine)

Therapeutic dosages:

Dosages vary greatly depending on the clinical situation

- 2-4 g/d in divided dosages for wound healing and general intestinal support**
- 10-40 g/d in divided dosages for critically ill and advanced disease**



Review

Curcumin, An Atoxic Antioxidant and Natural NF κ B, Cyclooxygenase-2, Lipooxygenase, and Inducible Nitric Oxide Synthase Inhibitor: A Shield Against Acute and Chronic Diseases

Stig Bengmark, MD, PhD, FRACS (hon), FRCR

From the Institute of Hepatology, University College, London Medical School, London, United Kingdom

J OF PAR AND ENT NUTRITION
Vol. 30,no.1, 2006,45-51

ABSTRACT. *Background:* The world suffers a tsunami of chronic diseases, and a typhoon of acute illnesses, many of which are associated with the inappropriate or exaggerated activation of genes involved in inflammation. Finding ther-

apeutic agents that can inhibit these genes, particularly nitric oxide synthase (NOS), significant preventive and/or curative effects have been observed in experimental animal models of a number of diseases, including arteriosclerosis, cancer, diabetes, respiratory, hepatic, pancreatic, intestinal and gas-

Turmeric, an approved food additive, or its component curcumin, has shown surprisingly beneficial effects in experimental studies of acute and chronic diseases characterized by an exaggerated inflammatory reaction. There is ample evidence to support its clinical use, both as a prevention and a treatment.

expected to double by 2011.¹ In order to prevent a total collapse of the system, preventive measures will be increasingly necessary.

The cost of medication is a large and growing part of health expenditure. This is one of many reasons why

fruits, kaempferol in white cabbage, myricetin in berries, quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine, and various curcumenoids found in turmeric (TU) curry.

Curcumin (CU): A Promising Tool

Interest in polyphenols, and especially in CU as a chemoprotective agent, has dramatically increased in recent years. CU, the most explored of the curcumenoids, has received increasing interest in recent years. The majority of studies reported thus far are

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Invited Review

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With all the focus on drug development and marketing, it is easy to forget that nutrition represents the world's earliest medicinal therapy. In the

The cell signaling effects of curcumin seem to be pleiotropic as administration of curcumin has been reported to modulate a host of other cytokines and signaling pathways, including inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9 (MMP-9), TNF, c-Jun N-terminal kinase (JNK), p38, Akt, Janus kinase (JAK), extracellular signal regulated protein kinase (ERK), and protein kinase C (PKC).

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polyphenols have been identified,⁴ in particular have a preponderance of evidence in the role of immune modulation and will be addressed in this review: resveratrol, epigallocatechin, curcumin, and boswellia. The findings of polyphenols to prevent and treat animal models of IBD are summarized in Table 1.^{3–22}

