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A review on the effects of flavan-3-ols, their metabolites, and their dietary sources on gut barrier integrity†

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Impairment of gut barrier integrity is associated with the pathogenesis of gastrointestinal diseases, including inflammatory bowel disease, colorectal cancer, and coeliac disease. While many aspects of diet have been linked to improved barrier function, (poly)phenols, a broad group of bioactive phytochemicals, are of potential interest. The (poly)phenolic sub-class, flavan-3-ols, have been investigated in some detail owing to their abundance in commonly consumed foods, including grapes, tea, apples, cocoa, berries, and nuts. This review summarises studies on the effects of flavan-3-ols, their microbiome-mediated metabolites, and food sources of these compounds, on gut barrier structure. Extensive evidence demonstrates that flavan-3-ol rich foods, individual flavan-3-ols (*e.g.*, (*epi*)catechin, *epi*(gallo)catechin-3-*O*-gallate, and pro(antho)cyanidins), and their related microbiota-mediated metabolites, could be effective in protecting and restoring the integrity of the gut barrier. In this context, various endpoints are assessed, including transepithelial electrical resistance of the epithelial layer and expression of tight junction proteins and mucins, in *ex vivo*, *in vitro*, and animal models. The differences in bioactivity reported for barrier integrity are structure–function dependent, related to the (poly)phenolic source or the tested compound, as well as their dose, exposure time, and presence or absence of a stressor in the experimental system. Overall, these results suggest that flavan-3-ols and related compounds could help to maintain, protect, and restore gut barrier integrity, indicating that they might contribute to the beneficial properties associated with the intake of their dietary sources. However, rigorous and robustly designed human intervention studies are needed to confirm these experimental observations.

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1. Introduction

Preservation of a functional gut barrier is fundamental to the effective absorption of nutrients as well as protection against antigens and pathogenic microorganisms present in the intestinal lumen.[1–8] This barrier comprises a single layer of homeostatically renewed epithelial cells,[4] joined by specific proteins, including tight junction proteins (TJs), adherens and gap junctions, and desmosomes.[1,2,5] It is separated from the gut lumen by a mucus layer formed from mucins, hydrated high molecular weight glycoproteins, creating a physical-immunological protection for the host, as well as an environmental niche and a source of nutrients for a sub-group of gut microorganisms.[6,7] The gut barrier structure is subject to deleterious factors, both endogenous and exogenous, such as intake of diets low in fibres and high in fat, consumption of advanced glycation end products (AGEs), inflammatory responses, obesity and, psychological stress, that could lead to unregulated destruction of TJs and excessive thinning of mucin coverage.[8] While beneficial factors include components of fruits and vegetables, such as (poly)phenols, fibres, minerals, and vitamins.[8,9]

(Poly)phenols are of particular interest in this respect: these are dietary phytochemicals which possess a structure with one

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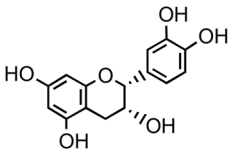
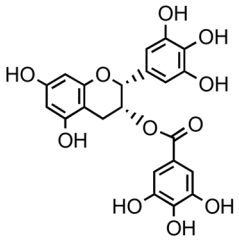
or more hydroxylated aromatic rings and sub-categorised based upon number of rings, their linkages, and chemical group moieties.[10,11] Flavonoids and non-flavonoids are the two main families of (poly)phenols.[10,11] The former are abundant in nature with flavan-3-ols representing the main dietary forms consumed.[11,12] Following intake, flavan-3-ols, which include (−)-epicatechin (**1**), (−)-epigallocatechin-3-*O*-gallate (**2**, ECGC), and pro(antho)cyanidins, among others, are extensively metabolised during their transit through the gastrointestinal tract. This review summarises the current evidence on the bioactive potential of flavan-3-ols and of their microbially derived metabolites with respect to gut barrier integrity in the presence or absence of stressors analysed in *ex vivo*, *in vitro* and animal models.



(−)-Epicatechin **1**



(−)-Epigallocatechin-3-*O*-gallate **2**

2. Flavan-3-ols and their metabolites

Despite the currently available information on the role of nutrition and (poly)phenols in reducing the occurrence and severity of gut barrier impairments,[9,13] a more in-depth analysis of the potential involvement of flavan-3-ols is warranted, especially when considering their dietary abundance. Tea, cocoa-derived products, wine, and pome fruits such as apples or pears, are key contributors to flavan-3-ol intake.[12,14,15] The National Diet and Nutrition Survey rolling programme (2008–2014) analysed the dietary intake of the UK population, noting consumption of flavan-3-ols gradually increases up to 483 ± 293 mg day^{-1} from childhood to adulthood, with the type of dietary sources differing in contribution between age groups.[12]

From a gastrointestinal perspective, following intake, flavan-3-ols remain relatively unaffected by the action of saliva enzymes[16–19] and limited modifications occur during the gastric phase, as indicated by studies where stomach metabolism was simulated *in vitro*, or naso-gastric sampling was performed.[20–23] Depending on the degree of polymerisation, and conjugation, up to ~90% of pro(antho)cyanidins transit through the small intestine without being metabolized or absorbed, while monomers are predominantly absorbed in the small intestine, with a portion being effluxed back into the intestinal lumen as phase II metabolites, a portion possibly through enterohepatic recirculation.[16,23–33] Phase II sulphate, methoxy, and/or glucuronide metabolites occur in the enterocytes and, after transport through the portal vein, in the liver.[34] The mechanism of absorption-conjugation-excretion in the small intestine was confirmed by the pivotal study of Actis-Goretta *et al.*,[35] who analysed intestinal perfusate collected following the intra-intestinal administration of (−)-epicatechin (**1**). Analysis of the (poly)phenolic content in ileal fluids following intake of flavan-3-ol sources by subjects with a ileostomy confirmed their relative stability with total intra-luminal presence of up to 2468 μmol of total flavan-3-ols over 24 h post-ingestion.[23,25,28–31,33] The (poly)phenolic profile of blood and urine samples collected from subjects with a full gastrointestinal tract after intake of flavan-3-ol-rich sources were in line with these observations with an average bioavailability estimated to be ~31%.[36] The *ca.* 70% of flavan-3-ol monomers that reach the colon, as either parent compounds or their metabolites, is then subjected to microbiota-mediated catabolism resulting in the production of phenyl-γ-valerolactones and phenylvaleric acids, unique products of flavan-3-ol monomers and pro(antho)cyanidins.[37,38] Phenolic acids including phenylpropanoic, phenylacetic, and benzoic acids can also be produced. All these catabolites, thus, have the potential to exert bioactivity within the colonic lumen as well as at a systemic level. It must be considered that bioavailability of flavan-3-ol compounds has been widely studies in rat and mice models. However, there are significant differences in their metabolism in comparison to humans, *e.g.*, absence of production of sulfated metabolites in rats,[39] which could represent a limit in translating findings in animal models to potential similar effects in humans.

3. Assessment of gut barrier integrity

Several direct and indirect methods are available to analyse the status of intestinal barrier integrity *via in vitro* and *ex vivo* models. Transepithelial electrical resistance (TEER) is a reference technique to quantitatively evaluate the permeability and integrity of the gut barrier *via* its electrical resistance,[40,41] thereby indirectly monitoring TJ functionality.[41] This technique can be applied both *in vitro* and *ex vivo*. Most commonly, TJ gene and protein expression and cellular localisation are measured, including zonula occludens (ZO), claudins, occludins, and junctional adhesion molecules (JAM). Permeability can be analysed *in vitro* through paracellular transport of fluorochrome markers, such as fluorescein isothiocyanate–dextran (FITC-Dx),[42,43] and, in animals, by monitoring circulating ovalbumin (OVA), glucagon-like peptide (GLP)-2, lipopolysaccharides (LPS) and LPS-binding protein (LBP) levels,[42,43] and by mannitol[42,44] and its ratio with lactulose.[45] In particular, these two monosaccharides cross the small intestinal barrier through trans- and para-cellular passage, therefore, their increased urinary excretion represents a marker of impaired permeability of this gastrointestinal section.[42,44] Faecal markers, including myeloperoxidase (MPO), which is specific for the neutrophil activity,[46] and calprotectin[42] are also used, while the presence of a healthy mucus layer can be assessed *via* analysis of mucin status and abundance of goblet cells. The interest in goblet cell density is mainly due to their ability to produce gel-forming mucins, which form the core struc-

Table 1 Examples of gut barrier stressors and models to simulate them in animals and cell models

Stressor	Model
Diabetes	High-fat diet + streptozotocin administration (a)
Inflammation	DSS administration (a), LPS, IL-1β, IL-6, and-or TNF-α exposure (c)
Coeliac disease	Transgenic DQ8 mice (a), gliadin exposure (c)
Obesity	Diet induced obesity (a)
CRC	Cancer treatment CTX (a)
Stress	Heat exposure, or water avoidance stress (a)
Age	Old mice (a)
Diet	High-fat and/or high-sugars diet (a)
Pathogens	*L. monocytogenes* exposure (c)

Stressor tested on a cell model (c), stressor tested on an animal model (a), colorectal cancer (CRC), cyclophosphamide (CTX), dextran sulphate sodium (DSS), interleukin (IL), lipopolysaccharides (LPS), tumour necrosis factor (TNF).

ture of the mucus layer.[6] The production of mucus differs between cell lines typically used for *in vitro* gut barrier studies and influences the type of cell line selected for use, based on the purpose of the study. For example, IPEC-J2 is a porcine intestinal cell line that does not produce mucus, which is a characteristic common to the Caco-2 human epithelial cell line cultured in normal conditions, whereas Caco-2 co-cultured with HT-29-MTX cells are characterised by mucus expression.[47] As revised by Martel and co-authors,[8] there are several factors that can trigger gut barrier integrity through several biological mechanisms. Examples are reported in Table 1.

4. Effects of flavan-3-ols, their metabolites, and their dietary sources

The studies covered in this review have been organised by type of (poly)phenolic source tested (*i.e.*, specific food source or individual compounds) with the main outputs summarised in Table 2 with more comprehensive experimental details provided in ESI Table 1.†

4.1. Cocoa (*Theobroma cacao* L.)

The (poly)phenolic profile of cocoa is characterised by a range of flavan-3-ols, from the unconjugated monomers to procyanidins with a degree of polymerisation >10 units,[48] and this composition is susceptible to effects of different processing methods.[49] Bitzer and co-workers[50] demonstrated *in vitro* that different fractions of cocoa extracts, containing mainly monomers, procyanidin oligomers (mainly dimers–hexamers), and polymers (mainly heptamers–decamers), exerted significant protection against a dextran sulphate sodium (DSS)-induced increase in permeability in Caco-2 cells. Moreover, the extracts containing mainly high molecular weight procyanidins showed significantly greater protective effects in comparison to the other fractions at the maximal concentration tested (100 μg mL^{-1}) and a protective effect was also observed at lower concentrations (10 and 25 μg mL^{-1}). Similarly, a cocoa extract containing mainly hexamers (10 μM), tested in the same cell model, protected against a decrease in ZO-1 protein expression and its cytoplasmic translocation induced by exposure to a stressor, the secondary bile acid deoxycholic acid (DCA, 0.2 mM).[51] While, in the absence of stress, the extract induced a significant time – (30–120 min) and concentration – (10–20 μM) dependent increase in TEER.[51] The latter effect was proposed to be the result of the adsorption of cocoa procyanidins to the cell membrane, that could lead to prolonged beneficial effects in the gut lumen,[51] with the procyanidins putatively also acting as a physical protective layer between the gut barrier and the intestinal lumen.

