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A Review of Complementary and Alternative Approaches to Immunomodulation

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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)- κ B pathway), cytokines, proinflammatory mediators, and disruption of bacterial flora. Using inflammatory bowel disease (IBD) as a model of inflammation, we explore the principal complementary and alternative medicine treatments that show promise in this regard, namely, resveratrol, green tea, curcumin, boswellia, fish oil, vitamin D, and probiotics. With each agent, we detail the mechanisms that have been described with regard to immune modulation, discuss the medical conditions for which it has been evaluated, 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

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 prevention is a rapidly growing field.¹ Who knows how many other agents are present in everyday foods that have not yet been tapped?

This article will aim to clarify what is known about alternative and nutrition therapies for immunomodulation. Obviously, this is a broad therapy, and so discussion will be restricted to a few key categories: polyphenols (including resveratrol, epigallocatechin, curcumin, and boswellia), 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 a 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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Table 1 Prophylactic and therapeutic effects of polyphenols in animal models of IBD

Polyphenol	No. of studies	Dose; route	Results
Resveratrol	2	5–10 mg/kg; 2/2 IG	2/2 Improvement: clinical, path, mediators, cytokines
EGCG	3	5 g/L, 50 mg/kg/d; 1 IP, 2 PO	3/3 Improvement: clinical, path, mediators, cytokines
Curcumin	6	2%, 30–300 mg/kg/d; 6 PO, 1 IP	6/6 Improvement: clinical, path, mediators, cytokines, markers; 4/7 ↑ survival
Boswellia	3	5.0–34.2 mg/kg/d; 2 PO, 1 IP	2/3 Improvement: clinical, macroscopic, microscopic, mediators; 1/3 no improvement

Resveratrol, EGCG, curcumin, and boswellia have been evaluated in mice for their ability to treat and prevent chemical-induced colitis. Quercetin has been evaluated in 6 trials, with mixed results, and was not included in the table for this reason.^{3–22}

↑, increased; EGCG, epigallocatechin gallate; IBD, inflammatory bowel disease; IG, intragastric; IP, intraperitoneal; PO, by mouth.

Resveratrol

Resveratrol, trans-3,5,4'-trihydroxy-trans-stilbene, is a phytochemical produced by plants. It has been identified in >70 plant species, including grapes, peanuts, berries, and pines; however, it is believed to be most abundant in the skin of red grapes, contributing to a high concentration in red wine and grape juice.²³ Since the initial report linking resveratrol to the possible cardioprotective benefits seen with red wine, hundreds of papers have been published showing purported health benefits.²⁴ These have encompassed a wide array of illnesses, including cardiovascular disease,^{25–29} cancer,^{23,30–33} immunomodulation,^{34–38} and longevity.^{39,40}

Numerous mechanisms for resveratrol have been proposed, including inhibition of cyclooxygenase (COX), hydroperoxidase, protein kinase C, Bcl-2 phosphorylation, Akt (an anti-apoptotic kinase), focal adhesion kinase, nuclear factor (NF)-κB, matrix metalloproteinase-9, and cell cycle regulators.²³ With regard to anti-inflammatory and immunomodulatory effects, the exact mechanism by which resveratrol works has not been clearly established; nevertheless, significant interest has been paid to this potential role, given that COX inhibitors are commonly used as anti-inflammatory drugs and resveratrol is a potent inhibitor of COX activity *in vivo*.^{41,42} However, the effect of resveratrol on the immune system does not seem to be mechanistically as simple as nonspecific inhibition of inflammation; resveratrol seems to enhance the immune response of mice treated with the arylating substance dinitrofluorobenzene and prevents immunosuppression by ethanol.³⁶ Resveratrol also appears to protect mice from infection with herpes simplex viruses.^{43,44} The exact mechanisms by which resveratrol differentially inhibits and enhances the immune system have not been clearly elucidated.

In rodent models of inflammatory colitis, intragastric resveratrol given acutely before and after colonic injury has been shown to reverse weight loss, increase stool consistency, improve mucosal appearance, improve histopathology, decrease inflammatory infiltrate, and decrease mucosal levels of inter-

leukin (IL)-1β, COX-2, and prostaglandin (PG) D₂.⁴⁵ In another study by the same group, intragastric resveratrol was given for a 14-day period after colonic injury and was shown to increase stool consistency; improve colonic appearance and histopathology; decrease tumor necrosis factor-α (TNFα), NFκB, and colonic myeloperoxidase (MPO) activity; and normalize prostaglandin E2 (PGE2) levels.⁴ To date, resveratrol has not yet been studied in human subjects with IBD; however, given its impressive results in the rodent model, it seems like a reasonable next step, if issues of cost, bioavailability, and toxicity can be ironed out.^{24,46}

Catechins

Catechins refer to monomers of flavonols with similar composition such as catechin, epicatechin, epigallocatechin, epicatechin gallate (EGC) and epigallocatechin gallate (EGCG). These compounds are particularly abundant in green (nonfermented) tea, whereas black tea contains theaflavins and thearubigins.^{47,48} Given that tea is the most consumed beverage in the world other than water,^{49,50} the health benefits present in these chemicals may translate to significant public health benefits on a global scale. Reports have linked green tea to beneficial effects in the prevention or treatment of cancer (breast,^{51,52} ovarian,⁵³ prostate,⁵⁴ stomach,^{55–57} and lung⁵⁸), hypertension,^{59–61} cardiovascular disease,^{56,62–66} oral health (dental caries, periodontal disease, and tooth loss),⁶⁷ skin disease,^{68,69} weight management,^{70,71} osteoporosis,⁴⁸ and glucose tolerance.^{72,73} There is also significant data evaluating the role of catechins in immune modulation, which will be detailed below.