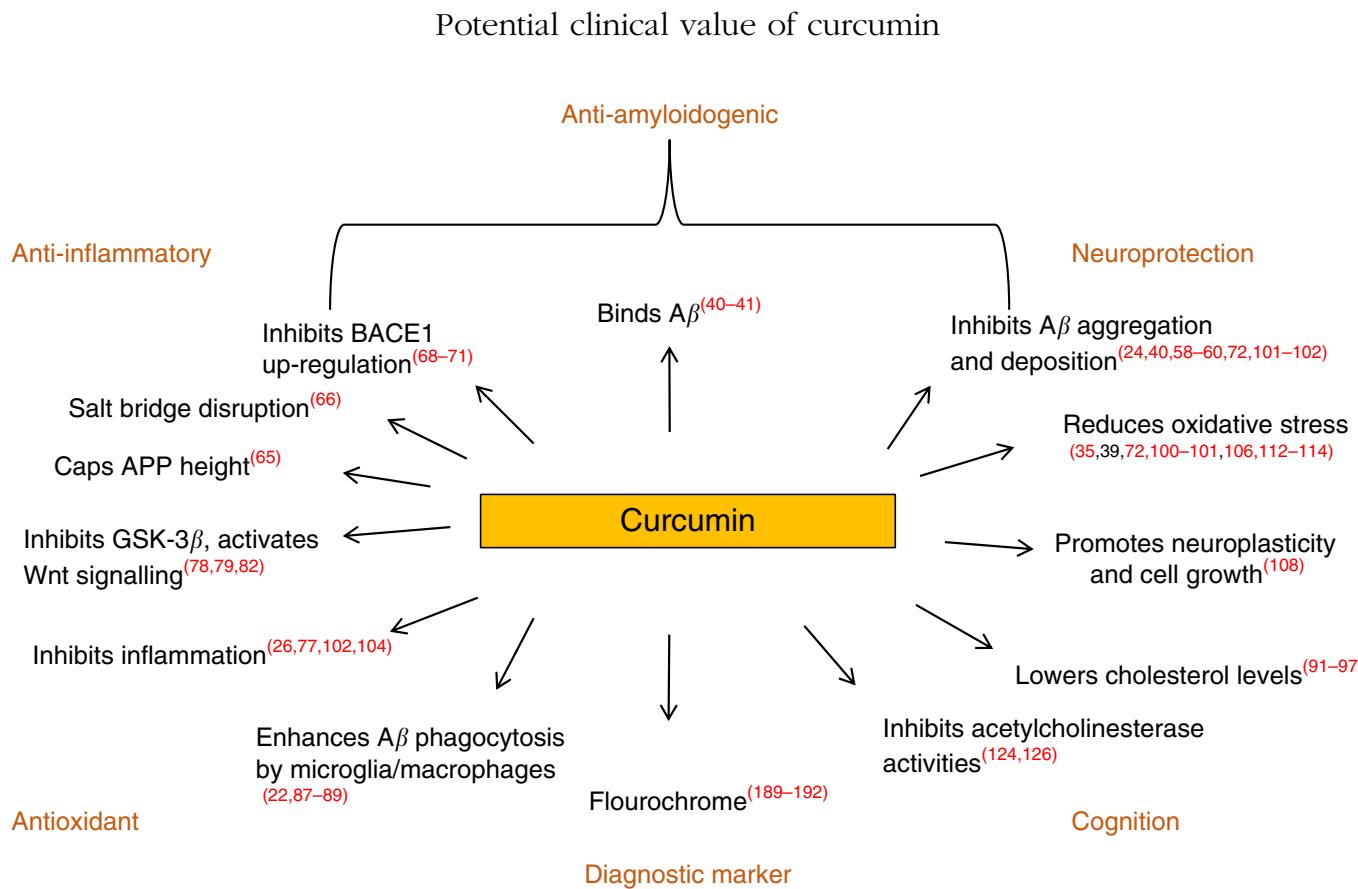
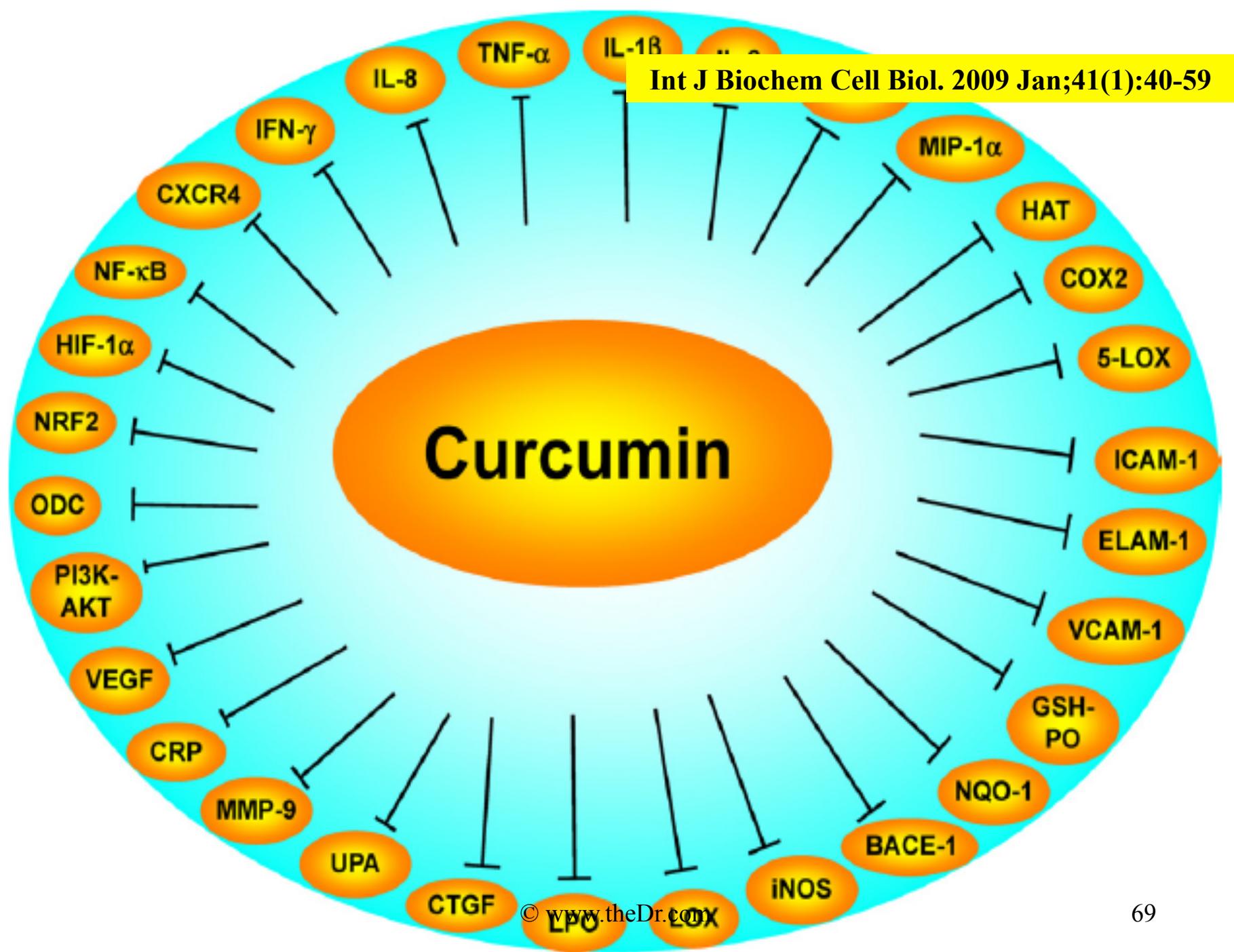


Fig. 1. Curcumin: reported mechanisms of action. BACE1, β -APP-cleaving enzyme-1; A β , β amyloid; APP, amyloid precursor protein.

Table 1. Studies using curcumin in Alzheimer's disease (AD): diagnosis, prevention and treatment

Study	Agent	Cohort	Dose	Duration	End points and brief summary of results
Baum <i>et al.</i> ⁽¹³⁷⁾ (NCT00164749)	Curcumin and ginkgo	Probable AD; 50 years+; n 30	1, 4 g daily	6 months	Safety and effects, biochemical and cognitive measures No differences detected between treatment groups in A β levels or MMSE scores
Ringman <i>et al.</i> ⁽¹⁴⁵⁾ (ACT00099710)	Curcumin C3 complex [®]	Mild/moderate AD; age 49 years+; n 30	2, 4 g daily	24 weeks plus 24 open label	Side effects, blood biomarkers and cognition No differences detected between treatment groups in clinical or biomarker efficacy measures; results also indicated low bioavailability
Hishikawa <i>et al.</i> ⁽¹⁵⁰⁾	Turmeric capsules	Severe AD; n 3	100 mg curcumin daily	12 months, tested after 12 weeks	MMSE and NPIQ; score on NPIQ decreased significantly, MMSE increased in 1/3
Poncha (NCT01001637)	Longvida TM	Moderate – severe AD; 50–80 years; n 160	2, 3 g twice daily	2 months	Efficacy and safety; blood and cognition
Martins & Goozee (ACTRN12613000681752)	Biocurcumax TM BCM-95	Retirement living, healthy 65–90 years; n 100	500 mg, thrice daily	12 months	Cognition, blood biomarkers/chemistry; lifestyle questionnaires; brain imaging (MRI, PET FDG and amyloid), retinal imaging
Martins (ACTRN12611000437965)	Biocurcumax TM BCM-95	Community living, healthy 55–75 years; n 100	500 mg, thrice daily	12 months	Cognition, blood biomarkers/chemistry; lifestyle brain imaging
Small (NCT01383161)	Theracurmin CR-031P TM	MCI/normal ageing n 132	90 mg/d twice daily	18 months	Cognition; blood; genetic profile
Frautschy (NCT018811381)	Longvida and yoga	Subjective cognitive complainers 55–90 years; n 80	400 mg, twice daily	6 months	Biochemistry, cognition and FDG PET
Cox <i>et al.</i> ⁽¹⁴⁴⁾ (ACTRN12612001027808)	Longvida TM	Healthy and cognitive decline 65–80 years; n 60	400, 800 mg daily	Phase 1: acute 1–3 h/ 4 weeks Phase 2: 8 weeks	Cognition, mood and anxiety; blood biomarkers fMRI; cognition
Patterson (NCT00595582 early termination)	Curcumin bioperine	MCI 55–85 years; n 10	900 mg twice daily	24 months	Cognition and size of metabolic lesions on the PET scan
Martins & Goozee (ACTRN12614001024639)	Biocurcumax TM BCM-95	Healthy and MCI 65–90 years; n 48	500 mg twice daily	3 months	Gene regulation and expression; and cognition
Verdooner & Martins (ACTRN12613000367741)	Longvida TM	Healthy, MCI, mild/moderate AD 50 years+; n 200	20 g daily (shake)	7 d	Diagnostics; curcumin fluorescence retinal imaging of A β plaques