Similar positive protective results were reported in mice following prolonged (*i.e.*, 8- or 18-weeks) daily intake of different formulations of cocoa powder (80 mg per g diet per day) with a high-fat diet, assessed *via* analysis of plasma markers of gut barrier integrity (*i.e.*, GLP-2, LPS, LBP, or FITC-Dx).[52,53] In rats, chocolate (50 mg day^{-1}) alone did not affect barrier functions, but, in combination with probiotics, which prove to have beneficial effects, inhibited the increase in ileum permeability caused by loperamide-induced constipation, a condition linked to possible impairments on the gut barrier structure, indicating an effect of the probiotics rather than the cocoa-derived compounds.[54]

4.2. Pome fruits

Apple consumption contributes to the intake of both fibres and flavan-3-ols, mainly proanthocyanidins.[55] Like in an earlier study by Bitzer *et al.*[50] with cocoa extracts, Wu and co-workers[56] analysed (poly)phenolic fractions extracted from Granny Smith apples in Caco-2 cells. The extract which contained (–)-epicatechin (**1**), (+)-catechin (**3**), 5-*O*-caffeoylquinic acid (**4**), and procyanidins B2 (**5**) and C1(**6**), attenuated decreases in ZO-1 and occludin protein expression in a concentration-dependent manner (12.5–150 μg L^{-1}) in response to a LPS challenge. Similarly, an increase in TJs (*i.e.,* ZO-1, occludin, and claudin-1) expression was reported using a IPEC-J2 small intestinal cell model incubated with apple (poly)phenols for 24 h.[57] Another apple (poly)phenolic extract exerted time (0–48 h)- and concentration (0.01–1%)-dependent increases in TEER of the Caco-2 cell monolayer.[58] While supplementation of pigs (49-day, three times per day) with similar products (400 and 800 mg kg^{-1}) induced an increase in the expression of the same TJ proteins in the small intestine and promoted villi tightness at the ileum and jejunum level.[57] Furthermore, Swiss mice fed an extract of the *Pyracantha fortuneana* (Maxim.) fruit rich in flavan-3-ols and other (poly)phenols,[59] for 8 weeks (0.4–1% dietary intake), led to significant dose-dependent attenuation in high-fat diet-induced decrease in colonic TJ expression, increased urinary lactulose/mannitol excretion, and widening of intestinal villi caused by the challenge diet.[60]

4.3. Berries

Berries contribute to the intake of flavan-3-ols but it should be noted that the levels vary, and that berries are also the main dietary source of other (poly)phenols, most notably anthocya-

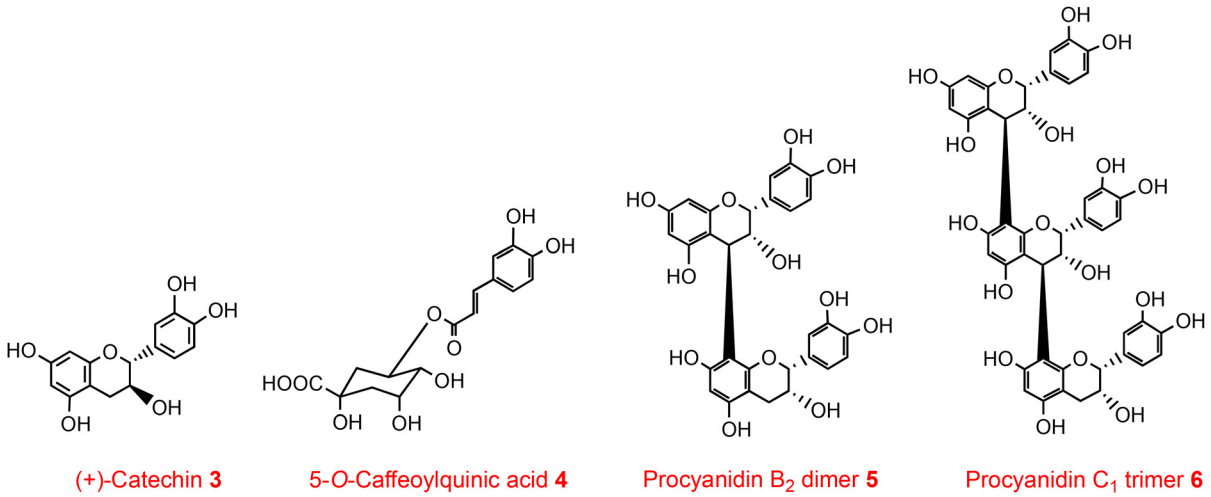


Table 2 Overview of studies reporting the effects of products containing flavan-3-ols and derivatives compounds, as well as these individual compounds, on selected markers of the gut barrier integrity, in presence (Y) or absence (N) of gut barrier stressors

PP source/type	Stress	Main significant outcomes	Ref.
Cocoa	N	TEER ↑	51
	Y	Permeability ↓, ZO-1 ↑, OCC ↓ or ↑, CL ↑ or ↑, Muc2 ↑	50–54, 156 and 157
Pome fruits	N	TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	57 and 58
	Y	Permeability ↓, ZO-1 ↑, OCC ↑, CL ↑	56, 57, 60 and 158
Berries	N	ZO-1 ↑	159
	Y	Permeability ↓, TEER ↑, ZO-1 ↑, JAM-1 ↑, OCC ↓ or ↑, CL ↑ or ↓, Muc2 ↑, Muc ↑	61–67, 69–73 and 159
Tea	N	Permeability ↓, TEER ↑, ZO-1 ↑ or ↓, OCC ↑ or ↓, CL ↑, Muc2 ↑	77, 81, 83, 93 and 123
	Y	Permeability ↓, TEER ↑, ZO-1 ↓ or ↑, OCC ↓ or ↑, CL ↑, Muc2 ↑	77, 81–83, 85–92 and 160
Grape	N	Permeability ↓ or ↑, TEER ↑, ZO-1 ↑, OCC ↑ or ↓, CL ↓ or ↑, Muc1 ↑, Muc2 ↑	98, 99, 101–106, 123, 161 and 162
	Y	Permeability ↓, TEER ↑, ZO-1 ↑, OCC ↑, CL ↑, E-cad ↑, Muc2 ↑	98, 99, 101, 102, 105–121 and 163
(−)-Epicatechin	N	Permeability ↑, TEER ↑, ZO-1 ↑.	125
	Y	Permeability ↓, TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	1, 128, 133 and 134
(−)-ECG	N	Muc17 ↑	129
(−)-EGCG	Y	Permeability ↓, TEER ↑, ZO-1 ↑, OCC ↑, CL ↑, TJ ↑, Muc2 ↑	130, 132, 135, 160, 164 and 165
(+)-Catechin	N	TEER ↑, ZO-1 ↑ or ↓, OCC ↑, CL ↑	41 and 125
	Y	TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	1, 41, 125, 160 and 166
Procyanidin B2	N	ZO-1 ↓, OCC ↑, CL ↑	41
	Y	ZO-1 ↑	41
Theaflavin-3′-*O*-gallate	N	Permeability ↓, TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	127
Theaflavin, theaflavin-3,3′-*O*-digallate, theaflavin-3-*O*-gallate	N	Permeability ↓	127
Theasinesins A, theasinesins B	N	Permeability ↓	138
Theabrownin	N	ZO-1 ↑, CL-1 ↑, Muc2 ↑	167
Procyanidin A1	Y	Permeability ↓, TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	168
3,4-Dihydroxy-BA	N	TEER ↑	169
2,4,6-Trihydroxy-BA	N	TEER ↓	169
3,4-Dihydroxy-BA	Y	ZO-1 ↑, Muc2 ↑	149
4-Hydroxy-3-methoxy-BA	Y	OCC ↑	170
Hippuric acid	Y	ZO-1 ↑	149
3′,4′-Dihydroxyphenylacetic acid	N	Permeability ↓, TEER ↑	101 and 125
	Y	TEER ↑	125
BA	N	ZO-1 ↑, OCC ↑	143
4-Hydroxy-BA	Y	OCC ↓, E-cad ↓	142
3-(3’,4’-Dihydroxyphenyl)propanoic acid	N	TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	125
	Y	TEER ↑	125
1,3,5-Trihydroxybenzene	N	TEER ↑, ZO-1 ↑, OCC ↑, CL ↑	125
	Y	TEER ↑	125
3,4,5-Trihydroxybenzoic acid	N	TEER ↓, CL ↓	144

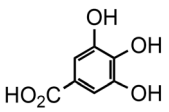
BA, benzoic acid; (−)-ECG, (−)-epicatechin-3-*O*-gallate; EGCG, (−)-epigallocatechin-3-*O*-gallate; PP, (poly)phenols; TEER, transepithelial electrical resistance; ↑, significant increase; ↓, significant decrease. Gene/protein expression of zonula occludens (ZO), occludin (OCC), claudin(s) (CL), and mucin (Muc) are reported. Results for paracellular or transcellular permeability were reported. For more experimental details see ESI Table S1.†

nins and ellagitannins.[10,11] Respectively, açai and aronia berries protected against reductions in TEER induced by LPS-[61] and a pro-inflammatory cytokines mix,[62] with a general consistent increase in TJ proteins observed in both studies.[61,62] An 8 weeks diet high in sugars and fats fed to obese mice increased serum LPS, an effect that was mitigated by supplementation of three (*i.e.*, cloudberry, alpine bearberry, and lingonberry) of five types of Arctic berries.[63] In addition, supplementation of a high fat diet with blueberry powder (10% w/w diet) for 8 weeks decreased circulating LBP, while promoting Muc2 expression at colonic level in a rodent model.[64] This agrees with protective effects exerted by wild blueberry (poly)phenolic fractions (17–53 mg (poly)phenols per day) against diet-induced thinning of the colonic mucus in mice, and albeit with inconsistent increases in goblet cells density.[65] Maqui berry-derived products (50–200 mg kg^{-1} day^{-1}) enhanced barrier integrity, occludin expression, mucin content, and goblet cell number in mice models of colitis (*i.e.*, DSS or TNBS induced), when supplemented intra-gastrically,[66] or orally.[67]

Ulcerative colitis and Crohn's disease can contribute to gut barrier disruption[8] and, although enteral nutrition represents one of the possible treatments for these conditions, it has been linked with side effects.[68,69] A significant dose-dependent (8–200 mg per kg BW per day) attenuation in the decrease of intestinal Muc2 expression and goblet cell number was observed following the addition of cranberry proanthocyanidins to enteral nutrition administered to mice (5 days).[69] Oral feeding of a cranberry extract (200 mg kg^{-1}),[70] or a freeze-dried cranberries (20% w/w diet)[71] improved barrier function in mice either challenged with a high fat or genetically-predisposed to colon-rectal cancer. Cranberry products not only increased Muc2 expression and content,[69–71] but promoted increases in ZO-1 and colon claudin-3 gene expression,[71] and attenuated the stress-induced increases in plasma levels of LPS.[70] Similar effects were observed by Heyman-Lindén *et al.*[72] after freeze-dried lingonberry supplementation to mice for 11 weeks decreased serum LBP and modulated occludin gene expression, albeit with some batch product variation being evident. Finally, an infusion of Chinese blackberry (*Rubus sauvissimus* S.) leaves mitigated against LPS-induced intestinal permeability in a mouse model while increasing expression of ZO-1 and JAM-1.[73]

