Polyphenols in the treatment of inflammatory bowel disease and acute pancreatitis

Haim Shapiro, Pierre Singer, Zamir Halpern and Rafael Bruck

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Polyphenols are phytochemicals that are abundant in food and beverages derived from plants. Although no deficiency state has been described for them, increased intake of polyphenols appears to protect against disease in virtue of their anti-inflammatory and vasculoprotective properties. This article focuses on four polyphenols with established anti-inflammatory properties: resveratrol, epigallocatechin gallate, curcumin and quercetin. In rodents, ingestion or systemic administration of these agents inhibits nuclear factor κ B-dependent gene expression and induces phase II antioxidant and detoxifying proteins. Conditions prevented and/or ameliorated by these polyphenols include inflammatory colitis and acute pancreatitis. Polyphenols also attenuate ischaemia-reperfusion injury and endotoxemic sepsis, which has a role in the development of multiple organ dysfunction in severe acute pancreatitis. Enteral nutrition has an important role in the management of inflammatory bowel disease (IBD)—mainly of Crohn’s disease, and of acute pancreatitis. Parenteral nutrition is reserved for refractory cases and disease-associated complications. Artificial nutrition attempts to safely administer the essential and otherwise beneficial constituents of food to patients with an impaired ability to ingest or digest food; yet, polyphenols are not included in the formulas. We suggest that the addition of polyphenols to artificial nutritional formulas would improve the outcome of patients with IBD and acute pancreatitis in need of enteral or parenteral nutrition.
PPLs’ effect on health is growing, it is more recent than the investigations dealing with the ramifications of LC ω-3 PUFA consumption. In addition, the growing list of identified PPLs, their variable distribution in different foods, their low bioavailability and their extensive and differential intestinal and hepatic metabolism have hampered defining their significance in the prevention of disease. Nevertheless, PPLs are increasingly recognised as health-promoting phytochemicals as: (1) they attenuate animal models of many human illnesses that have an inflammatory component; (2) their consumption by humans on a healthful plant-based diet is approximately 1 g a day—considerably higher than that of vitamins C and E and β-carotene; (3) they have anti-inflammatory, antioxidative and insulin-sensitising effects and have enhanced endothelial function in clinical trials; and (4) they have reduced cardiovascular disease in epidemiological studies.

**POLYPHENOLS INHIBIT PRO-INFLAMMATORY TRANSCRIPTION FACTORS AND ENHANCE CYTOPROTECTIVE ONES IN VIVO**

PPLs are powerful free radical scavengers in vitro, but present opinion holds that their in vivo anti-inflammatory effect stems from their interaction with proteins involved in signal transduction and gene expression. One important target of PPLs’ action in vivo is the pivotal inflammatory transcription factor, nuclear factor κ B (NFκB; fig 1). Usually bound to and inactivated by the cytoplasmic inhibitor of κ B (IκB), NFκB is released from its association with the latter by activated IκB kinases (IκKs). Pathogen-associated molecular patterns (eg, endotoxin), inflammatory cytokines (eg, tumour necrosis factor-α (TNFα)), T-cell-activating signals and reactive oxygen species trigger signal transduction cascades that converge on, phosphorylate and rapidly activate IκKs. Released NFκB is then translocated into the nucleus where it promotes the expression of inflammatory gene products such as TNFα, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, intercellular adhesion molecule and induces inflammatory activation of lymphocytes, monocyte/macrophages and endothelial cells. Although it may protect parenchymal cells from apoptosis, NFκB is considered to be a target for the treatment of diverse pathological conditions with an inflammatory component. By inhibiting IκK phosphorylation and/or preventing proteasomal degradation of IκB, numerous PPLs attenuate the in vivo NFκB activation induced in inflammatory disease states. These include resveratrol, which is found in grapes and wine and probably contributes to their cardioprotective effects; epigallocatechin gallate (EGCG), an anti-inflammatory component of green tea; curcumin, the major anti-inflammatory PPL in turmeric; and quercetin, which is found in apples, onions, leafy green vegetables and tea. Interestingly, the anti-inflammatory properties of NSAIDs and salicylates are also partially attributable to inhibition of IκK.

As PPLs do not appear to prevent COX-1-mediated synthesis of constitutive/protective prostaglandins, they may be safer, if less powerful, anti-inflammatory agents.

In addition to down-regulating the expression of inflammatory mediators, preneoplastic lesions also induce in vivo the transcription of cytoprotective phase II antioxidant and detoxifying molecules, such as haem-oxygenase-1 (HO-1) and glutathione-related enzymes (fig 1). These are part of the endogenous defence system against xenobiotic and chemical toxicity and protect from carcinogenesis and inflammatory and autoimmune diseases. Electrophilic PPLs release nuclear factor E2-related factor (Nrf2) from its complex with the cytoskeleton-associated protein Keap1, through an interaction with thiols in Keap1. Nrf2 can then bind to the antioxidant responsive element, a regulatory element of phase II genes. Interestingly, the Nrf2 pathway is physiologically activated by the very mediators of inflammatory pathways, such as increased oxidative stress, certain protein kinase(s) C and mitogen-activated protein kinases, perhaps as a counter-regulatory mechanism to reduce collateral tissue injury during inflammation. Thus, through differential modulation of gene expression, PPLs inhibit the injurious consequences of cell injury, oxidative stress and inflammation while enhancing cytoprotective responses. Other genomic and non-genomic actions of different PPLs are reviewed elsewhere.

