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Review article: The complex interplay between diet and *Escherichia coli* in inflammatory bowel disease

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Summary

Background: Although no causative microbe has been yet identified or successfully targeted in the treatment of inflammatory bowel disease (IBD), the role of *Escherichia coli* in the pathogenesis of Crohn's disease has attracted considerable interest.

Aim: In this review, we present a literature overview of the interactions between diet and *E. coli* and other Proteobacteria in the aetiology, outcomes and management of IBD and suggest future research directions.

Methods: An extensive literature search was performed to identify in vitro studies and research in animal models that explored mechanisms by which dietary components can interact with *E. coli* or Proteobacteria to initiate or propagate gut inflammation. We also explored the effect diet and dietary therapies have on the levels of *E. coli* or Proteobacteria in patients with IBD.

Results: Preclinical data suggest that the Western diet and its components influence the abundance, colonisation and phenotypic behaviour of *E. coli* in the gut, which may in turn initiate or contribute to gut inflammation. In contrast, the Mediterranean diet and specific dietary fibres may abrogate these effects and protect from inflammation. There are limited data from clinical trials, mostly from patients with Crohn's disease during treatment with exclusive enteral nutrition, with findings often challenging observations from preclinical research. Data from patients with ulcerative colitis are sparse.

Conclusions: Preclinical and some clinical trial data suggest that *E. coli* and other Proteobacteria interact with certain dietary components to promote gut inflammation. Well-designed clinical trials are required before dietary recommendations for disease management can be made.

The Handling Editor for this article was Professor Peter Gibson, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are characterised by a complex interaction between host immunity, genetic risk, intestinal microbiota and environmental factors.[1,2] The prevalence of IBD is more common in westernised countries in North America, Northern Europe and Oceania, but disease incidence is increasing in low- and medium-income societies in economic growth.[1,3,4] This rapid increase in the incidence of IBD points to a pivotal role for environmental factors in the underlying disease pathogenesis, including influences from diet.[5]

Modern lifestyle, globalisation and technological advances in the food industry have introduced extensive changes to our habitual diet with eating habits shifting from a predominantly plant-based, low-meat diet to one limited in fibre and high in refined carbohydrates, red meat, ultra-processed food, saturated fats and protein.[6] This dietary pattern often labelled as the Western diet has been associated with an increased risk of developing CD and UC,[7-10] and preclinical research in animal models and in vitro studies suggests mechanisms via which certain food ingredients modify host–microbiota interactions with a potential impact on the initiation and severity of gut inflammation.[11-14]

A dysbiotic microbiota of low diversity is the commonest feature of patients with CD.[15] Facultative anaerobes from *Enterobacteriaceae*, *Enterococci* and *Streptococci* are increased while *Ruminococcaceae*, *Lachnospiraceae* and other butyrate-producing bacteria are observed in much lower abundance than in healthy individuals.[16,17] Although no causative microbe has been identified yet, the role of adherent-invasive *Escherichia coli* (AIEC) in the pathogenesis of CD has attracted considerable interest over the past two decades. The AIEC pathovar was first characterised in 1999 by Boudeau et al. and has emerged since, as a potential candidate in initiation of gut inflammation in CD.[18] AIEC are more frequently isolated from patients with ileal CD than healthy individuals although mucosa-associated *E. coli* which possess the AIEC characteristics were also detected in a high number of CD colonic biopsies.[13] AIEC can also be found in the gut of patients with UC; albeit they are less common compared with patients with CD.[19] In vitro studies have described the ability of AIEC to adhere to and invade epithelial cells, translocate across M cells lining the epithelia, and to survive and replicate in macrophages, hence making them candidate organisms in the pathogenesis of CD.[20,21] *E. coli* strains can typically be assigned to one of eight major phylogroups, and the dominant strains isolated from human intestinal mucosa largely belong to phylogroup B2. Members of phylogroup B2 possess more virulence factors than strains from other phylogroups, and 64% of AIEC belong to this phylogroup.[11] To date, AIEC strains are difficult to identify due to the lack of a specific genotype, and their identification depends on phenotypic traits of cell invasion and replication in macrophages, although the latter ability is common to other human *E. coli* pathotypes.[22] A variety of cell lines have been used to characterise the phenotypic characteristics of AIEC, in vitro, which may explain, at least in part, the failure to identify reproducible genetic markers associated with the AIEC pathotype.

Like almost all members of the gut microbial community, *E. coli* growth, virulence and phenotypic behaviour are highly reliant on the diet of the host. However, there are little data on the potential effects of host diet on *E. coli* levels, phenotypes and virulence, and the consequences these effects may have in IBD intestinal lesions. The purpose of this review is to provide a critical overview on the current literature exploring interactions between diet and *E. coli*/*Enterobacteriaceae*/Proteobacteria in IBD. We reviewed literature on: (1) in vitro studies and animal models that explored mechanisms by which dietary components can interact with *E. coli* or Proteobacteria to initiate or propagate gut inflammation, and (2) the effect dietary components have on the levels of *E. coli* or Proteobacteria and the phenotypic properties of AIEC, in patients with IBD.

2 | LITERATURE REVIEW

A literature search was performed on PubMed (restricted to abstracts and titles) with the following Medical Subject Heading terms: (Crohn's OR colitis OR "inflammatory bowel disease") AND (e. coli OR Escherichia OR *proteobact* OR enterobact*) AND (diet* OR nutrition OR nutrient* OR food)). The initial search query returned 889 studies. Eligible studies included intervention and observational studies investigating the effect of diet on *E. coli*/*Enterobacteriaceae*/Proteobacteria in both adult and paediatric patients with IBD. Research using in vitro and animal models of IBD was considered too. Studies with a primary focus on interventions with probiotics were excluded. We also excluded non-English articles and studies assessing the effect of different types of drugs on the gut microbiome in CD.

During a second screening step, only studies aiming to explore the interactions between dietary components with the abundance of *E. coli*/*Enterobacteriaceae*/Proteobacteria and AIEC virulence in IBD were retained. After assessing the full text of 135 publications, 65 studies met the inclusion criteria and were included in the current review. These articles included 44 studies in animals (Figure 1), 9 in vitro experiments (Figure 2), and 12 clinical trials in patients with IBD (Tables 1–3, respectively).

Literature was subsequently grouped under five thematic sections: the effect of (a) high-fat/high-sugar diets; (b) food additives and sweeteners; (c) prebiotics and fibre; (d) fruit, vegetables and polyphenol sources; and (e) vitamins and minerals on *E. coli*/*Enterobacteriaceae*/Proteobacteria in animal models, in vitro intestinal tissues, and patients with CD and UC. Finally, we report research which explored the effect of protein, selected amino and fatty acids, exclusive enteral nutrition (EEN) and food-based therapies on the abundance and phenotype of CD-associated *E. coli* strains and Proteobacteria. Our research findings suggest that there are sparse data ($n = 2$) from clinical studies which explored the interactions between diet with *E. coli* or other Proteobacteria in patients with UC.

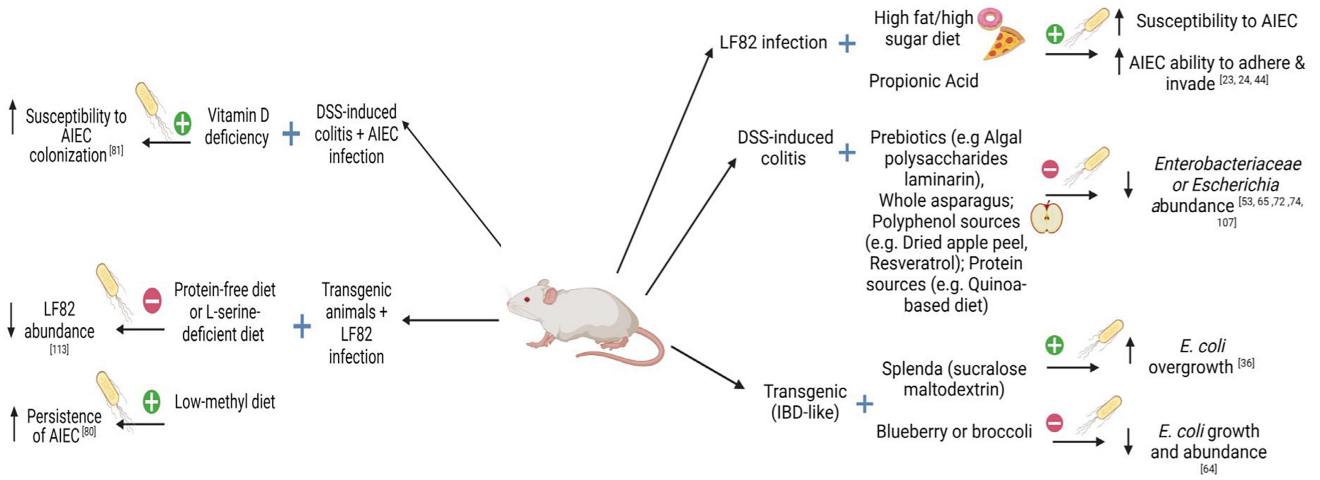

FIGURE 1 Summary of in vivo studies of the effect of dietary components on *Escherichia coli* and adherent-invasive *Escherichia coli*. ↑, increase; ↓, decrease; ⊕, enhance; ⊖, decrease; AIEC, adherent-invasive *Escherichia coli*; IBD, inflammatory bowel diseases; LF82, AIEC strain.

