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Polyphenols in the treatment of inflammatory bowel disease and acute pancreatitis: the missing ingredient in enteral and parenteral nutrition formulas?

Alternative/running title:
Enrichment of artificial nutrition formulas with polyphenols: a rationale

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Abbreviations used in this article
PPLs: polyphenols; LC ω-3 PUFA: Long-Chain Omega-3 Polyunsaturated Fatty Acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; NFκB: Nuclear Factor Kappa B; IkB: IkB kinase; LPS: lipopolysaccharide; ROS: reactive oxygen species; PKC: protein kinase C; MAPK: mitogen activated protein kinase(s); TNF-α: tumor necrosis factor alpha; IL: interleukin; COX: cyclo-oxygenase; iNOS: inducible nitric oxide synthase; ICAM: intercellular adhesion molecule; Nrf-2: NF-E2-related factor; HO-1: heme-oxygenase-1; EGCG: epigallocatechin gallate; EN: enteral nutrition; PN: parenteral nutrition; CD: Crohn’s disease; UC: ulcerative colitis; AP: acute pancreatitis; SAP: severe acute pancreatitis; TNBS: trinitro-benzene-sulphonic acid; DNBS: dinitro-benzene-sulphonic acid; DSS: dextran sodium sulphate; i.g. : intragastric (gavage); PG: prostaglandin; MPO: myeloperoxidase; rGSH: reduced glutathione; GSSG: oxidized glutathione; IFN-γ: Interferon gamma; SAA: serum amyloid A; Hct: Hematocrit; MAPK: mitogen activated protein kinase; pΦ: peritoneal macrophage; GM-CSF: granulocyte macrophage-colony stimulating factor; 15d-PGJ2: 15-deoxy-D 12,14-prostaglandin J2; MDA: malondialdehyde; NO: nitric oxide; Bu’OOH: tert-butyl hydroperoxide; RES: rough endoplasmic reticulum; AP-1 activator protein-1; HSP70: heat shock protein; CYP: cytochrome P450

Keywords: polyphenols, inflammatory bowel disease, acute pancreatitis, enteral nutrition, parenteral nutrition

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Competing interest: none declared
Abstract
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 vasculo-protective 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 Kappa B-dependent gene expression and induces Phase II anti-oxidant and detoxifying proteins. Conditions prevented and/or ameliorated by these polyphenols include inflammatory colitis and acute pancreatitis. Polyphenols also attenuate ischemia-reperfusion injury and endotoxemic sepsis, which play a role in the development of multiple organ dysfunction in severe acute pancreatitis. Enteral nutrition plays an important role in the management of inflammatory bowel disease—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 inflammatory bowel disease and acute pancreatitis in need of enteral or parenteral nutrition.
1. Polyphenols, a group of secondary plant metabolites, are non-essential nutrients that probably contribute to human health