**LET ARTIFICIAL NUTRITION BE THY MEDICINE**

Artificial nutrition formulas are an attempt to partially reconstruct food from its essential and healthful components, in a form that can be safely administered by the enteral or parenteral route. Over the years, formulas have been modified in an attempt to replicate healthful food intake, correct malnutrition, attenuate catastabilism, inflammation and immunosuppression and to enhance disease resolution and healing. To this end, formulas may include pharmacological doses of nutrients (eg, glutamine and ω-3 PUFAs), non-essential constituents of food with healthful and disease-modifying properties (eg, dietary fibre, prebiotics and probiotics), and even molecules not related to food (eg, transforming growth factor-β). Yet, a patient who temporarily or permanently becomes dependent on enteral or parenteral nutrition is deprived of PPLs that she/he may have previously obtained from fruit, vegetables, tea, wine, chocolate or spices. Although consumption of phytochemicals as a supplement does not necessarily confer the same benefit as ingesting foods rich in these compounds, addition of PPLs to otherwise complete nutritional formulas would bring them a step closer to what has been termed the “entire biological package” of food.

By inhibiting NFκB, inclusion of the PPLs discussed here in artificial nutritional formulas may boost their therapeutic effect in acute and chronic diseases that necessitate enteral nutrition or parenteral nutrition and in which NFκB activation is implicated, such as sepsis, acute respiratory distress syndrome, postoperative organ dysfunction, cachexia, IBD and acute pancreatitis.

1As olives are rich in lipophilic PPLs, olive oil-based formulas may contain remnants that have not been removed during processing. Olive PPLs are antioxidative, anti-inflammatory and vasculoprotective in humans and it has been suggested that they, rather than the mono-unsaturated fatty acids, are the anti-inflammatory component found in dietary olive oil and in nutritional formulas based on it. If this is the case, it would further support a beneficial role for combining PPLs in artificial nutrition.
It has previously been proposed that phytochemicals other than vitamins may be important for patients receiving artificial nutrition. The rest of this article reviews the literature suggesting that administration of the four above-mentioned PPLs is beneficial in IBD and acute pancreatitis, thus offering a rationale for their inclusion in artificial nutrition formulas for patients with these conditions.

**POLYPHENOLS FOR IBD**

Crohn’s disease and ulcerative colitis, the two forms of IBD, are multifactorial disorders resulting from a dysfunctional epithelial, innate and adaptive immune response to intestinal microorganisms. Pharmacological treatment typically targets the ensuing robust autoimmune and inflammatory response that damages the gastrointestinal mucosa, impairing its absorptive and protective barrier function. Most patients with IBD will suffer at some stage a degree of nutritional deficiency, owing to any combination of anorexia, malabsorption, enteropathic protein and blood loss, and a systemic inflammatory-catabolic response. These have deleterious intestinal and extraintestinal consequences.

Paediatric and adult patients with Crohn’s disease and malnutrition may need enteral nutrition and rarely parenteral nutrition to replenish macronutrients and micronutrients and enhance anabolism and growth. In patients with active Crohn’s disease, enteral nutrition is effective as a remission-inducing and a glucocorticoid-sparing treatment to maintain remission. Parenteral nutrition may benefit malnourished patients before major surgery, those with spontaneous or postsurgical enterocutaneous fistulas and possibly also glucocorticoid-resistant patients. Patients with Crohn’s disease having short bowel syndrome after extensive resection of the intestines often depend on artificial nutrition as a source of nutrients. The benefit of nutritional support in ulcerative colitis has received less interest and is presently less supported.

Studies in rodent models of IBD indicate that administration of PPLs is effective in preventing and treating intestinal inflammation and injury. Acute or chronic colitis was induced in these studies by intrarectal administration of dinitrobenzene sulphate or trinitrobenzene sulphate, addition of dextran sulphate sodium (DSS) to the drinking water, or by knock-out of the interleukin-2 gene (IL-2-/- mice). Rodents were treated with PPLs before, during and/or after...
**Table 1** Prophylactic and therapeutic effects of polyphenol administration in rodent models of inflammatory colitis

