Review

Dietary fiber, low-molecular-weight food constituents and colo-rectal inflammation in animal models – A review

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This review provides an overview over studies in experimental animals aimed at elucidating the influence of dietary constituents on colo-rectal inflammation. Human studies as well as *in vitro* investigations will not be covered. In experimental animals, a variety of chemical treatments and genetic modifications, lead to various types of gut inflammation. In a number of these models, there is good evidence for an anti-inflammatory action of dietary tocopherols, certain polyphenols, and curcumin at relatively high oral doses. It has also been established, that oral application of fats and oils rich in n-3 PUFAs and/or conjugated linoleic acid (CLA) can attenuate certain types of colitis in experimental animal models. While the effect of dietary calcium on experimental colitis is less clear, there are hints indicating that certain high-fiber diets or diets rich in digestion-resistant carbohydrates ("fiber") can attenuate experimental colitis in animals, although contradictory results have been reported. In summary, the anti-inflammatory potency of dietary constituents on colon inflammation in experimental animals seems to be rather limited. The reasons for this lack of activity seem to be manifold including pharmacokinetic limitations and intestinal degradation of the compounds, in particular insufficient local, *i.e.*, intra- or sub-mucosal levels of the effective compounds, and general limitations of animal models.

Keywords: Animal models / Anti-inflammatory factors / Colo-rectal inflammation / Nutrition

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1 Introduction

This review provides an overview over studies in experimental animals aimed at elucidating the influence of dietary constituents on colo-rectal inflammation. Human studies as well as *in vitro* investigations will not be covered. Colon inflammation is a local and also a frequent systemic reaction mediated by the immune system responding to external factors such as infectious microorganisms, their toxins, and other chemicals as well as internal factors, *e.g.*, as part of autoimmunity reactions. Frequently, acute inflammatory responses are observed which are directed against a sudden challenge by oral infection or certain other constituents of the diet. Chronic or acute/chronic intermittent inflammation may result from the same stimuli reflecting either persistent exposure to the inflammatory stimulus or a shift to inflammation which became independent of the presence of the external noxious factor. Autoimmune diseases are a typical example of this type of inflammation.

The inflammatory response of the colon is characterized by the immigration of a variety of inflammatory cells [1 – 3] which release a broad spectrum of mediators of inflammation such as reactive oxygen species (ROS), lipids and their metabolites, cytokines, and proteases [4 – 6]. Among the chronic inflammatory diseases of the colon, the inflammatory bowel diseases (IBD) Crohn's disease (CD), and ulcerative colitis (UC) have gained much attention. The underlying patho-mechanisms are subject to intensive research which have led to certain hypotheses. Cornerstones of these hypotheses are the T helper (Th) cell paradigms suggesting that UC-like inflammation is mediated by Th type 2 (Th2)

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Abbreviations: CD, Crohn's disease; **CLA,** conjugated linoleic acid; **COX,** cyclooxygenase; **DSS,** dextran sulfate sodium; **GSH,** glutathione; **IBD,** inflammatory bowel disease; **IFN-γ**, interferon γ; **iNOS,** inducible nitric oxide synthase; **LTB_4,** leukotriene B_4; **MPO,** myeloperoxidase; **NF-κB,** nuclear factor κB; **PG,** prostaglandin; **PPAR,** peroxisome proliferator activated receptor; **Th cell,** T helper cell; **TNBS,** trinitrobenzene sulfonic acid; **TNF-α**, tumor necrosis factor α; **UC,** ulcerative colitis