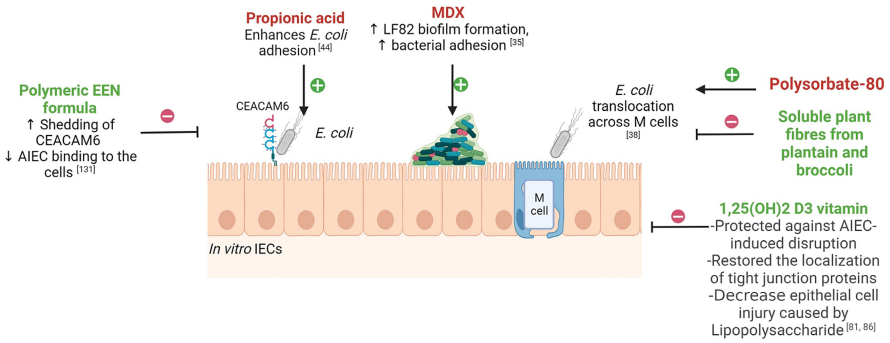

FIGURE 2 Summary of in vitro studies of the effect of dietary components on *Escherichia coli* and adherent-invasive *Escherichia coli*. ↑, increase; ↓, decrease; ⊕, enhance; ⊕, inhibit; AIEC, adherent-invasive Escherichia coli; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; IECs, intestinal intestinal epithelial cells; LF82, AIEC strain; MDX, maltodextrin.

3 | HIGH-FAT/HIGH-SUGAR DIET

Three studies investigated the effect of high-sugar/high-fat Western-type diets on the gut microbiota in animal models of colitis, including changes in *E. coli* populations.[23-25] Martinez-Medina et al.[24] and Agus et al.[23] observed an increase in *E. coli* from mucosal biopsies in CEABAC10 mice following a high-fat/high-sugar diet. These transgenic mice express the human carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), which serves as a receptor for AIEC adherence via type 1 pili and is abnormally overexpressed in patients with ileal CD.[26] AIEC colonisation via CEACAM6 induces intestinal inflammation in CEABAC10 transgenic mice, and when fed with a high-fat/high-sugar diet, they show a higher susceptibility to AIEC colonisation at the colonic intestinal mucosa, release of proinflammatory cytokines and initiation of inflammation[23,24,27] (Table 1, Figure 1). A decrease in mucus layer thickness, lower concentration of short-chain fatty acids and increased intestinal permeability was associated with dysbiosis in CEABAC10 mice.[24]

Mice (C57BL6) fed a high-fat diet (60% fat, 20% protein and 20% carbohydrate) were more susceptible to chemical-induced colitis and developed severe colonic inflammation with expansion of Proteobacteria and *Atopobium* in faecal samples compared to a group of mice fed chow providing 13% fat, 25% protein and 62% carbohydrate.[25] Likewise, Kim et al.[28] reported that long-term feeding with a high-fat diet increased faecal Proteobacteria abundance in C57BL6 mice, and these changes were also associated with an increase in proinflammatory cytokine production and levels of faecal lipopolysaccharide which may have mechanistic implications in the initiation of gut inflammation. Collectively, these findings suggest that a high-sugar/high-fat diet enhances low-grade inflammation, increases levels of *E. coli* and facilitates AIEC colonisation of the intestinal mucosa to initiate colonic inflammation.

A recent study utilising a mucin-2-deficient mouse model of colitis observed that mice fed a diet containing 40% corn oil (n-6 polyunsaturated fat) had a higher prevalence of mucin-degrading bacteria including *Akkermansia muciniphila* and *Enterobacteriaceae* in colon samples compared to those animals fed a Mediterranean diet providing the same amount of fat but of different composition (high monounsaturated, 2:1 n-6: n-3 polyunsaturated and moderate saturated fat). Interestingly, a dietary blend of fats mimicking the composition of Mediterranean diet reduced disease activity, improved histopathological scores and inflammation-related biomarkers such as the cytokines RELM-ß and IL-6, and improved metabolic parameters and

TABLE 1 Experiments in animal models reporting the effects of dietary components and patterns on Proteobacteria and E. coli populations with respect to intestinal inflammation.

Diet Category	Reference	Animal model	Control group	Dietary intervention	Effect on inflammation	Effect on proteobacteria
Western diet	Martinez-Medina et al, 2014[24]	CEABAC10 and WT mice + LF82 infection	Conventional diet	High-fat/high-sugar diet for 12 weeks	↑	Increase in *E. coli* population in mucosal biopsies, increased ability of AIEC to colonise
	Agus et al., 2016[23]	CEABAC10 and WT mice + LF82 infection	Conventional diet	High-fat/high-sugar diet for 18 weeks	↑	Overgrowth of mucosal Proteobacteria and *E. coli*, increased susceptibility to AIEC infection
	Lee et al., 2017[25]	C57BL6 mice, DSS-induced colitis	Normal diet (13% fat, 25% protein and 62% carbohydrate)	High-fat diet inducing obesity (60% fat, 20% protein and 20% carbohydrate) for 15 weeks	↑	Expansion of faecal Proteobacteria in high-fat diet group
	In Kim et al. 2019[146]	C57BL6 J mice	Normal diet (15% fat)	High-fat (45% fat) for 10 or 20 weeks	Changes in gut microbiota (associated with high proinflammatory cytokines)	Increase in faecal Proteobacteria in high-fat diet group
	Haskey et al., 2022[29]	Mucin 2 gene (Muc 2−/−) with spontaneous colitis	40% fat corn oil (n-6 polyunsaturated-rich) or olive oil (monounsaturated-rich) or milk fat (saturated-rich)	Mediterranean diet (MD) (40% fat, isocaloric, isonitrogenous diet high in monounsaturated, 2:1 n-6:n-3 polyunsaturated and moderate saturated fat)	MD resulted in lower clinical and histopathological inflammatory scores and induced intestinal barrier repair	Corn oil showed a higher prevalence of mucin degraders including *A. muciniphila* and *Enterobacteriaceae* in colon samples compared to Mediterranean diet
Prebiotics and fibre	Koleva et al (2012)[49]	HLA-B27 transgenic rats	Conventional diet	Inulin and fructooligosaccharides (FOS) for 12 weeks	↓	Decrease of gene copies of *Enterobacteriaceae* in faeces in the FOS group
	Koleva et al., 2014[50]	HLA-B27 transgenic rats	AIN-76A diet	Chemically defined diet AIN-76A containing sucrose + FOS for 12 weeks	FOS had no anti-inflammatory effect when added to AIN-76A diets	*Enterobacteriaceae* in caecal contents were stimulated by FOS
	O'Shea et al., 2016[53]	Pigs (DSS-induced colitis or distal water)	Conventional diet	Algal polysaccharides laminarin for 56 days	↓	Laminarin + DSS group had reduced *Enterobacteriaceae* in digesta of proximal colon relative to the DSS group
	Kittana et al., 2018[59]	C57BL6 mice (Cr-induced colitis), control (no treatment and not infected)	Equivalent water	Galactooligosaccharides for 2 weeks	↓	Neither reduced the adherence of *C. rodentium* to the distal colon nor decreased its dissemination to systemic organs
	Cai et al., 2019[57]	Rat model of colitis induced by TNBS Ethanol enema for control group	Equivalent saline	Compound polysaccharides containing yam polysaccharide and inulin for 16 days	↓	Decreased faecal Proteobacteria

(Continues)

TABLE 1 (Continued)