Plants, like other single- and multi-cellular organisms contain ubiquitous organic molecules (e.g. amino acids, carbohydrates and fatty acids) termed primary metabolites that are essential to cell structure and basic metabolism. These compounds also serve as substrates for the synthesis of an array of chemicals called secondary plant metabolites, which are accumulated at lower concentrations and are more variably distributed among different species. Once thought to be waste products, these agents are now considered to play a role in ecological interactions with friendly and hostile micro- and macro-organisms, and protection from environmental stressors. Following their ingestion, certain secondary metabolites from edible plants interact beneficially with the regulatory domains of functional proteins that are shared by plants and herbivores, due to evolutionary conservation. Vitamins, for instance, act as enzyme co-activators and their insufficient intake results in disease.[1][2][3] Polyphenolic substances (PPLs), the subject of this review, belong to an ill-defined group of secondary plant metabolites called phytochemicals or bioactive compounds in food, for which a deficiency-state has not been described (denying them the title of essential micro-nutrient) but that have attracted attention as mediators of the disease-preventative effect of a healthful diet.[4][5][6][7][8][9][10][11][12][13][14] PPLs’ status as a non-essential, but an established health-promoting dietary constituent is approaching that of the marine life-derived, Long Chain ω-3 Polynsaturated Fatty Acids (LC PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): These can be synthesized to some extent from the shorter-chain, plant-derived, essential ω-3 PUFA, alpha-linolenic acid. Thus EPA and DHA are not considered essential nutrients for adults.[8] Yet since the initial interest in their vasculoprotective properties during the 1970’s, a formidable body of knowledge from mechanistic, epidemiologic and large clinical studies has evolved, defining a role for the LC ω-3 PUFAs in the secondary prevention of cardiovascular disease.[15][16] A number of studies have also shown the importance of supplementing artificial nutrition formulas with these fatty acids, by showing that they reduce morbidity, and possibly mortality, in several clinical scenarios.[17][18] Thus modern nutritional science has expanded its focus from overt nutrient-deficiency states to the relationship of diet and nutritional status to the industrialized world’s common diseases, including the benefit derived from consuming certain non-essential bioactive components of food.[8][19] Although interest in PPLs’ effect on health is growing, it is more recent[20] than investigations dealing with the ramifications of LC ω-3 PUFAs 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.[11][12][13][14][20][21] The current level of evidence precludes recommending that patients take PPL-containing supplements to treat or prevent disease, rather than eat a variety of healthful foods, with emphasis on plant sources.[8][12][20] Still, PPLs are increasingly recognized as health-promoting phytochemicals since: 1) they attenuate animal models of many human illnesses that have an inflammatory component,[12][20] 2) their consumption by humans on a healthful plant-based diet is approximately 1 gram a day- considerably higher than that of vitamins C and E and beta carotene[12] 3) - has anti-inflammatory, anti-oxidative and insulin-sensitizing effects and has enhanced
endothelial function in clinical trials[22][23][24][25][26][27], and 4) reduced cardiovascular disease in epidemiological studies.[28]

2. Polyphenols inhibit pro-inflammatory transcription factors and enhance cytoprotective ones in vivo

PPLs are powerful free radical scavengers in vitro,[12] but present opinion holds that their in vivo anti-inflammatory effect stems from their interaction with proteins involved in signal transduction and gene expression.[11][12][20][21][29] One important target of PPLs’ action in vivo is the pivotal inflammatory transcription factor Nuclear Factor Kappa B (NFκB) (Figure 1). Usually bound to and inactivated by the cytoplasmic inhibitor of κB (IκB), NFκB is released from its association with the latter by activated IκB kinases (IκKs). Pathogen-associated molecular patterns (e.g. endotoxin), inflammatory cytokines (e.g. TNF-α), 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 TNF-α, iNOS, COX-2, ICAM and induces inflammatory activation of lymphocytes, monocyte/macrophages and endothelial cells.[30] Although it may protect parenchymal cells from apoptosis, NFκB is considered a target for the treatment of diverse pathologic conditions with an inflammatory component.[30][31] By inhibiting IκK phosphorylation and/or preventing proteasomal degradation of IκB, numerous PPLs attenuate the in vivo NFκB activation induced in inflammatory disease states.[11][12] These include resveratrol, which is found in grapes and wine and probably contributes to their cardio-protective effects,[32][33] epigallocatechin gallate (EGCG), an anti-inflammatory component of green tea,[34] curcumin, the major anti-inflammatory PPL in turmeric,[35][36] and quercetin, which is found in apples, onions, leafy green vegetables and tea.[37] Interestingly, the anti-inflammatory properties of NSAIDS and salicylates are also partially attributable to inhibition of IκK.[38] Since 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, PNLs also induce in vivo the transcription of cytoprotective Phase II anti-oxidant and detoxifying molecules, such as heme-oxygenase-1 (HO-1) and glutathione-related enzymes.[39][40][41][42] (Fig 1) These are part of the endogenous defense system against xenobiotic and chemical toxicity and protect from carcinogenesis and inflammatory and auto-immune disease.[43] Electrophilic PPLs release Nuclear-factor-E2-related factor (Nrf-2) from its complex with the cytoskeleton-associated protein Keap1, through an interaction with thiols in Keap1. Nrf-2 can then bind to the antioxidant responsive element (ARE), a regulatory element of Phase II genes.[42] Interestingly, the Nrf-2 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.[43] Thus, via 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.[11][12][28][32][33][34][35][41]
3. 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.[44] Over the years formulas have been modified in an attempt to replicate healthful food intake, correct malnutrition, attenuate catabolism, inflammation and immunosuppression and to enhance disease resolution and healing.[44][45] To this end, formulas have come to include pharmacological doses of nutrients (e.g. glutamine and ω-3 PUFAs), non-essential constituents of food with healthful and disease-modifying properties (e.g. dietary fiber, pre- and probiotics), and even molecules not related to food (e.g. TGF-β).[45][46][47][48] Yet a patient who temporarily or permanently becomes dependent on enteral or parenteral nutrition (PN) is deprived of PPLs that she/he may have previously obtained from fruit, vegetables, tea, wine, chocolate or spices1.