<table>
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<tr>
<th>Polyphenol</th>
<th>Model, reference</th>
<th>Route, dose, duration and timing of administration</th>
<th>Outcome</th>
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<tr>
<td>Resveratrol</td>
<td>TNBS enema in Wistar rats</td>
<td>i.g. 5 or 10 mg/kg resveratrol 48, 24 and 1 h before and 24 h after TNBS</td>
<td>Reversal of weight loss; ↑ stool consistency; ↓ colonic macropathology (presence and degree of hyperaemia, ulceration, inflammation, adhesions); ↓ colonic histopathology (presence and degree of necrosis, inflammatory infiltrate and mucus depletion); ↓ mucosal PGE2, COX-2, PGD2, levels; ↓ colonic MPO activity</td>
<td>PGE2 levels were not significantly reduced; 5 mg/kg resveratrol improved fewer parameters than 10 mg/kg</td>
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<td></td>
<td>TNBS enema in Wistar rats</td>
<td>i.g. 10 mg/kg/day resveratrol for 14 days starting 24 h after TNBS</td>
<td>↑ Steal consistency; colonic macropathology (weight, presence and degree of hyperaemia, ulceration, inflammation, adhesions); ↓ colonic histopathology (presence and degree of necrosis, inflammatory infiltrate, fibrosis and mucus depletion); ↓ mucosal TNFα and p65 NFκB; ↓ colonic MPO activity; ↑ mucosal PGE2; ↑ epithelial apoptosis</td>
<td>PGE2 levels were reduced during the chronic stage of colitis in untreated animals; resveratrol normalised PGE2 levels</td>
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<td>EGCG/green tea polyphenol extract</td>
<td>DNBS enema, in Sprague-Dawley rats</td>
<td>p.o. green tea polyphenol extract 1 day before and 4 days after DNBS</td>
<td>Reversal of weight loss; ↓ diarrhoea; ↓ colon weight and macropathology; ↓ histopathology (presence and degree of oedema, necrosis, neutrophil infiltrate, haemorrhage); ↓ colonic TNFα, ICAM-1 and nitrotyrosine levels; ↓ colonic MPO activity; ↑ Colonic HO-1</td>
<td>Colonic glutathione status not significantly improved</td>
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<td>DSS in drinking water, in BALB/C mice</td>
<td>p.o. green tea polyphenol extract (in food) for 3 days before and 7 days after DSS</td>
<td>↓ Weight loss and diarrhoea; ↑ colon length; ↑ histopathology (presence and degree of inflammatory infiltrate, mucosal expansion, crypt epithelium disruption, ulceration); ↑ epithelial cytoskeleton distortion/fragmentation (as per laser scanning confocal microscopy); ↓ serum rGSH, SAA, TNFα, ↑ serum Hct and GSSG</td>
<td>IL-2−/− mice spontaneously develop autoimmune disease characterised by colitis, haemolytic anaemia and cachexia; all components respond to green tea intake</td>
</tr>
<tr>
<td>IL-2−/− C57BL/6J mice</td>
<td>p.o. green tea polyphenol extract (5 g/l in drinking water) for 6 weeks after disease establishment</td>
<td>↑ Weight gain, ↓ colon weight; ↓ histopathology (presence and degree of inflammatory infiltrate, epithelial hyperplasia, goblet cell depletion, erosions, ulcerations and crypt abscesses); ↓ ex vivo colonic TNFα and IFNγ, ↓ plasma SAA levels, ↑ Hct</td>
<td>IL-2−/− mice spontaneously develop autoimmune disease characterised by colitis, haemolytic anaemia and cachexia; all components respond to green tea intake</td>
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<td>Curcumin</td>
<td>TNBS enema in Wistar rats</td>
<td>p.o. curcumin (2% in food) for (a) 3 days before or (b) 14 days after TNBS</td>
<td>↑ Survival; ↓ weight loss; ↓ colon histopathology (presence and degree of inflammatory infiltrate, thickening of colon wall, goblet cell depletion); ↓ colonic iNOS; ↓ colonic NfκB activation and IL-1β mRNA (both groups)</td>
<td>Prophylactic (group a) and therapeutic (group b) curcumin showed similar efficacy to prophylactic sulphasalazine</td>
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<td>TNBS enema in BALB/c mice</td>
<td>i.g. curcumin at 25, 50, 100 or 300 mg/kg/day for 10 days before and 8 days after TNBS administration</td>
<td>↓ Weight loss; ↓ diarrhoea; ↓ colon weight and macropathology (presence and degree of inflammatory and ulceration); ↓ histopathology (presence and degree of inflammatory infiltrate, thickening of colon wall, goblet cell depletion); ↓ colon MPO activity; ↓ colon iNOS; (groups b-d); ↓ colon serum protease and NfκB activity; ↓ colon iNOS mRNA, IL-12 mRNA, IL-4 mRNA (assessed in group b only)</td>
<td>Doses of 50–300 mg/kg/day were similarly effective, but 25 mg/kg/day did not significantly improve colitis. Curcumin attenuated the expression of T-helper 1 profile of cytokines</td>
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<td>TNBS enema in C57BL/6 and BALB/c mice</td>
<td>p.o. curcumin in food at (a) 2% for 3 days before; (b) 0.5% for 7 days after; (c) 2% for 7 days after; (d) 5% for 7 days after TNBS administration or (e) 2% for 5 days starting 2 days after TNBS</td>
<td>↑ Survival (group a); ↓ weight loss (groups a–d); ↓ histopathology (presence and degree of inflammatory infiltrate, vascularity, thickening of colon wall (groups a,c,d)); ↓ colonic CYP2C11; ↑ cell infiltration, NfκB activation and levels of IL-6, IL-12, TNFα and IFNγ mRNA (assessed in group a only)</td>
<td>Curcumin tended to be more effective than both dexamethasone 2 mg/kg/day and combined dexamethasone and curcumin. Only curcumin increased formation of PGE2 and granulation tissue</td>
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<td>TNBS enema in Sprague–Dawley rats</td>
<td>i.p. 30 mg/kg/day curcumin for 14 days after TNBS</td>
<td>↑ Survival; ↓ weight loss; macropathology (hyperaemia, ulceration, inflammation, adhesions); ↓ microphagocytosis (epithelial necrosis, destruction of glands, inflammatory infiltrate); ↓ granulation tissue; ↓ colonic IL-1, TNFα, IFNγ mRNA, ↓ colonic IL-4 mRNA; ↑ Colonic PPAR-γ and 15d-PGJ2</td>
<td>Curcumin tended to be more effective than both dexamethasone 2 mg/kg/day and combined dexamethasone and curcumin. Only curcumin increased formation of PGE2 and granulation tissue</td>
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Table 1 Continued