4.4. Tea (*Camellia sinensis* L.)

Green and black teas, major sources of flavan-3-ols and their derived products,[74,75] are consumed widely by the adult population of many countries.[76] Green tea has been reported to alleviate the detrimental effects of coeliac disease on the gut barrier.[77,78] Avoiding gluten intake is the only current treatment against this disease,[77,79,80] but complete adherence to this restricted diet is often not fulfilled.[79,80] In an *in vitro* Caco-2 model, a decaffeinated green tea extract (1 mg mL^{-1}) improved gut permeability and prevented a gliadin-induced decrease in TEER up to 24 h post-incubation.[77] Dias *et al.*[78] showed that attenuation of gliadin-induced morphological changes in colonic crypts, and villi of gluten-sensitive DQ8 transgenic mice, were reduced by green tea extract consumption (50 mg kg^{-1} day^{-1}) over a 45-day period. In the absence of stressors, a 12-weeks oral supplementation of a green tea extract (2% w/w diet) did not significantly change colonic TJ expression (*i.e.*, ZO-1, occludin, claudin-1), nor FITC-Dx permeability in mice, although serum and portal vein endotoxemia were decreased significantly.[81] Furthermore, daily supplementation of animals with green tea-derived products significantly prevented or ameliorated impairments of the gut barrier caused by a high-fat diet, in terms of permeability to endotoxin and TJ expression.[81–84] Broadly in line with these results are the outputs reported for fu brick tea,[85] pu-erh tea[86] and its ripened version,[87,88] raw bowl tea,[89] and other tea-derived products.[86] As with lingonberries,[72] batch effects were evident in the efficacy of ripened pu-erh tea (year of production 2006 *vs.* 2010) with respect to attenuation of DSS-induced ZO-1 protein expression decrease, but not in the modulation of MPO activity.[90]



3,4,5-Trihydroxybenzoic acid **7**

Alcohol is also a known cause of gut barrier impairment,[8] and an aqueous extract of fu brick tea (400 mg per kg BW per day) was assessed for efficacy in mice supplemented daily for 12-weeks with alcohol (40%).[91] The treatment improved the alcohol-impaired gut barrier function, up-regulating epithelial TJ expression and reducing circulating LPS concentrations.[91] In addition, intra-gastric gavage with a tea flower extract (200 mg per kg BW per day) significantly mitigated against changes in markers of gut barrier disruption caused by intraperitoneal supplementation of the cancer treatment cyclophosphamide (CTX) in mice.[92] Furthermore, daily consumption for 22 days of a green tea catechin extract (0.1–0.5% w/v in drinking water) by Wistar rats significantly increased ileal mucins and decreased the sialomucins/sulfomucins ratio, although it did not affect the content of mucins in either the jejunum or colon.[93] Similarly, 3,4,5-trihydroxybenzoic acid (**7**, aka gallic acid), present in tea both as the free acid and conjugated to monomeric and polymeric flavan-3-ols, inhibited the increase in colonic sialic acid containing mucins as a consequence of sub-cutaneous exposure to 1,2-dimethylhydrazine (DMH).[94] In contrast to (–)-epicatechin (**1**), EGCG (**2**), one of the main monomeric flavan-3-ols in green tea, can cross-link with gastric (MUC5Ac) and duodenal (Muc2) porcine mucins *in vitro*.[95] Conjugated flavan-3-ols can also form multilayer-EGCG structures *via* interactions with other similar molecules already adsorbed to the mucus.[96]

4.5. Grape (*Vitis vinifera* L.)

Cultivated grapes are a dietary source rich in proanthocyanidins,[11] which occur predominantly in skin and seeds.[97] Grape

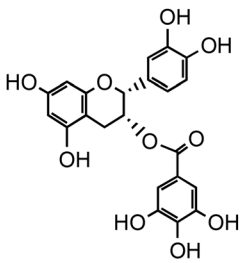
seed (12.5 μg L^{-1})[98] and red wine (60 μg mL^{-1})[99] extracts decrease the permeability of fluorescent markers and increase TEER *in vitro*, improving the barrier function of the intestinal cell layer. This permeability decrease was not always associated with increased expression of TJ proteins.[99–101] Similarly, in a porcine model, grape proanthocyanidins fed (100 and 250 mg kg^{-1}) for up to 28 days promoted a decrease in intestinal permeability in weaned piglets,[102,103] while a combined oral and intra-gastric supplementation of grape seed extract decreased faecal calprotectin, but not blood endotoxemia in rats.[104] Despite differences in (poly)phenolic composition, in the concentrations tested of grape-derived products, and in the duration of interventions, there seemed to be a general trend to protect against stress-induced increase in gut barrier permeability[99,102,105–114] or decreased TJ expression[99,102,105–119] caused by inflammatory[98,99,113] and oxidative challenges,[105] the microbial pathogen *L. monocytogenes*,[119] ulcerative colitis,[106,108,116–118,120] antibiotic treatment,[102] weaning,[105] or westernised dietary patterns characterised by a high content of sugars and fats.[106,107,109–112,114,115] Studies report significant protection mediated by grape-derived products on some of the monitored markers of gut barrier disruption.[99,109,110,114,116,121] Absence of beneficial protection was observed for a grape skin powder[116] and a table grape extract rich in (poly)phenols.[109] However, their effects improved when fractions obtained from the same original products, but differing in flavan-3-ol profiles, were tested.[109,116] Moreover, a decrease in claudin-1 caused by a cafeteria diet was prevented by intermittent supplementation of a grape seed procyanidin extract, but not when the intake of the extract occurred prior to stress exposure,[111] highlighting the potential importance of frequency of (poly)phenol intakes in the framework of stress exposure.

4.6. Other sources of flavan-3-ols or their metabolites

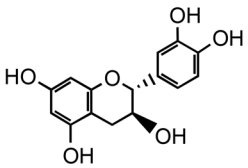
Studies on the effects of other dietary sources of flavan-3-ols on gut barrier function include peanut skin and other nut or derived products. Procyanidins from peanut skin significantly mitigated gut barrier impairments in mice affected by type 2 diabetes caused by a high-fat diet and streptozotocin.[122] However, downregulation of claudin-1 caused by stressors of the gut barrier was not prevented by supplementation with peanut skin procyanidins.[122] In contrast, a chestnut extract exhibited a dose-dependent decrease in TEER, which was accompanied by a significant decrease in claudin-2 expression.[123] However, it did not impact other monitored TJs, namely ZO-1, occludin, claudin-3 and -15, JAM-1.[123]

4.7. Individual compounds and metabolites

When models were analysed in absence of stressor-related perturbations, a general absence of significant changes in markers of gut barrier integrity, TJs or mucin expression has been reported following intestinal cell line incubations, animal supplementation, and *ex vivo* exposure to (–)-epicatechin (**1**),[124–128] (–)-epicatechin-3-*O*-gallate (**8**),[127,129] and EGCG (**2**).[127,130–132] Protective effects of (–)-epicatechin (1–20 μM) occur *in vitro* independent of the tested stress-source,[1,128,133,134] while its effect against dysbiosis in the gut barrier of mice caused by high-fat diet was concentration-dependent upon oral supplementation (2–20 mg per kg BW).[128] Inhibition of stress-induced decrease in TEER and ZO-1 protein expression in mono-cell lines was caused by (+)-catechin (**9**) (10–50 μM) incubation.[1,125,135] In contrast, these effects were not observed in a more complex Caco-2/HT-29 MTX co-culture model when (+)-catechin was tested at a 50 μM concentration.[41] Moreover, the protective activities exerted by EGCG (**2**) were dependent on the concentration,[78,132] stressor type,[130] and route of administration.[135] Regarding the latter aspect, a study by Wu and co-workers[135] highlighted that, in mice, the metabolism of EGCG (50 mg per kg BW per day) may represent a critical step for observing significant effects against DSS-induced changes in MPO plasma activity, disruption of TJs, and mucosal damages, as these properties were absent following rectal administration of the gallated flavan-3-ol.