cytokines such as IL-4 and IL-13 while CD-like inflammation implies Th type 1 (Th1) activity. A large number of studies have been focused on the role and interplay of cytokine receptors, cytokines such as interferon-γ, transforming growth factor-β, *etc.*, in IBD [7–9]. Less is known about patho-physiologic mechanisms leading to the relatively common diagnosis of irritable bowel syndrome (IBS) which is also assumed to include inflammatory responses, *e.g.*, towards food allergens or as a result of intolerance towards certain constituents of the diet [10]. Finally, it is noteworthy that chronic inflammation of the colo-rectum is considered as a relevant risk factor for colo-rectal cancer, the major contributor to overall cancer mortality in Western industrialized countries. The probable importance of this relationship for the risk of sporadic colo-rectal cancer is emphasized by epidemiologic findings on the reduction of colo-rectal cancer by a long-term treatment with non-steroidal anti-inflammatory drugs [11]. Even the impact of known risk factors for colo-rectal cancer such as overweight, obesity, and lack of physical activity have been linked to metabolic stress and chronic low-grade inflammation under these conditions [12]. The diagnostic and clinical features of these diseases will not be presented and discussed here.

This review tries to compile and discuss the available information giving hints to possible attenuating effects of certain dietary constituents on acute, sub-chronic, or chronic colonic inflammation of any origin. In animal experiments, a major challenge in the interpretation of positive results on anti-inflammatory effects is to differentiate between direct anti-inflammatory effects of a constituent and effects mediated via changes in the microflora of the colon. Furthermore, it is usually unknown if the parent constituent or (a) metabolite/s formed during the gastro-intestinal passage is/are the active principles. Finally, it usually cannot be excluded that an anti-inflammatory dietary constituent acts not only via the luminal space but also or primarily after systemic absorption and delivery to the colon via the circulation.

Here, the broad field of microbial-gut interactions influenced by nutritional microorganisms ("prebiotics") and the effects of dietary constituents on the pattern of organisms in the colonic microflora are not discussed. These issues have been covered in review articles [13]. The focus of this review is on direct anti-inflammatory effects in the colon elicited by dietary constituents and/or their metabolites as well as on the role of dietary fiber, a substrate for microbial SCFA (short chain fatty acid) formation in the colon, on colonic inflammation.

2 Studies in experimental animals

A number of experimental models of colitis in animals use oral or local treatment with certain agents which have been shown to act in the colon in a pro-inflammatory way [14]. Common models to induce colitis in experimental models include the oral application of dextran sulfate sodium (DSS), *e.g.*, in the drinking water [15]. Typical features of the DSS model, thus resembling human UC, are mucosal lesions, and diarrhea (Table 1). Furthermore, a slower body weight gain, and a decreased ratio of colon length/diameter are observed. DSS-treated wild-type mice show a robust production of interferon γ (IFN-γ) in the gut, while IFN-γ-deficient mice do not develop DSS colitis. Furthermore, IFN-γ-dependent IFN-γ inducible protein-10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) are strongly increased in wild-type but not on IFN-γ (–/–)-mice treated with DSS [16].

Local administration of trinitrobenzene sulfonic acid (TNBS) results in a spectrum of inflammatory responses (Table 1) which share several features with CD in humans [17]. Typically, epithelial damage, neutrophilic infiltration, a decreased ratio of colon length/diameter, and increased pro-inflammatory cytokine expression are observed. Most notably, IL-6 levels are significantly enhanced.

Other, less frequently used animal models using pro-inflammatory agents are the administration of cholic acid [18], oxazolone, acetic acid, or indomethacin [19]. Application of methotrexate (MTX) in combination with an elemental diet [20] to rats increases the intestinal permeability for bacteria and bacterial metabolites and is considered as an experimental model for enterocolitis.

An increasing number of genetically modified mice strains are generated which bear certain defects mainly in regulatory proteins of the immune system, regulators of inflammation, or factors required for an intact epithelial barrier [21–23]. In particular, IL-10 null mice [24] have been used for the study of putative anti-inflammatory effects of dietary constituents.