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<tr>
<td>TNBS enema in Sprague–Dawley rats</td>
<td>i.p. 30 or 60 mg/kg/day for 14 days after TNBS</td>
<td>† Survival; † macrophagia (hyperaemia, ulceration, inflammation, adhesion); † macrophagia (epithelial necrosis, destruction of glands, inflammatory infiltrate); † colon MPO activity; † colonic iNOS, COX-2, TNF-α, IFN-γ mRNA, PGE2 (30 and 60 mg/kg/day); † colon macrophagia (presence and degree of hyperaemia, bowel wall thickening, ulceration, inflammation, colonic histopathology (presence and degree of inflammatory infiltrate, ulceration, necrosis); † colonic IL-1β; † colonic MPO, p38 MAPK and NFκB activity</td>
<td>p.r. quercetin 10 μM/day was ineffective. PO rutin and PR quercetin were as effective as PO sulphasalazine and PR 5-ASA; rutin was metabolised to quercetin by colonic microbial glycosidases</td>
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<td>DNBS enema in C3H mice</td>
<td>p.o. curcumin (0.25% in food) for 5 days before and 5 days after DNBS</td>
<td>† Macrophagia (presence and degree/extent of hyperaemia, inflammation ulceration, scabbing, stricture, serosal adhesion); † colon MPO activity (rutin and quercetin 25–100 μM/day)</td>
<td>† Macrophagia (presence and degree/extent of hyperaemia, inflammation ulceration, scabbing, stricture, serosal adhesion); † colon MPO activity (rutin and quercetin 25–100 μM/day)</td>
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<td>Quercetin and its naturally occurring glycones, quercitrin and rutin</td>
<td>TNBS enema in Sprague–Dawley rats</td>
<td>(a) i.g. rutin 10 mg/kg/day from day 1 to 6 after TNBS; (b) p.r. quercetin (enema) 10, 25, 50 or 100 μM/day from day 1 to 6 after TNBS</td>
<td>† Macrophagia (presence and degree/extent of hyperaemia, inflammation ulceration, scabbing, stricture, serosal adhesion); † colon MPO activity (rutin and quercetin 25–100 μM/day)</td>
<td>No reduction in colon MPO activity, perhaps due to the single dose and/or insufficient time for pharmacological effect 125–0.5 mg/kg and 10–50 mg/kg were not effective in acute colitis; quercetin 1 and 5 mg/kg did not reduce markers of inflammation and oxidative stress in chronic colitis despite reduced macrophagia</td>
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<td>TNBS enema in Wistar rats</td>
<td>i.g. quercetin 1 or 5 mg/kg (single dose) 2 h before TNBS</td>
<td>† Colonic alkaline phosphatase and NOS activity; † colonic water and electrolyte absorption; † colonic MDA (1 and 5 μM/kg)</td>
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<td>TNBS enema in Wistar rats</td>
<td>Acute colitis: i.g. quercetin 0.125, 0.25, 0.5, 1, 5, 10, 25 or 50 mg/kg 2 h before to and 24 h after TNBS; Chronic colitis: i.g. quercetin 1 or 5 mg/kg, 2 h before to and daily for 2–4 weeks after TNBS</td>
<td>Acute colitis: † diarrhoea, † colon macrophagia, † colon MPO and AP activity. † colon glutathione content, † colon fluid absorption. (1 and 5 mg/kg only)</td>
<td>Chronic colitis: † diarrhoea, † colon macrophagia, † colon fluid absorption (1 and 5 mg/kg/day)</td>
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<td>DSS in drinking water, in Wistar rats</td>
<td>1 mg/kg/day for 10 days with DSS.</td>
<td>† Disease activity index (weight loss, diarrhoea, blood in faeces), † colon MPO and NFκB activity, † colonic IL-1β, TNF-α, iNOS (quercetin)</td>
<td>† Disease activity index (weight loss, diarrhoea, blood in faeces), † colon MPO and NFκB activity, † colonic IL-1β, TNF-α, iNOS (quercetin)</td>
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<td>DSS in drinking water, in ICR mice</td>
<td>p.o. quercetin or rutin (0.1% in food) for 7 days before and 7 days concurrently with DSS</td>
<td>† Weight loss; † colonic shortening; † histopathology (presence and degree/extent of oedema, inflammation, regenerative changes, fibrosis); † colon and p38 MAPK and p38 MAPK and NFκB activity</td>
<td>i.g. quercetin was ineffective. Quercetin is metabolised by colonic microbial glucosidases to the active quercetin</td>
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<tr>
<td>DSS in drinking water, in Sprague–Dawley rats</td>
<td>p.o. quercetin in drinking water: (a) 1 mg/kg/day together with DSS for 8 days; (b) 5 mg/kg/day together with DSS for 8 days; (c) 1 mg/kg/day after 10 days of DSS, for 5 days</td>
<td>† Disease activity index (weight loss, stool consistency, rectal bleeding) (all groups); † histopathology (presence and degree/extent of inflammatory infiltrate, ulceration, mucus depletion, mitotic activity in crypts, oedema, vasculature, fibrin deposition) (a,c); † colon MPO and iNOS activity (a,c); † colon glutathione content (all groups); † colon NFκB activation (assessed in group c only)</td>
<td>Early administration of quercetin at 1 mg/kg/day improved more parameters than did 5 mg/kg/day; colon LTβR levels were not reduced by quercetin</td>
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**AP**, alkaline phosphatase; **ASA**, 5-aminosalicylic acid; **CCG-8**, cholecystokinin octapeptide; **COX**, cyclooxygenase; **CYP**, cytochrome P450; **EGCG**, epigallocatechin gallate; **ICAM**, intercellular adhesion molecule; **IFN**, interferon; i.g., intragastric; i.p., intraperitoneal; p.o., oral; i.v., intravenous; s.c., subcutaneous; **iNOS**, inducible nitric oxide synthase; **MAPK**, mitogen-activated protein kinase; **MDA**, malondialdehyde; **MPO**, myeloperoxidase; **NFκB**, nuclear factor κB; **PPAR**, peroxisome proliferator-activated receptor; **SAA**, serum amyloid A; **TNBS**, trinitrobenzene sulphate; **TNF**, tumour necrosis factor.
ENRICHMENT OF ARTIFICIAL NUTRITION FORMULAS WITH POLYPHENOLS