Diet Category	Reference	Animal model	Control group	Dietary intervention	Effect on inflammation	Effect on proteobacteria
	Xie et al., 2019[54]	DSS-induced colitis rats	Equivalent saline	Ganoderma lucidum polysaccharide for 3 weeks	↓	Ganoderma lucidum polysaccharide reduced *Escherichia/Shigella* in both the small intestine and caecal samples of rat
	Li et al., 2020[55]	C57BL6 mice with DSS-induced colitis or control group	Equivalent saline	Human milk oligosaccharides and the main component, 2′-fucosyllactose (2′-FL) for 11 days	↓	Inhibited the overgrowth of *Escherichia/Shigella* in faecal samples
	Zou et al., 2020[56]	C57BL6 mice with DSS-induced colitis or control group	Equivalent saline	Ficus carica polysaccharide: mulberry family for 5 weeks	↓	Lower abundance of mucosal *Escherichia* at the genus level
	Wang et al., 2019[51]	(IL-10−/−) mice with spontaneous chronic colitis, WT control	Conventional diet	Multifibre mix diet (48.8% Galactooligosaccharides) for 4 weeks	↓	Reduced Proteobacteria in faecal samples
	Desai et al., 2016[62]	Germ-free and wild-type Swiss Webster mice colonised with a synthetic human gut microbiota	Rich fibre diet	Low dietary fibre (chronic or intermittent) for 4 weeks	↑	Dietary fibre deprivation promotes greater epithelial access to Cr
	Araki et al., 2000[52]	Sprague–Dawley rats, DSS-induced colitis	3% DSS in cellulose diets	Germinated barley foodstuff for 5 days	↓	Faecal *Enterobacteriaceae* significantly lower in rats fed germinated barley foodstuff than in the control group
	Chen et al., 2022[63]	DSS-induced colitis mouse model (BALB/C WT)	Gavage of saline	Gavage of soybean + carbohydrates such as sucrose and raffinose family oligosaccharide for 8 days	↑	Higher relative abundance of *Enterobacteriaceae* in soybean group compared to control, isolated *E. coli* and purified LPS from soybean group showed high macrophage toxicity to inhibit pathogen clearance
Food additives and sweeteners	Chassaing et al., 2015[32]	WT, IL10−/− and TLR5−/− mice	Equivalent water	CMC and P-80 via drinking water for 12 weeks	↑	In IL10−/− mice, both CMC and P80 enriched mucosa-associated Proteobacteria
	Rousta et al., 2021[37]	Ex-germ-free IL10−/− mice colonised by pooled faecal transplant from patients with IBD	Equivalent water	CMC (1% w/v), P80 (1% v/v) for 31 days	↑	CMC did not impact bacterial composition, while P80 exposure nonsignificantly increased the abundance of Actinobacteria and Proteobacteria

TABLE 1 (Continued)

Diet Category	Reference	Animal model	Control group	Dietary intervention	Effect on inflammation	Effect on proteobacteria
	Rodriguez-Palacios et al., 2018[36]	CD-like ileitis SAMP1/YitFc (SAMP) mice, AKR and C57BL6J mice	Equivalent water	Splenda (sucralose maltodextrin) for 6 weeks	Did not increase the severity of ileitis Trigger dysbiosis	Expansion of Proteobacteria in faeces in all mice, and *E. coli* overgrowth with increased bacterial infiltration into the ileal lamina propria of SAMP mice
	Hrncirova et al., 2019[39]	Human-associated gut microbiota WT and Nod2-deficient C57BL6 mice	Equivalent water	Sodium benzoate, sodium nitrite, and potassium sorbate for 2 months	Trigger gut microbiota dysbiosis in both wild-type and Nod2-deficient	Expansion of Proteobacteria in faecal samples of both wild-type and Nod2-deficient mice
	Ormsby et al., 2020[44]	C57BL6 mice + LF82 infection	Equivalent saline	Propionic acid for 3 days prior to infection	NR	Propionic acid in vivo increased ability of AIEC strains to adhere to and invade intestinal epithelial cells and form biofilms in vitro
Fruit and vegetables	Paturi et al., 2012[64]	mdr1a−/− mice (IBD mouse model)	Conventional diet	Supplemented control diet with either 10% blueberry or broccoli for 21 weeks	Altered the composition and metabolism of the caecal microbiota	Inhibited growth of *E. coli* Decrease in caecal *E. coli* vs. control
	Varshney et al. 2013[67]	C57BL6 mice, Cr-induced colitis	Conventional diet	White button mushrooms for 6 weeks	↓	Increased populations of Epsilon, Delta and Gamma Proteobacteria in faecal samples
	Power et al., 2016[65]	C57BL6 mice (DSS-induced colitis)	Conventional diet	Whole asparagus and its flavonoid glycoside, rutin for 2 weeks prior to and during colitis	↓	Reduced mucosal *Enterobacteriaceae* and *Bacteroides*
	Smith et al., 2019[66]	C3H/He mice with Cr-induced colitis	Water	Pomegranate peel extract for 2 weeks	↓	No effect on Cr colon colonisation and clearance
	Ahmed et al., 2021[68]	C57Bl/6 and C3H/HeNHsd (C3H) inbred mice with Cr-induced colitis	Standard AIN-93 diets (with cellulose)	Pectin diet (modified AIN-93 diet: 335.686 g corn starch, 60 g pectin and no cellulose) or Tributyrin diet at 3rd day postinfection till 12 days	↓	Pectin diet: a significant decrease in faecal *Enterobacteriaceae*, an increase in S24-7 bacteria and the abundance of butyrate-producing bacteria Tributyrin diet: a relative increase in faecal *Firmicutes* with a reduction in *Proteobacteria*
Polyphenol sources	Larrosa et al., 2009[72]	DSS-induced colitis rats	Conventional diet	Resveratrol for 25 days	↓	Diminished the increase of faecal enterobacteria upon DSS treatment

(Continues)

TABLE 1 (Continued)

Diet Category	Reference	Animal model	Control group	Dietary intervention	Effect on inflammation	Effect on proteobacteria
	Denis et al., 2016[74]	C57BL6 mice (DSS-induced colitis)	Conventional diet	Dried apple peel powder for 10 days pre- and post-DSS treatment	↓	Mucosal *Enterobacteriaceae* was slightly decreased in dried apple peel-treated mice
	Wang et al., 2017[76]	Rats with a Western-style diet (high protein and fat) (DSS-induced colitis)	Western-style diet with 0% Propolis	Propolis (honeybees' product) for 21 days	↓	0.3% propolis supplementation increased microbial diversity, significant increase in bacteria belonging to the Proteobacteria in caecal samples
	Zhang et al., 2019[75]	DSS-induced colitis mice	Equivalent water	Phloretin (from apples and strawberries) for 21 days	↓	*E. coli* level in faeces was rebalanced after phloretin treatment
	Grosu et al., 2020[73]	Piglets with DSS-induced colitis	Grape seed meal (GSM), no DSS	Grape seed meal for 30 days	No significant change	GSM treatment with no DSS: increased faecal Proteobacteria, DSS and GSM: a lower relative abundance of Proteobacteria
Vitamins and minerals	Denizot et al., 2015[80]	CEABAC10 transgenic mice + LF82 infection	Conventional diet	Low-methyl diet	Abnormal CEACAM6 overexpression	Increased persistence of AIEC colonisation in faeces
	Assa et al., 2015[81]	57BL6 mice (DSS-induced colitis) + AIEC infection	Vitamin D-sufficient diet	Vitamin 1,25(OH)2 D3 deficient diet for 5 weeks	↑	Vitamin D-deficient C57BL6 mice were more susceptible to AIEC colonisation
	Zhu et al., 2019[82]	57BL6 mice (DSS-induced colitis)	Equivalent saline	Cyanocobalamin or methylcobalamin vit. B12 for 5 days	↑	Cyanocobalamin increased the proportion of faecal *Enterobacteriaceae* through riboswitch and enzyme systems
	Gimier et al, 2020[83]	CEABAC10 mice	Conventional diet	Methyl-supplemented diet for 6–8 weeks	↓	Decrease in faecal AIEC load in methyl-supplemented diet-fed mice compared to control diet-fed ones 2 and 3 days postinfection
	Mahalhal et al., 2018[84]	C57BL6 mice (with and without DSS-induced colitis)	100 ppm and 200 ppm iron diet	Dietary iron 400 ppm for 10 days	↑	Dietary iron at 400 ppm increased faecal Proteobacteria

TABLE 1 (Continued)

Diet Category	Reference	Animal model	Control group	Dietary intervention	Effect on inflammation	Effect on proteobacteria
	Ellermann et al., 2019[85]	IL10−/− mice, WT	Control and low-iron diet	High-iron diet for 4 weeks	↓	In control and low-iron diet groups, the relative faecal abundances of Proteobacteria and *Enterobacteriaceae* including *E. coli* were significantly higher than the high-iron diet group in WT and transgenic mice
Protein and peptides; fatty acids	Jia et al., 2017[147]	C57BL6J mice, DSS-induced colitis	Conventional diet	Fine powder of eggshell membrane supplemented diet for 7 days, after colitis	↓	Decreased absolute numbers of faecal *Enterobacteriaceae* and *E. coli*
	W. Liu et al., 2018[107]	C57BL6 mice, DSS-induced colitis	Conventional diet	Quinoa-based diet for 1 weeks	↓	Decreased abnormal expansion of Proteobacteria and decreased *Escherichia/Shigella* in caecum
	S. Wang et al., 2019[108]	Dogs with chronic inflammatory enteropathy	Healthy dogs	Hydrolysed protein diet for 2 weeks	↓	Decreased abundance of faecal *E. coli* and increased levels of the secondary bile acids that inhibit *E. coli* growth
	Ma et al., 2019[111]	*Cr*-induced colitis mice	Conventional diet + no *Cr* infection	Peptides derived from egg albumin transferrin, IRW and IQW for 14 days	↓	Proteobacteria was higher in the *Cr* group, compared to control group Proteobacteria returned to normal in mice treated with IRW and IQW
	Singh et al., 2019[112]	C57BL6 mice, (DSS) model and Cr-infected	Conventional diet	Dietary arginine for 14 days	↓	Faecal proteobacteria not affected by the change in diet
	Kitamoto et al., 2020[113]	Germ-free B6, Il10−/− mice + co-inoculated with AIEC LF82 and commensal *E. coli* MG1655 (DSS-induced colitis)	Amino acid-defined diet (control)	Protein-free diet (PFD) or L-serine-deficient diet (SDD) for 14 days	Restriction of dietary serine significantly attenuated colitis induced by the CD microbiota in Il10−/− mice	Inflammation-induced blooms of *E. coli* LF82 were significantly blunted when L-serine removed from the diet in germ-free B6 mice