The mechanisms by which catechins achieve their beneficial effects is still not entirely clear; however, there is mounting evidence that they likely work through a combination of both antioxidant effect and alteration of intracellular signaling (primarily through inhibition of the NFκB pathway). Catechins, particularly EGCG, are effective free radical scavengers *in vitro*⁷⁴; however, it has been suggested by some researchers that these compounds may play a relatively minor role as antioxidants *in*

in vivo due to low circulating levels and rapid metabolism.⁷⁵ This has led to investigation into the role of catechins in cell signaling, and it has now been demonstrated that EGCG can modulate and inhibit NF κ B activity.⁷⁶ Given that expression of IL-8, a major human inflammatory mediator, is dependent on IL-1 β activation of NF κ B, it stands to reason that inhibition of the NF κ B cascade may result in a profound effect on inflammation. To support this, studies have shown that administration of EGCG can affect and inhibit the infiltration of CD8+ T cells into sites of inflammation.⁷⁷

Using IBD as a marker of a chronic inflammatory disease, the current data on catechin administration are promising. Using a murine colitis model with IL-2 deficiency, investigators were able to show that oral administration of green tea extract for 6 weeks after disease presentation resulted in weight gain, improved colonic histopathology, decreased colonic weight, and increased hematocrit (Table 1).⁶ In another study involving a murine IBD model, it was shown that green tea polyphenol extract given for 3 days before and 7 days after a caustic trigger resulted in decreased weight loss, improved diarrhea, improved histopathology, decreased serum inflammatory cytokines, and improved hematocrit.⁵ Similar findings were reported in a rat model of colitis given green tea polyphenols extract for a period of 5 days.³ An *in vitro* study involving human colonic tissue showed that administration of EGCG resulted in decreased proinflammatory cytokine production and down-regulation of genes involved in inflammation.⁷⁸ To date, there are no *in vivo* human studies evaluating the role of green tea extract in IBD; however, given the encouraging results above and the excellent safety profile of these agents, it is hard to imagine that these studies are far away.

Curcumin

Turmeric, the major spice in curry, is a natural spice made from the herb *Curcuma longa*, a member of the ginger family. Besides being a culinary staple, it has been used in Ayurvedic medicine since ancient times. The major chemical constituents of turmeric are curcuminoids, the most prominent of which is curcumin. In traditional medicine, it has been used as an oral and topical agent to treat a wide variety of ailments, including—but not limited to—pain, rheumatism, amenorrhea, liver disease, common colds, and pulmonary diseases.^{79–81} Given the longstanding history of this medication, patient preference for a “natural” remedy and the excellent safety profile in studies to date,^{82,83} research has exploded in the use of curcumin for medicinal treatment, and there is emerging literature for gastrointestinal disease. To date, over 1900 papers have been published on curcumin (and most of these have been published in the last 4 years). Studies to date have suggested possible benefits in the prevention or treatment of numerous diseases, including atherosclerosis,^{84,85}

cancer,^{86,87} neurodegenerative diseases including Alzheimer’s dementia,^{88,89} pancreatitis,^{90,91} and rheumatoid arthritis.^{92,93}

The number of mechanisms by which curcumin acts seems to be rivaled only by the number of disease processes in which it has been shown to be of benefit. Its antioxidant activity was initially demonstrated in 1976,⁹⁴ and it has been shown to be a potent free radical scavenger both *in vitro* and *in vivo*.⁹⁵ Recently, investigational focus has shifted toward the role of curcumin as an intracellular signaling agent, and studies have demonstrated that curcumin, much like green tea polyphenols, is an inhibitor of NF κ B^{96,97} and leads to downstream regulation and inhibition of proinflammatory genes and cytokines (Figure 1).⁴⁷ Interestingly, the cell signaling effects of curcumin seem to be pleiotropic as administration of curcumin has also been reported to modulate a host of other cytokines and signaling pathways, including inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9 (MMP-9), TNF α , c-Jun N-terminal kinase (JNK), p38, Akt, Janus kinase (JAK), extracellular signal-regulated protein kinase (ERK), and protein kinase C (PKC).^{47,98,99} Given the wide array of pathways affected by curcumin, it is difficult to distinguish whether the anti-inflammatory effects of this agent are due primarily to inhibition of one specific pathway or due to the combination of multiple interlocked systems. Hopefully, this will be clarified with ongoing and future research.

Given that curcumin may act through NF κ B inhibition and would be expected to down-regulate proinflammatory genes and decrease cytokines involved in inflammation, it would stand to reason that IBD would be a natural avenue to explore for possible therapeutic efficacy. Not surprisingly, the studies to date examining this have been encouraging. Studies involving curcumin to date in the field of IBD have been consistently positive. Four studies involving curcumin administration to murine colitis models showed clinical and histopathological improvement and, where measured, decreased inflammatory cytokine production.^{8,9,12,100} These findings were echoed in 3 studies involving rodent models of colitis.^{7,10,11} The natural next step would be a pilot study in human subjects with IBD. Holt and colleagues¹⁰¹ reported in 2005 the preliminary results of a pilot study involving open-label administration of curcumin preparation to 5 patients with ulcerative colitis and 5 patients with Crohn’s disease. Of the 10 patients, 9 reported improvement at the conclusion of the 1-month study. Four of the 5 patients with ulcerative colitis were able to decrease or eliminate their medications. In a larger, randomized, double-blind, multicenter trial involving 89 patients with quiescent ulcerative colitis, administration of 1 g of curcumin twice daily resulted in both clinical improvement and a statistically significant decrease in the rate of relapse.¹⁰² Given its excellent safety profile, plausible mechanism for