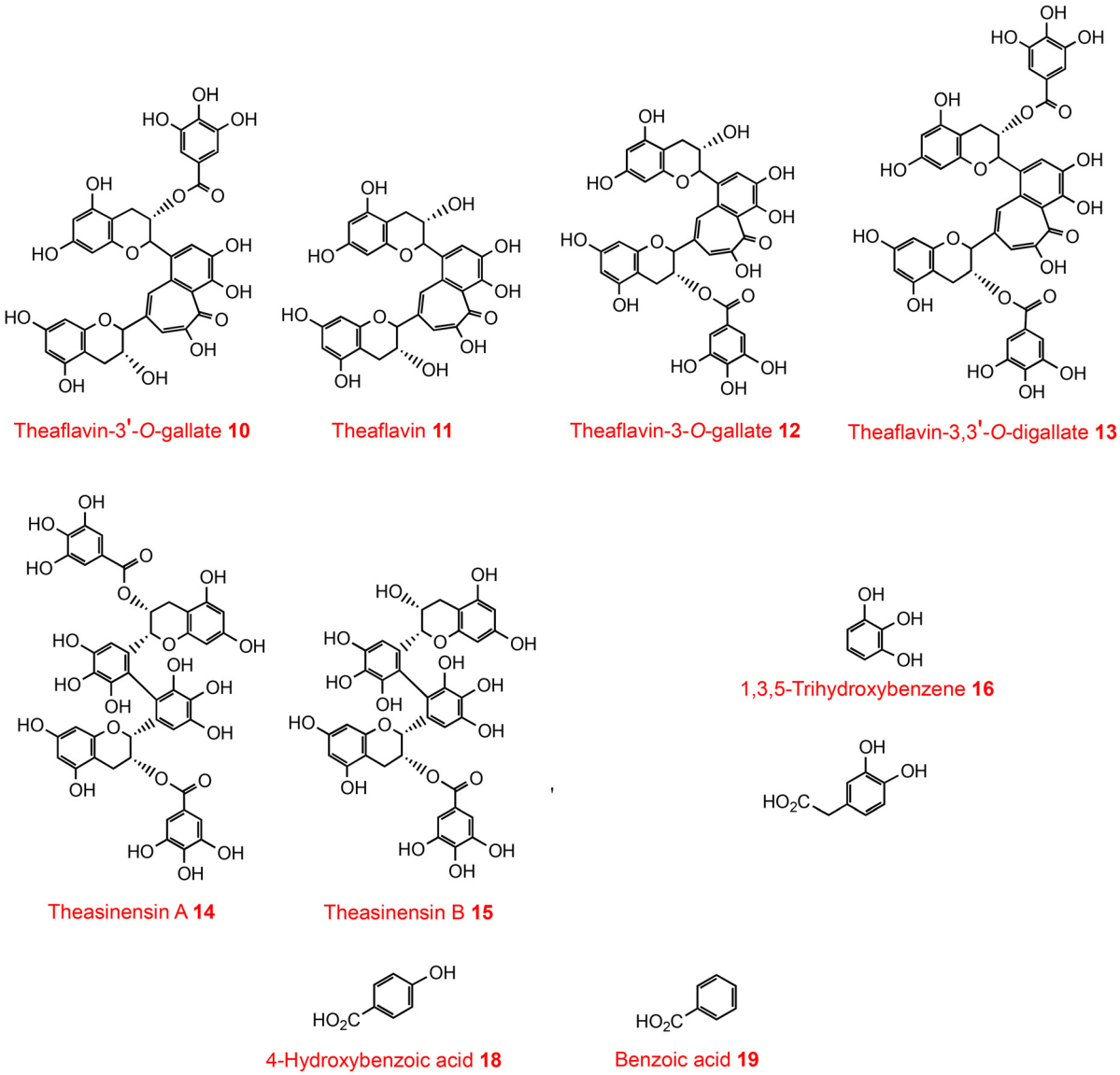
(–)-Epicatechin-3-*O*-gallate **8**



(+)-Catechin **9**

An increase in TEER was reported upon incubation of Caco-2 cells with theaflavin-3′-*O*-gallate (**10**) (10–50 μM)[127] or a mixture of procyanidins with different degrees of polymerisation,[136] suggesting their possible effects as gut barrier strengthening factors. Indeed, all the studies testing bioactivity of pro(antho)cyanidins on cell models of gut barrier applied these compounds in their free form, and not bound to proteins which can modulate and mediate their bioactive potential.[137] Moreover, a decrease in the permeability of Caco-2 monolayers has been reported followed incubation with theaflavin-3′-*O*-gallate, theaflavin (**11**), theaflavin-3-*O*-digallate (**12**), theaflavin-3,3′-*O*-digallate (**13**),[127] theasinesin A (**14**), and theasinesin B (**15**).[138] Similar effects were observed for compounds with lower molecular weight namely 1,3,5-trihydroxybenzene (**16**, aka phloroglucinol)[125] and 3′,4′-dihydroxyphenylacetic acid (**17**).[1] With a combined *in vitro* and *in silico* model involving the use of a porcine gastric mucin type III, Brandão and co-workers[139] observed that a grape seed fraction, containing mainly procyanidin B4 and a tetramer, could interact with the mucins, through hydrogen bonds and hydrophobic interactions, similarly to that reported for EGCG.[95,96]

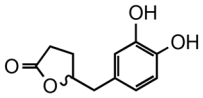
As reviewed by other authors,[37,140,141] flavan-3-ols undergo extensive metabolism during their transit through the gastrointestinal tract and, especially in the colon where they are catabolised to simple phenolic catabolites. Significant dose-depen-



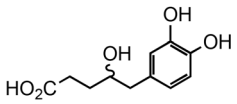
dent mitigation against stress-induced impairment of gut barrier integrity has been reported for, 4-hydroxybenzoic acid (**18**), (10–40 mg kg^{-1} day^{-1}),[142] benzoic acid (**19**) (2–5 g kg^{-1} diet),[143] and 3,4,5-trihydroxybenzoic acid (**7**) (5–50 μM).[144] Moreover, time-dependent protection exerted by phenolic compounds against stressors of this key intestinal structure,[125,145,146] as well as the absence or partial protective effects, have been described.[1,62,86,142,147–150] For example, none of the simple phenolic compounds individually tested *in vitro* by Valdez and collaborators[62] effectively protected Caco-2 cells against an inflammatory insult, suggesting that the (poly)phenolic fraction of aronia berry powder, having a mixture of these compounds, might not be the unique factor responsible for the beneficial effects attributed to the whole food extract. These results confirm the importance of elucidating the contribution of individual compounds to the overall effects observed in complex matrixes as food products and their extracts, as noted by Bianchi *et al.*[41]

5. Conclusions

The studies included in this review were mainly conducted employing cell models, with the colorectal adenocarcinoma Caco-2 cell line being the most frequently utilised, and in animals, typically mice and rats. Modulation or strengthening of the gut barrier was assessed by testing the flavan-3-ols, their metabolites, or their dietary sources in the absence of stress, or prior to a stress challenge. Their capacity to reduce the severity of damage and dysfunction, or to facilitate the re-establishment of gut barrier integrity following stress-induced impairment, were analysed by tests in mixed temporal models, or after challenge exposure. However, it is important that human interventions are carried out with healthy and patient groups to confirm these protective effects. Several human studies are ongoing,[9] and a recent investigation by Del Bo' *et al.*[151] analysed the impact of a diet rich in (poly)phenols on the gut barrier integrity of older subjects *via* monitoring their serum zonulin levels and reported potential promising findings.



(*R*/*S*)-5-(3',4'-Dihydroxyphenyl)-γ-valerolactone **20**



(*R*/*S*)-4-Hydroxy-5-(3',4'-dihydroxyphenyl)-valeric acid **21**

Greater elucidation of the potential benefits derived from flavan-3-ol phase II metabolites and their characteristic phenyl-γ-valerolactones (**20**) and phenylvaleric acid (**21**) colonic catabolites[37] will be essential in the context of person-to-person variations in the fate of flavan-3-ols within the gastrointestinal tract. *In vitro* and *in silico* analyses of the mechanisms and stability of the interactions between these compounds and the epithelial and mucus layers are needed to define their putative mechanism(s) of action. While analysis of the stability of tested compounds in the media used for cell models has been identified as a critical step in the assessment of their bioactivity,[152] this has been investigated with a only a limited number of (poly)phenolic sources with the majority of incubations only up to 24 hours duration. Moreover, artifacts due to the addition of these (poly)phenolic compound to the cell models should be also monitored as they can mediate oxidative stress response *via*, *e.g.*, hydrogen peroxide generation,[153] as recently reported by Mahmutović *et al.*[154] Therefore, it might be advisable that future research implements experimental protocols to consider these factors. For this purpose, the analysis of the concentration of metabolites present in the culture media during incubations requires investigation.[41,152] Furthermore, a more complete analysis of the intra-luminal availability of flavan-3-ols and their metabolites, both in terms of chemical structure and available concentrations, could better support future design of studies aiming at investigate the bioactivity of these compounds on the gut barrier. While a harmonised way to report the compounds name and tested quantity would benefit comparison between studies. Finally, the potential synergies of (poly) phenols with the resident microbiota in maintaining gut barrier functions also deserves attention.[65,155] In this regard, designing and testing functional foods or supplements to improve and maintain a healthy epithelial and mucus layer, including probiotics together with flavan-3-ols, represents a field of importance for future research. There are considerable differences in the metabolism of flavan-3-ols between animals and humans.[39] Therefore, clinical human studies are needed to further clarify the potential impact of these (poly)phenols on human gut health. The results reported in this review, in terms of possible promising compounds and concentrations to be tested, could represent a starting point for their design.

Author contributions

SD, LKP, NGT, DDR, and CIRG were involved in the generation of the topic. SD was involved in data review and writing of the review article. LKP, NGT, GJMD, GPC, LB, PM, TMA, AC, KMT, DDR, and CIRG critically revised and edited the manuscript. All the authors have read and approved the final manuscript.

Data availability

Refer to literature references for data availability of each study included in the current work. No new data was generated.

Conflicts of interest

The authors declare on conflicts of interest.

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References

1 H. Bergmann, D. Rogoll, W. Scheppach, R. Melcher and E. Richling, The Ussing type chamber model to study the intestinal transport and modulation of specific tight–junction genes using a colonic cell line, *Mol. Nutr. Food Res.*, 2009, **53**, 1211–1225.
2 C. Zihni, C. Mills, K. Matter and M. S. Balda, Tight junctions: from simple barriers to multifunctional molecular gates, *Nat. Rev. Mol. Cell Biol.*, 2016, **17**, 564–580.
3 A. A. Bhat, S. Uppada, I. W. Achkar, S. Hashem, S. K. Yadav, M. Shanmugakonar, H. A. Al-Naemi, M. Haris and S. Uddin, Tight Junction Proteins and Signaling Pathways in Cancer and Inflammation: A Functional Crosstalk, *Front. Physiol.*, 2019, **9**, 1942.
4 S. C. Bischoff, G. Barbara, W. Buurman, T. Ockhuizen, J.-D. Schulzke, M. Serino, H. Tilg, A. Watson and J. M. Wells, Intestinal permeability – a new target for disease prevention and therapy, *BMC Gastroenterol.*, 2014, **14**, 189.
5 A. A. Bhat, N. Syed, L. Therachiyil, S. Nisar, S. Hashem, M. A. Macha, S. K. Yadav, R. Krishnankutty, S. Muralitharan, H. Al-Naemi, P. Bagga, R. Reddy, P. Dhawan, A. Akobeng, S. Uddin, M. P. Frenneaux, W. El-Rifai and M. Haris, Claudin-1, A Double-Edged Sword in Cancer, *Int. J. Mol. Sci.*, 2020, **21**, 569.