rutin) reduced mortality rates, attenuated colonic (eg, diarrhoea, bloody stools) and extracolonic (eg, weight loss) signs of disease, colon macrophathy and micropathy (eg, hyperaemia, ulcerations, inflammatory infiltrate, serosal adhesions) and/or indices of inflammation and autoimmunity (eg, colonic myeloperoxidase and NFκB activity, increased TNFα, IL-1β, IL-12, iNOS and reduced IL-10, Crohn’s disease 4 T cell and neutrophil infiltration). In studies that assessed several dosages, the ratio between the highest and lowest effective dose ranged between 2 and 6, suggesting a relatively wide therapeutic window.

Quercetin (3-rhamnosylquercetin) and rutin (3-O-rhamnosyl-glucosyl-quercetin), the two commonly occurring glycones of quercetin, lack anti-inflammatory properties in vitro but act as pro-drugs when ingested for the treatment of colitis. They are not well absorbed in the small intestine and are metabolised in the colon to the locally active aglycone form, quercetin, by microbial rhamnosidasases. Quercetin was found to be effective when administered intrarectally, but its ingestion failed to ameliorate colitis despite the efficacy of its glycosides, probably due to its avid absorption in the small bowel. Protection against small intestinal disease was not discussed in these studies, but their findings suggest that ingestion of PPL glycones may not be beneficial for inflammation proximal to the colon.