2.1 Low-molecular-weight secondary plant constituents/anti-oxidative vitamins/plant extracts

In colon-derived permanent cell lines, mostly originating from human or animal tumors, a broad spectrum of dietary plant constituents and vitamins can suppress certain cellular activities related to inflammation. It has to be kept in mind, however, that colonic inflammation is not restricted to a primary response of epithelial cells, but to a complex interaction between many cell types, most notably cells belonging to the immune system. In the human intestinal carcinoma cell line Caco-2, the human colon cancer cell line HT-29 [25, 26], and in a number of other cell lines derived from colon tumors [27], a broad number of dietary plant constituents have been shown to ameliorate the formation or levels of pro-inflammatory factors such as eicosanoids, leukotrienes, cytokines, *etc.*, [25, 28]. The meaning of these findings for the *in vivo* situation has to be established. In case of positive *in vivo* results, these studies can be helpful, how-

Table 1. Major colitis models in experimental animals, dietary constituents with demonstrated anti-inflammatory effects, and possible/probable targets (see also main text)

Colitis model	Major features	Anti-inflammatory dietary constituents	Possible/probable targets	Reference(s)
DSS (drinking water)	Crypt and epithelial damage, Granulocyte and mononuclear cell infiltration, Edema and ulceration, Th1- and Th2-cell-mediated, ↑Macrophage-derived cytokines (IL-1β, IL-6, and TNF-α), *etc.*,↑$CD4^+$T-cells (IFN-γ, IL-4), *etc.*	Tocopherols	↓Oxidative stress, ↓IL-1β	30
		β-Caryophyllene	↓MPO activity, ↓IL-6	38
		Oil rich in conjugated linoleic acid (CLA)	↑PPAR-γ activity, ↓TNF-alpha	48, 49
		Lactulose	↓MPO activity, ↓TNF-α, leukotrienes	63, 64
		Fermented rice/fermented barley	↓MPO activity	66, 70, 71
TNBS/ethanol (rectal)	Hapten formation, Transmural inflammation, Edema, Th1-cell-mediated (↑IL-12), ↑TNF-α, IFN-γ, IL-6, IL-16, IL-18R1, IL-22, *etc.*	Quercetin	↓Recruitment of NF-κB to proinflammatory gene promoters	29
		Quercitrin	↓Oxidative stress, ↓iNOS	34
		EGCG	↓MPO activity, NF-κB, AP-1	36
		Curcumin	↓TNF-α, MPO activity, COX2, ↓iNOS, MAPKp38	32
		Resveratrol	↓COX2, IL-1β	31
		Theaflavin-3,3′-gallate	↓TNF-α, IL-12, IFN-γ, iNOS, ↓Nuclear level of NF-κB, ↓Cytosolic IKK activity, +/− IκB-α	35
		n-3 PUFA-rich oils	↓AP, γ-GT activity, ↓PGE_2, LTB_4, ↓Lymphocyte proliferation, ↓Th1 clonal expansion	43–47, 52
		Lactulose	↓MPO activity, ↓TNF-α, leukotrienes	63, 64
		Fructooligosaccharides	↓MPO activity, ↓LTB_4, ↓iNOS expression	65
Acetic acid		Rutoside	↓GSH depletion	33
		Ginger extract	↓Oxidative stress, ↓MPO activity, ↓TNF-alpha, PGE_2	39
Methotrexate		Pectin	↓MPO activity	20
HLA-B27 transgenic rat		Seeds of *Plantage ovata*	↓NO formation, ↓LTB_4, TNF-α	60
		Long-chain inulin/oligofructose	↓Cecal IL-1β, ↑Cecal TGF-β	61
IL-2 (−/−) mouse		Green tea extract	↓IFN-γ, TNF-α secretion in explant local lymphocytes	40
IL-10(−/−) mouse		Calcium/1α,25-dihydroxyvitamin D3	↓TNF-α dependent genes	71

ever, to understand the possible modes of action of the respective compounds [29].

The major types of low-molecular-weight plant constituents tested for beneficial effects in colon inflammation are anti-oxidative vitamins, and polyphenols.