1 [Since olives are rich in lipophytic PPLs, olive oil-based formulas may contain remnants that have not been removed during processing. Olive PPLs are anti-oxidative, anti-inflammatory and vasculoprotective in humans [23] [26] 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 upon it.[4] [49] If this is the case, it would further support a beneficial role for combining PPLs in artificial nutrition.]

Whereas 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.[50]

By inhibiting NFκB, the inclusion of the PPLs discussed here in artificial nutritional formulas may boost their therapeutic effect in acute and chronic diseases that necessitate EN or PN and in which NFκB activation is implicated, such as sepsis,[51] Acute Respiratory Distress Syndrome,[52] post-operative organ dysfunction,[53] cachexia,[54] inflammatory bowel disease (IBD)[55] and acute pancreatitis (AP).[56]

It has previously been proposed that phytochemicals other than vitamins may be important for patients receiving artificial nutrition.[44] The rest of this article reviews the literature suggesting that administration of the four above-mentioned PPLs is beneficial in IBD and AP, thus offering a rationale for their inclusion in artificial nutrition formulas for patients with these conditions.

4. Polyphenols for Inflammatory Bowel Disease

Crohn’s Disease (CD) and Ulcerative Colitis (UC), the two forms of Inflammatory Bowel Disease (IBD) are multi-factorial disorders resulting from a dysfunctional epithelial, innate and adaptive immune response to intestinal micro-organisms. Pharmacological treatment typically targets the ensuing robust autoimmune and inflammatory response that damages the gastrointestinal mucosa, impairing its absorptive and protective barrier function.[57] Most IBD patients will suffer at some stage from 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 extra-intestinal consequences.[57][58][59]
Pediatric and adult CD patients suffering from malnutrition may need EN and rarely PN in order to replenish macro- and micronutrients and enhance anabolism and growth. In active CD, EN is effective as a remission-inducing and a glucocorticoid-sparing treatment to maintain remission. PN may benefit malnourished patients before major surgery, those with spontaneous or post-surgical enterocutaneous fistulas and possibly also glucocorticoid-resistant patients. CD patients with Short Bowel Syndrome following extensive resection of the intestines often depend on artificial nutrition as a source of nutrients. The benefit of nutritional support in UC has received less interest and is presently less supported. [57][58][59]