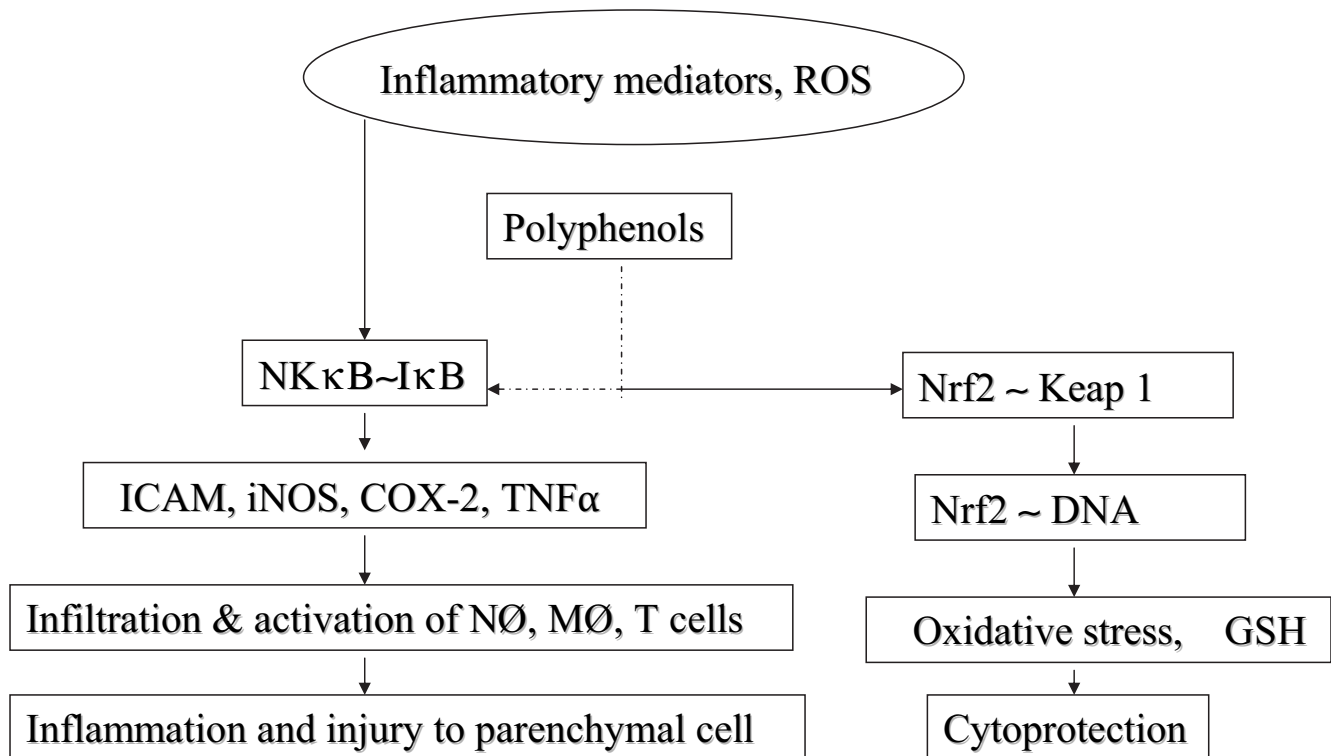


Figure 1. Polyphenols attenuate inflammation and injury. Polyphenols attenuate injury to parenchymal cells by down-regulating inflammatory genes and up-regulating cytoprotective ones. COX-2, cyclooxygenase-2; DNA, deoxyribonucleic acid; GSH, reduced glutathione; HO-1, haem-oxygenase-1; IκB, inhibitor of κB; ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; NFκB, nuclear factor κB; Nrf2, nuclear factor E2-related factor; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α.

affecting inflammation, and the results above, curcumin is poised to have a prominent role in the future management of IBD.

Boswellia

The lipophilic fraction of the gum from the tree *Boswellia serrata*, termed “frankincense,” is a traditional Ayurvedic remedy. It has been used in Asia and Africa as a medical therapy for at least 3500 years and has been used to treat a wide variety of ailments, including respiratory problems, diarrhea, constipation, flatulence, central nervous system disorders, rheumatism, liver disease, wound healing, fat reduction, and fevers. It has also been used as a mental tonic, taste enhancer, and even as an aphrodisiac.^{103,104}

When the resin of different *Boswellia* species is analyzed, over 200 different compounds can be identified. However, the main biologic effects of the *Boswellia* species are thought to be derived from a group of chemicals referred to as tetracyclic triterpenes and pentacyclic triterpenes. These substances are referred to commonly as boswellic acids (BA).

How these agents work is not completely understood. It has been shown that BA interfere with the 5-lipoxygenase pathway, with a resultant decrease in leukotriene formation (Figure 2).

This has been demonstrated in a number of *in vitro* experiments^{103,105}; however, there is considerable debate as to whether suppression of 5-lipoxygenase and leukotriene production is of pharmacologic relevance *in vivo*.¹⁰³ Other postulated molecular targets for BA include human leukocyte elastase, CYP 2C8/2C9/3A4, topoisomerase I, topoisomerase IIa, and IKK α/β. In addition, recent reports have also suggested that BA may also exert some effect through calcium mobilization and mitogen-activated protein kinase phosphorylation.¹⁰³ A recent paper has also shown that BA, similar to the previously discussed polyphenols, may have a role in inhibition of NFκB and down-regulation of the proinflammatory cascade.¹⁰⁶ The relative contribution of each of the above mechanisms to the *in vivo* anti-inflammatory activity of *Boswellia* has not been clearly established at this time.