Within the group of *anti-oxidative vitamins*, tocopherols have been shown to suppress the experimental colonic inflammation. In TNBS-treated male Wistar rats, vitamin E supplementation of the diet (300 mg/kg diet) reduced colon damage, lipid peroxidation, and diarrhea, reduced IL-1β levels and preserved glutathione reductase activity, and total glutathione (GSH) levels [30]. However, myeloperoxidase activity, indicative of neutrophile infiltration was not modified by the supplementation.

Polyphenols tested include flavonoids, resveratrol, curcumin, and related compounds. In TNBS colitis in male Wistar rats, 5–10 mg resveratrol/kg b.w. per day, given orally, significantly reduced the degree of colonic injury, neutrophilic infiltration, and the level of IL-1β [31]. The increased PGE_2 levels were not reverted but a significant

decrease in PGD_2 was found. Immunohistochemical staining for cyclooxygenase 1 (COX-1) was unchanged while that for COX-2 was found to be reduced. Oral application of curcumin (50 – 100 mg/kg b.w. per day) to TNBS-treated male and female Wistar rats reduced the epithelial damage in the colon and attenuated the rise in myeloperoxidase (MPO) activity and tumor necrosis factor α (TNF-α) levels [32]. It also reduced nitrite levels, down-regulated COX-2 and inducible nitric oxide synthase (iNOS) expression, and decreased the activation of mitogen-activated protein kinase (MAPK) p38. At 25 and 100 mg/kg b.w. the flavonoid rutoside reduced colon injury and prevented the increase in AP activity and the depletion of glutathione in the rat model (male Wistar rats) of acetic acid-induced colitis [33]. However, MPO activity and leukotriene B_4 (LTB_4) levels were not changed. Sanchez de Medina *et al.* [34] reported that quercitrin (1 and 5 mg/kg b.w., p.o.) prevented increases in colonic malondialdehyde levels, and iNOS and alkaline phosphatase activities but had no effects on observable damage in the colon of TNBS-treated female Wistar rats. No effect of quercitrin on enhanced MPO activity was observed. Theaflavin-3,3′-digallate (5 mg/kg b.w., by gavage), a polyphenolic antioxidant from black tea, improved TNBS-colitis in female BALB/c mice and decreased mRNA and protein levels of TNF-α, IL-12, IFN-γ, and iNOS in colonic mucosa [35]. Furthermore, TNBS-induced increases in nuclear localization of nuclear factor κB (NF-κB), and cytosolic inhibitor of NF-κB kinase (IKK) activity were reduced, and IκB-α was preserved in colon tissue under treatment with theaflavin-3,3′-gallate. A major green tea polyphenol, epigallocatechin-3-gallate (EGCG), given intraperitoneally at a daily dose of (2×10 mg/kg b.w) to TNBS-treated C57BL/6 mice, attenuated colitis, and significantly reduced MPO activity, NF-κB and activator protein 1 (AP-1) activation in colon tissue [36]. However, plasma cytokine levels were not reduced.

In male Sprague – Dawley rats treated with azoxymethane, subsequently treated with a high fat diet rich in omega-6 fatty acids (20% corn oil in the diet), quercetin (0.5% in the diet) or β-carotene (0.05% in the diet) supplementation did not result in a significant reduction in colonic expression of iNOS or COX-2 [37].

Other low-molecular-weight plant constituents with anti-inflammatory potency in experimental colitis comprise a broad spectrum of chemical structures. The plant sesquiterpene β-caryophyllene reduced colon inflammation in DSS-treated male BALB/c mice at a relatively high oral dose of 300 mg/kg b.w. per day [38]. The sesquiterpene also reduced MPO activity, and suppressed the level of IL-6 mRNA in the colon. Furthermore, the serum level of IL-6 was reduced by 55%.