Inhibition of NFκB and of leucocyte and T-cell infiltration and activation probably contributes to PPLs’ therapeutic effect in colitis. PPL induction of HO-1, which reduces oxidative stress and increases carbon monoxide formation, may also blunt injury in IBD. A 2-week treatment with curcumin, itself a peroxisome proliferator-activated receptor-γ agonist, increased the intestinal level of this transcription factor and its endogenous agonist 15-deoxy-D12, 14-prostaglandin J2. Thus, intestinal peroxisome proliferator-activated receptor-γ activation, which inhibits NFκB and attenuates colitis, may also underlie curcumin’s therapeutic action. PGE2 levels are reduced in some models of chronic colitis, and may be increased by PPLs, despite reduced transcription of COX-2. In one study, curcumin, but not dexamethasone, increased the formation of granulation tissue 2 weeks after induction of trinitrobenzene sulphate colitis. Thus, PPLs may somehow modulate the eicosanoid response such as to promote the resolution of inflammation and enhance wound healing.

Animal studies suggest that PPLs improve graft function and survival after organ transplantation, acting alone or synergistically with cyclosporine or mycophenolate mofetil, suggesting that they have immunosuppressive properties as well. Oral curcumin and quercetin reduced acute rejection and immunosuppressive-drug side effects in a double-blind study on cadaveric renal transplant recipients. Also of pertinence to the nutritional support of patients with IBD in a catabolic state is the finding that intraperitoneal administration of resveratrol for 10 days attenuated skeletal muscle cachexia in tumour-bearing mice. A small pilot study showed that oral curcumin therapy improved clinical symptoms, histopathology and laboratory indices in all five patients with ulcerative colitis and four out of five patients with Crohn’s disease who had an insufficient response to conventional treatments. The patients with ulcerative colitis received 550 mg curcumin twice a day for 1 month followed by the same dose once a day for another month. Patients with Crohn’s disease were treated with 360 mg curcumin three times a day for 1 month followed by 360 mg four times a day for two additional months. Finally, the preliminary results from a 6-month placebo-controlled trial of curcumin therapy in 89 patients with ulcerative colitis in remission were recently presented. All patients were on 5-aminosalicylic acid therapy. Relapse was seen in 5% of curcumin-treated and 21% of placebo-treated patients, and no serious adverse effects were reported.

POLYPHENOLS FOR ACUTE PANCREATITIS

Acute pancreatitis is an inflammatory process triggered by a number of instigating factors, with variable involvement of peri-pancreatic tissues and remote organs. After initial acinar cell injury by a specific pathogenic agent or process, the release and activation of proteases and leucocyte infiltration exacerbate a destructive autodigestive and inflammatory cascade. Most cases are mild and resolve spontaneously within 48 h with supportive therapy. But in patients with severe acute pancreatitis (SAP), spillover of inflammatory molecules can initiate early or late multiple organ dysfunction syndrome. Early enteral nutrition, rather than nothing per os or parenteral nutrition, is the recommended approach for patients with severe, and especially necrotising acute pancreatitis, despite the rationale behind avoiding stimulation of the pancreas in such a scenario. Parenteral nutrition is reserved for patients with SAP that develop critical illness and in whom attempts at administering enteral nutrition have failed.

PPLs are protective in experimental acute pancreatitis induced either by injection of tert-butyl hydroperoxide or sodium taurocholate into the pancreatic duct, intraperitoneal injection of DL-ethionine or intravenous cholecystokinin octapeptide (CCK-8) together with oral ethanol (table 2). Resveratrol, EGCG/green tea PPL extract and curcumin attenuate acute pancreatitis in rodents when administered before, concomitantly to or after the instigating agent. Pancreatic damage (pancreatic macropathology and micropathology, neutrophil infiltrate, trypsin activity, lipoperoxides and inflammatory cytokines) was reduced in all studies except for two that were performed by the same group, and in which curcumin did reduce serum amylose, TNFα and IL-6 as well as bacterial translocation.

Inhibition of NFκB and enhanced expression of HO-1 may mediate PPLs’ protective effects in acute pancreatitis. Some evidence suggests that administration of PPLs early in the course of acute pancreatitis may prevent the development of multiple organ dysfunction and septic shock: resveratrol attenuated SAP-associated acute respiratory distress syndrome. Prophylactic administration of PPLs attenuates ischaemia-reperfusion injury to the bowel, which has been implicated in bacterial translocation, pancreatic infection and development of sepsis in SAP. PPLs also protect against ischaemia-reperfusion injury to the kidneys, liver and heart and may thus reduce dysfunction of these organs in the context of the severe inflammatory response syndrome. Finally, pre-emptive administration of PPLs significantly improves survival rates in rodent models of endotoxemia, whereas intravenous curcumin treatment attenuates the liver injury, systemic inflammation and mortality associated with caecal ligation and puncture, even when initiated 5 h after the puncture.
Table 2  Prophylactic and therapeutic effects of polyphenol administration in rodent models of acute pancreatitis