Abbreviations: ↑, increased inflammation with equal/lower efficacy indicators in intervention diet group, compared to the control group; ↓, improved intestinal inflammation with higher efficacy parameters in the intervention diet group, compared to the control group; AIEC, adherent-invasive *Escherichia coli*, CD, Crohn's disease, CMC, carboxymethylcellulose; Cr-induced colitis, infection with *Citrobacter Rodentium*; DSS, dextran sulphate sodium; HF/HS, high fat/high sugar; NR, not reported; P-80, polysorbate-80; TNBS, 2,4,6-trinitrobenzenesulfonic acid; WT, wild type.

intestinal permeability. The same types of fats also induced tolerogenic CD103+ CD11b+ dendritic, Th22 and IL-17+ IL-22+ cells which are important for intestinal barrier repair.[29] Collectively, these data provide mechanistic evidence to show that different fat composition modifies differently the risk of gut inflammation in animal models of colitis, and by proxy risk of IBD development in humans, and this effect may be mediated by certain members of the gut microbiome, including *Enterobacteriaceae*.

4 | FOOD ADDITIVES AND SWEETENERS

Use of food additives in food industry has greatly increased in recent years.[30] Food additives and preservatives have been studied as putative dietary initiators of gut inflammation in IBD.[31-34] Five in vivo and four in vitro studies have been included in the current review (Tables 1 and 2). Polysaccharide-based food additives, such as maltodextrin (MDX), xanthan gum and carboxymethylcellulose

TABLE 2 Experiments in in vitro studies reporting the effects of dietary components on E. coli and adherent-invasive E. coli strains.

Diet category	Reference	In vitro supplementation	In vitro model	Effect on *E. Coli*
Food additives and sweeteners	Roberts et al., 2010[38]	Emulsifier polysorbate-80	Co-culture of Caco2-cl1 and Raji B cells, and human Peyer's patches	↑ *E coli* translocation through M cells
	Nickerson et al, 2012[35]	Maltodextrin (MDX)	Human intestinal epithelial cell monolayers (HT29 and Caco2), biofilm formation assays, type 1 Pili expression analysis, and cell adhesion and invasion assays	↑ LF82-specific biofilm formation. ↑ Type I pili expression ↑ Bacterial adhesion to cell line
	Ormsby et al., 2020[44]	Propionic acid	Caco-2 human intestinal epithelial cell line, LF82 obtained from propionic acid-fed mice	↑ 16-fold adhesion to the Caco-2 human intestinal epithelial cell line compared to WT LF82
	Gerasimidis et al., 2020[48]	Cinnamaldehyde, sucralose and carrageenan-kappa	Faecal samples fermentation from healthy individuals	↑ The abundance of *Escherichia/Shigella*
Prebiotics	Chen et al, 2020[58]	Tea flower polysaccharide	Intestinal microecology of normal people or patients with IBD under anaerobic environment (fermentation of tea flower polysaccharide for 24 h)	↑ *Escherichia/Shigella* in IBD faeces
Fruit and vegetables	Roberts et al., 2010[38]	Soluble plant fibres from plantain and broccoli	Co-culture of Caco2-cl1 and Raji B cells, and human Peyer's patches	↓ *E. coli* translocation across M cells
Vitamins	Assa et al., 2015[81]	1,25(OH)2 D3 vitamin	Caco-2-bbe cells	Vit. D protected against AIEC-induced disruption of transepithelial electrical resistance.
	Chen et al., 2015[86]	1,25(OH)2 D3 vitamin	Caco-2 cell monolayers	Restored the expression and localization of tight-junction proteins and ↓ Epithelial cell injury caused by lipopolysaccharide, a major component of gram-negative bacteria
EEN	Keenan et al., 2014[131]	Polymeric formula	Caco-2 human adenocarcinoma cell line with (CEACAM6) expression	↑ The expression of CEACAM6 ↑ Losing of CEACAM6 ↓ AIEC binding to the surface of Caco-2 cells

Abbreviations: ↑, increase; ↓, decrease; CD, Crohn's disease; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule-6 receptor; EEN, exclusive enteral nutrition; IBD, inflammatory bowel disease; WT, wild type.

(CMC), were studied to explore their effects on CD-associated AIEC. In ileal CD, analysis of mucosa-associated bacteria showed an increase in the prevalence of *malX*, an important gene for MDX metabolism.[35] Nickerson and McDonald[35] further showed that increased exposure to MDX, but not CMC or xanthan gum, promoted AIEC LF82-specific biofilm formation, enhanced type 1 pili expression and increased bacterial adhesion in human intestinal epithelial cell monolayers (i.e., Caco2 and HT29) (Figure 2). Adhesion of LF82 in this study, which was promoted by MDX, was independent of the expression of the AIEC receptor CEACAM6 on Caco2 cell lines with endogenous knocked-down CEACAM6 expression and on HT29 cells with no detectable CEACAM6. These findings suggest a novel mechanism of epithelial cell adhesion of AIEC in the presence of MDX and propose a hypothesis by which diet influences AIEC phenotypes that may promote disease development. Rodriguez-Palacios et al.[36] tested the effect of 6-week supplementation of the artificial sweetener Splenda, a source of sucralose and maltodextrin, on ileitis in SAMP1/YitFc (SAMP) mice. They observed an expansion of faecal Proteobacteria in all animals and overgrowth of *E. coli* with increased bacterial infiltration into the murine ileal lamina propria.

The effect of CMC and polysorbate-80 (P80) to initiate colitis and affect human microbiota was tested in germ-free IL10−/− mice colonised with pooled faecal transplant from three patients with active IBD. Treatment with CMC increased histologic inflammatory scores

TABLE 3 Summary of food-based dietary therapies, exclusive enteral nutrition and dietary supplements which have been used to induce or maintain clinical remission in patients with IBD in studies included changes in Proteobacteria and E. coli.

Diet category	Reference, setting	Cohort, sample size	Dietary intervention	Control group	Effect on *E. Coli*
Vitamins	Garg et al., 2018, Australia[87]	UC (active, FC ≥100 μg/g) $n=8$	40,000 units of vitamin D/week for 8 weeks	Non-IBD controls $n=8$, Inactive UC [FC <100 μg/g] $n=9$	Reduced intestinal inflammation in patients with active UC ↑ *Enterobacteriaceae* but no change in overall faecal microbial diversity
	Von Martels et al., 2019, the Netherlands[88]	CD (2 groups: high FC >200 μg/g) and low FC <200 μg/g) $n=70$	100 mg riboflavin/days for 3 weeks	N/A	Anti-inflammatory and antioxidant effects in CD ↓ *Enterobacteriaceae* in faeces in patients with low FC levels. No effects on diversity or taxonomy of the faecal microbiome
EEN	D'Argenio et al., 2013, Italy[117]	CD (case report) = 1	8-weeks polymeric EEN for disease induction	HC = 1	*Enterobacteriaceae* (ileal biopsy) during EEN reached a level similar to the HC
	Gerasimidis et al., 2014, UK[130]	CD = 15	8-weeks polymeric EEN for disease induction	HC = 21	No significant change in faecal *E. coli* level during EEN
	Quince et al., 2015, UK[119]	CD = 23	8-weeks polymeric EEN for disease induction	HC = 21	Genus level Shannon diversity ↓ during EEN No change in *Escherichia/Shigella* in faecal samples
	Guinet-Charpentier et al., 2016, France[129]	CD = 4	6-weeks polymeric EEN for disease induction	PEN group = 22 No EEN group = 8	↓ Proteobacteria (*Escherichia/Shigella* and *Sutterella*) at weeks 2 and 6 EEN in faecal samples γ-Proteobacteria positively correlated with Harvey–Bradshaw index of CD
	Dunn et al., 2016, Canada[120]	CD = 10	12-weeks polymeric EEN for disease induction	Controls (CD relatives) on normal diet = 5	Nonsustained remission group was associated with predominant *Enterobacteriaceae* (including *Klebsiella*) in faecal samples Proteobacteria ↑ further in nonsustained remission patients over EEN course
	De Meij et al., 2018, the Netherlands[124]	Treatment-naïve paediatric IBD patients CD = 63	6-weeks polymeric EEN for disease induction	HC = 61	↓ Proteobacteria over time in CD faecal samples
	Hart et al., 2020, Canada[127]	CD = 16	8 weeks of polymeric EEN for disease induction	CS = 14; 10 UC, 4 CD	EEN ↓ *Escherichia/Shigella* and *Fusobacterium* genera in faecal samples CS ↓ *Alistipes* and *Fusobacterium* genera
	Sahu et al., 2021,India[133]	UC = 62 ($n=27$ with microbiome data)	7 days of EEN semielemental as adjunctive therapy to intravenous steroids	UC = 30 on intravenous steroids	EEN influenced ($p=0.06$) microbiome with clustering explained by certain bacterial groups including *Enterobacteriaceae*
CDED	Levine et al., 2019, Israel[125]	Children with mild to moderate CD = 40	6-weeks CDED + 25% PEN (recommended: chicken, eggs, potatoes, fruits and vegetables; excluded: gluten, dairy products, red and processed meat, food additives, coffee and alcohol)	Free diet with 25% PEN = 38	↓ Proteobacteria with EEN or CDED in faecal samples