There are now emerging data to suggest that *Boswellia* may have a role to play in the management of IBD. In a study involving a rat model of colitis, investigators showed that oral administration of *Boswellia* extract or acetyl-11-keto-β-BA (AKBA) over a 2-day period resulted in a dose-dependent decrease in rolling (up to 90%) and adherent (up to 98%) leukocytes. In addition,

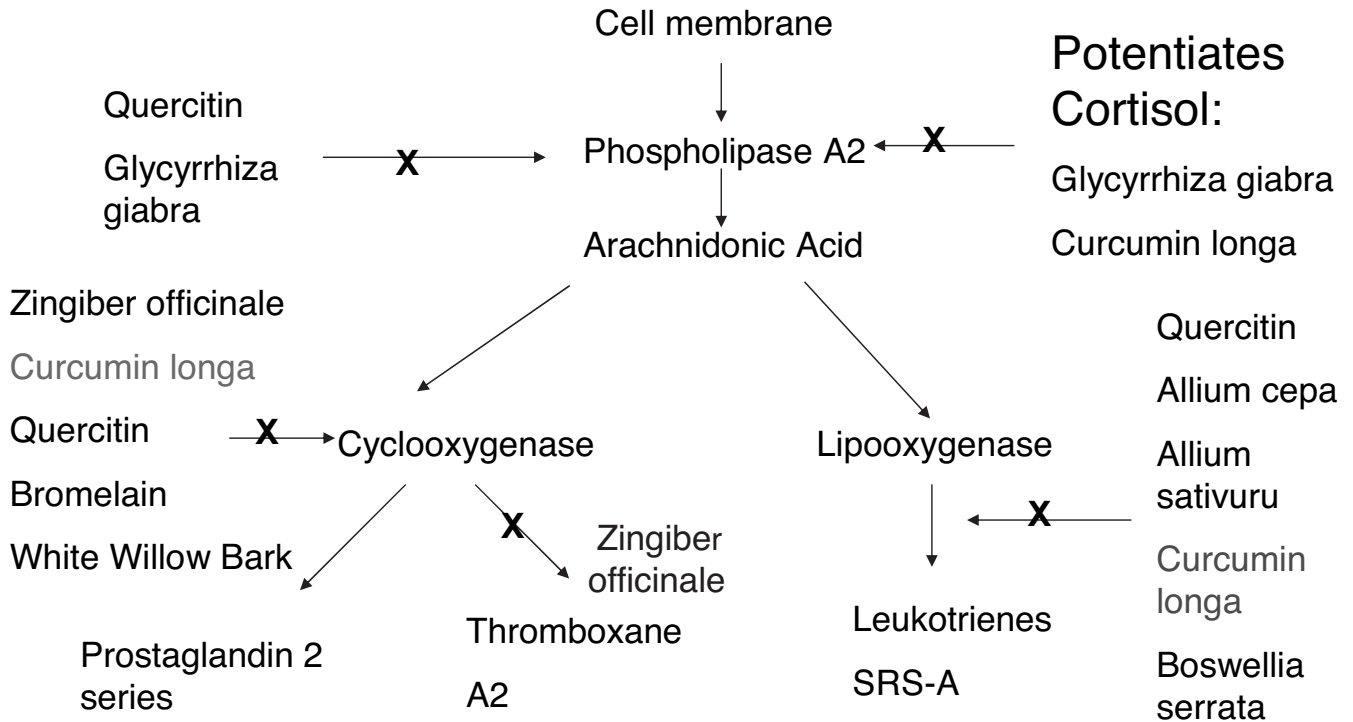


Figure 2. Botanical modulation of arachidonic acid cascade. Polyphenols have a number of different mechanisms for down-regulating inflammation and modulating immunity. A number of botanicals, including polyphenols (curcumin, boswellia, quercetin, and ginger) interfere with the production of noxious proinflammatory eicosanoids such as prostaglandin-2 series (PGE2), leukotrienes (LTB) such as slow reactive releasing substance (SRS-A) and thromboxane A2 (TXA2) via inhibition of the enzymes cyclooxygenase-2 (COX-2) and 5'-lipoxygenase (5'LPO).

necropsy showed improvement of inflammatory changes on both a macroscopic and microscopic level.²⁰ In a murine model of colitis, a semisynthetic form of AKBA was shown to blunt disease activity both grossly and histologically, reduce recruitment of adherent leukocytes and platelets, and prevent up-regulation of P-selectin (normally observed with this particular model of colitis). These anti-inflammatory effects were comparable to effects seen in the same murine model treated with corticosteroids.²² However, a benefit was not observed in a study by a different investigational group evaluating the effects of BA on a murine model of chemically-induced colitis, although the formulation by which BA was derived varied and this may have partially explained the negative results of this study.²¹

Few studies have been performed evaluating the role of *Boswellia* in human subjects with IBD. Researchers from India compared administration of *Boswellia* (350 mg 3 times daily for 6 weeks) to sulfasalazine (1 g 3 times daily for 6 weeks) and found similar improvement in clinical, laboratory, and histopathological parameters.¹⁰⁷ The same investigators reported a subsequent study comparing 30 patients treated with *Boswellia* or sulfasalazine (at the same doses as above). Of the 20 patients treated with *Boswellia*, 18 (90%) had improvement in at least 1 secondary endpoint, and 14 (70%) went

into remission. In contrast, in the 10 patients treated with sulfasalazine, only 6 (60%) had improvement in at least 1 secondary endpoint and only 4 (40%) went into remission.¹⁰⁸ Investigators from Germany compared *B serrata* extract H15 with mesalazine for the treatment of Crohn's disease in a randomized, double-blind controlled trial involving 102 patients. The primary outcome was the change in the Crohn's Disease Activity Index, which decreased by 90 in the H15-treated group and decreased by 53 in the mesalazine-treated group. The authors concluded that *B serrata* extract H15 "appears to be superior over mesalazine in terms of a benefit-risk-evaluation"¹⁰⁹; however, as the study was powered only to be a noninferiority study, these conclusions must be interpreted with caution, and further research, hopefully in the form of a multicenter, randomized, controlled trial, is necessary to definitively evaluate the role of *Boswellia* in the therapeutic armamentarium of IBD.