A β , β amyloid; MMSE, Mini Mental State Examination; PET, positron emission tomography; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; NPIQ, Neuro-Psychiatric Inventory-Brief Questionnaire; fMRI, functional MRI.



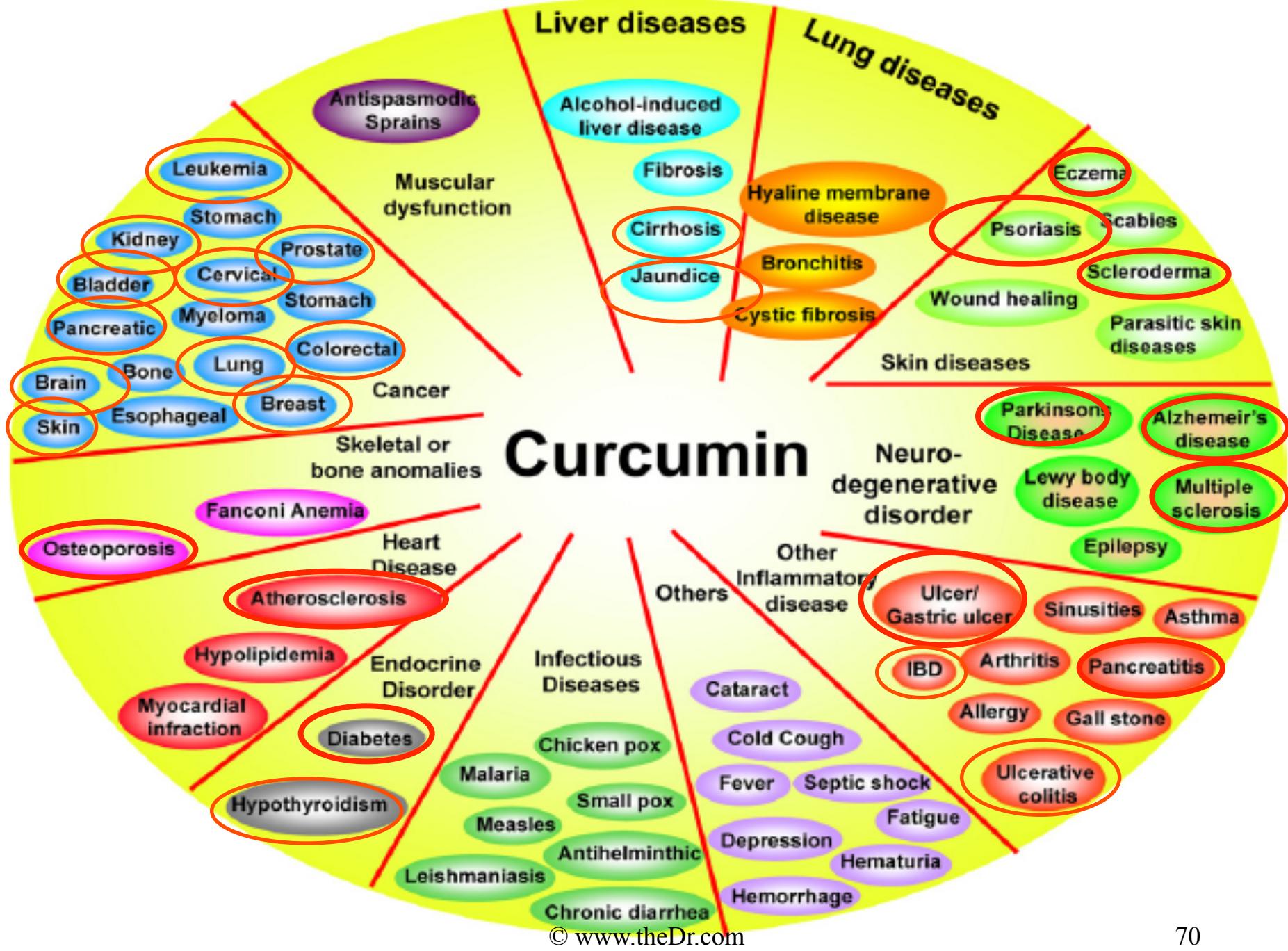


Fig. 2. Effect of curcumin on various proinflammatory diseases.