<table>
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<th>Polyphenol</th>
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<tr>
<td>Resveratrol</td>
<td>Bu’OOH injection into pancreatic duct of Wistar rats&lt;sup&gt;14&lt;/sup&gt;</td>
<td>i.p. resveratol 2 mg/day for 8 days before Bu’OOH injection (rats weighed ~300 g)</td>
<td>↓ Pancreatic weight, ↓ pancreatic histopathology (acinar vacuolisation, focal oedema, necrosis, haemorrhage), ↓ pancreatic carbonyl and SH groups, ↓ acinar RES cistern dilation and mitochondrial swelling (per electron microscopy), ↓ serum amylase activity</td>
<td>Administration of diethylstilbestrol, a synthetic analogue of resveratrol, was equally effective</td>
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<td>Taurocholate injection into pancreatic duct of Sprague-Dawley rats&lt;sup&gt;16&lt;/sup&gt;</td>
<td>i.p. resveratrol 30 mg/kg (single dose) after taurocholate injection</td>
<td>↓ Pancreatic histopathology (haemorrhage, microthrombi, exudates, inflammatory infiltrate), ↓ pancreatic NF-kB activity, ↓ pancreatic TNF-α and IL-8, ↓ lung histopathology (alveolar septum thickening, interstitial oedema, inflammatory infiltrate), ↓ lung water content and capillary permeability, ↓ lung MPO activity, ↓ lung ICAM-1, ↓ blood viscosity</td>
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<tr>
<td>EGCG/green tea polyphenol extract</td>
<td>s.c. CCK-8 in Wistar rats&lt;sup&gt;49&lt;/sup&gt;</td>
<td>i.p. 10 mg/kg resveratrol 30 min before CCK-8</td>
<td>↓ Macropathology (oedema, necrosis, haemorrhage, saponification), ↓ amount and turbidity of ascitic fluid, ↓ micropathology (intralobular and interlobular oedema, inflammatory infiltrate, haemorrhage, necrosis), ↓ P450 and NF-kB activation and iNOS activity, ↓ serum TNF-α, IL-1β and NO</td>
<td></td>
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<td>EGCG/green tea polyphenol extract</td>
<td>i.p. green tea polyphenol extract (in drinking water) for 10 days before i.p. cerulein</td>
<td>↓ Pancreatic wet weight, ↓ pancreatic histopathology (acinar cell vacuolisation, intralobule and interlobule oedema, inflammatory infiltrate)</td>
<td></td>
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<td>i.p. DL-ethionine in Wistar rats&lt;sup&gt;54&lt;/sup&gt;</td>
<td>p.o. green tea polyphenol extract (in drinking water) for 10 days before i.p. DL-ethionine</td>
<td>↓ Pancreatic wet weight, ↓ pancreatic histopathology (acinar cell necrosis, intralobule and interlobule oedema), ↓ pancreatic MDA, ↓ serum amylase activity</td>
<td></td>
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<tr>
<td>Curcumin</td>
<td>Taurocholate injection into pancreatic duct of Wistar rats&lt;sup&gt;55&lt;/sup&gt;</td>
<td>(a) i.p. curcumin 100 mg/kg/day for 20 days before and 6 days after taurocholate administration; (b) as in group (a) and i.p. ciprofloxacin and metronidazole for 6 days after taurocholate administration</td>
<td>↓ Bacterial translocation, ↓ serum amylase, MDA and NO</td>
<td>Combination of curcumin and antibiotics produced better results than curcumin alone, but neither groups reduced pancreatic histopathologic scores</td>
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<td>Taurocholate injection into pancreatic duct of Wistar rats&lt;sup&gt;56&lt;/sup&gt; (1) i.v. cerulein or (2) p.o. ethanol + i.v. CCK-8 in Sprague-Dawley rats&lt;sup&gt;57&lt;/sup&gt;</td>
<td>i.v. curcumin 200 mg/kg (single dose) concomitantly to cerulein/CCK-8</td>
<td>↓ Pancreatic histopathology, ↓ pancreatic trypsin activity, ↓ neutrophil infiltration, ↓ pancreatic NF-κB and AP-1 activation, ↑ pancreatic IL-6, ↑ pancreatic IL-6, ↑ TFN-α, ↑ NO activity, ↑ serum amylase and lipase</td>
<td>Curcumin did not reduce tissue injury</td>
</tr>
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</table>

CCK-8, cholecystokinin octapeptide; EGCG, epigallocatechin gallate; ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; i.g., intragastric; i.p., intraperitoneal; p.o., oral; i.v., intravenous; s.c., subcutaneous; MDA, malondialdehyde; MPO, myeloperoxidase; NF-κB, nuclear factor κ B; SOD, sphincter of Oddi dysfunction; TNF, tumour necrosis factor.
SOME CONSIDERATIONS FOR FUTURE RESEARCH AND DEVELOPMENT

Beyond confirming their efficacy, the animal studies reviewed here contribute little to the formulation of a PPL extract (ie, which PPL(s), what dosage(s) would be effective when administered with enteral nutrition/parenteral nutrition). Effective dosage(s) varied among different models, rodent species and studies. Controlled clinical studies of PPL supplementation should provide a closer approximation, but the slow coadministration of PPLs together with nutrient-rich enteral nutrition/parenteral nutrition formulas may influence PPLs’ pharmacodynamics. For instance, quercetin supplementation potentiates ω-3 PUFAs’ anti-inflammatory effect in DSS-induced colitis but quercetin inhibits the induction of heat shock protein 70 (Hsp70), which partially mediates the beneficial response to glutamine. What then would be the sum effect of combining quercetin (or its glycosides) with an “immunonutritional” package containing glutamine and ω-3 PUFAs? Other PPLs actually induce Hsp70 or at least do not interfere with its cytoprotective properties.