TABLE 3 (Continued)

Diet category	Reference, setting	Cohort, sample size	Dietary intervention	Control group	Effect on *E. Coli*
Mediterranean diet	Zhang et al., 2020, Canada[114]	CD in remission Nondiversified diet group = 15	12-weeks dietary intervention: Mediterranean diet included increased intake of plant-based foods, fatty fish and olive oil, and limiting food additives, alcohol and saturated fat	Diversified diet control group on conventional diet = 25	↓ Faecal *Proteobacteria* and *Escherichia/Shigella* in the Nondiversified diet group
CDED + PEN	Verburgt et al., 2022, the Netherlands[132]	Children with CD reaching remission after nutritional therapy = 54	Group 1: CDED phase 1 (50% PEN for the 6 weeks, followed by phase 2 diet (25% PEN for the next 6 weeks) Group 2: Standard EEN for 6 weeks followed by 25% PEN during weeks 6–12, with gradual reintroduction of foods between weeks 6 and 9. (All patients were exposed to PEN + free diet by week 12.1)	HC = 26	Faecal *Proteobacteria* reached relative abundance levels of healthy controls except for *E. coli*.

Abbreviations: ↑, increase; ↓, decrease; CD, Crohn's disease; CDED, Crohn's disease exclusion diet; CS, corticosteroids; EEN, exclusive enteral nutrition; FC, faecal calprotectin; HC, healthy control; IBD, inflammatory bowel disease; N/A, not applicable; PEN, partial enteral nutrition; UC, ulcerative colitis.

and colonic inflammatory cytokine gene expression compared with P80 and water controls but with no impact on bacterial composition. However, P80 exposure nonsignificantly increased the abundance of both Proteobacteria and Actinobacteria.[37] Roberts et al. showed that the food emulsifier P80 increased *E. coli* translocation in Caco2-cl1 cells, M cells and across human Peyer's patches.[38] Likewise, Chassaing et al.[32] demonstrated that the emulsifiers CMC and P80 promoted low-grade inflammation and obesity/metabolic syndrome in wild-type (WT) mice and induced colitis in IL10−/− and TLR5−/− transgenic mice. In IL10−/− mice, both CMC and P80 exhibited a marked reduction in microbial diversity and increased mucosa-associated Proteobacteria. Similar findings were observed by Hrncirova et al.[39] with the food preservatives sodium benzoate, sodium nitrite and potassium sorbate. These food additives were shown to induce gut microbial dysbiosis and expand Proteobacteria in faeces from both WT- and Nod2-deficient mice in which oral bacterial challenge or infection can initiate a systemic inflammatory response.

AIEC require their own metabolic niche to survive and proliferate within the competitive environment of the gut microbiota. Since *E. coli* are microaerophilic rather than strictly anaerobic, they are more likely to be at close proximity to the mucosa where there is relatively high oxygen tension and higher levels of oxygen free radicals in inflamed tissue.[40] Nonetheless, subsets of genes which are required for AIEC colonisation are associated with acquisition and metabolism of essential nutrients, many of which originate from the diet of the host.[41] Propionic acid is produced by gut microbiota though the fermentation of dietary fibre and is also widely used in agriculture in the animal feed industry and in bakery products as a broad-spectrum food preservative with bactericidal, fungicidal and insecticidal properties.[42,43] Propionic acid has been shown to function as a signalling molecule for AIEC LF82 to increase virulence in vivo and in vitro. LF82 recovered after passage through propionic acid-fed mice showed a 16-fold higher adhesion to Caco-2 human intestinal epithelial cells than the WT parent strain and increased biofilm formation.[44] In addition, propionic acid altered AIEC metabolism and enhanced use of ethanolamine,[45] an intestinal metabolite that is known to be utilised during inflammation by pathogens.[46,47] Ethanolamine increased intracellular AIEC growth, altered carbon source utilisation and upregulated genes involved in biofilm formation, stress response, metabolism and membrane integrity.[45] Interestingly, it was shown that metabolism of ethanolamine by *E. coli* was higher in paediatric CD during active disease compared to the same patients when they entered in clinical remission following treatment with EEN and when compared with healthy controls.[45] The effect of various food additives on the faecal microbiome and its fibre fermentation capacity was tested also using in vitro batch faecal cultures. Food additives and artificial sweeteners such as cinnamaldehyde, sucralose and carrageenan-kappa increased the baseline abundance of *Escherichia/Shigella* spp. and induced microbial dysbiosis, thus offering mechanistic insights on how food industrialisation may modify the risk of CD pathogenesis.[48]

5 | PREBIOTICS AND FIBRE

Nine in vivo studies and one in vitro study assessed the effect of fibre/prebiotic supplementation on *E. coli* levels and gut

inflammation (Tables 1 and 2). No relevant studies in patients with IBD were identified. Koleva et al.[49] showed that colitis was significantly reduced in HLA-B27 transgenic rats fed with fructooligosaccharides (FOS). Most important, this effect was associated with a decrease in the levels of *Enterobacteriaceae* in faeces following supplementation. A subsequent study by the same group reported that FOS reduced colitis in animals fed normal chow, but when added to modified diets containing sucrose no anti-inflammatory effect was observed, and the levels of *Enterobacteriaceae in caecal contents* increased in parallel.[50] Together these observations suggest that background diet composition can abrogate the protective properties of FOS. Wang et al.[51] investigated the effectiveness of a 4-week multifibre mix diet, including 49% FOS, in IL-10−/− mice with spontaneous colitis. A significant decrease in colitis was observed which was associated with reduction of Th1/Th17 cells in lamina propria, reduced inflammatory cytokines and chemokines, and a decrease in members of Proteobacteria in faecal samples. Likewise, germinated barley foodstuff, a source of fibre, effectively prevented bloody diarrhoea, mucosal damage and decreased levels of faecal *Enterobacteriaceae* in rats with dextran sulphate sodium (DSS)-induced colitis.[52]

The algal polysaccharide laminarin has been shown to reduce *Enterobacteriaceae* in digesta from the proximal colon and reduce body weight loss and diarrhoea associated with DSS-induced colitis in pigs.[53] Other studies showed that several polysaccharides and oligosaccharides can attenuate intestinal inflammation and suppress the abundance of *Escherichia*, such as *Ganoderma lucidum* polysaccharide in caecal samples in rats with DSS-induced colitis,[54] human milk oligosaccharides and their component, 2′-fucosyllactose in C57BL6 mice faecal samples with DSS-induced colitis,[55] and *Ficus carica* polysaccharide from mulberry fruit in C57BL6 mice mucosa with DSS-induced colitis.[56] In addition, Cai et al.[57] tested the efficacy of a combination of yam polysaccharide and inulin in reducing inflammation in a rat model of colitis induced by 2,4,6-trinitrobenzenesulfonic acid. These polysaccharides reduced inflammation and reversed 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced gut dysbiosis by decreasing Proteobacteria, *Bacteroides* and sulphate-reducing bacteria in faeces. This effect was paralleled by a reduction in oxidative stress, cell motility and signal transduction.