6 P. Paone and P. D. Cani, Mucus barrier, mucins and gut microbiota: the expected slimy partners?, *Gut*, 2020, **69**, 2232–2243.
7 O. I. Coleman and D. Haller, Microbe–Mucus Interface in the Pathogenesis of Colorectal Cancer, *Cancers*, 2021, **13**, 616.
8 J. Martel, S.-H. Chang, Y.-F. Ko, T.-L. Hwang, J. D. Young and D. M. Ojcius, Gut barrier disruption and chronic disease, *Trends Endocrinol. Metab.*, 2022, **33**, 247–265.
9 S. Bernardi, C. Del Bo', M. Marino, G. Gargari, A. Cherubini, C. Andrés-Lacueva, N. Hidalgo-Liberona, G. Peron, R. González-Dominguez, P. Kroon, B. Kirkup, M. Porrini, S. Guglielmetti and P. Riso, Polyphenols and Intestinal Permeability: Rationale and Future Perspectives, *J. Agric. Food Chem.*, 2020, **68**, 1816–1829.
10 C. Manach, A. Scalbert, C. Morand, C. Rémésy and L. Jiménez, Polyphenols: food sources and bioavailability, *Am. J. Clin. Nutr.*, 2004, **79**, 727–747.
11 D. Del Rio, A. Rodriguez-Mateos, J. P. E. Spencer, M. Tognolini, G. Borges and A. Crozier, Dietary (Poly)phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases, *Antioxid. Redox Signal.*, 2013, **18**, 1818–1892.
12 N. Ziauddeen, A. Rosi, D. Del Rio, B. Amoutzopoulos, S. Nicholson, P. Page, F. Scazzina, F. Brighenti, S. Ray and P. Mena, Dietary intake of (poly)phenols in children and adults: cross-sectional analysis of UK National Diet and Nutrition Survey Rolling Programme (2008–2014), *Eur. J. Nutr.*, 2019, **58**, 3183–3198.
13 M. Fortea, M. Albert-Bayo, M. Abril-Gil, J.-P. Ganda Mall, X. Serra-Ruiz, A. Henao-Paez, E. Expósito, A. M. González-Castro, D. Guagnozzi, B. Lobo, C. Alonso-Cotoner and J. Santos, Present and Future Therapeutic Approaches to Barrier Dysfunction, *Front. Nutr.*, 2021, **8**, 718093.
14 L. Johannot and S. M. Somerset, Age-related variations in flavonoid intake and sources in the Australian population, *Public Health Nutr.*, 2006, **9**, 1045–1054.
15 V. Knaze, R. Zamora-Ros, L. Luján-Barroso, I. Romieu, A. Scalbert, N. Slimani, E. Riboli, C. T. M. Van Rossum, H. B. Bueno-de-Mesquita, A. Trichopoulou, V. Dilis, K. Tsiotas, G. Skeie, D. Engeset, J. Ramón Quirós, E. Molina, J. M. Huerta, F. Crowe, E. Wirfält, U. Ericson, P. H. M. Peeters, R. Kaaks, B. Teucher, G. Johansson, I. Johansson, R. Tumino, H. Boeing, D. Drogan, P. Amiano, A. Mattiello, K.-T. Khaw, R. Luben, V. Krogh, E. Ardanáz, C. Sacerdote, S. Salvini, K. Overvad, A. Tjønneland, A. Olsen, M.-C. Boutron-Ruault, G. Fagherazzi, F. Perquier and C. A. González, Intake estimation of total and individual flavan-3-ols, proanthocyanidins and theaflavins, their food sources and determinants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, *Br. J. Nutr.*, 2012, **108**, 1095–1108.
16 K. Kahle, M. Kempf, P. Schreier, W. Scheppach, D. Schrenk, T. Kautenburger, D. Hecker, W. Huemmer, M. Ackermann and E. Richling, Intestinal transit and systemic metabolism of apple polyphenols, *Eur. J. Nutr.*, 2011, **50**, 507–522.
17 C. S. Yang, M.-J. Lee and L. Chen, Human Salivary Tea Catechin Levels and Catechin Esterase Activities: Implication in Human Cancer Prevention Studies, *Cancer Epidemiol. Biomarkers Prev.*, 1999, **8**, 83–89.
18 I. Hasslauer, A. Oehme, S. Locher, A. Valotis, G. Van't Slot, H. Humpf and P. Schreier, Flavan–3—ol *C* –glycosides – Preparation and model experiments mimicking their human intestinal transit, *Mol. Nutr. Food Res.*, 2010, **54**, 1546–1555.
19 M. Rogozinska and M. Biesaga, Decomposition of Flavonols in the Presence of Saliva, *Appl. Sci.*, 2020, **10**, 7511.
20 Q. Y. Zhu, R. R. Holt, S. A. Lazarus, J. L. Ensunsa, J. F. Hammerstone, H. H. Schmitz and C. L. Keen, Stability of the Flavan-3-ols Epicatechin and Catechin and Related Dimeric Procyanidins Derived from Cocoa, *J. Agric. Food Chem.*, 2002, **50**, 1700–1705.
21 L. Y. Rios, R. N. Bennett, S. A. Lazarus, C. Rémésy, A. Scalbert and G. Williamson, Cocoa procyanidins are stable during gastric transit in humans, *Am. J. Clin. Nutr.*, 2002, **76**, 1106–1110.
22 A. P. Neilson, A. S. Hopf, B. R. Cooper, M. A. Pereira, J. A. Bomser and M. G. Ferruzzi, Catechin Degradation with Concurrent Formation of Homo- and Heterocatechin Dimers during *in Vitro* Digestion, *J. Agric. Food Chem.*, 2007, **55**, 8941–8949.
23 K. Kahle, W. Huemmer, M. Kempf, W. Scheppach, T. Erk and E. Richling, Polyphenols Are Intensively Metabolized in the Human Gastrointestinal Tract after Apple Juice Consumption, *J. Agric. Food Chem.*, 2007, **55**, 10605–10614.
24 K. Kahle, M. Kraus, W. Scheppach and E. Richling, Colonic availability of apple polyphenols - A study in ileostomy subjects, *Mol. Nutr. Food Res.*, 2005, **49**, 1143–1150.
25 C. Auger, W. Mullen, Y. Hara and A. Crozier, Bioavailability of Polyphenon E Flavan-3-ols in Humans with an Ileostomy4, *J. Nutr.*, 2008, **138**, 1535S–1542S.
26 S. Roowi, A. Stalmach, W. Mullen, M. E. J. Lean, C. A. Edwards and A. Crozier, Green Tea Flavan-3-ols: Colonic Degradation and Urinary Excretion of Catabolites by Humans, *J. Agric. Food Chem.*, 2010, **58**, 1296–1304.
27 A. Stalmach, H. Steiling, G. Williamson and A. Crozier, Bioavailability of chlorogenic acids following acute ingestion of coffee by humans with an ileostomy, *Arch. Biochem. Biophys.*, 2010, **501**, 98–105.
28 S. Hagl, H. Deusser, B. Soyalan, C. Janzowski, F. Will, H. Dietrich, F. W. Albert, S. Rohner and E. Richling, Colonic availability of polyphenols and D –(–)–quinic acid after apple smoothie consumption, *Mol. Nutr. Food Res.*, 2011, **55**, 368–377.
29 A. Stalmach, C. A. Edwards, J. D. Wightman and A. Crozier, Gastrointestinal stability and bioavailability of (poly)phenolic compounds following ingestion of Concord grape juice by humans, *Mol. Nutr. Food Res.*, 2012, **56**, 497–509.

30 G. Borges, M. E. J. Lean, S. A. Roberts and A. Crozier, Bioavailability of dietary (poly)phenols: a study with ileostomists to discriminate between absorption in small and large intestine, *Food Funct.*, 2013, **4**, 754.
31 E. M. Brown, S. Nitecki, G. Pereira-Caro, G. J. McDougall, D. Stewart, I. Rowland, A. Crozier and C. I. R. Gill, Comparison of *in vivo* and *in vitro* digestion on polyphenol composition in lingonberries: Potential impact on colonic health, *BioFactors*, 2014, **40**, 611–623.
32 D. Mueller, K. Jung, M. Winter, D. Rogoll, R. Melcher and E. Richling, Human intervention study to investigate the intestinal accessibility and bioavailability of anthocyanins from bilberries, *Food Chem.*, 2017, **231**, 275–286.
33 J. I. Ottaviani, R. Y. Fong, G. Borges, J. Kimball, J. L. Ensunsa, V. Medici, L. K. Pourshahidi, E. Kane, K. Ward, R. Durkan, S. Dobani, R. Lawther, G. O'Connor, C. I. R. Gill, H. Schroeter and A. Crozier, Flavan-3-ol-methylxanthine interactions: Modulation of flavan-3-ol bioavailability in volunteers with a functional colon and an ileostomy, *Free Radicals Biol. Med.*, 2023, **196**, 1–8.
34 M. Monagas, M. Urpi-Sarda, F. Sánchez-Patán, R. Llorach, I. Garrido, C. Gómez-Cordovés, C. Andres-Lacueva and B. Bartolomé, Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites, *Food Funct.*, 2010, **1**, 233.
35 L. Actis-Goretta, A. Lévèques, M. Rein, A. Teml, C. Schäfer, U. Hofmann, H. Li, M. Schwab, M. Eichelbaum and G. Williamson, Intestinal absorption, metabolism, and excretion of (–)-epicatechin in healthy humans assessed by using an intestinal perfusion technique, *Am. J. Clin. Nutr.*, 2013, **98**, 924–933.
36 G. Di Pede, P. Mena, L. Bresciani, M. Achour, R. M. Lamuela-Raventós, R. Estruch, R. Landberg, S. E. Kulling, D. Wishart, A. Rodriguez-Mateos, A. Crozier, C. Manach and D. Del Rio, Revisiting the bioavailability of flavan-3-ols in humans: A systematic review and comprehensive data analysis, *Mol. Aspects Med.*, 2023, **89**, 101146.
37 P. Mena, L. Bresciani, N. Brindani, I. A. Ludwig, G. Pereira-Caro, D. Angelino, R. Llorach, L. Calani, F. Brighenti, M. N. Clifford, C. I. R. Gill, A. Crozier, C. Curti and D. Del Rio, Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity, *Nat. Prod. Rep.*, 2019, **36**, 714–752.
38 G. Williamson, C. D. Kay and A. Crozier, The Bioavailability, Transport, and Bioactivity of Dietary Flavonoids: A Review from a Historical Perspective, *Compr. Rev. Food Sci. Food Saf.*, 2018, **17**, 1054–1112.
39 J. I. Ottaviani, G. Borges, T. Y. Momma, J. P. E. Spencer, C. L. Keen, A. Crozier and H. Schroeter, The metabolome of [2-14C](–)-epicatechin in humans: implications for the assessment of efficacy, safety and mechanisms of action of polyphenolic bioactives, *Sci. Rep.*, 2016, **6**, 29034.
40 B. Srinivasan, A. R. Kolli, M. B. Esch, H. E. Abaci, M. L. Shuler and J. J. Hickman, TEER Measurement Techniques for In Vitro Barrier Model Systems, *SLAS Technol.*, 2015, **20**, 107–126.
41 M. G. Bianchi, M. Chiu, G. Taurino, F. Brighenti, D. Del Rio, P. Mena and O. Bussolati, Catechin and Procyanidin B2 Modulate the Expression of Tight Junction Proteins but Do Not Protect from Inflammation-Induced Changes in Permeability in Human Intestinal Cell Monolayers, *Nutrients*, 2019, **11**, 2271.
42 M. Vancamelbeke and S. Vermeire, The intestinal barrier: a fundamental role in health and disease, *Expert Rev. Gastroenterol. Hepatol.*, 2017, **11**, 821–834.
43 I. Schoultz and Å. V. Keita, The Intestinal Barrier and Current Techniques for the Assessment of Gut Permeability, *Cells*, 2020, **9**, 1909.
44 J. Grootjans, Non-invasive assessment of barrier integrity and function of the human gut, *World J. Gastrointest. Surg.*, 2010, **2**, 61.
45 M. Linsalata, G. Riezzo, B. D'Attoma, C. Clemente, A. Orlando and F. Russo, Noninvasive biomarkers of gut barrier function identify two subtypes of patients suffering from diarrhoea predominant-IBS: a case-control study, *BMC Gastroenterol.*, 2018, **18**, 167.
46 M. Kosek, R. Haque, A. Lima, S. Babji, S. Shrestha, S. Qureshi, S. Amidou, E. Mduma, G. Lee, P. P. Yori, R. L. Guerrant, Z. Bhutta, C. Mason, G. Kang, M. Kabir, C. Amour, P. Bessong, A. Turab, J. Seidman, M. P. Olortegui, J. Quetz, D. Lang, J. Gratz, M. Miller and M. Gottlieb, Fecal Markers of Intestinal Inflammation and Permeability Associated with the Subsequent Acquisition of Linear Growth Deficits in Infants, *Am. Soc. Trop. Med. Hyg.*, 2013, **88**, 390–396.
47 *The Impact of Food Bioactives on Health*, ed. K. Verhoeckx, P. Cotter, I. López-Expósito, C. Kleiveland, T. Lea, A. Mackie, T. Requena, D. Swiatecka and H. Wichers, Springer International Publishing, Cham, 2015.
48 S. Langer, L. J. Marshall, A. J. Day and M. R. A. Morgan, Flavanols and Methylxanthines in Commercially Available Dark Chocolate: A Study of the Correlation with Nonfat Cocoa Solids, *J. Agric. Food Chem.*, 2011, **59**, 8435–8441.
49 J. Oracz, E. Nebesny, D. Zyzelewicz, G. Budryn and B. Luzak, Bioavailability and metabolism of selected cocoa bioactive compounds: A comprehensive review, *Crit. Rev. Food Sci. Nutr.*, 2020, **60**, 1947–1985.
50 Z. T. Bitzer, S. L. Glisan, M. R. Dorenkott, K. M. Goodrich, L. Ye, S. F. O'Keefe, J. D. Lambert and A. P. Neilson, Cocoa procyanidins with different degrees of polymerization possess distinct activities in models of colonic inflammation, *J. Nutr. Biochem.*, 2015, **26**, 827–831.
51 A. G. Erlejman, G. Jaggers, C. G. Fraga and P. I. Oteiza, TNFα-induced NF-κB activation and cell oxidant production are modulated by hexameric procyanidins in Caco-2 cells, *Arch. Biochem. Biophys.*, 2008, **476**, 186–195.
52 Y. Gu, S. Yu, J. Y. Park, K. Harvatine and J. D. Lambert, Dietary cocoa reduces metabolic endotoxemia and adipose tissue inflammation in high-fat fed mice, *J. Nutr. Biochem.*, 2014, **25**, 439–445.