Studies in rodent models of IBD[60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76] (Table 1) indicate that administration of PPLs is effective in preventing and treating intestinal inflammation and injury. Acute or chronic colitis were induced in these studies by intrarectal administration of dinitrobenzene sulphate [62][70] or trinitrobenzene sulphate[60][61][65][66][67][68] [70][71][72] (DNBS, TNBS), addition of dextran sulfate sodium (DSS) to the drinking water, [63] [74][75][76] or by knock-out of the interleukin-2 gene[64] (IL-2⁺ mice). Rodents were treated with PPLs before, during and/or after induction of colitis, by oral (added to food or drinking water or via an oro-gastric tube),[60][61][63][64][65][66][67][69][70][71][72][73][74][75][76] rectal[71] or intraperitoneal[62][68][69] administration. They were sacrificed, and indices of disease were assessed between 48 hrs and 6 weeks following induction of colitis. Resveratrol,[60][61] EGCG/ green tea PPL extract,[62][63][64] curcumin[65][66][67][68][69][70] and quercetin and its naturally occurring glycones[71][72][73][74][75][76] (quercetin and rutin) reduced mortality rates, attenuated colonic (e.g. diarrhea, bloody stools) and extra-colonic (e.g. weight loss) signs of disease, colon macro- and micropathology (e.g. hyperemia, ulcerations, inflammatory infiltrate, serosal adhesions) and/or indices of inflammation and auto-immunity (e.g. colonic MPO and NFκB activity, elevated TNF-α, IL-1β, IL-12, iNOS, and reduced IL-10, CD4⁺ 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 metabolized in the colon to the locally active aglycone form, quercetin, by microbial rhamnosidases.[71] [74] Quercetin was found to be effective when administered intra-rectally,[71] but its ingestion failed to ameliorate colitis despite the efficacy of its glycosides,[71][72][73][74][75][76] probably due to its avid absorption in the small bowel. Protection against small intestinal disease was not addressed 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 leukocyte and T-cell infiltration and activation probably contributes to PPLs’ therapeutic effect in colitis.[55] PPL induction of HO-1,[40][41] which reduces oxidative stress and increases carbon monoxide formation, may also blunt injury in IBD.[76][77][78] Two weeks treatment with curcumin, itself a PPAR-γ agonist, [79][80][81] increased the intestinal level of this transcription factor and its endogenous agonist 15d-PGJ2.[68] Thus intestinal PPAR-γ activation, which inhibits NFκB and attenuates colitis,[82] may also underlie curcumin’s therapeutic action. PGE₂ levels are reduced in some models of chronic colitis, and was increased by
PPLs, despite reduced transcription of COX2. In one study, curcumin, but not dexamethasone, increased the formation of granulation tissue two weeks following induction of TNBS 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 following 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 IBD patients in a catabolic state is the finding that i.p. administration of resveratrol for 10 days attenuated skeletal muscle cachexia in tumor-bearing mice. A small pilot study showed that oral curcumin therapy improved clinical symptoms, histopathology and laboratory indices in five out of five UC patients and four out of five CD patients with an insufficient response to conventional treatments. The UC patients received 550 mg curcumin twice a day for one month followed by the same dose once a day for another month. Patients with CD were treated with 360 mg curcumin three times a day for one month followed by 360 mg four times a day for 2 additional months. Finally, the preliminary results from a 6 month placebo-controlled trial of curcumin therapy in 89 UC patients in remission were recently presented. All patients were on 5-ASA therapy. Relapse was seen in 5% of curcumin-treated patients and in 21% of placebo-treated patients, and no serious adverse effects were reported.
**Table 1:** Prophylactic and therapeutic effects of polyphenol administration in rodent models of inflammatory colitis