With respect to *plant extracts*, El-Abhar *et al.* [39] found an attenuating effect of oral application of Ginger extract (100, 200, and 400 mg/kg b.w., given orally) on acetic acid-induced (single local treatment) colonic inflammation in male Wistar rats. In particular, histopathologic findings, mucosal parameters of lipid peroxidation, and myeloperoxidase activity pointed to decreased inflammatory changes. Furthermore, inflammation-related colonic levels of TNF-α and PGE_2 were significantly decreased. Application of a green tea polyphenol extract (5 g/L in the drinking water) to IL-2 (−/−)-mice showing spontaneous colitis, led to lower histologic scores of colitis and decreased wet weights of the colon [40]. Explant colon and lamina propria lymphocyte cultures of mice treated with green tea extract showed lower spontaneous IFN-γ and TNF-α secretion.

2.2 Dietary fat/fatty acids/fish oils

There is increasing evidence that long-chain n-3 PUFAs suppress colonic inflammation [41, 42]. It still remains unclear if this effect is due to the formation of bioactive eicosanoids, effects on nuclear receptors, or changes in membrane lipid composition and function. Shoda *et al.* [43] reported that an elemental diet supplemented with 2% n-3 PUFA-rich perilla oil significantly suppressed plasma LTB_4 and intestinal ulcer index in TNBS-induced colitis in male Sprague – Dawley rats when compared to a diet supplemented with 2% n-6 PUFA-rich oil. In a similar study, perilla oil significantly decreased the arachidonic acid level in the colonic phospholipid fraction but increased the eicosapentaenoic acid level [44]. In the TNBS colitis model in male Wistar rats, Nieto *et al.* [45] found that dietary administration of n-3 PUFAs (in fish oil; 30% of total fat in the diet) led to a higher histologic recovery, a minimum stenosis score, lower colonic alkaline phosphatase and γ-glutamyl transpeptidase (γ-GT) activity, and lower mucosal levels of PGE_2 and LTB_4. However, a decrease in the colonic anti-oxidative enzymes GSH transferase, GSH reductase, GSH peroxidase, and catalase when compared to supplementation with mono-unsaturated fatty acids was found. Kuratko [46] isolated colonic lymphocytes from male BALB/c mice fed a diet high in either corn oil (20% of total diet) rich in n-6 PUFAs or fish oil (19% of total diet) rich in n-3 PUFAs. Cultured lymphocytes from the fish oil group showed lower rates of proliferation upon cytokine stimulation (IL-1β, IL-2, TNF-α) than lymphocytes from the corn oil group. Recently, it was reported that feeding of fish oil (4% of total diet) rich in n-3 PUFAs alters the balance between Th1 and Th2 cells by directly suppressing the Th1 cell clonal expansion [47].

In pigs, treated with DSS to induce colitis, Bassaganya-Riera and Hontecillas [48] and Hontecillas *et al.* [49] found a delayed onset and attenuated activity of colitis when the animals were fed conjugated linoleic acid (CLA), 1.3% added to the diet. In contrast, supplementation with n-3 polyunsaturated acids (PUFAs) as fish oil, failed to protect from inflammation but led to a faster recovery. Interestingly, CLA but not PUFAs activated colonic peroxisome proliferator activated receptor-γ (PPAR-γ) and down-regu-

lated TNF-α expression. PPAR-γ is discussed as playing a role in suppressing colonic inflammation, a function which may be impaired in IBD patients [10]. However, the PPAR-γ agonist rosiglitazone aggravated colonic inflammation in the DSS-model in female C57BL/6 mice [50]. In the same model, Ramakers *et al.* [51] found no increase in major parameters of colitis (weight and length of the colon, histologic scores, cytokine levels) in animals receiving an arachidonic acid-supplemented diet (1% in the diet). Myeloperoxidase activity in plasma and polymorphonuclear cell infiltration in the colon were lower in animals having received a fish oil-supplemented diet.

In female Wistar rats treated over 15 days with DSS in the drinking water, a synergistic attenuating effect of a combined diet based on olive oil with fish oil and 1 mg/kg b.w. per day of quercitrin on various parameters of colonic inflammation was found [52]. Most notably, the diet decreased inflammation-related colonic myeloperoxidase and alkaline phosphatase activities, nitric oxide synthase and COX-2 expression, and LTB_4, TNF-α, and IL-1β levels in the colon.