Essential Fatty Acids

Essential fatty acids (EFA) refer to dietary constituents that cannot be synthesized endogenously and must be obtained *via* the diet for optimal health. By definition, these EFA can be subdivided into ω -3 and ω -6 polyunsaturated fatty acids according to the position of the initial double bond from the methyl

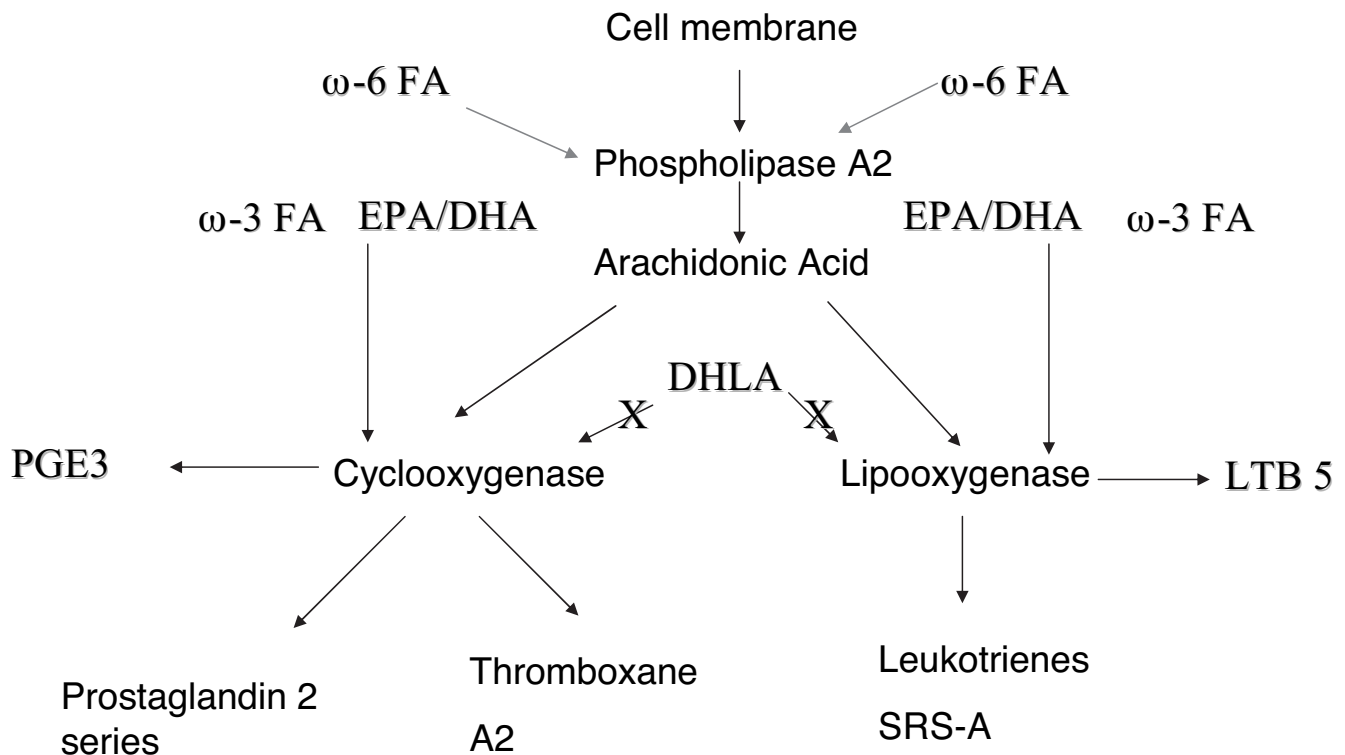


Figure 3. ω -3 Modulation of the arachidonic acid cascade. ω -6 Fatty acids appear to promote the production of phospholipase A2 (PLP A2), arachidonic acid (AA) and production of noxious proinflammatory eicosanoids such as prostaglandin-2 series (PGE2), leukotrienes (LTB) such as slow reactive releasing substance (SRS-A), and thromboxane A2 (TXA2). ω -3 Fatty acids, in contrast, downregulate production of proinflammatory eicosanoids by competitive inhibition of the enzymes cyclooxygenase-2 (COX-2) and 5'-Lipoxygenase (5'/LPO) for AA, thus leading to preferential production of the prostaglandin-3 series (PGE3) and leukotriene-5 series (LTB5).

end of the fatty acid. ω -6 EFA are markedly more common in the current Western diet and may have a proinflammatory effect. Although ω -3 EFA are found in a wide variety of foods, including wild plants, eggs, nuts, and berries, they are particularly abundant in fish, and, not surprisingly, ω -3 EFA supplementation has become synonymous with fish oil.^{110,111} Typical fish oil is extracted from fish bodies and is composed of a variety of long-chain ω -3 EFA. The 2 most common EFA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which comprise 18% and 12% of fish oil, respectively, in typical marine fish.^{112,113} Fish oil can also be obtained from cod liver; however, cod liver oil has slightly less EPA (10%) and DHA (10%) than other marine oils and can be associated with vitamin A toxicity at high doses. Administration of fish oil has not been associated with any serious acute treatment-related syndromes; however, long-term use raises theoretical concerns for possible increased bleeding, lipid peroxidation, and toxicity of mercury and halogenated biphenyls.^{112,114} Fish oil can be administered as either raw fish oil or as an enteric-coated capsule. A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption.¹¹²

The health benefits of fish oil in a broad array of disease processes are widely heralded. Hu and col-

leagues have reported that in a cohort of 84,688 women enrolled in the Nurses' Health Study and followed for a period of 16 years, deaths related to cardiovascular disease were 50% lower in women who consumed fish 5 times per week, and a significant reduction in cardiovascular disease was noted even with fish consumption as infrequently as 1–3 times per month.¹¹⁵ In fact, a PubMed search of "fish oil" and "cardiovascular disease" results in more than 2000 entries. Other disease processes in which fish oil has been postulated to be of benefit include hyperlipidemia,^{116,117} asthma,^{118,119} cystic fibrosis,^{120,121} rheumatoid arthritis,¹¹³ depression,^{122,123} and dementia.^{124,125} This is by no means an exhaustive list, as more than 11,000 papers have been published to date on the benefits of fish oil.