<table>
<thead>
<tr>
<th>Polyphenol</th>
<th>Model, Reference</th>
<th>Route, dose, duration and timing of administration</th>
<th>Outcome</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Resveratrol</td>
<td>TNBS enema in Wistar rats [60]</td>
<td>i.g. 5 or 10 mg/kg resveratrol 48, 24 and 1 hr before and 24 hr after TNBS</td>
<td>reversal of weight loss; ↑ stool consistency, ↓ colonic macropathology (presence and degree/extent of hyperemia, ulceration, inflammation, adhesions), ↓ colonic histopathology (presence and degree/extent of necrosis, inflammatory infiltrate and mucus depletion); ↓ mucosal IL-1β, 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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<tr>
<td>EGCG/ green tea polyphenol extract</td>
<td>DNBS enema, in Sprague-Dawley rats [62]</td>
<td>i.p. 50 mg/kg/day green tea polyphenol extract 1 day before and 4 days after DNBS</td>
<td>reversal of weight loss; ↓ diarrhea; ↓ colon weight and macropathology; ↓ histopathology (presence and degree/extent of edema, necrosis, neutrophil infiltrate, hemorrhage); ↓ colonic TNF-α, ICAM-1 and nitrotyrosine levels; ↓ colonic MPO activity; ↑ colonic HO-1</td>
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<tr>
<td>Treatment</td>
<td>Route</td>
<td>Compound</td>
<td>Description</td>
<td>Effects</td>
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<td>DSS in drinking water, in BALB/C mice [63]</td>
<td>p.o.</td>
<td><em>green tea polyphenol extract</em> (in food) for 3 days before and 7 days after DSS</td>
<td>↓ weight loss and diarrhea; ↑ colon length; ↓ histopathology (presence and degree/extent of inflammatory infiltrate, mucosal expansion, crypt epithelium disruption, ulceration); ↓ epithelial cytoskeleton distortion/fragmentation (as per laser scanning confocal microscopy); ↓ serum rGSH, SAA, TNF-α; ↑ serum Hct and GSSG</td>
<td>Colonic glutathione status not significantly improved</td>
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<tr>
<td>IL-2−/− C57BL/6J mice [64]</td>
<td>p.o.</td>
<td><em>green tea polyphenol extract</em> (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); ↓ <em>ex vivo</em> colonic TNF-α and IFN-γ, ↓ plasma SAA levels, ↑ Hct</td>
<td>IL-2−/− mice spontaneously develop autoimmune disease characterized by colitis, hemolytic anemia and cachexia; all components responded to green tea intake</td>
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<td>curcumin</td>
<td>TNBS enema in Wistar rats [65]</td>
<td>p.o.</td>
<td><em>curcumin</em> (2% in food) for a) 3 days before or b) 14 days after TNBS</td>
<td>↑ survival; ↓ weight loss; ↓ colon histopathology (presence and degree/extent of inflammatory infiltrate, thickening of colon wall, goblet cell depletion); ↑ colonic IkB; ↓ colonic NFκB activation and IL-1β mRNA (both groups)</td>
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<td>curcumin</td>
<td>TNBS enema in BALB/c mice [66]</td>
<td>i.g.</td>
<td><em>curcumin</em> at 25, 50, 100 or 300 mg/kg/day for 10 days before and 8 days after TNBS administration</td>
<td>↓ weight loss; ↓ diarrhea; ↓ colon weight and macropathology (presence and degree/extent of inflammation and ulceration); ↓ histopathology (presence and degree/extent of inflammatory infiltrate, thickening of colon wall, goblet cell depletion); ↓ colon MPO activity; ↓ colon NO, O₂⁻ (groups b-d). ↓ colon serine protease and NFκB activity; ↓ colon IFN-γ, IL-12 mRNA, ↑ IL-4 mRNA (assessed in group b only).</td>
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<tr>
<td>Study</td>
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<td>TNBS enema in C57BL/6 and BALB/c mice [67]</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]; ↓ mucosal CD4+ T-cell infiltration, NFκB activation and levels of IL-6, IL-12, TNF-α and IFN-γ mRNA [assessed in group a only]</td>
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<td>TNBS enema in Sprague-Dawley rats [68]</td>
<td>i.p. 30 mg/kg/day curcumin for 14 days following TNBS</td>
<td>↑survival; ↓weight loss; macropathology (hyperemia, ulceration, inflammation, adhesions); ↓ micropathology (epithelial necrosis, destruction of glands, inflammatory infiltrate, ↑granulation tissue); ↓colonic IL-1, TNF-α, IFN-γ mRNA, ↑colonic IL-4 mRNA; ↑ colonic PPAR-γ and 15d-PGJ2</td>
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<td>TNBS enema in Sprague-Dawley rats [69]</td>
<td>i.p. 30 or 60 mg/kg/day curcumin for 14 days following TNBS</td>
<td>↑survival; ↓macropathology (hyperemia, ulceration, inflammation, adhesions); ↓ micropathology (epithelial necrosis, destruction of glands, inflammatory infiltrate); ↓ colon MPO activity; ↓colonic iNOS, COX2, TNF-α, IFN-γ mRNA, ↑PGE2 [30 and 60 mg/kg/day]</td>
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<td>DNBS enema in C3H mice [70]</td>
<td>p.o curcumin (0.25% in food) for 5 days before and 5 days after DNBS</td>
<td>↓ colon macropathology (presence and degree of hyperemia, bowel wall thickening, ulceration, inflammation; ↓ colon histopathology (presence and degree of inflammatory infiltrate, ulceration, necrosis); ↓colonic IL-1β; ↓colonic MPO, p38 MAPK and NFκB activity</td>
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<td>quercetin and its naturally occurring glycones, quercetrin and rutin</td>
<td>TNBS enema in Sprague-Dawley rats [71]</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>↓ colon macropathology (presence and degree/extent of hyperemia, inflammation ulceration, scabbing, stricture, serosal adhesion); ↓ colon MPO activity [rutin and quercetin 25-100 µM/day]</td>
<td>p.r. quercetin 10 µM/day was ineffective. PO rutin and PR quercetin were as effective as PO sulfasalazine and PR 5-ASA; rutin was metabolized to quercetin by colonic microbial glycosidases</td>
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<td>TNBS enema in Wistar rats [72]</td>
<td>i.g. quercetin 1 or 5 mg/kg (single dose) 2 hours before TNBS</td>
<td>↓ colonic alkaline phosphatase and NOS activity; ↑ colonic water and electrolyte absorption; ↓ colonic MDA [1 and 5 mk/kg].</td>
<td>No reduction in colonic MPO activity, perhaps due to the single dose and/or insufficient time for pharmacological effect</td>
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<td></td>
<td>TNBS enema in Wistar rats [73]</td>
<td>Acute colitis: i.g. quercitrin 0.125, 0.25, 0.5, 1, 5, 10, 25 or 50 mg/kg 2 hours before to and 24 hours after TNBS; Chronic colitis: i.g. quercitrin 1 or 5 mg/kg, 2 hours before to and daily for 2-4 weeks after TNBS</td>
<td>Acute colitis: ↓ diahroea, ↓ colon macropathology, ↓ colon MPO and AP activity, ↑ colon glutathione content, ↑ colon fluid absorption [1 and 5 mg/kg only]. Chronic colitis: ↓ diahroea, ↓ colon macropathology, ↑ colon fluid absorption [1 and 5 mg/kg/day]</td>
<td>0.125 – 0.5 mg/kg and 10-50 mg/kg were not effective in acute colitis; quercetrin 1 and 5 mg/kg did not reduce markers of inflammation and oxidative stress in chronic colitis despite reduced macropathology</td>
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<td>DSS in drinking water, in Wistar rats [74]</td>
<td>i.g. quercetin or quercetrin, 1 mg/kg/day for 10 days with DSS.</td>
<td>↓ disease activity index (weight loss, diarrhea, blood in feces), ↓ colonic MPO and NFκB activity, ↓ colonic IL-1β, TNF-α, iNOS [quercetrin]</td>
<td>i.g. quercetin was ineffective. Quercetrin is metabolized by colonic microbial rhamnosidases to the active quercetin</td>
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</tbody>
</table>
### 5. 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. Following initial acinar cell injury by a specific pathogenic agent or process, the release and activation of proteases and leukocyte infiltration exacerbate a destructive auto-digestive and inflammatory cascade. Most cases are mild and resolve spontaneously within 48 hours with supportive therapy. But in patients with severe acute pancreatitis (SAP), spillover of inflammatory molecules can initiate early or late multiple organ dysfunction syndrome.[89] Early EN, rather than nothing per os or PN, is the recommended approach to patients with severe, and especially necrotising AP, despite the rationale behind avoiding stimulation of the pancreas in such a scenario. PN is reserved for patients with SAP that develop critical illness and in whom attempts at administering EN have failed.[90][91]