Male C57BL/6 mice fed a high-fat diet were more susceptible to DSS-induced colitis than those fed a normal diet [53]. They had higher numbers of non-CD1d-restricted natural killer T-cells in the colonic epithelium. These cells expressed TNF-α and IFN-γ. Furthermore, the levels of colonic T_{reg} cells were decreased.

In IL-10 null mice, an olive oil supplemented diet inhibited COX-2 expression in the colon, while supplementation with fish oil exacerbated colitis [54]. Replacement of sunflower oil in a standard diet by 50% coconut oil/50% sunflower oil (medium chain fatty acid diet) reduced colitis scores, IL-6 and interferon γ levels, and the number of intraepithelial $CD3^+$ and lamina propria $CD3^+/CD4^+$ lymphocytes in the colon of IL-10 null mice [55].

2.3 Dietary fiber

Certain types of dietary fiber are considered as so-called "probiotics", *i.e.*, having a beneficial effect on the composition and/or function on the intestinal microflora. A hallmark of such a beneficial action is an increased formation of butyrate, which is, together with other short-chain fatty acids (SCFAs) a typical fermentation product formed by the microflora of the lower gut [56]. Major substrates for butyrate formation are non-digestable carbohydrates which remain (partially) intact during the upper gastro-intestinal passage and reach the colon. Butyrate is a major nutritive factor for the colonic enterocytes and is rapidly absorbed and metabolized there. It exhibits a broad spectrum of cellular effects on the mucosa such as enhanced differentiation, apoptosis, and changes in gene expression. Furthermore, butyrate is supposed to exert local anti-inflammatory effects [57]. The underlying mechanisms have been suggested to include inhibition of NF-κB activation and suppression of histone deacetylation. In isolated human subepithelial myofibroblasts butyrate significantly reduced IFN-γ and TNF-α stimulated secretion of IP-10, a mediator of chronic inflammation in IBD [58].

With respect to dietary fiber resistant or partially resistant to digestion in the upper gastrointestinal tract, a variety of studies have addressed effects on animal models of colonic inflammation. Mao *et al.* [20] reported that addition of 1% pectin to an intragastric infusion of elemental diet reduced intestinal myeloperoxidase levels, body weight loss, and colon water content in the MTX/elemental diet model in male Sprague–Dawley rats. Jacobasch *et al.* [59] reported an earlier recovery from TNBS-colitis in male Wistar rats when resistant starch was added to the diet. Dietary high-amylose cornstarch (15 or 30% in the diet over 10 days) partially protected the colon from TNBS-induced inflammation in male Sprague–Dawley rats [60]. A fiber-supplemented diet containing 5% seeds of *Plantago ovata* ameliorated the development of colonic inflammation in HLA-B27 transgenic mice [61]. This effect was associated by a decrease in NO formation, and LTB_4 and TNF-α levels in the colon. In intestinal contents significantly higher levels of butyrate and propionate were found. Also in HLA-B27 rats, dietary supplementation with a 1:1 mixture of long-chain inulin and short-chain inulin fraction oligofructose (5 g/kg b.w. per day in the drinking water over 7 weeks) significantly decreased inflammatory histologic scores in the cecum and colon [62], decreased cecal IL-1β, and increased cecal TGF-β concentrations. Levels of SCFAs were not analyzed in this study. In weaning piglets, a diet supplemented with a combination of four fermentable carbohydrates (20 g/kg lactulose, 7.5 g/kg inulin, 50 g/kg sugarbeet pulp, and 50 g/kg wheat starch) induced an up-regulation of IL-6 and IL-1β mRNA [63]. These changes were correlated with increased fermentation products, most notably branched-chain fatty acids. Camuesco *et al.* [64] found that dietary lactulose (2.5% in the drinking water) reduced MPO activity, and TNF-α and leukotriene levels in the colon of TNBS-treated female Wistar rats. Similar attenuating effects of lactulose (1000 mg/kg b.w., given orally, twice daily for 6 days) on experimental colitis were reported in DSS-treated male Wistar rats [65]. Lara-Villoslada *et al.* [66] found that short-chain fructooligosaccharides added to the diet (5 g/kg) reduced colonic MPO activity, LTB_4 levels and iNOS expression in the mucosa of TNBS-treated female Wistar rats.