ω -3 EFA seem to work through a plethora of mechanisms. To begin with, eicosanoids seem to affect both the COX pathway (primarily COX-2) and the 5-lipoxygenase pathway (Figure 3). Prostaglandin E₂ is a proinflammatory, nociceptive factor that is produced through the COX-2 pathway. Arachidonic acid (AA) is the usual substrate for this pathway. EPA is a chemical homolog that differs from AA by only the presence of the ω -3 double bond. Therefore, EPA represents both an inhibitor of AA and an alternate substrate for COX. In addition,

through similar means, EPA also results in inhibition of the 5-lipoxygenase pathway and decreased production of leukotriene B₄.^{112,125} In addition to decreasing production of proinflammatory mediators, it has been recently shown that EPA and DHA can act themselves as substrates for the formation of novel protective mediators, termed E- and D-series resolvins, that may have direct anti-inflammatory effects.^{127–129} ω -3 EFA are also thought to play a role in the control of transcription factors such as peroxisome proliferator-activated receptors (PPARs), with resultant down-regulation of inflammatory processes. Through these, and possibly other mechanisms, ω -3 EFA inhibit NF κ B and decrease the release of the proinflammatory cytokines IL-1 β and TNF α .^{113,130}

Fish oil and inflammation are closely intertwined. A PubMed search for the 2 terms results in more than 600 publications and, given the mechanisms detailed above, this is hardly surprising. Although there are abundant data evaluating multiple disease models of inflammation, including rheumatoid arthritis, asthma, and multiple sclerosis, the discussion in this paper will be restricted to IBD. Interestingly, the rate of IBD has traditionally been very low in the Japanese population; however, this appears to be changing, and one theory as to why this change is occurring is the dietary shift from an ω -3 EFA-based diet to an ω -6 EFA-based diet.¹³¹

Numerous studies have evaluated the effects of fish oil on ulcerative colitis. Several early studies supported the notion that enteral fish oil supplements led to improvement in IBD in animal models,^{132,133} and these findings were corroborated in small clinical trials.^{134–136} Although a variety of studies have been performed exploring the roles of ω -3 EFA in the treatment of ulcerative colitis, the methodology and endpoints have been varied, and it is difficult to directly compare the results obtained. When clinical scores were used as an outcome (Disease Activity Index, Ulcerative Colitis Activity Index, or undefined “clinical score”),¹³⁷ 3 of 5 studies showed significant clinical improvement in the fish oil arm of the study at some point during the course of therapy^{138–140} (although only 2^{138,140} of these 3 studies showed significant benefit at the predetermined endpoint of the study). Two studies showed no significant change between the 2 groups.^{134,141} When endoscopic endpoints were used to evaluate the role of fish oil in the treatment of ulcerative colitis, 3 of 3 studies showed statistically significant improvement in the study group that received fish oil supplementation^{134,140,141} (although it should be noted that one of the studies¹³⁴ included patients with both ulcerative colitis and Crohn’s disease and statistical significance was not met when the 2 subgroups were analyzed individually). When examining the endpoint of histologic improvement, only 1¹⁴¹ of 3^{138,141,142} studies reported significant improvement in the fish oil-treated arm of the study.¹³⁷ However, the data that pertain to the

effects of ω -3 fatty acids on steroid requirements suggest that ω -3 fatty acids may reduce the need or dose for corticosteroids among patients with IBD. Future studies should assess the effects of pharmaceutical grade enteric-coated ω -3 fatty acids on clinical outcomes in IBD, including requirements for corticosteroids.¹⁴²

Recently, a randomized, controlled trial evaluated a “nutritionally balanced oral supplement enriched with fish oil, fructooligosaccharides, gum arabic, vitamin E, vitamin C, and selenium” on disease activity and medication use in patients with mild to moderate ulcerative colitis. A total of 121 patients were randomized to this dietary supplement or placebo. The subjects were instructed to consume 18 oz of the oral supplement daily for a 6-month period, with a resultant planned fish oil intake of 3.27 g of EPA and 1.38 g of DHA daily. Clinical and histologic parameters, as well as medication usage, were assessed at 3 and 6 months. Eighty-six patients completed the study. Both treatment groups (oral supplement and placebo) showed similar improvement in clinical and histologic indices. However, the group treated with the supplement containing fish oil showed a significantly greater rate of decrease in the dose of prednisone required to control clinical symptoms when compared with the group that received placebo.¹⁴⁴ This type of integrated approach with synergistic nutraceuticals may achieve superior outcomes in future IBD studies.

The relationship of fish oil and Crohn’s disease has also been extensively evaluated. The Cochrane Collaboration recently published a systematic review evaluating this topic.¹⁴⁵ A total of 214 publications were evaluated and 15 randomized, controlled trials were identified. After exclusionary criteria (including the use of non-enteric-coated fish oil supplementation), the researchers felt that 4 studies were of sufficient quality to be included in the analysis.^{146–149} When all 4 studies were reviewed, the Cochrane Collaboration found that enteric-coated ω -3 EFA supplementation reduced the 1-year relapse rate by half with an absolute risk reduction of 31% and a number needed to treat (NNT) of only 3. The conclusion of the review was that the limited available data suggests that daily oral therapy with enteric-coated ω -3 EFA supplementation is safe and may be effective for maintenance of remission in Crohn’s disease. However, emphasis was made that the data are limited and a larger multicenter, randomized, controlled trial is needed to definitively evaluate the issue.¹⁴⁵

Vitamin D

Vitamin D is recognized as essential for optimal bone mineralization and the maintenance of a healthy skeleton. Normal acquisition is *via* direct exposure to sunlight, which induces the production of cholecalciferol (vitamin D₃). Vitamin D can also be