53 D. K. Weikart, V. V. Indukuri, K. C. Racine, K. M. Coleman, J. Kovac, D. W. Cockburn, H. Hopfer, A. P. Neilson and J. D. Lambert, Effect of processing on the anti-inflammatory efficacy of cocoa in a high fat diet-induced mouse model of obesity, *J. Nutr. Biochem.*, 2022, **109**, 109117.

54 C. S. Lee, P. L. Tan, J. Y. Eor, D. H. Choi, M. Park, S. K. Seo, S. Yoon, S. Yang and S. H. Kim, Prophylactic use of probiotic chocolate modulates intestinal physiological functions in constipated rats, *J. Sci. Food Agric.*, 2019, **99**, 3045–3056.

55 A. Koutsos, K. Tuohy and J. Lovegrove, Apples and Cardiovascular Health—Is the Gut Microbiota a Core Consideration?, *Nutrients*, 2015, **7**, 3959–3998.

56 H. Wu, T. Luo, Y. M. Li, Z. P. Gao, K. Q. Zhang, J. Y. Song, J. S. Xiao and Y. P. Cao, Granny Smith apple procyanidin extract upregulates tight junction protein expression and modulates oxidative stress and inflammation in lipopolysaccharide-induced Caco-2 cells, *Food Funct.*, 2018, **9**, 3321–3329.

57 T. Huang, Q. Che, X. Chen, D. Chen, B. Yu, J. He, H. Chen, H. Yan, P. Zheng, Y. Luo and Z. Huang, Apple Polyphenols Improve Intestinal Antioxidant Capacity and Barrier Function by Activating the Nrf2/Keap1 Signaling Pathway in a Pig Model, *J. Agric. Food Chem.*, 2022, **70**, 7576–7585.

58 M. J. McCann, C. I. R. Gill, G. O′ Brien, J. R. Rao, W. C. McRoberts, P. Hughes, R. McEntee and I. R. Rowland, Anti-cancer properties of phenolics from apple waste on colon carcinogenesis in vitro, *Food Chem. Toxicol.*, 2007, **45**, 1224–1230.

59 L. Wang, R. Li, Q. Zhang, J. Liu, T. Tao, T. Zhang, C. Wu, Q. Ren, X. Pu and W. Peng, Pyracantha fortuneana (Maxim.) Li: A comprehensive review of its phytochemistry, pharmacological properties, and product development, *Front. Sustain. Food Syst.*, 2022, **6**, 940900.

60 H. Xu, C. Zhao, Y. Li, R. Liu, M. Ao, F. Li, Y. Yao, Z. Tao and L. Yu, The ameliorative effect of the *Pyracantha fortuneana* (Maxim.) H. L. Li extract on intestinal barrier dysfunction through modulating glycolipid digestion and gut microbiota in high fat diet-fed rats, *Food Funct.*, 2019, **10**, 6517–6532.

61 K. J. Kim, Y. Kim, S. G. Jin and J. Y. Kim, Acai berry extract as a regulator of intestinal inflammation pathways in a Caco–2 and RAW 264.7 co–culture model, *J. Food Biochem.*, 2021, e13848.

62 J. C. Valdez, J. Cho and B. W. Bolling, Aronia berry inhibits disruption of Caco-2 intestinal barrier function, *Arch. Biochem. Biophys.*, 2020, **688**, 108409.

63 F. F. Anhê, T. V. Varin, M. Le Barz, G. Pilon, S. Dudonné, J. Trottier, P. St-Pierre, C. S. Harris, M. Lucas, M. Lemire, É. Dewailly, O. Barbier, Y. Desjardins, D. Roy and A. Marette, Arctic berry extracts target the gut–liver axis to alleviate metabolic endotoxaemia, insulin resistance and hepatic steatosis in diet-induced obese mice, *Diabetologia*, 2018, **61**, 919–931.

64 S. Lee, K. I. Keirsey, R. Kirkland, Z. I. Grunewald, J. G. Fischer and C. B. De La Serre, Blueberry Supplementation Influences the Gut Microbiota, Inflammation, and Insulin Resistance in High-Fat-Diet–Fed Rats, *J. Nutr.*, 2018, **148**, 209–219.

65 M.-C. Rodríguez-Daza, L. Daoust, L. Boutkrabt, G. Pilon, T. Varin, S. Dudonné, É. Levy, A. Marette, D. Roy and Y. Desjardins, Wild blueberry proanthocyanidins shape distinct gut microbiota profile and influence glucose homeostasis and intestinal phenotypes in high-fat high-sucrose fed mice, *Sci. Rep.*, 2020, **10**, 2217.

66 G. Zhou, L. Chen, Q. Sun, Q.-G. Mo, W.-C. Sun and Y.-W. Wang, Maqui berry exhibited therapeutic effects against DSS-induced ulcerative colitis in C57BL/6 mice, *Food Funct.*, 2019, **10**, 6655–6665.

67 T. Ortiz, F. Argüelles-Arias, M. Illanes, J.-M. García-Montes, E. Talero, L. Macías-García, A. Alcudia, V. Vázquez-Román, V. Motilva and M. De-Miguel, Polyphenolic Maqui Extract as a Potential Nutraceutical to Treat TNBS-Induced Crohn's Disease by the Regulation of Antioxidant and Anti-Inflammatory Pathways, *Nutrients*, 2020, **12**, 1752.

68 N. Narula, A. Dhillon, D. Zhang, M. E. Sherlock, M. Tondeur and M. Zachos, Enteral nutritional therapy for induction of remission in Crohn's disease, *Cochrane Database Syst. Rev.*, 2018, **4**, CD000542.

69 J. F. Pierre, A. F. Heneghan, R. P. Feliciano, D. Shanmuganayagam, D. A. Roenneburg, C. G. Krueger, J. D. Reed and K. A. Kudsk, Cranberry Proanthocyanidins Improve the Gut Mucous Layer Morphology and Function in Mice Receiving Elemental Enteral Nutrition, *J. Parenter. Enter. Nutr.*, 2013, **37**, 401–409.

70 F. F. Anhê, D. Roy, G. Pilon, S. Dudonné, S. Matamoros, T. V. Varin, C. Garofalo, Q. Moine, Y. Desjardins, E. Levy and A. Marette, A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice, *Gut*, 2015, **64**, 872–883.

71 D. Jin, T. Liu, W. Dong, Y. Zhang, S. Wang, R. Xie, B. Wang and H. Cao, Dietary feeding of freeze-dried whole cranberry inhibits intestinal tumor development in *Apc* min/+ mice, *Oncotarget*, 2017, **8**, 97787–97800.

72 L. Heyman-Lindén, D. Kotowska, E. Sand, M. Bjursell, M. Plaza, C. Turner, C. Holm, F. Fåk and K. Berger, Lingonberries alter the gut microbiota and prevent low-grade inflammation in high-fat diet fed mice, *Food Nutr. Res.*, 2016, **60**, 29993.

73 H. Zhang, R. Qi, Y. Zeng, R. Tsao and Y. Mine, Chinese Sweet Leaf Tea (*Rubus suavissimus*) Mitigates LPS-Induced Low-Grade Chronic Inflammation and Reduces the Risk of Metabolic Disorders in a C57BL/6J Mouse Model, *J. Agric. Food Chem.*, 2020, **68**, 138–146.

74 D. Del Rio, A. J. Stewart, W. Mullen, J. Burns, M. E. J. Lean, F. Brighenti and A. Crozier, HPLC-MS ^{n} Analysis of Phenolic Compounds and Purine Alkaloids in

Green and Black Tea, *J. Agric. Food Chem.*, 2004, **52**, 2807–2815.

75 A. Crozier, M. Clifford and D. Rio, *Flavonoids and Related Compounds*, CRC Press, 20120210, 2012.

76 D. L. McKay and J. B. Blumberg, The Role of Tea in Human Health: An Update, *J. Am. Coll. Nutr.*, 2002, **21**, 1–13.

77 C. B. Van Buiten, N. H. Yennawar, C. N. Pacheco, E. Hatzakis and R. J. Elias, Physicochemical interactions with (−)-epigallocatechin-3-gallate drive structural modification of celiac-associated peptide α_2-gliadin (57–89) at physiological conditions, *Food Funct.*, 2019, **10**, 2997–3007.

78 R. Dias, P. Bergamo, F. Maurano, V. Rotondi Aufiero, D. Luongo, G. Mazzarella, C. Bessa-Pereira, M. Pérez-Gregorio, M. Rossi and V. Freitas, First morphological-level insights into the efficiency of green tea catechins and grape seed procyanidins on a transgenic mouse model of celiac disease enteropathy, *Food Funct.*, 2021, **12**, 5903–5912.

79 N. Abu-Janb and M. Jaana, Facilitators and barriers to adherence to gluten–free diet among adults with celiac disease: a systematic review, *J. Hum. Nutr. Diet.*, 2020, **33**, 786–810.

80 M. D. L. Moreno, Á. Cebolla, A. Muñoz-Suano, C. Carrillo-Carrion, I. Comino, Á. Pizarro, F. León, A. Rodríguez-Herrera and C. Sousa, Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing, *Gut*, 2017, **66**, 250–257.

81 P. Dey, G. Y. Sasaki, P. Wei, J. Li, L. Wang, J. Zhu, D. McTigue, Z. Yu and R. S. Bruno, Green tea extract prevents obesity in male mice by alleviating gut dysbiosis in association with improved intestinal barrier function that limits endotoxin translocation and adipose inflammation, *J. Nutr. Biochem.*, 2019, **67**, 78–89.

82 J. Li, T. N. Sapper, E. Mah, M. V. Moller, J. B. Kim, C. Chitchumroonchokchai, J. D. McDonald and R. S. Bruno, Green tea extract treatment reduces NFκB activation in mice with diet-induced nonalcoholic steatohepatitis by lowering TNFR1 and TLR4 expression and ligand availability, *J. Nutr. Biochem.*, 2017, **41**, 34–41.

83 J. Li, G. Y. Sasaki, P. Dey, C. Chitchumroonchokchai, A. N. Labyk, J. D. McDonald, J. B. Kim and R. S. Bruno, Green tea extract protects against hepatic NFκB activation along the gut-liver axis in diet-induced obese mice with nonalcoholic steatohepatitis by reducing endotoxin and TLR4/MyD88 signaling, *J. Nutr. Biochem.*, 2018, **53**, 58–65.

84 P. Dey, Targeting gut barrier dysfunction with phytotherapies: Effective strategy against chronic diseases, *Pharmacol. Res.*, 2020, **161**, 105135.

85 F. Zhou, Y.-L. Li, X. Zhang, K.-B. Wang, J.-A. Huang, Z.-H. Liu and M.-Z. Zhu, Polyphenols from Fu Brick Tea Reduce Obesity via Modulation of Gut Microbiota and Gut Microbiota-Related Intestinal Oxidative Stress and Barrier Function, *J. Agric. Food Chem.*, 2021, **69**, 14530–14543.

86 X. Gao, Q. Xie, P. Kong, L. Liu, S. Sun, B. Xiong, B. Huang, L. Yan, J. Sheng and H. Xiang, Polyphenol- and Caffeine-Rich Postfermented Pu-erh Tea Improves Diet-Induced Metabolic Syndrome by Remodeling Intestinal Homeostasis in Mice, *Infect. Immun.*, 2018, **86**, e00601–e00617.