Feeding of a diet rich in fermented brown rice, a fiber-rich food, reduced the development of ulcers, and attenuated the inflammatory damage and MPO levels in DSS-treated male Wistar rats [67]. In DSS-treated male Sprague–Dawley rats, dietary inulin (1% in drinking water or 400 mg/day), an effective precursor of butyrate formation, reduced colonic inflammation [68].

In contrast to the aforementioned studies, Moreau *et al.* [69] could not observe any positive effects of dietary short-

chain fructo-oligosaccharides (63 g/kg in the diet) on DSS-induced colitis in male Sprague – Dawley rats. In another study, galacto-oligosaccharides (4 g/kg b.w. per day) were ineffective in modifying TNBS colitis in male outbred HY/WIST rats [70].

A more complex fiber-rich food item is germinated barley foodstuff (GBF). Its major constituents are proteins with a high content of glutamine and polyglucane-fiber rich in hemicelluloses. In two studies [71, 72], feeding of GBF to rats attenuated DSS-mediated colitis in male Sprague – Dawley rats.

2.4 Calcium/vitamin D

Dietary calcium is considered to have some protective effect against colon cancer. Its role in colonic inflammation is poorly understood, however. In DSS-induced colitis in male BALB/c mice, Pele *et al.* [73] found that low dietary calcium increased crypt scores and elevated mucosal caspase expression while high dietary calcium had no effect. In IL-10 null mice, removal of calcium from the diet increased the severity of gut inflammation, while the animals fed calcium and 1α,25-dihydroxyvitamin D3 had the mildest form of bowel inflammation [74]. The anti-inflammatory effect was associated with a reduced expression of several TNFα-related genes. Double knockout mice lacking IL-10 and the vitamin D receptor suffered from fulminating inflammation in the gastrointestinal tract suggesting that the anti-inflammatory action of D vitamins in the colon is receptor mediated [73, 74].

3 Summary and conclusions

In experimental animals, a variety of treatment regimens and, more recently, of genetic modifications, lead to various types of IBD. The major models used for the study of effects of dietary constituents are the DSS- and TNBS-models. More recently, regimens using acetic acid, bile acids, *etc.*, were established. With the exception of the bile acid model, most of these models use compounds which are not of primary relevance in human IBD, although they can generate patterns of inflammatory responses which resemble certain types of human IBD such as ulcerous colitis or Crohn's colitis.

In TNBS- and/or DSS-treated animals, there is good evidence for an anti-inflammatory action of dietary tocopherols, certain polyphenols, and curcumin at relatively high oral doses. More studies are needed, however, to find out if a high consumption of food items rich in these constituents can prevent human IBD or extent remission phases in patients with IBD. There is also good evidence, that oral application of fats and oils rich in n-3 PUFAs and/or CLA can attenuate certain types of colitis in experimental animal models. While the effects of dietary calcium on colitis are relatively unclear, there are hints indicating that certain high-fiber diets or diets rich in digestion-resistant carbohydrates can attenuate experimental colitis in animals although contradictory results have been reported. Fermentation products such as butyrate, formed by the intestinal flora, may play a role in these effects.

In summary, the anti-inflammatory potency of dietary constituents on gut inflammation in animals seems to be limited. It remains open if a diet can be developed which, as a result of its anti-inflammatory constituents, can be used in effective treatment of active IBD. The reasons for this lack of activity seem to be manifold including pharmacokinetic limitations and intestinal degradation of the compounds, in particular insufficient local, *i. e.*, intra- or sub-mucosal levels of the effective compounds, and, most notably, an (unknown) etiology of human IBD which most likely differs from the mechanisms leading to experimental colitis in animal models.

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