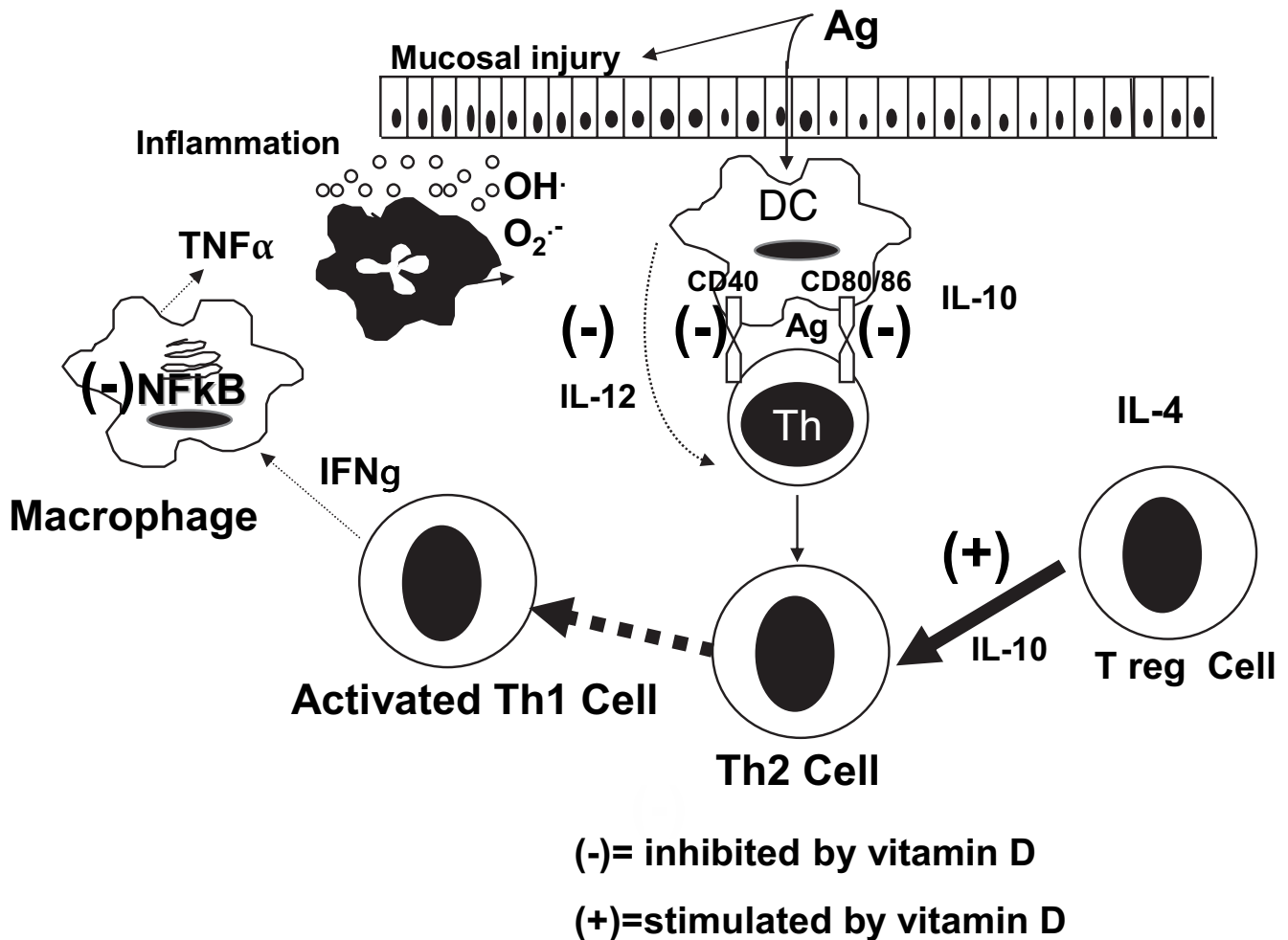


Figure 4. Immunomodulatory role of vitamin D in inflammatory bowel disease. In Crohn's disease, bacterial antigens drive antigen-presenting cells (DCs) to produce cytokines such as interleukin-12 (IL-12) to drive a T-helper 1 (Th1) proinflammatory response to induce macrophages, which produce $\text{TNF}\alpha$ and neutrophil chemoattractive agents, which ultimately result in the production of noxious agents and tissue injury. The damaged intestinal tissue is more permeable to antigens that drive the vicious cycle of antigen-presentation, local immune activation, and tissue injury. Anti-inflammatory cytokines such as interleukin-10 (IL-10), made by regulatory T cells (T regs) antagonize Th1 proinflammatory processes by stimulating T-helper 2 function. Vitamin D antagonizes Th1 proinflammatory responses by interfering with antigen-presentation and Th1 activation, up-regulating Th2 cytokines, and down-regulating $\text{NF}\kappa\text{B}$ in macrophages.

ingested orally as either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3). Recently, there has been recognition that vitamin D receptors are present in tissues not believed to be involved with calcium and phosphate metabolism. This has led to renewed investigation into the role of vitamin D, and there is now increasing evidence that vitamin D is involved in regulation of the immune system and cancer prevention.¹⁵⁰

The mechanisms by which vitamin D modulates the immune system are being studied extensively. Vitamin D receptors have been identified on almost all cell types involved in immune modulation. Currently, it is believed that the main mechanism by which vitamin D affects inflammation is through T-cell regulation, specifically through modulation of the Th1 and Th2

pathways (Figure 4). Vitamin D deficiency favors a Th1, or proinflammatory, response, whereas supplementation of vitamin D (at least *in vitro*) appears to shift T-cell activity toward a Th2 response. Numerous studies have been done to elucidate these mechanisms, and these studies have recently been reviewed by one of the authors, along with the role of Th1/Th2 responses in IBD (G.E.M.).^{150,151} In addition, like most of the substances reviewed in this paper, vitamin D has also recently been shown to be an inhibitor of the $\text{NF}\kappa\text{B}$ pathway (with resultant decrease in proinflammatory cytokines).¹⁵²