Treatment Protocols

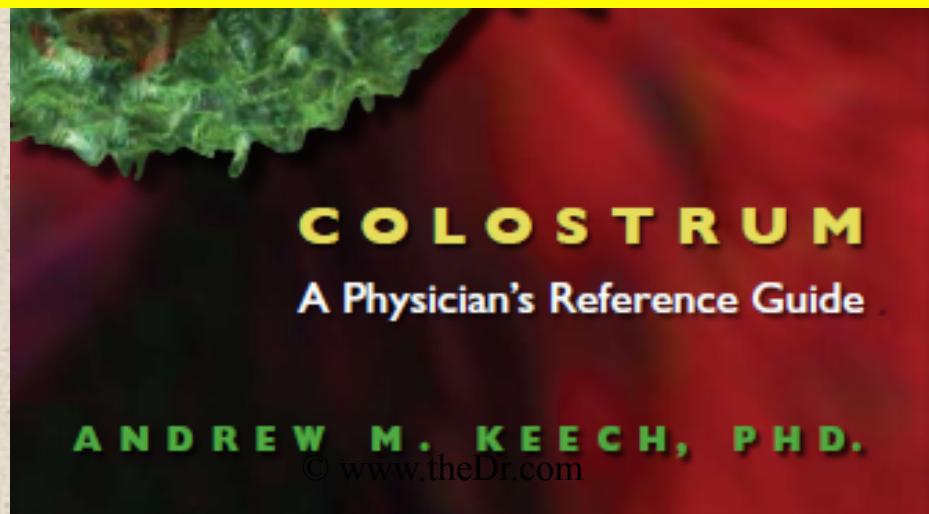
(personal recommendations-Curcumin)

Therapeutic dosages:

**Turmeric (*Curcuma longa*) standardized to
curcuminoids 500mg TID up to 4g daily**

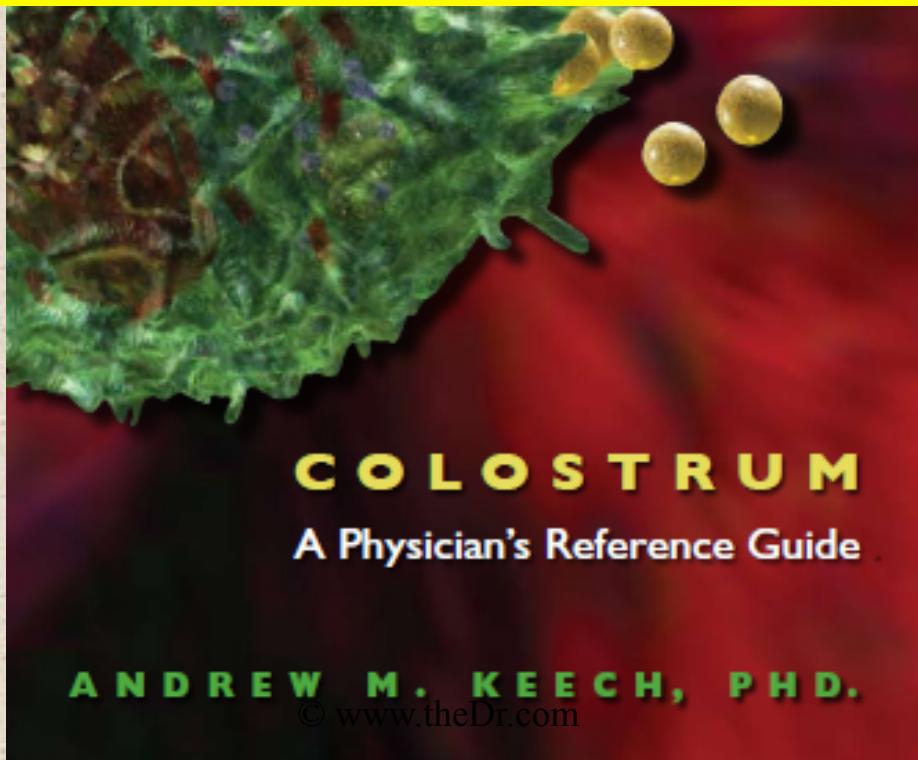
Peptide Immunotherapy

High intestinal permeability is a normal feature of newborn gut ecology. Colostrum functions to reduce inflammation protect against irritation from toxins and check any potential infection, while promote epithelial growth and repair.



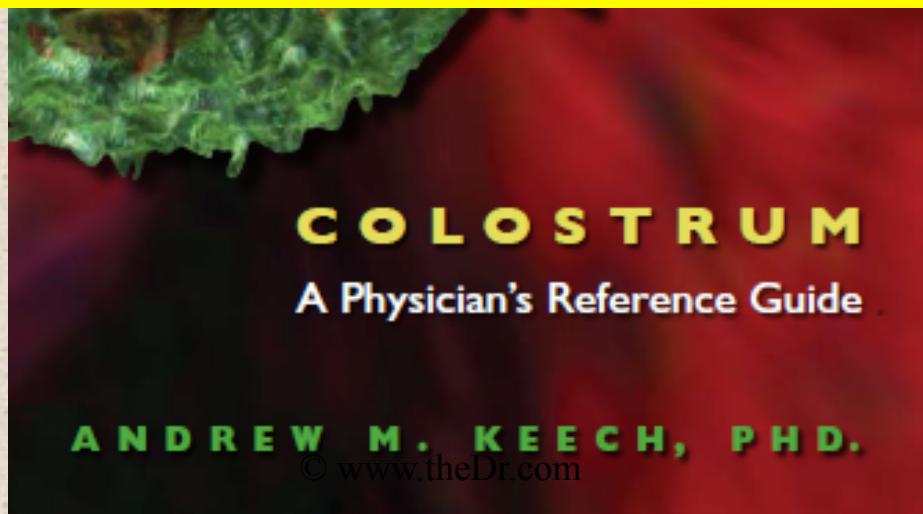
Peptide Immunotherapy

**Colostrum also promotes re-colonization
of the bowel by the friendly flora.**



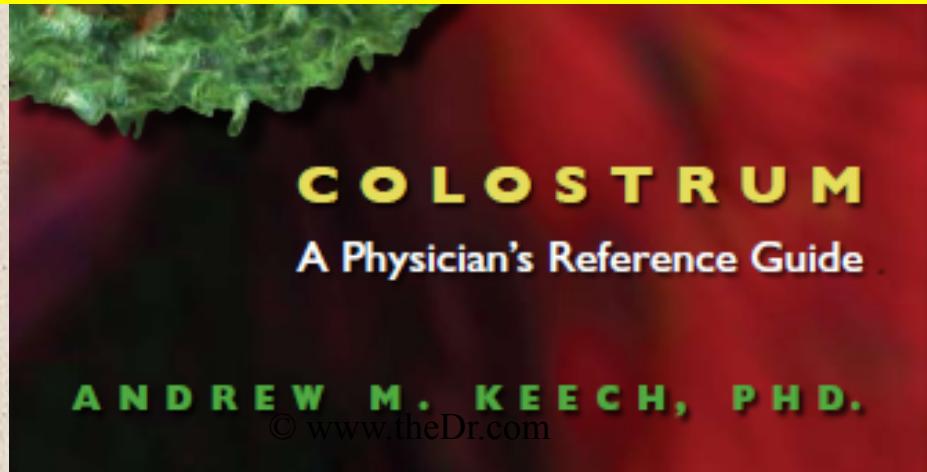
Peptide Immunotherapy

Colostrum is the best remedy known for all-around gut health. Colostrum restores leaky gut to normal permeability levels. It contains growth factors and hormones to help repair damage to the intestinal lining, and restore gut integrity.