87 X. Lu, J. Liu, N. Zhang, Y. Fu, Z. Zhang, Y. Li, W. Wang, Y. Li, P. Shen and Y. Cao, Ripened Pu-erh Tea Extract Protects Mice from Obesity by Modulating Gut Microbiota Composition, *J. Agric. Food Chem.*, 2019, **67**, 6978–6994.

88 J. Ye, Y. Zhao, X. Chen, H. Zhou, Y. Yang, X. Zhang, Y. Huang, N. Zhang, E. M. K. Lui and M. Xiao, Pu-erh tea ameliorates obesity and modulates gut microbiota in high fat diet fed mice, *Food Res. Int.*, 2021, **144**, 110360.

89 B. Liu, J. Zhang, P. Sun, R. Yi, X. Han and X. Zhao, Raw Bowl Tea (Tuocha) Polyphenol Prevention of Nonalcoholic Fatty Liver Disease by Regulating Intestinal Function in Mice, *Biomolecules*, 2019, **9**, 435.

90 S. Hu, S. Li, Y. Liu, K. Sun, L. Luo and L. Zeng, Aged Ripe Pu-erh Tea Reduced Oxidative Stress-Mediated Inflammation in Dextran Sulfate Sodium-Induced Colitis Mice by Regulating Intestinal Microbes, *J. Agric. Food Chem.*, 2021, **69**, 10592–10605.

91 Y. Du, C. Yang, D. Ren, H. Shao, Y. Zhao and X. Yang, Fu brick tea alleviates alcoholic liver injury by modulating the gut microbiota–liver axis and inhibiting the hepatic TLR4/NF-κB signaling pathway, *Food Funct.*, 2022, **13**, 9391–9406.

92 D. Chen, Y. Ding, G. Chen, Y. Sun, X. Zeng and H. Ye, Components identification and nutritional value exploration of tea (Camellia sinensis L.) flower extract: Evidence for functional food, *Food Res. Int.*, 2020, **132**, 109100.

93 Y. Ito, T. Ichikawa, T. Iwai, Y. Saegusa, T. Ikezawa, Y. Goso and K. Ishihara, Effects of Tea Catechins on the Gastrointestinal Mucosa in Rats, *J. Agric. Food Chem.*, 2008, **56**, 12122–12126.

94 A. Shree, J. Islam, A. Vafa, S. Mohammad Afzal and S. Sultana, Gallic acid prevents 1, 2−Dimethylhydrazine induced colon inflammation, toxicity, mucin depletion, and goblet cell disintegration, *Environ. Toxicol.*, 2020, **35**, 652–664.

95 P. Georgiades, P. D. A. Pudney, S. Rogers, D. J. Thornton and T. A. Waigh, Tea Derived Galloylated Polyphenols Cross-Link Purified Gastrointestinal Mucins, *PLoS One*, 2014, **9**, e105302.

96 Y. Zhao, L. Chen, G. Yakubov, T. Aminiafshar, L. Han and G. Lian, Experimental and Theoretical Studies on the Binding of Epigallocatechin Gallate to Purified Porcine Gastric Mucin, *J. Phys. Chem. B*, 2012, **116**, 13010–13016.

97 N. Unusan, Proanthocyanidins in grape seeds: An updated review of their health benefits and potential uses in the food industry, *J. Funct. Foods*, 2020, **67**, 103861.

98 R. Nallathambi, A. Poulev, J. B. Zuk and I. Raskin, Proanthocyanidin-Rich Grape Seed Extract Reduces Inflammation and Oxidative Stress and Restores Tight Junction Barrier Function in Caco-2 Colon Cells, *Nutrients*, 2020, **12**, 1623.

99 C. Nunes, V. Freitas, L. Almeida and J. Laranjinha, Red wine extract preserves tight junctions in intestinal epithelial cells under inflammatory conditions: implications for intestinal inflammation, *Food Funct.*, 2019, **10**, 1364–1374.

100 I. Zorraquín-Peña, D. Taladrid, A. Tamargo, M. Silva, N. Molinero, D. G. De Llano, B. Bartolomé and M. V. Moreno-Arribas, Effects of Wine and Its Microbial-Derived Metabolites on Intestinal Permeability Using Simulated Gastrointestinal Digestion/Colonic Fermentation and Caco-2 Intestinal Cell Models, *Microorganisms*, 2021, **9**, 1378.

101 D. Taladrid, D. González de Llano, I. Zorraquín-Peña, A. Tamargo, M. Silva, N. Molinero, M. V. Moreno-Arribas and B. Bartolomé, Gastrointestinal Digestion of a Grape Pomace Extract: Impact on Intestinal Barrier Permeability and Interaction with Gut Microbiome, *Nutrients*, 2021, **13**, 2467.

102 M. Han, P. Song, C. Huang, A. Rezaei, S. Farrar, M. A. Brown and X. Ma, Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model, *Oncotarget*, 2016, **7**, 80313–80326.

103 Q. H. Li, H. S. Yan, H. Q. Li, J. J. Gao and R. R. Hao, Effects of dietary supplementation with grape seed procyanidins on nutrient utilisation and gut function in weaned piglets, *Animal*, 2020, **14**, 491–498.

104 K. M. Goodrich, G. Fundaro, L. E. Griffin, A. Grant, M. W. Hulver, M. A. Ponder and A. P. Neilson, Chronic administration of dietary grape seed extract increases colonic expression of gut tight junction protein occludin and reduces fecal calprotectin: a secondary analysis of healthy Wistar Furth rats, *Nutr. Res.*, 2012, **32**, 787–794.

105 P. Song, R. Zhang, X. Wang, P. He, L. Tan and X. Ma, Dietary Grape-Seed Procyanidins Decreased Postweaning Diarrhea by Modulating Intestinal Permeability and Suppressing Oxidative Stress in Rats, *J. Agric. Food Chem.*, 2011, **59**, 6227–6232.

106 H. Wang, Y. Xue, H. Zhang, Y. Huang, G. Yang, M. Du and M. Zhu, Dietary grape seed extract ameliorates symptoms of inflammatory bowel disease in IL 10–deficient mice, *Mol. Nutr. Food Res.*, 2013, **57**, 2253–2257.

107 D. E. Roopchand, R. N. Carmody, P. Kuhn, K. Moskal, P. Rojas-Silva, P. J. Turnbaugh and I. Raskin, Dietary Polyphenols Promote Growth of the Gut Bacterium *Akkermansia muciniphila* and Attenuate High-Fat Diet–Induced Metabolic Syndrome, *Diabetes*, 2015, **64**, 2847–2858.

108 G. Yang, Y. Xue, H. Zhang, M. Du and M.-J. Zhu, Favourable effects of grape seed extract on intestinal epithelial differentiation and barrier function in IL10-deficient mice, *Br. J. Nutr.*, 2015, **114**, 15–23.

109 B. Collins, J. Hoffman, K. Martinez, M. Grace, M. A. Lila, C. Cockrell, A. Nadimpalli, E. Chang, C.-C. Chuang, W. Zhong, J. Mackert, W. Shen, P. Cooney, R. Hopkins and M. McIntosh, A polyphenol-rich fraction obtained from table grapes decreases adiposity, insulin resistance and markers of inflammation and impacts gut microbiota in high-fat-fed mice, *J. Nutr. Biochem.*, 2016, **31**, 150–165.

110 K. Gil-Cardoso, I. Ginés, M. Pinent, A. Ardévol, L. Arola, M. Blay and X. Terra, Chronic supplementation with dietary proanthocyanidins protects from diet–induced intestinal alterations in obese rats, *Mol. Nutr. Food Res.*, 2017, **61**, 1601039.

111 K. Gil-Cardoso, I. Ginés, M. Pinent, A. Ardévol, M. Blay and X. Terra, The co-administration of proanthocyanidins and an obesogenic diet prevents the increase in intestinal permeability and metabolic endotoxemia derived to the diet, *J. Nutr. Biochem.*, 2018, **62**, 35–42.

112 C. González-Quilen, K. Gil-Cardoso, I. Ginés, R. Beltrán-Debón, M. Pinent, A. Ardévol, X. Terra and M. T. Blay, Grape-Seed Proanthocyanidins are Able to Reverse Intestinal Dysfunction and Metabolic Endotoxemia Induced by a Cafeteria Diet in Wistar Rats, *Nutrients*, 2019, **11**, 979.

113 H. Arie, T. Nozu, S. Miyagishi, M. Ida, T. Izumo and H. Shibata, Grape Seed Extract Eliminates Visceral Allodynia and Colonic Hyperpermeability Induced by Repeated Water Avoidance Stress in Rats, *Nutrients*, 2019, **11**, 2646.

114 Z. Gao, H. Wu, K. Zhang, I. Hossen, J. Wang, C. Wang, D. Xu, J. Xiao and Y. Cao, Protective effects of grape seed procyanidin extract on intestinal barrier dysfunction induced by a long-term high-fat diet, *J. Funct. Foods*, 2020, **64**, 103663.

115 J. Baldwin, B. Collins, P. G. Wolf, K. Martinez, W. Shen, C.-C. Chuang, W. Zhong, P. Cooney, C. Cockrell, E. Chang, H. R. Gaskins and M. K. McIntosh, Table grape consumption reduces adiposity and markers of hepatic lipogenesis and alters gut microbiota in butter fat-fed mice, *J. Nutr. Biochem.*, 2016, **27**, 123–135.

116 L. H. Maurer, C. B. B. Cazarin, A. Quatrin, N. M. Minuzzi, E. L. Costa, J. Morari, L. A. Velloso, R. F. Leal, E. Rodrigues, V. C. Bochi, M. R. M. Júnior and T. Emanuelli, Grape peel powder promotes intestinal barrier homeostasis in acute TNBS-colitis: A major role for dietary fiber and fiber-bound polyphenols, *Food Res. Int.*, 2019, **123**, 425–439.

117 K. Sheng, G. Zhang, M. Sun, S. He, X. Kong, J. Wang, F. Zhu, X. Zha and Y. Wang, Grape seed proanthocyanidin extract ameliorates dextran sulfate sodium-induced colitis through intestinal barrier improvement, oxidative stress reduction, and inflammatory cytokines and gut microbiota modulation, *Food Funct.*, 2020, **11**, 7817–7829.

118 G. C. Pistol, C. V. Bulgaru, D. E. Marin, A. G. Oancea and I. Taranu, Dietary Grape Seed Meal Bioactive Compounds Alleviate Epithelial Dysfunctions and Attenuates Inflammation in Colon of DSS-Treated Piglets, *Foods*, 2021, **10**, 530.

119 G. Gerardi, M. D. Rivero-Pérez, M. Cavia-Saiz, B. Melero, A. Salinero-Zorita, M. L. González-SanJosé and P. Muñiz, Wine Pomace Product Inhibit Listeria monocytogenes

Invasion of Intestinal Cell Lines Caco-2 and SW-480, *Foods*, 2021, **10**, 1485.

120 S. Bibi, Y. Kang, G. Yang and M.-J. Zhu, Grape seed extract improves small intestinal health through suppressing inflammation and regulating alkaline phosphatase in IL-10-deficient mice, *J. Funct. Foods*, 2016, **20**, 245–252.

