**Figure 44.1.** Interaction of various factors contributing to chronic intestinal inflammation in a genetically susceptible host.

**Figure 44.2.** Pathogenesis of IBD. An unknown initiating event causing injury to the gut permits the translocation of bacterial antigens across the breached mucosal barrier into the mucosal immune system. A genetically determined aberrant immune response elaborates an imbalance in T-helper-1 (Th1) and T-helper-2 (Th2) cytokines which drives the proinflammatory response into chronicity. Luminal contents which breach the impaired intestinal barrier then perpetuate a viscous cycle of immune hyperreactivity, inflammation and tissue injury.
Figure 44.3. Impaired Cellular Defense Mechanisms in IBD

Figure 44.4. Omega-3 Modulation of Arachidonic Acid Cascade
Figure 44.5. The Role of Fish Oil on Inflammatory Mediators. Vegetable oils such as corn oil (n6) promote the metabolism of arachidonic acid into PGE2, SRSA (low releasing substance of anaphylaxis), and LTB4, which provoke inflammation via proinflammatory cytokines and NFkB. As white blood cells and neutrophils degranulate and destroy tissues, biochemicals called resolvins and protectins are produced to further limit the inflammatory cascade. N3 fatty acids facilitate the “clean up” or resolution phase though resolvin and protectin production.

Figure 44.6 Omega 3 Fatty Acids for Maintenance of Crohn’s Disease: EPIC-1 and EPIC-2 Trials. A much larger RCT asked whether n3 fatty acids could sustain remission once it is achieved. EPIC-1 (US-based) and EPIC-2 (European-Canadian based). Two randomized, double-blind, placebo-controlled studies (Epanova Program in Crohn’s Study 1 [EPIC-1] and EPIC-2) conducted between January 2003 and February 2007 at 98 centers in Canada, Europe, Israel, and the United States. Data from 363 and 375 patients with quiescent Crohn’s disease were evaluated in EPIC-1 and EPIC-2, respectively. Patients with a Crohn’s Disease Activity Index (CDAI) score of less than 150 were randomly assigned to receive either 4 g/d of omega-3 free fatty acids or placebo for up to 58 weeks. No other treatments for Crohn’s disease were permitted. Clinical relapse, as defined by a CDAI score of 150 points or greater and an increase of more than 70 points from the baseline value, or initiation of treatment for active Crohn’s disease.

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Inflammatory mediators, ROS

Polyphenols

NKxB–IxB

↑ ICAM, iNOS, COX-2, TNFα

Infiltration & activation of NØ, MØ, T cells

Inflammation and injury to parenchymal cell

Nrf2 – Keap 1

Nrf2 – DNA

↓ Oxidative stress, ↑ GSH

Cytoprotection

Potentiates cortisol:
- Glycyrrhiza gabra
- Curcumin longa

Cell membrane

Phospholipase A2

Arachidonic acid

Cyclooxygenase

Lipoxygenase

Zingiber officinale

Curcumin longa

Quercitin

Glycyrrhiza gabra

Zingiber officinale

Curcumin longa

Quercitin

Bromelain

White willow bark

Prostaglandin 2 series

Thromboxane A2

Leukotrienes SRS-A

Figure 44.7. Polyphenols attenuate inflammation and injury. Polyphenolic compounds attenuate inflammation by downregulating NFkB and upregulating Nrf2 DNA, which induces glutathione peroxidase and diminishes oxidative stress, producing a concomitant cytoprotective effect.

Figure 44.8. Botanical Modulation of the Arachidonic Cascade. The pathway by which arachidonic acid in plasma membranes is metabolized to proinflammatory eicosanoids such as PGE2, thromboxane A2, etc. Medications that are given for IBD work, in large part, by their ability to attenuate this pathway. However, botanicals found in nature and food, at therapeutic doses, can also work on the exact same pathways and block the metabolism of arachidonic acid into proinflammatory mediators.
REFERENCES


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