Peptide Immunotherapy

Colostrum is unmatched as an immune system stimulant and modulator. There are numerous “one note” products lining the shelves of natural food stores that claim to stimulate the immune system. Only colostrum, however, plays the whole symphony.



**Gut Microbiome and Brain-Gut Axis in Autism —
Aberrant Development of Gut-Brain Communication
and Reward Circuitry**

Elizabeth M. Sajdel-Sulkowska and
Romuald Zabielski

Additional information is available at the end of the chapter

The two key developmental time-points in the regulation of the GIT both occur postnatally,

- the first few days after birth when all gut digestive functions are launched by first colostrum ingestion and**
- the second at weaning when the digestive system has to modify its function following a switch from mother's milk to solid food.**

toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

This chapter attempts to bridge basic animal studies with clinical findings pertaining to the brain-gut and gut microbiome in autism, and includes a discussion of various strategies in managing autistic symptoms. The discussion also includes possible changes in the reward

Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry, Published: March 6, 2013

Chapter 4

Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry

Elizabeth M. Sajdel-Sulkowska and
Romuald Zabielski

Additional information is available at the end of the chapter

The first time-point is particularly relevant for all mammalian species since it is associated with a complex of dynamic changes in the GIT structure and function leading to a temporary drop in the gut permeability barrier.

hormones involved in the regulation of food intake, such as cholecystokinin (CCK), ghrelin, leptin and insulin, and by the immunological signaling pathway involving cytokines. Recent studies indicate that the vagus nerve is involved in immunomodulation as suggested by its ability to attenuate the production of proinflammatory cytokines in experimental models of inflammation (de Jonge and Ullola, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

This chapter attempts to bridge basic animal studies with clinical findings pertaining to the brain-gut and gut microbiome in autism, and includes a discussion of various strategies in managing autistic symptoms. The discussion also includes possible changes in the reward



Gut on FIRE! Body on Fire

- Eliminate Inflammatory Foods
- Prebiotics
- Apple Pectin
- Bone Broth
- Fermented Foods
 - Probiotics
- Vitamin D
- Glutamine
- EPA/DHA
- Curcumin
- Colostrum

**Note: There are many other beneficial anti-inflammatories that
can be used. These are foundational recommendations**

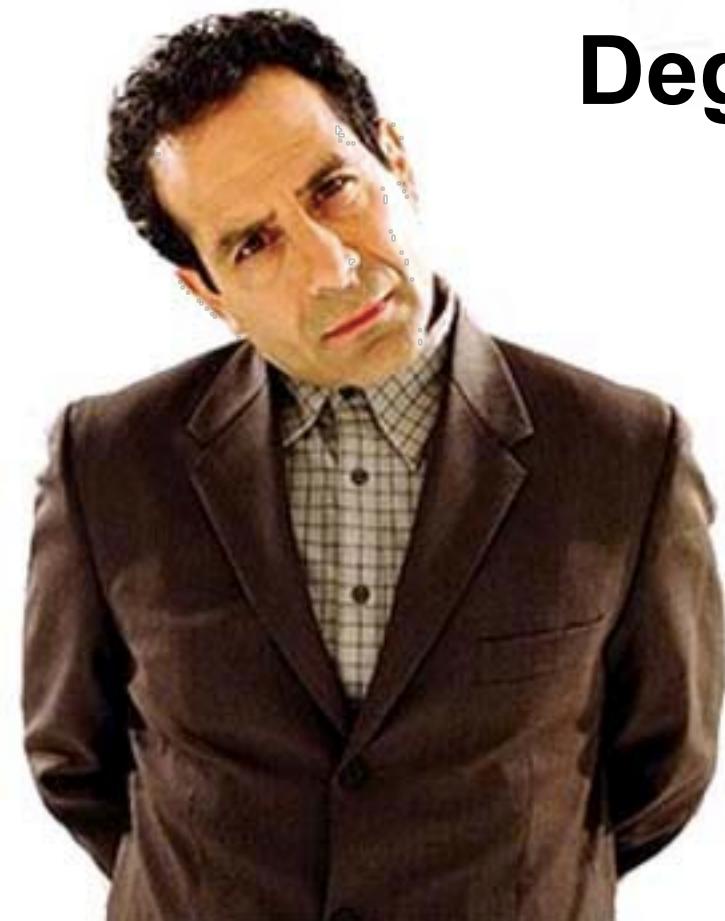


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Premise #1

**Why Such a Delay in
Recognizing that Autoimmune
Disease is the Platform of
Degenerative Diseases?**



Detective Adrian Monk



The answer is 17 years, what is the question: understanding time lags in translational research

J R Soc Med 2011 104: 510

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²RAND Europe, Cambridge CB4 1YG, UK

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DECLARATIONS

Summary

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.

RESEARCH

Programme in the Department of Health. The views expressed are not necessarily those of the Department

Ethical approval
Not applicable

Guarantor
JG

Contributorship
ZSM designed, conducted and analysed the literature review, and drafted and revised the paper;
JG initiated the project, drafted and revised the paper, and has led a number of studies cited that attempted to measure lags; SW revised the paper

face difficulties in knowing what they should or can do to reduce time lags.

This effectively 'blindfolds' investment decisions and risks wasting effort.

The study concludes that understanding lags first requires agreeing models, definitions and measures, which can be applied in practice. A second task would be to develop a process by which to gather these data.