PPLs are protective in experimental AP[92][93][94][95][96][97][98][99][100][101][102][103] induced either by injection of tert-butyl hydroperoxide[78] or sodium taurocholate into the pancreatic duct,[80][81] i.p.[82] or i.v.[85] injection of cerulein, i.p. injection of DL-ethionine[83] or i.v. CCK-8 together with oral ethanol (Table 2).[85] Resveratrol,[78][79][80][81] EGCG/ green tea PPL extract,[82][83] and curcumin[84][85] attenuates AP in rodents when administered prior to, concomitantly to, or following the instigating agent. Pancreatic damage (pancreatic macro- and micro-pathology, neutrophil infiltrate, trypsin activity, lipoperoxides and inflammatory cytokines) was reduced in all studies except for two that were performed by the same group,[101][102] and in which curcumin did reduce serum amylase, TNF-α and IL-6 as well as bacterial translocation.
Inhibition of NFκB[56] and enhanced expression of HO-1[104] may mediate PPLs’ protective effects in AP. Some evidence suggests that administration of PPLs early in the course of AP may prevent the development of multiple organ dysfunction and septic shock: resveratrol attenuated SAP-associated acute respiratory distress syndrome.[94][95] Prophylactic administration of PPLs attenuates ischemia-reperfusion injury to the bowel,[105][106] which has been implicated in bacterial translocation, pancreatic infection and development of sepsis in SAP.[107][108]. PPLs also protect against ischemia-reperfusion injury to the kidneys, liver and heart,[109][110][111][112][113][114][115] 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 endotoxinemia,[116][117][118] whereas intravenous curcumin treatment attenuates the liver injury, systemic inflammation, and mortality associated with cecal ligation and puncture, even when initiated five hours following the puncture.[79]