The effect of tea flower polysaccharide on the intestinal microecology of faeces from healthy people or patients with IBD was tested under anaerobic conditions in vitro. The abundance of *Escherichia*, *Enterococcus*, *Lactobacillus* and *Bifidobacterium* increased whereas the abundance of *Enterobacter*, *Streptococcus*, *Bacteroides* and *Clostridium XlVa* decreased in faeces of IBD patients following 24-hour fermentation in the presence of tea flower polysaccharide.[58] However, Kittana et al.[59] observed that galactooligosaccharides neither reduced the adherence of *Citrobacter rodentium*, an enteric mouse-specific pathogen used to model human pathogenic *Escherichia coli* infections, to the distal colon nor decreased its spread to systemic organs in C57BL6 mice.[60]

In conditions of reduced dietary fibre intake, data from animal experiments show that the gut microbiota shifts to utilisation of the glycoprotein-rich mucus layer of the intestinal wall as an alternative source of energy. This layer acts as a first line of innate immunity against pathogens, pathobionts and commensals thus preventing invasion and colonisation.[61] Dietary fibre deprivation in mice fed with low dietary fibre for 4 weeks promoted greater epithelial access to *C. rodentium* and increased its ability to cause inflammation.[62] A recent study by Chen et[63] showed that gavage with soybean carbohydrates such as sucrose and raffinose family oligosaccharides worsened inflammation in a DSS-induced colitis BALB/C mouse model compared to saline gavage. In the same study, isolated *E. coli* and purified LPS from mice administered soybean carbohydrates exhibited high macrophage toxicity to inhibit pathogen clearance.

Collectively, these findings indicate that low fibre intake has detrimental effects on gut barrier function and integrity, hence increasing the proximity of pathobionts, such as *E. coli*, to the intestinal epithelium and provoking inflammation. However, different prebiotics and polysaccharides exert different effects on gut inflammation which may also be dependent on the disease model used, and some of these effects can be influenced by the background diet of the host and can also be deleterious. It is therefore important to test such preclinical signals in clinical trials in healthy humans at risk of IBD development as well as in those with existing IBD where the role of diet and its interactions the gut microbiome may be different.

6 | FRUIT AND VEGETABLES

Five animal studies (Table 1) and one in vitro study (Table 2) investigated the role of fruit and vegetables or their ingredients on *Enterobacteriaceae* during inflammation. Paturi et al.[64] demonstrated inhibition of *E. coli* growth in the *mdr1a*−/− mouse model when fed a diet supplemented with either 10% blueberry or broccoli for 21 weeks. *E. coli* growth was most inhibited in broccoli-fed mice, which showed a 2-$\log_{10}$ decrease in caecal *E. coli* levels compared to control animals. Power et al.[65] demonstrated that asparagus and its equivalent content of purified flavonoid glycoside, rutin, might be helpful in attenuating colitis severity and enhancing colonic mucosal repair in DSS-induced colitis mice by decreasing levels of mucosal *Enterobacteriaceae* and *Bacteroides*. Roberts et al.[38] tested the effect of soluble plant fibres on AIEC isolates from colonic mucosal biopsies of patients with CD using co-cultures with Caco2-cl1 and Raji B cells, and human Peyer's patches. The authors found that soluble nonstarch polysaccharides from plantain and broccoli markedly reduced *E. coli* translocation across M cells. Conversely, neither leek- nor apple-soluble fibres had a significant effect.

Smith et al.[66] showed, in C3H/He mice, that administration of pomegranate peel extract for 2 weeks decreased *C. rodentium*-induced colon damage but did not affect *C. rodentium* colon colonisation and clearance. Varshney et al.[67] showed that white button mushrooms fed to C57BL6 mice with *C. rodentium*-induced colitis

reduced the severity of colitis and infiltration of inflammatory cells in the intestinal mucosa. Of note, this effect was associated with an increase in populations of faecal Epsilon, Delta, and Gamma Proteobacteria. A recent study observed that administration of pectin in mice with *C. rodentium*-induced colitis reduced the severity of colitis, restoring faecal levels of *Firmicutes* and *Bacteroidetes*, increasing mucus production and decreasing levels of *Enterobacteriaceae*.[68]

7 | POLYPHENOL SOURCES

Five in vivo studies report the effect of supplementation of polyphenols on *Enterobacteriaceae* levels in the gut (Table 1). Resveratrol is a polyphenol-rich source which is found in various plants, grape skins and red wine.[69] It has potent antioxidant, antimicrobial and anti-inflammatory properties in vitro and in vivo.[70,71] Larrosa et al.[72] showed that standard chow supplemented with 1 mg/kg/day of resveratrol (>99% purity) significantly protected the colonic mucosa architecture, reduced body weight loss and reduced markers of systemic inflammation in a rat model of DSS-induced colitis. This improvement was associated with decreasing the high levels of faecal Enterobacteria upon DSS treatment. Grosu et al.[73] observed that the relative abundance of faecal Proteobacteria increased significantly in piglets fed grape seed meal (8% grape seed meal within diet), but not treated with DSS, while a decrease in the abundance of Proteobacteria was shown in piglets fed with grape meal and treated with DSS, showing different effects dependent on the presence or absence of gut inflammation.

Mice treated with dried apple peel powder showed enhanced antioxidant and anti-inflammatory action in the intestine with a slight decrease in levels of mucosal-associated *Enterobacteriaceae*.[74] Zhang et al.[75] found that the elevated levels of commensal *E. coli* in faeces of mice with DSS-induced colitis decreased after administration of phloretin, a naturally occurring phytochemical which is abundant in apples and strawberries and belongs to the chalcone class of flavonoids. Supplementation with propolis, a polyphenol-rich product from honeybees, was shown to attenuate DSS-induced colitis and increase microbial diversity in a rodent model with rats fed on a Western-style diet. Interestingly, in this study levels of Proteobacteria were increased in caecal samples following propolis treatment.[76]

8 | VITAMINS AND MINERALS

Micronutrient deficiencies are common in patients with IBD particularly those with CD and are more present in active disease than during periods of remission.[77] Previous research associated micronutrient deficiencies with adverse disease outcomes, and there is some evidence that host intake in micronutrients can influence microbiome composition and function with important downstream implications for health.[78,79] Six in vivo studies[80-85] (Table 1), two in vitro experiments[81,86] (Table 2) and two clinical studies[87,88] in patients with IBD (Table 3) reported the effect of vitamins or minerals on alterations to *E. coli* populations and gut inflammation.

Patients with CD often present deficiencies in serum methyl-donor molecules such as folate and vitamin $B_{12.}$[89,91] Denizot et al.[80] found that the AIEC receptor gene CEACAM6 is regulated by a DNA methylation-dependent pathway. CEABAC10 transgenic mice fed on a low-methyl diet and orally challenged with AIEC LF82 were found to display hypomethylation of the CEACAM6 promoter, resulting in abnormal CEACAM6 overexpression and consequent AIEC persistence and colonisation in faeces.[80] A recent study by the same group demonstrated that CEABAC10 mice fed a methyl-donor-supplemented diet for 6–8 weeks had a significant decrease in CEACAM6 gene expression and faecal *E. coli* levels when compared to mice fed a control diet. In addition, there was a decrease in AIEC load, 2 and 3 days postinfection, associated with a decreased expression of calprotectin subunits S100a8 and S100a9 in transcriptomic analysis.[83] These observations suggest certain dietary components can modulate the expression of key genes in the host that can in turn influence colonisation by AIEC in the gut. However, Zhu et al.[82] found that cyanocobalamin (a synthetic analogue of vitamin B_{12}), but not methylcobalamin (a natural form of vitamin B_{12}) supplementation for 5 days, aggravated colitis through increasing the proportion of *Enterobacteriaceae* in C57BL6 mice faecal samples with DSS-induced colitis.

Substantial evidence indicates that there might be a connection between IBD and vitamin D status as an environmental factor in disease pathogenesis.[92] In addition to the classical role of vitamin D in bone homeostasis, and promoting intestinal absorption of calcium and phosphate,[95] its physiological effects also extend to regulation of immune function by inducing anti-inflammatory T-cell pathways and stimulating the antimicrobial effects of macrophages.[96,97] Vitamin D appears to have a role in maintaining the integrity of the intestinal epithelial barrier against inflammatory and infectious insults. Vitamin D-deficient C57BL6 mice showed epithelial barrier dysfunction and were more susceptible to AIEC colonisation when challenged with DSS-induced colitis and AIEC.[81] Human colonic Caco-2 cells supplemented with 1,25$(OH)_2$ vitamin D_3 were protected against AIEC-induced disruption of monolayer permeability.[81] A similar study demonstrated that Caco-2 cell monolayers incubated with 1,25$(OH)_2$ vitamin D_3 restored the expression and localization of tight-junction proteins and decreased epithelial cell injury caused by lipopolysaccharide, a major outer membrane component of the gram-negative bacteria.[86] A mixture of krill oil, the probiotic *Lactobacillus reuteri* and vitamin D (D_3) decreased adherence and invasiveness of AIEC in an in vitro adhesion/invasion assay, decreased TNF-α and IL-8 mRNA expression and increased expression of the vitamin D receptor.[98] Animal models have shown that a lack of vitamin D receptor signalling results in murine gut microbial dysbiosis, whereas vitamin D therapy in mice with DSS-induced colitis preserved gut microbiome composition.[99,100] 8-week supplementation with vitamin D_3 in 16 healthy volunteers increased bacterial richness in the upper gastrointestinal tract (gastric corpus, antrum and duodenum) and decreased the relative abundance of Gammaproteobacteria

including *Escherichia/Shigella* spp.[101] In a pilot study, vitamin D supplementation in patients with active UC for 8 weeks decreased intestinal inflammation and paradoxically increased *Enterobacteriaceae* but without any change in overall faecal microbial diversity.[87]

Iron is an essential mineral that is required by most living organisms.[102] Acquisition of dietary iron by bacteria including members of *Enterobacteriaceae*, such as *E. coli* and *Salmonella*, is an important process for colonisation and establishment of successful infection.[103] Mahalhal et al.[84] found that an iron intake of 400 ppm exacerbated DSS-induced colitis in C57BL6 mice and led to changes in intestinal microbial diversity with a significant reduction in the faecal abundance of Firmicutes and Bacteroidetes, and a parallel increase of Proteobacteria. These changes were not observed with a lower dietary intake of iron (100 ppm), suggesting a dose-dependent effect. In contrast, in another study, the relative abundance of *Enterobacteriaceae* in faeces, including *E. coli*, was significantly higher in wild-type mice with low-iron diet compared to a high-iron diet group. However, there was no effect on the faecal microbiota of Il10 −/− mice during iron supplementation versus the control diet.[85] Further research is needed to understand the underlying mechanisms by which micronutrients influence gut inflammation and whether any effects are mediated by modulation of the intestinal microbiota including *E. coli*.