Introduction

Timely realization of the benefits of expensive medical research is an international concern attracting considerable policy effort around 'translation'.^{1,2} Policy interventions to improve translation respond to a vast empirical literature on the difficulties of getting research across research phases and into practice.^{3–11}

Both literature and policy tend to assume that speedy translation of research into practice is a good thing. Delays are seen as a waste of scarce resources and a sacrifice of potential patient benefit.¹² Although some lag will be necessary to ensure the safety and efficacy of new interventions or advances, in essence we should aim to optimize lags. One recent study (of which JG and SW were co-authors) estimating the economic benefit of cardiovascular disease (CVD) research in the UK between 1975 and 2005, found an internal rate of return (IRR) of CVD research of 39%.¹³ In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits

equivalent to earning £0.39 per year in perpetuity. Of this, 9% was attributable to the benefit from health improvements, which is the focus of this paper. (The remaining 30% arose from 'spillovers' benefiting the wider economy.) This level of benefit was calculated using an estimated lag of 17 years. Varying the lag time from 10 to 25 years produced rates of return of 13% and 6%, respectively, illustrating that shortening the lag between bench and bedside improves the overall benefit of cardiovascular research. What is notable is that all the above calculations depended upon an estimated time lag; estimated because, despite longstanding concerns about them,¹⁴ time lags in health research are little understood.

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.^{1,3,15} Balas and Bohen,¹⁶ Grant¹⁷ and Wratschko¹⁸ all estimated a time lag of 17 years measuring different points of the process. Such convergence around an 'average' time lag of 17 years hides complexities that are relevant to

Premise #2

**We Have To Wake Up and ‘up our game’
in How We Look at Our Predicament**



Detective Adrian Monk



Trends differ in the different systems, with

- terrestrial systems declining by 38%,**
- marine systems declining by 36% and**
- freshwater being reduced by more than 75% of their abundance in 1970.**

Report 2016

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in a new era**

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Premise #3

Where does Autoimmunity Initiate



Detective Adrian Monk

Letter to Editor

How Macrophages are Converted to Foam Cells

We agree with Nicolaou *et al.* in their view about the conversion of macrophages to foam cells¹⁾. Foam cell formation cannot be caused by the uptake of oxi-

pathogens. Accordingly, *in vitro* experiments have shown that LPS from *Chlamydia pneumoniae* and also from several periodontal pathogens is able to convert

It has also been demonstrated that human LDL inactivates up to 90% of *Staphylococcus aureus* alpha-toxin and even a larger fraction of bacterial lipopolysaccharide (LPS)

that "increased lipid uptake and reduced cholesterol efflux" are responsible¹⁾.

It is not widely known that lipoproteins are able to bind and inactivate microbes and their toxins effectively by complex formation, as documented by more than a dozen research groups^{2, 3)}. For instance, complex formation between all lipoprotein subclasses and both bacteria and viruses has been demonstrated by electron microscopy, enzyme-linked immunoabsorbance assay, and column chromatography²⁾. It has also been demonstrated that human LDL inactivates up to 90% of *Staphylococcus aureus* alpha-toxin and even a larger fraction of bacterial lipopolysaccharide (LPS)²⁾.

The protective effect of lipoproteins has also been demonstrated in animal experiments. For instance, compared with normal rats, hypocholesterolemia induced by LDL depletion in all three

tivate phagocytosed pathogens by producing oxygen radical species, promoting LDL oxidation⁷⁾.

As suggested by Nicolaou *et al.*¹⁾, conversion of macrophages to foam cells by bacteria indicates that these pathogens contribute to the development of atherosclerosis. We have suggested that sufficiently large complexes between microorganisms and lipoproteins may occlude the *vasa vasorum* because of high extracapillary pressure and because of endothelial dysfunction induced by hyperhomocysteinemia⁷⁾, producing ischemia of the arterial wall and vulnerable plaques of the arteries^{2, 8)}.

Both authors declare that we have no conflict of interest.

Premise #4

What are the Antigenic Agents Passing Through a Permeable Intestine?



Detective Adrian Monk

Epidemiology of *Helicobacter pylori* infection among the healthy population in Iran and countries of the Eastern Mediterranean Region: A systematic review of prevalence and risk factors

It has been estimated that more than 50% of the population aged 5 years is infected and this rate may exceed 90% during adulthood.

pital, Shiraz University of Medical Sciences, Shiraz 71345-1744, Iran

Author contributions: Eshraghian A sorely contributed to this paper.

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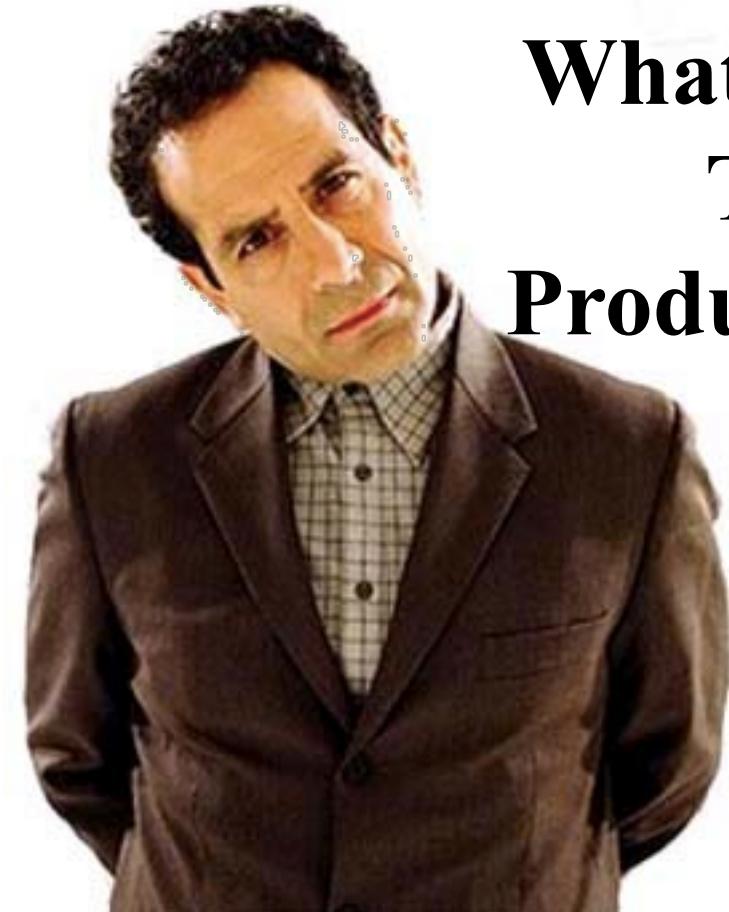
Published online: December 14, 2014

Kingdom of Saudi Arabia, 4 studies from Egypt, 2 from the United Arab Emirates, and one study from Libya, Oman, Tunisia, and Lebanon, respectively. The overall prevalence of *H. pylori* infection in Iran, irrespective of time and age group, ranged from 30.6% to 82%. The overall prevalence of *H. pylori* infection, irrespective of time and age group, in other EMRO countries ranged from 22% to 87.6%.