**Table 2:** Prophylactic and therapeutic effects of polyphenol administration in rodent models of acute pancreatitis

<table>
<thead>
<tr>
<th>polyphenol</th>
<th>model and reference</th>
<th>route, dose, duration and timing of administration</th>
<th>outcomes</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>resveratrol</td>
<td>Bu'OOH injection into pancreatic duct of Wistar rats [93]</td>
<td>i.p. resveratrol 2 mg/day for 8 days prior to Bu'OOH injection (rats weighed ~300 grams)</td>
<td>↓pancreatic weight, ↓pancreatic histopathology (acinar vacuolization, focal edema, necrosis, hemorrhage), ↓pancreatic carbonyl and SH groups, ↓acinar RES cistem dilation and mitochondrial swelling (per electron microscopy), ↓serum amylase activity</td>
<td>Administration of diethylstilbesterol, a synthetic analogue of resveratrol, was equally effective</td>
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<tr>
<td>taurocholate injection into pancreatic duct of Sprague Dawley rats [94][95]</td>
<td>i.p. <strong>resveratrol</strong> 30 mg/kg (single dose) following taurocholate injection</td>
<td>↓ pancreatic histopathology (hemorrhage, microthrombi, exudates, inflammatory infiltrate), ↓ pancreatic NFκB activity, ↓ pancreatic TNF-α and IL-8, ↓ lung histopathology (alveolar septum thickening, interstitial edema, inflammatory infiltrate), ↓ lung water content and capillary permeability, ↓ lung MPO activity, ↓ lung ICAM-1, ↓ blood viscosity</td>
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<tr>
<td>taurocholate injection into pancreatic duct of Sprague Dawley rats [96]</td>
<td>i.v. 10 mg/kg <strong>resveratrol</strong> 5 min after sodium taurocholate</td>
<td>↓ micropathology (intra- and interlobular edema, inflammatory infiltrate, hemorrhage, necrosis); ↓ PΦ NFκB activation and iNOS activity; ↓ serum TNF-α, IL-1β and NO</td>
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<td></td>
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<tr>
<td>Treatment</td>
<td>Dose/Protocol</td>
<td>Effects</td>
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<tr>
<td>Taurocholate injection into pancreatic duct of Sprague Dawley rats [97]</td>
<td>iv 20 mg/kg resveratrol after sodium taurocholate</td>
<td>↓ macropathology (edema, necrosis, hemorrhage, saponification); ↓ amount and turbidity of ascitic fluid; ↓ micropathology (intra- and interlobular edema, inflammatory infiltrate, hemorrhage, thrombosis, necrosis); ↓ pancreatic TBARS, ↓ pancreatic MPO activity, ↑ pancreatic SOD</td>
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<td>s.c. CCK-8 in Wistar rats [98]</td>
<td>i.p. 10 mg/kg resveratrol 30 min before CCK-8</td>
<td>↓ pancreatic wet weight, ↓ pancreatic histopathology (acinar cell vacuolization, intra- and inter-lobule edema, inflammatory infiltrate)</td>
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<tr>
<td>EGCG/ green tea polyphenol extract</td>
<td>i.p. cerulein in Wistar rats [99]</td>
<td>p.o. green tea polyphenol extract (in drinking water) for 10 days prior to i.p. cerulein</td>
<td>↓ pancreatic wet weight, ↓ pancreatic histopathology (acinar cell vacuolization, intra- and inter-lobule edema), ↓ pancreatic MDA, ↓ serum amylase</td>
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<tr>
<td>i.p. DL-ethionine in Wistar rats [100]</td>
<td>p.o. green tea polyphenol extract (in drinking water) for 10 days prior to i.p. DL-ethionine)</td>
<td>↓ pancreatic wet weight, ↓ pancreatic histopathology (acinar cell necrosis, intra- and interslobule edema), ↓ pancreatic MDA, ↓ serum amylase</td>
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<td>curcumin injection into pancreatic duct of Wistar rats [101]</td>
<td>a) i.g. curcumin 100 mg/kg/day for 20 days before and 6 days after taurocholate administration; b) as in group a) plus i.p. ciprofloxacin and metronidazole for 6 days after taurocholate administration</td>
<td>↓ bacterial translocation; ↓ serum amyase, 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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<tr>
<td>taurocholate injection into pancreatic duct of Wistar rats [102]</td>
<td>i.g. curcumin 100 mg/kg/day for 20 days before and 6 days after taurocholate administration</td>
<td>↓ serum TNF-α and IL-6</td>
<td>Curcumin did not reduce tissue injury</td>
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<tr>
<td>1) i.v. cerulein or 2) p.o. ethanol + i.v. CCK-8 in Sprague-Dawley rats [103]</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 NFκB and AP-1 activation, ↑ pancreatic IκB, ↓ pancreatic IL-6, TNF-α, iNOS mRNA, ↓ serum amyase and lipase</td>
<td>Curcumin did not reduce CCK-mediated amylase secretion, suggesting that the reduced pancreatic trypsin activity is due to its anti-neutrophil effect</td>
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</table>