One interesting observation that may suggest a role for vitamin D in the pathogenesis of IBD is the fact that the prevalence of IBD appears to be highest in North America and Northern Europe, where

direct sunlight exposure is lower.¹⁵³ Further, vitamin D deficiency is common in patients with IBD, even when their disease is well controlled.^{154,155} To date, there have been at least 3 animal experiments that have evaluated the role of either vitamin D elimination (*via* knockout of vitamin D receptors) or vitamin D supplementation on the development and severity of IBD. All 3 studies have shown a consistent link between the presence of vitamin D and either improved parameters or delayed development of colitis.^{156–158}

Probiotics

The gastrointestinal tract is a sterile environment at the time of birth; thereafter, the situation rapidly changes and the human gastrointestinal system is colonized by at least 300–500 different bacterial species, with concentrations of bacteria in the large intestine that can reach 10^{12} cells/g of luminal contents.¹⁵⁹ This dynamic system of intestinal microflora plays a vital role in the maintenance of intestinal health, and, increasingly, data are emerging to show that this community plays an important role in the regulation of the mucosal inflammatory cascade.

Probiotics are defined as “living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond those of basic nutrition.”¹⁶⁰ Although the concept of oral consumption of bacteria was initially described over a century ago by the Russian Nobel Prize winner Metchnikoff (who espoused the benefits of yogurt consumption on longevity), it is only in recent years that this theory has gained credence and received serious scientific attention.¹⁶¹ In the past 5 years, over 2000 papers have been published on probiotics and a wide variety of medical conditions, including, but not limited to, IBD, pouchitis, traveler’s diarrhea, hepatic encephalopathy, nosocomial infections, prevention of infection after pancreatitis, allergic diseases, irritable bowel syndrome, prevention of preterm labor, asthma, and other etiologies.

The mechanisms by which probiotics exert their effect are not entirely clear and several theories abound. In patients with IBD, the bacterial microflora become aberrant, and this may contribute to some extent to the underlying pathogenesis of the disease.¹⁶² One route by which probiotics may exert benefit is through competition with the native microbial pathogens for limited epithelial receptors, resulting in inhibited epithelial attachment and, thus, decreased intracellular invasion by a large variety of toxic bacteria.¹⁶³ Probiotics can also stabilize the intestinal barrier and epithelial tight junctions.¹⁶⁴ However, it seems that probiotics act in a systemic manner and do not simply perform a barrier function. There is now evidence to suggest that probiotics modulate the mucosal immune response to IBD through a number of different pathways, including inhibition of NF κ B, modulation

Table 2 Immunomodulator effects of probiotics in IBD

Up-regulate Th2 cytokines (IL-10)
Down-regulate Th1 cytokines (IL-12)
Inhibit IFN γ by T cells
Inhibit NF κ B
Stabilize I κ B levels
Induce T-regs

Probiotics have been shown to modulate the ability of T-regs to rebalance cytokines in the mucosal immune system. T-regs induce anti-inflammatory cytokines such as IL-10 to antagonize Th1 proinflammatory processes mediated by IFN- γ and IL-12 by stimulating T-helper 2 function. Probiotics also down-regulate the expression of NF κ B and stabilizing I κ B, which results in dampening proinflammatory responses.

IBD, inflammatory bowel disease; IL, interleukin; INF, interferon; I κ B, inhibitors of κ B; NF κ B, nuclear factor κ B; T-regs, T-regulatory cells.

of PepT1 activity, reduction of the number of CD4 intraepithelial lymphocytes, regulation of the anti-inflammatory effect *via* the Toll-like receptor-9 (TLR9) signaling pathway, modulation of immune cell apoptosis and proliferation *via* TLR2 signaling, and modulation of the PPAR- γ pathway (Table 2). In addition, certain probiotics may be active secretors of antimicrobial agents and may serve a role in decomposition of luminal pathogenic antigens.¹⁶²

Over 20 trials have been published in the last few years evaluating the role of probiotics in the prevention, treatment, and maintenance of IBD, and several excellent reviews have been recently published on the matter.^{161,165–167} The results to date have been mixed, with probiotics thus far benefiting ulcerative colitis more so than Crohn’s disease.^{168–176} The reader is referred to these excellent reviews for a full analysis of this topic.

Conclusion

Over 30% of the Western population are now using some form of CAM.¹⁷⁷ In the field of IBD, these numbers are estimated to be even higher (50%), given the data present in this discipline and the questionable efficacy of existing medical therapies.¹⁷⁸ Although many of the treatments in this paper are not included in the texts of most medical training institutions, it is important to recognize that there is a mountain of scientific data behind these supplements. A PubMed search for resveratrol, green tea, curcumin, boswellia, fish oil, vitamin D, or probiotics results in over 50,000 publications, and the quality of the data, in many cases, is excellent.

The immune system is a complicated process, and there are many ways to disrupt and gently modulate this equilibrium. Polyphenols, fish oil, probiotics, and vitamin D all promise a novel approach to attenuation and possible reversal of the inflammation cascade and do so from the safety of (in some cases) centuries of usage. Rigorous randomized, controlled, multicenter studies are needed to clarify the

role of these agents in the armamentarium of Western therapy; however, the data are promising, and these therapies should be considered as adjunct therapies for select patients with IBD and other inflammatory conditions.

With increasing data regarding these agents, it is tempting to speculate on a world in which patients would supplement their diet with natural agents designed to treat their individual ailments and modify their diets early in life according to familial and environmental risk factors. Inflammation would be a carefully regulated phenomenon acting at the discretion of the patient, rather than being an unwieldy albatross. A new term would have to be devised for CAM as it would be neither complementary nor alternative any longer. The term "integrative medicine," devised by Dr Andrew Weil for incorporating aspects of sound diet, lifestyle factors, and nutraceuticals, together with conventional care for superior outcomes, may be the future direction for clinical trials and patient care. Given the exciting research detailed above, perhaps this day is coming sooner than we think.

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