CONCLUSION: The prevalence of *H. pylori* in EMRO countries is still high in the healthy asymptomatic population. Strategies to improve sanitary facilities, educational status, and socioeconomic status should be

Premise #5

What is the One Identifiable and
Treatable Trigger in the
Production of Antibodies To Self?



Detective Adrian Monk

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90

REVIEW

www.nature.com/clinicalpractice/gasthep

Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

SUMMARY

The primary function

perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur. This neuroepidemiologic evidence

NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9

means that they are the third most common category of diseases in the US after cancer and heart disease. They can affect virtually every site in the body, including the gastrointestinal tract. At least 15 diseases are known to be the direct result of an autoimmune response, and circumstantial evidence links more than 80 conditions to autoimmunity.¹

CLASSICAL THEORIES ON THE

The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.

"autoimmunity", "tight junctions", "toll", "innate immunity", "occludin", "claudin", "claudins", and "intestinal AND disease AND permeability". Only full papers published in English were considered. Additional searches were performed using Retro Search and Google.

A Fasano is Professor of Pediatrics, Medicine, and Physiology, and Director of the Mucosal Biology Research Center and the Center for Celiac Research, and T Shea-Donohue is Professor of Medicine and Physiology and a member of the Mucosal Biology Research Center, at the University of Maryland School of Medicine, Baltimore, MD, USA.

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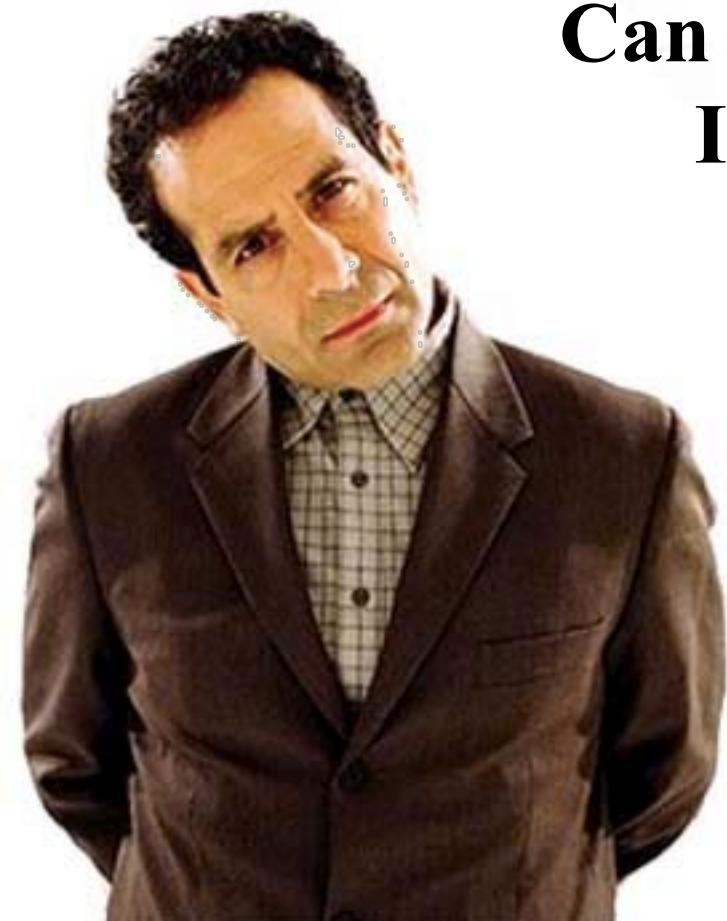
www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep0259

It becomes independent of continuous exposure to the environmental trigger, and is therefore self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbial antigens and self-antigens has been shown in some animal models to initiate autoimmunity.³ Conversely, in most human autoimmune diseases, molecular mimicry seems to be a factor in the progression of a pre-existing subclinical autoimmune response, rather than in the initiation of autoimmunity.³

Another theory suggests that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infection, and that this leads to the development of autoimmunity. This mechanism has been referred to as the 'bystander effect', and it occurs only when the new antigen is presented with the

Premise #6

Can Foods Trigger Pathogenic Intestinal Permeability



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Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity

Conclusions: Increased intestinal permeability after gliadin exposure occurs in all individuals.

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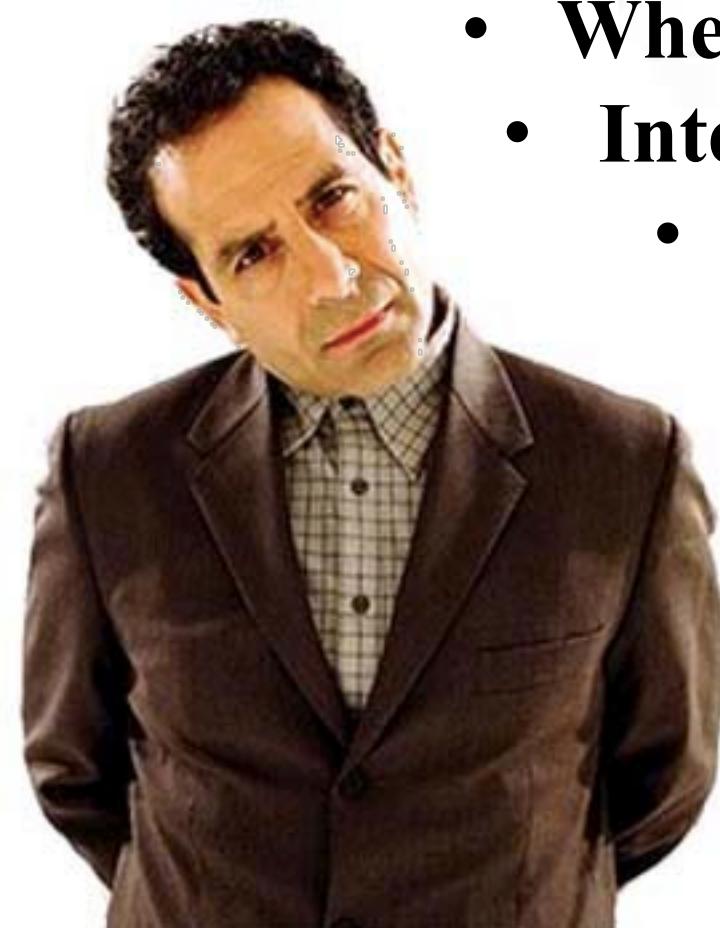
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Premise #7