There are very few studies which explored the effect of micronutrient supplementation on the microbiome of patients with IBD and which have reported any changes on *E. coli* populations. In a prospective clinical trial, daily oral supplementation with riboflavin (vitamin B_2) for 3 months had several anti-inflammatory and antioxidant effects in patients with CD, such as a decrease in IL-2 levels in patients with low faecal calprotectin levels (<200 μg/g) and a decrease in C-reactive protein in patients with high faecal calprotectin levels (>200 μg/g). Riboflavin supplementation decreased *Enterobacteriaceae* levels in the group with low levels of faecal calprotectin at baseline. However, there were no effects on microbial diversity, taxonomy or metabolic pathways of the faecal microbiome based on shotgun metagenomic analysis.[88]

9 | PROTEINS AND AMINO AND FATTY ACIDS

High intake of protein, especially of animal source has been associated with increased risk of CD and UC onset and risk of disease relapse in nutritional epidemiological studies, but the underlying mechanisms remain unknown.[104] In the absence of inflammation, Mu et al.[105] demonstrated that the administration of a high-protein diet (45% protein and 30% carbohydrate) in Wistar rats for 6 weeks increased levels of faecal *Escherichia/Shigella*. A positive correlation was also observed between *Escherichia/Shigella* levels and a set of upregulated genes involved in chemotaxis, antigen presentation and cell adhesion, hence suggesting that a protein-rich diet may influence *E. coli* dynamics and contribute to disease pathogenesis. In contrast, Liu et al.[106] observed no significant differences in faecal *Enterobacteriaceae* abundance between rats fed on either a normal-protein diet (14% protein) or a high-protein isocaloric diet (53% protein) for 15 days.

Quinoa, a high plant protein food, suppressed dysbiosis, decreased abnormal expansion of Proteobacteria and *Escherichia/Shigella*, in the caecum, and improved clinical symptoms induced by DSS compared to mice fed a standard diet.[107] Hydrolysed protein induced remission in a dog model of chronic inflammatory enteropathy by decreasing the abundance of pathobionts *E. coli* and *Clostridium perfringens* in faecal samples and increasing the levels of the secondary bile acids which inhibit *E. coli* growth.[108] A few studies have also explored the regulatory roles of amino acid and peptide administration in intestinal inflammation.[109,110] In a *C. rodentium*-induced colitis mouse model, peptides derived from egg albumin, transferrin, the tripeptides IRW and IQW were found to regulate intestinal bacteria associated with colonic inflammation including Proteobacteria in the colon.[111] After *C. rodentium* infection, there was an increase in L-glutamine, gentisic acid and L-acetylcarnitine while these metabolites were at normal levels with IRW and IQW treatment.[111] Singh et al.[112] reported that arginine supplementation for 7 days prior to the induction of colitis with DSS and *C. rodentium*, protected from colitis onset, an effect mediated by restoration of the faecal microbiome composition. However, faecal Proteobacteria levels were not affected by the change in diet. It has also been found that the AIEC strain *E. coli* LF82 shifts its metabolism to catabolise amino acids, particularly L-serine in the inflamed intestine.[113] The main source of luminal L-serine, which is used by pathogenic *Enterobacteriaceae* originates from host diet. It is therefore possible that restriction of dietary L-serine may prevent expansion of *Enterobacteriaceae* in the environment of the inflamed gut.[113]

Zhang et al. investigated the effect of diets of different composition on the faecal microbial composition of patients with CD in remission.[114] Patients were classified into two groups: (a) a non-diversified diet group (defined as a low plant-based [dietary fibre intake ≤ 15 g/day or total fruit and vegetables servings ≤3/day]), (b) a high red and processed meat-based diet [≥3/week]) and (c) the diversified diet control group which received conventional management (patient not meeting the criteria above). The nondiversified group received a 12-week structured dietary intervention based on the principles of the Mediterranean diet and limited intake of food additives, alcohol and saturated fat. At baseline, Proteobacteria levels positively correlated with red meat intake, while fibre and total vegetable and fruit intake were negatively correlated with Proteobacteria and *Escherichia/Shigella* in faeces. Following 12-week dietary intervention, the microbiome structure of the nondiversified diet intervention group shifted towards that of the control group with a reduction of Proteobacteria and *Escherichia/Shigella* and enrichment of *Faecalibacterium*. This study suggested that changes in *Escherichia/Shigella* or Proteobacteria, in faeces, may depend on the baseline abundance of these microbes, and this can help improve the concept of personalised nutritional management in patients with CD.

10 | EXCLUSIVE ENTERAL NUTRITION (EEN) AND NOVEL DIETARY THERAPIES IN CD

Exclusive enteral nutrition, a diet based on exclusive consumption of liquid supplements for 6–8 weeks, is an established dietary therapy for Crohn's disease. Early studies support a mechanism of EEN mediated by modulation of the intestinal microbiota.[115,116] Since EEN has been used mostly in the management of paediatric CD, most of studies have been conducted in children, except for one which was carried out in adults (Table 3). Comparing findings across different studies is challenging due to differences in cohort characteristics, specimens used for microbiota analysis (stool vs. mucosal biopsy) and methodology aspects such as the type of EEN formula used and sequencing platforms or bioinformatic analysis. However, a few consistent patterns have emerged. Among all studies published, five ([117-121]), including a study which profiled the mucosal microbiome of a single patient, reported a significant reduction in diversity during treatment with EEN. In contrast, four studies[122-125] showed no change during EEN, and two recent studies[126,127] observed an increase in overall diversity in faeces. Two studies also observed that β diversity, a metric of microbial community structure, clustered away from its baseline or healthy controls during EEN, all performed in faecal samples.[125,128]

Several studies have reported on taxonomic changes during treatment with EEN. Five studies[117,124,125,127,129] reported a decrease in Proteobacteria levels, and two studies demonstrated that Proteobacteria levels were high in patients who did not respond to EEN or associated with a rapid subsequent relapse after successful treatment with EEN.[120,125] However, other research noted no significant changes in Proteobacteria abundance with EEN.[119,130] In vitro, EEN induced the expression of CEACAM6 in Caco-2 cell lines but also increased the release of soluble CEACAM6 leading to a decrease in AIEC binding to the cell surface in the presence of the polymeric EEN formula.[131] In a recent RCT, Levine et al.[125] evaluated the efficacy of the CD exclusion diet (CDED) coupled with 50% partial enteral nutrition (PEN) in patients with CD for induction and maintenance of clinical remission. This diet excludes foods which were previously associated with dysbiosis and colonic inflammation in preclinical research. The authors found that the abundance of faecal Proteobacteria in the patient group on CDED+50%PEN as well as in the control group on EEN decreased, and this effect coincided with disease improvement and reduction of biomarkers of gut inflammation. Interestingly, another recent study, based on the same patient cohort, showed that CDED+PEN or EEN decreased the overall relative abundance of Proteobacteria in children with CD reaching remission. However, among Proteobacteria genera, levels of *Escherichia* and *Sutterella*, in stool samples, remained more abundant in patients with CD, treated with EEN or CDED+PEN and remained at significantly higher levels than healthy controls, suggesting that 12 weeks of diet was not enough to achieve complete correction of dysbiosis.[132] Collectively, there is good evidence to suggest that the effectiveness of established and novel dietary therapies of CD may be mediated by the changes in the gut microbiome including a decrease in the abundance of *E. coli* and its adherence to the intestinal epithelium but more research is required to explore the mucosal-associated microbiota including changes in the levels and phenotype of AIEC. The latter is particularly important as CD with ileal involvement, where AIEC are more commonly identified, responds better to treatment with EEN. Our literature search has identified a single case report where the higher abundance of Proteobacteria in the ileum of a child with CD decreased after EEN, and the composition of the ileum microbiome was similar to that seen in the healthy control.[117]