### 6. 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 (i.e. which PPL(s), what dosage(s)) would be effective when administered with EN/PN. Effective dosage(s) varied among different models, rodent species and studies. Controlled clinical studies of PPL supplementation [89] should provide a closer approximation, but the slow co-administration of PPLs together with nutrient-rich EN/PN formulas may influence PPLs’ pharmacodynamics. For instance, quercetin supplementation potentiates omega-3 PUFAs’ anti-inflammatory effect in DSS-induced colitis [119] but quercetin inhibits the induction of heat shock protein 70 (hsp70), [120] which partially mediates...
the beneficial response to glutamine. What then would be the sum effect of combining quercetin (or its glycones) 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 EN/PN should help identify therapeutic regimens.

Food-drug interactions are another issue needed to be addressed. Quercetin inhibits cytochrome P450 (CYP) 3A4 and elevates 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- 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 AP and may safely enhance the therapeutic effect of enteral and parenteral nutrition in patients with these conditions. Further pre-clinical and clinical studies are indicated.

Acknowledgement.

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135. Satyanarayana PS, Singh D, Chopra K. Quercetin, a bioflavonoid, protects against oxidative stress-related renal dysfunction
by cyclosporine in rats. 


Figure 1 title and legend:

**Figure 1:** Polyphenols attenuate injury to parenchymal cells by down-regulating inflammatory genes and up-regulating cytoprotective ones

The body responds to cell injury by initiating an inflammatory response aimed at immobilizing, 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 respectively enhance 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 anti-oxidative and anti-inflammatory ones.
Inhibited by polyphenols
Activated by polyphenols

Inflammatory mediators, reactive oxygen species

Polyphenol

NFκB–IκB

Nrf2–Keap1

NFκB–DNA

Nrf2–DNA

↑ ICAM, iNOS, COX-2, TNF-α, etc
Adhesive endothelium; infiltration and activation of neutrophils, macrophages and T-cells

Oxidative stress, ↑ CO production

↑ HO-1, glutathione system enzymes

Inflammation and injury to parenchymal cell

Cytoprotection

Inhibited by polyphenols
Activated by polyphenols