Breakthroughs in Identifying:

- Wheat Related Disorders
 - Intestinal Permeability
 - Autoimmunity



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RESEARCH ARTICLE

Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays

Rok Seon Choung¹, Eric V. Marietta¹, Carol T. Van Dyke¹, Tricia L. Brantner¹, John Rajasekaran², Pankaj J. Pasricha³, Tianhao Wang², Kang Bei², Karthik Krishna², Hari K. Krishnamurthy², Melissa R. Snyder⁴, Vasanth Jayaraman^{2†}, Joseph A. Murray^{1‡*}

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We identified 2 distinct discontinuous gliadin sequence sets that, when combined, significantly improved the sensitivity (IgG, 97%; IgA, 99%) and specificity (IgG, 98%; IgA, 100%) ($P < .001$) for the diagnosis of CD.

OPEN ACCESS

Citation: Choung RS, Marietta EV, Van Dyke CT, Brantner TL, Rajasekaran J, Pasricha PJ, et al. (2016) Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays. PLoS ONE 11(1): e0147777. doi:10.1371/journal.pone.0147777

Editor: Massimo Pietropaolo, Baylor College of Medicine, UNITED STATES

Background

Most antibodies recognize conformational or discontinuous epitopes that have a specific 3-dimensional shape; however, determination of discontinuous B-cell epitopes is a major challenge in bioscience. Moreover, the current methods for identifying peptide epitopes often involve laborious, high-cost peptide screening programs. Here, we present a novel microarray method for identifying discontinuous B-cell epitopes in celiac disease (CD) by using a silicon-based peptide array and computational methods.

Premise #8

How do we Arrest Pathogenic Intestinal Permeability



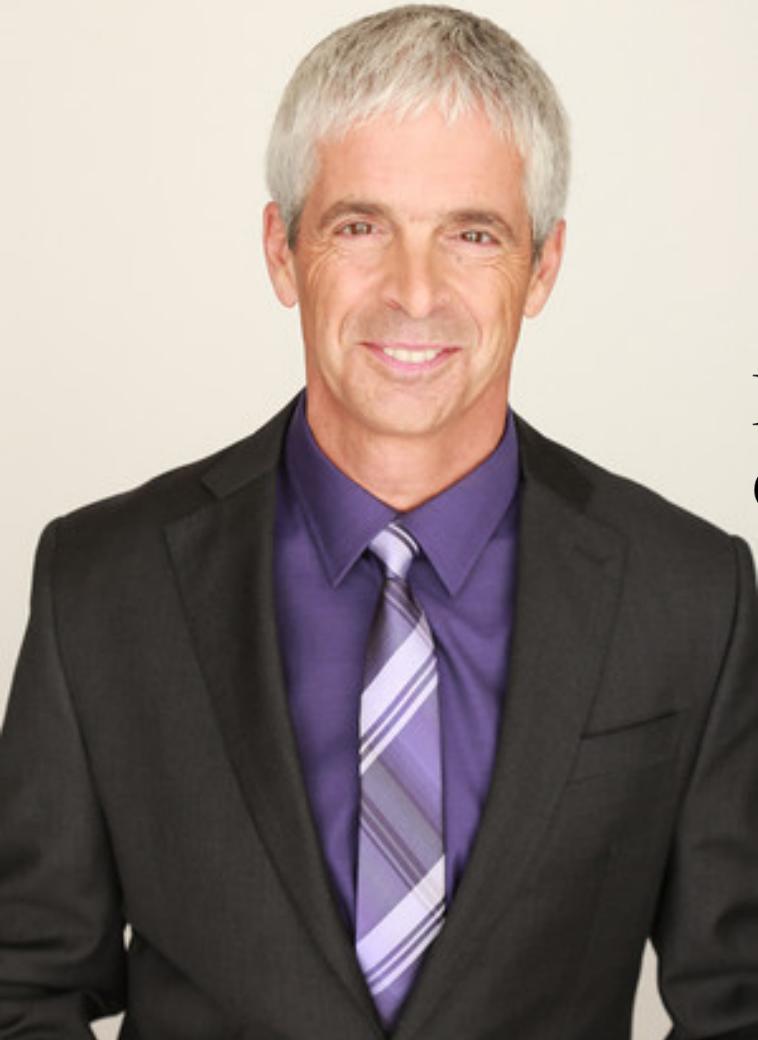
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- Bone Broth
- Fermented Foods
 - Probiotics
- Vitamin D
- Glutamine
- EPA/DHA
- Curcumin
- Colostrum

**Note: There are many other beneficial anti-inflammatories that
can be used. These are foundational recommendations**



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JEFFREY S. BLAND, PH.D.

WITH SARA H. BENUM, M.A.

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“Thank You for Your Kind Attention”



A scenic landscape featuring a vibrant field of pink and red flowers in the foreground, rolling green hills in the middle ground, and a majestic mountain range under a dramatic sunset sky in the background.

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The medical community is unable to reach consensus on what to do with America's health insurance situation.

The Allergists were in favor of scratching it, but the Dermatologists advised not to make any rash moves.

The Chiropractors tried to straighten out the whole mess.

The Gastroenterologists had sort of a gut feeling about it, but the Neurologists thought the Administration had a lot of nerve.

Meanwhile, Obstetricians felt certain everyone was laboring under a misconception, while the Ophthalmologists considered the idea shortsighted.

Pathologists yelled, "Over my dead body!" while the Pediatricians said, "Oh, grow up!"

The Psychiatrists thought the whole idea was madness, while the Radiologists could see right through it.

Surgeons decided to wash their hands of the whole thing and the Internists claimed it would indeed be a bitter pill to swallow.

The Plastic Surgeons opined that this proposal would "put a whole new face on the matter."

The Podiatrists thought it was a step forward, but the Urologists were pissed off at the whole idea.

Anesthesiologists thought the whole idea was a gas, and those lofty Cardiologists didn't have the heart to say no.

In the end, the Proctologists won out, leaving the entire decision up to the assholes in Washington.