A single RCT also explored the effectiveness of EEN as adjunct therapy to intravenous corticosteroids in patients with acute severe UC. The authors of this study observed a modest ($p=0.06$) effect of treatment with EEN on microbiome community structure with clustering explained by certain taxonomic groups including *Enterobacteriaceae*.[133]

11 | DISCUSSION

The primary aim of this narrative review was to summarise the literature on the interplay between diet and *E. coli* in the underlying pathogenesis of gut inflammation in IBD. Most studies identified were preclinical studies in animals or in vitro studies with a notable lack of clinical research, particularly in patients with UC where only two clinical trials were identified. Collectively, there is evidence to suggest that certain dietary components or dietary patterns may influence the abundance, colonisation and phenotype of AIEC and other *Enterobacteriaceae*, which in turn may modify risk of development of gut inflammation. Components that increase the abundance of *E. coli*/*Enterobacteriaceae*/Proteobacteria and/or change their phenotype and subsequently increase risk of inflammation in animal models include a diet high in sugar, fat and protein, food additives such as MDX, P80 and CMC emulsifiers, and an increased intake of certain micronutrients such as cyanocobalamin and iron. Underlying mechanisms involve expansion of AIEC levels and increased virulence, adhesion and invasion under the influence of luminal substrates. In contrast, certain dietary components such as fibre and a Mediterranean type of diet abrogate these effects and protect from inflammation. Likewise, vitamin D, white button mushroom and polyphenol sources including grape seed and propolis extract have been found to increase levels of Proteobacteria or *Enterobacteriaceae* with a paradoxical improvement in gut inflammatory markers. Such findings could reflect the diversity of Proteobacteria and *Enterobacteriaceae* with some species/strains playing a benign commensal role and other exerting a pathogenic role under specific conditions and under the influence of other modifying factors such as host diet. A deep genomic and/or phenotypic analysis of bacterial isolates was not performed in any of the studies reviewed here.

Experiments in animal models greatly advance our understanding of the underlying pathogenesis of IBD and help towards the

development of effective treatments. However, caution should always be exercised when translating preclinical research findings to recommendations for prevention or management of human IBD. This literature review has highlighted several examples where hypotheses generated from preclinical research, in animals or in vitro, were not confirmed or even contradicted by clinical studies of IBD. Prime examples include the preclinical evidence linking the role of fibre or food additives and their interaction with *E. coli* in protection against or initiation of gut inflammation, respectively.[32,49] These findings are challenged by clinical experience and research evidence showing that a fibre-free and food additive-rich treatment with EEN induces clinical remission and mucosal healing and that dietary interventions with prebiotics or fibre in patients with IBD fail to provide positive results.[134] The efficacy of EEN in improving active disease in paediatric CD offers an opportunity to study the critical role of *E. coli* and its interaction with food ingredients in the initiation and management of gut inflammation in humans. The fact that the composition of EEN feeds is listed, and feeds include numerous food additives, including those proposed to interact with *E. coli* causing gut inflammation in preclinical models, strongly suggests that they are not important candidate food components to pursue any further, at least in the context of disease management. In contrast, focus should be redirected to other components which are excluded during treatment with EEN, like fibre. For example, propionate, originating from the anaerobic fermentation of fibre, promotes the virulent phenotype of CD-associated AIEC whereas genes encoding propanediol utilisation, produced from sugars such as fucose and rhamnose through bacterial fermentation, are overrepresented in AIEC relative to non-pathogenic *E. coli*.[135]

The ability of AIEC to rapidly evolve in the gut further complicates our efforts to understand its role in IBD pathogenesis. Elhenawy et al.[136] assessed the adaptive evolution of AIEC in a murine model of chronic colonisation across multiple hosts and transmission events. The transit of AIEC across multiple mice led to the selection of isolates with improved utilisation of the short-chain fatty acid acetate as a carbon source enabling the evolved strain to outcompete the parent strain in co-infected mice. Interestingly, *E. coli* isolates from patients with CD had increased acetate utilisation compared to isolates from healthy controls suggesting that AIEC may evolve differently within the host than commensal strains and acquire a metabolic advantage. Further studies may be required to investigate the effect of individual nutrients and food additives on their long-term, as opposed to their acute or short-term, ability to adapt and promote inflammation in the gut of people with established disease or at high risk of development of IBD.

In general, different disease models have produced different results for the same nutrient studied. Several factors could attribute to this difference such as luminal pH, nutrient dosage and concentration, duration of intake, fermentation site for prebiotics/fibre, the baseline composition of the gut microbiota and background diet of the host as reported in the current article.[137] Results from experimental colitis models on the effectiveness of prebiotics demonstrate that not all prebiotics confer a benefit, and their effects may depend on the colitis model used and are not always associated with changes in *E. coli* populations. So far only FOS, galactooligosaccharides, lactulose and inulin are considered prebiotics.[138,139] Other components might be claimed to be prebiotics but with only preliminary data for their protective effects. Examples of these substrates are algal polysaccharides laminarin and *Ficus carica* polysaccharide. Importantly, this literature review failed to identify clinical research on the effect of dietary prebiotics linking *E. coli*/Proteobacteria populations with clinical disease outcomes. There is also mechanistic evidence in animals to show in the presence of active gut inflammation fibre and fibre-originating short-chain fatty acids may be harmful[140,141] and damage the intestinal mucosa, an effect which opposes to the well-established benefits of the same molecules in cases of intestinal health homeostasis. A recent elegant study showed that β-fructan may have detrimental effects in select patients with active IBD who lack fibre-fermenting species.[142] Collectively, these data highlight once again that belief that the same diet–microbiome interactions may have very different consequences in development or management of gut inflammation in IBD.

It is currently unclear whether AIEC or other *E. coli* strains directly initiate gut inflammation and lead to disease or act as an aggravating factor in promoting intestinal inflammation. The balance of current evidence suggests that AIEC strains are pathobionts that promote disease only under the influence of specific host genetic or environmental factors. Thus, diet may affect the host and the intestinal barrier and may enhance the ability of AIEC to colonise and translocate the intestinal epithelium. Likewise, diet can enhance the adhesion and colonisation of AIEC indirectly by affecting the composition of the commensal gut microbiota or directly through guiding the expression of different AIEC virulence factors, as is the case with L-serine and propionic acid.[44,113] Food additives such as MDX and propionic acid can also enhance the virulence phenotypes of AIEC leading to enhanced persistence, colonisation and metabolic capabilities.[35,44] There is also evidence that AIEC invasion has the ability to alter epithelial barrier function by displacing ZO-1, a necessary protein for the formation of apical tight junctions.[143] It is also possible that different dietary, microbial or environmental factors are responsible for IBD development compared to its management. In part, this may explain the lack of replication of findings from preclinical studies, which largely explore the role of diet and microbes in onset of gut inflammation.

Most of the studies included in this review are based on animal models and in vitro studies. There are significant limitations of using animal models in the study of human gut microbiota and disease, which present complex interactions between genetic, immune and environmental factors. The main feature of most of these models is acute colitis, which does not involve the chronic injury of small intestine, an important feature in CD, where the ileum is the major site where AIEC are isolated from patients. In transgenic and knockout mice, the imposed genetic mutations may not mirror the actual aetiology of human CD which is still elusive.[144] In addition, the excessively high doses of some nutrients or food additives used in animal studies may affect the outcomes observed, but similar effects may not be observed with the much lower dietary intake in humans. Consequently, there is an urgent need to design

high-quality clinical interventions targeting dietary components which have been shown in preclinical trials to interact with *E. coli* and cause gut inflammation. The effect of dietary patterns associated with reduced risk of IBD development, like the Mediterranean diet, on *E.coli* colonisation, virulence and phenotypic traits is important areas to study in patients with IBD as well as in those at risk of disease development. An alternative approach to reducing *E. coli* levels in the gut could be the development of targeted antimicrobials with a specific activity against *E. coli*. Recent work has demonstrated that *E. coli*-specific protein antibiotics known as colicins can be successfully formulated for targeted oral delivery and controlled release to reduce AIEC LF82 levels in an in vivo murine model of *E. coli* colonisation. In the future, it is possible that concomitant therapy with such antimicrobial agents and effective dietary therapies, like EEN, will have better synergistic effectiveness than each of these therapeutics in isolation.[145]

In conclusion, there are preclinical and some clinical trial data to propose that *E. coli* and other *Enterobacteriaceae* interact with certain dietary components in CD to promote gut inflammation. Nonetheless, for some dietary components, patterns or therapies the evidence is inconsistent and currently none of these studies can prove a causal relationship. Well-designed clinical trials are required before dietary recommendations for disease management can be made.

AUTHOR CONTRIBUTIONS

Nojoud Faqerah: Methodology (lead); writing – original draft (lead). **Daniel Walker:** Supervision (equal); writing – review and editing (equal). **Konstantinos Gerasimidis:** Conceptualization (lead); methodology (equal); supervision (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

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