Uncertainties notwithstanding, the animal studies do suggest that PPLs have a wide therapeutic window, and that potentially, numerous combinations/dosages would be beneficial. PPLs generally remain non-toxic, even at relatively high doses and safety studies in healthy volunteers, followed by dose-finding/safety studies in patients receiving enteral nutrition/parenteral nutrition should help identify therapeutic regimens.

Food-drug interactions are another issue which needs to be discussed. Quercetin inhibits cytochrome P450 (CYP) 3A4 and increases blood levels of cyclosporine (which is occasionally used to treat IBD) in healthy volunteers. Consumption of a green tea extract did not interfere with CYP3A4-mediated or 2D6-mediated drug metabolism. To the best of our knowledge, the effect of curcumin and resveratrol on clinically relevant pharmacokinetics in humans has not been assessed. Despite their potential to increase cyclosporine levels, the PPLs reviewed here actually protect against cyclosporine-induced nephrotoxicity, while enhancing its therapeutic immunosuppressive effect (in organ transplantation).

In conclusion, PPLs are anti-inflammatory and cytoprotective constituents of plant-derived food that reduce the severity of experimental IBD and acute pancreatitis and may safely enhance the therapeutic effect of enteral and parenteral nutrition in patients with these conditions. Further preclinical and clinical studies are indicated.

The body responds to cell injury by initiating an inflammatory response aimed at immobilising, destroying and removing the injurious agent, and by cytoprotective adaptations that reduce direct and co-lateral damage to parenchymal cells. Numerous injurious agents initiate intracellular cascades that converge on transcription factors, such as NFκB and Nrf2, allowing their translocation to the nucleus where they enhance, respectively, the transcription of pro-inflammatory and cytoprotective genes. Through their divergent effect on NFκB and Nrf2, PPLs inhibit the synthesis of potentially injurious mediators while enhancing that of antioxidative and anti-inflammatory ones.

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REFERENCES

6. Mozaffarian D. Estimated phytochemical content of the dietary approaches to stop hypertension (DASH) diet is higher than in the Control Study Diet. Am J Med 2004; 117(Suppl 1): 31S–33S.
factor beta containing formulas.}

experimentally induced colitis model.}

colonic inflammation in rats. Biochem Pharmacol

grapes, suppresses oxidative damage and stimulates apoptosis during early

pathogenesis of pulmonary diseases: implications for therapy. Br J Surg

lactobacillus and fibre supplement to early enteral nutrition in patients with acute

intestinal inflammation. Ann Surg

glomerulonephritis through up-regulation of heme oxygenase 1.

{\textit{k}}appa B activation, and iNOS overexpression in liver of streptozotocin-

signaling pathways. Ann N Y Acad Sci

a shield against acute and chronic diseases.

animal studies. J Nutr Biochem

in the infarcted rat myocardium through the induction of thioredoxin-1, heme


{\textit{k}}appa B system: a treasure trove for drug development. Mol Nutr Food Res

chronic inflammatory diseases.

et al.]. Plant polyphenols: modifiers of immune function and risk of


et al.]. Antioxidants as novel therapy in a murine

et al.]. An important role of Nrf2-ARE pathway in the cellular

et al.]. A beginner’s guide to NF-{\textit{k}}appa B


et al.]. Resveratrol, a polyphenol found in

et al.]. Inflammatory bowel disease. In:

et al.]. Induction of transcription factor NF-\textit{k}appa B in inflammatory bowel disease.

et al.]. Curcumin, the major component of food

et al.]. Curcumin, a promising drug for long-

et al.]. Pancreatitis. Lancet

et al.]. Induction of proteasome expression in skeletal

et al.]. Pancreatitis.

et al.]. Natural antioxidants in a murine

et al.]. Probiotics and the gut flora in critically ill patients.

et al.]. Pancreatitis: the role of diet and lifestyle.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

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et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.

et al.]. Pancreatitis.
ENRICHMENT OF ARTIFICIAL NUTRITION FORMULAS WITH POLYPHENOLS


Mojzis J, Hvissova K, Germanova D, et al. Effective protective of acetaminophen on 10 April 2007 gut.bmj.com


Chander M, Turrier N, Chopra K. Resveratrol, a polyphenolic phytoalexin protects against cyclosporine-induced nephropathy through nitric oxide dependent mechanism. Toxicology 2005;210:55–64.


www.gutjnl.com