121 H. Segú, F. Jalševac, M. Pinent, A. Ardévol, X. Terra and M. T. Blay, Intestinal Morphometric Changes Induced by a Western-Style Diet in Wistar Rats and GSPE Counter-Regulatory Effect, *Nutrients*, 2022, **14**, 2608.

122 M. Liu, B. Huang, L. Wang, Q. Lu and R. Liu, Peanut skin procyanidins ameliorate insulin resistance via modulation of gut microbiota and gut barrier in type 2 diabetic mice, *J. Sci. Food Agric.*, 2022, **102**, 5935–5947.

123 A. Toschi, A. Piva and E. Grilli, Phenol-Rich Botanicals Modulate Oxidative Stress and Epithelial Integrity in Intestinal Epithelial Cells, *Animals*, 2022, **12**, 2188.

124 A. Barcelo, Mucin secretion is modulated by luminal factors in the isolated vascularly perfused rat colon, *Gut*, 2000, **46**, 218–224.

125 D. Rogoll, H. Bergmann, D. Hellenschmidt, J. Heinze, W. Scheppach, R. Melcher and E. Richling, Influence of apple polyphenols on the intestinal barrier in a colonic cell model, *J. Appl. Bot. Food Qual.*, 2010, **83**, 110–117.

126 T. Yamamoto, H. Takahashi, K. Suzuki, A. Hirano, M. Kamei, T. Goto, N. Takahashi and T. Kawada, Theobromine enhances absorption of cacao polyphenol in rats, *Biosci. Biotechnol. Biochem.*, 2014, **78**, 2059–2063.

127 H.-Y. Park, Y. Kunitake, N. Hirasaki, M. Tanaka and T. Matsui, Theaflavins enhance intestinal barrier of Caco-2 Cell monolayers through the expression of AMP-activated protein kinase-mediated Occludin, Claudin-1, and ZO-1, *Biosci. Biotechnol. Biochem.*, 2015, **79**, 130–137.

128 E. Cremonini, Z. Wang, A. Bettaieb, A. M. Adamo, E. Daveri, D. A. Mills, K. M. Kalanetra, F. G. Haj, S. Karakas and P. I. Oteiza, (-)-Epicatechin protects the intestinal barrier from high fat diet-induced permeabilization: Implications for steatosis and insulin resistance, *Redox Biol.*, 2018, **14**, 588–599.

129 T. Volstatova, A. Marchica, Z. Hroncova, R. Bernardi, I. Doskocil and J. Havlik, Effects of chlorogenic acid, epicatechin gallate, and quercetin on mucin expression and secretion in the Caco–2/HT29–MTX cell model, *Food Sci. Nutr.*, 2019, **7**, 492–498.

130 J. L. Watson, S. Ansari, H. Cameron, A. Wang, M. Akhtar and D. M. McKay, Green tea polyphenol (–)-epigallocatechin gallate blocks epithelial barrier dysfunction provoked by IFN-γ but not by IL-4, *Am. J. Physiol.: Gastrointest. Liver Physiol.*, 2004, **287**, G954–G961.

131 T. Sergent, N. Piront, J. Meurice, O. Toussaint and Y.-J. Schneider, Anti-inflammatory effects of dietary phenolic compounds in an in vitro model of inflamed human intestinal epithelium, *Chem. – Biol. Interact.*, 2010, **188**, 659–667.

132 R. Wei, X. Liu, Y. Wang, J. Dong, F. Wu, G. G. Mackenzie and Z. Su, (–)-Epigallocatechin-3-gallate mitigates cyclophosphamide-induced intestinal injury by modulating the tight junctions, inflammation and dysbiosis in mice, *Food Funct.*, 2021, **12**, 11671–11685.

133 T. C. Contreras, E. Ricciardi, E. Cremonini and P. I. Oteiza, (–)-Epicatechin in the prevention of tumor necrosis alpha-induced loss of Caco-2 cell barrier integrity, *Arch. Biochem. Biophys.*, 2015, **573**, 84–91.

134 Z. Wang, M. C. Litterio, M. Müller, D. Vauzour and P. I. Oteiza, (-)-Epicatechin and NADPH oxidase inhibitors prevent bile acid-induced Caco-2 monolayer permeabilization through ERK1/2 modulation, *Redox Biol.*, 2020, **28**, 101360.

135 Z. Wu, S. Huang, T. Li, N. Li, D. Han, B. Zhang, Z. Z. Xu, S. Zhang, J. Pang, S. Wang, G. Zhang, J. Zhao and J. Wang, Gut microbiota from green tea polyphenol-dosed mice improves intestinal epithelial homeostasis and ameliorates experimental colitis, *Microbiome*, 2021, **9**, 184.

136 S. Deprez, I. Mila, J.-F. Huneau, D. Tome and A. Scalbert, Transport of Proanthocyanidin Dimer, Trimer, and Polymer Across Monolayers of Human Intestinal Epithelial Caco-2 Cells, *Antioxid. Redox Signal.*, 2001, **3**, 957–967.

137 C. González-Quilen, E. Rodríguez-Gallego, R. Beltrán-Debón, M. Pinent, A. Ardévol, M. T. Blay and X. Terra, Health-Promoting Properties of Proanthocyanidins for Intestinal Dysfunction, *Nutrients*, 2020, **12**, 130.

138 J. Qiu, Y. Kitamura, Y. Miyata, S. Tamaru, K. Tanaka, T. Tanaka and T. Matsui, Transepithelial Transport of Theasinensins through Caco-2 Cell Monolayers and Their Absorption in Sprague–Dawley Rats after Oral Administration, *J. Agric. Food Chem.*, 2012, **60**, 8036–8043.

139 E. Brandão, M. Santos Silva, I. García-Estévez, N. Mateus, V. De Freitas and S. Soares, Molecular study of mucin-procyanidin interaction by fluorescence quenching and Saturation Transfer Difference (STD)-NMR, *Food Chem.*, 2017, **228**, 427–434.

140 E. Márquez Campos, P. Stehle and M.-C. Simon, Microbial Metabolites of Flavan-3-Ols and Their Biological Activity, *Nutrients*, 2019, **11**, 2260.

141 G. Di Pede, P. Mena, L. Bresciani, T. M. Almutairi, D. Del Rio, M. N. Clifford and A. Crozier, Human colonic catabolism of dietary flavan-3-ol bioactives, *Mol. Aspects Med.*, 2023, **89**, 101107.

142 X. Xu, A. Luo, X. Lu, M. Liu, H. Wang, H. Song, C. Wei, Y. Wang and X. Duan, p-Hydroxybenzoic acid alleviates inflammatory responses and intestinal mucosal damage in DSS-induced colitis by activating ERβ signaling, *J. Funct. Foods*, 2021, **87**, 104835.

143 J. L. Chen, P. Zheng, C. Zhang, B. Yu, J. He, J. Yu, J. Q. Luo, X. B. Mao, Z. Q. Huang and D. W. Chen, Benzoic acid beneficially affects growth performance of weaned pigs which was associated with changes in gut bacterial populations, morphology indices and growth factor gene expression, *J. Anim. Physiol. Anim. Nutr.*, 2017, **101**, 1137–1146.

144 M. Tretola, G. Bee and P. Silacci, Gallic acid affects intestinal-epithelial-cell integrity and selected amino-acid

uptake in porcine *in vitro* and *ex vivo* permeability models, *Br. J. Nutr.*, 2021, **126**, 492–500.

145 Y. Chen, Y. Niu, W. Hao, W. Zhang, J. Lu, J. Zhou, L. Du and W. Xie, Pineapple Leaf Phenols Attenuate DSS-Induced Colitis in Mice and Inhibit Inflammatory Damage by Targeting the NF-κB Pathway, *Molecules*, 2021, **26**, 7656.

146 H. Lan, L.-Y. Zhang, W. He, W.-Y. Li, Z. Zeng, B. Qian, C. Wang and J.-L. Song, Sinapic Acid Alleviated Inflammation-Induced Intestinal Epithelial Barrier Dysfunction in Lipopolysaccharide- (LPS-) Treated Caco-2 Cells, *Mediators Inflammation*, 2021, **2021**, 1–10.

147 S. He, Y. Guo, J. Zhao, X. Xu, J. Song, N. Wang and Q. Liu, Ferulic acid protects against heat stress-induced intestinal epithelial barrier dysfunction in IEC-6 cells via the PI3 K/Akt-mediated Nrf2/HO-1 signaling pathway, *Int. J. Hyperthermia*, 2018, **35**, 112–121.

148 F. Wan, R. Zhong, M. Wang, Y. Zhou, Y. Chen, B. Yi, F. Hou, L. Liu, Y. Zhao, L. Chen and H. Zhang, Caffeic Acid Supplement Alleviates Colonic Inflammation and Oxidative Stress Potentially Through Improved Gut Microbiota Community in Mice, *Front. Microbiol.*, 2021, **12**, 784211.

149 L. Song, T. Wu, L. Zhang, J. Wan and Z. Ruan, Chlorogenic acid improves the intestinal barrier by relieving endoplasmic reticulum stress and inhibiting ROCK/MLCK signaling pathways, *Food Funct.*, 2022, **13**, 4562–4575.

150 H. Diao, Z. Gao, B. Yu, P. Zheng, J. He, J. Yu, Z. Huang, D. Chen and X. Mao, Effects of benzoic acid (VevoVitall®) on the performance and jejunal digestive physiology in young pigs, *J. Anim. Sci. Biotechnol.*, 2016, **7**, 32.

151 C. Del Bo', S. Bernardi, A. Cherubini, M. Porrini, G. Gargari, N. Hidalgo-Liberona, R. González-Domínguez, R. Zamora-Ros, G. Peron, M. Marino, L. Gigliotti, M. S. Winterbone, B. Kirkup, P. A. Kroon, C. Andres-Lacueva, S. Guglielmetti and P. Riso, A polyphenol-rich dietary pattern improves intestinal permeability, evaluated as serum zonulin levels, in older subjects: The MaPLE randomised controlled trial, *Clin. Nutr.*, 2021, **40**, 3006–3018.

152 G. Aragonès, F. Danesi, D. Del Rio and P. Mena, The importance of studying cell metabolism when testing the bioactivity of phenolic compounds, *Trends Food Sci. Technol.*, 2017, **69**, 230–242.

153 B. Halliwell, Cell culture, oxidative stress, and antioxidants: Avoiding pitfalls, *Biomed. J.*, 2014, **37**, 99–105.

154 L. Mahmutović, A. Sezer, E. Bilajac, A. Hromić-Jahjefendić, V. N. Uversky and U. Glamočlija, Polyphenol stability and bioavailability in cell culture medium: Challenges, limitations and future directions, *Int. J. Biol. Macromol.*, 2024, **279**, 135232.

155 D. Qin, Y. Ma, Y. Wang, X. Hou and L. Yu, Contribution of Lactobacilli on Intestinal Mucosal Barrier and Diseases: Perspectives and Challenges of Lactobacillus casei, *Life*, 2022, **12**, 1910.

156 D. Álvarez-Cilleros, S. Ramos, M. E. López-Oliva, F. Escrivá, C. Álvarez, E. Fernández-Millán and M. Á. Martín, Cocoa diet modulates gut microbiota composition and improves intestinal health in Zucker diabetic rats, *Food Res. Int.*, 2020, **132**, 109058.

157 J. Y. Eor, P. L. Tan, S. M. Lim, D. H. Choi, S. M. Yoon, S. Y. Yang and S. H. Kim, Laxative effect of probiotic chocolate on loperamide-induced constipation in rats, *Food Res. Int.*, 2019, **116**, 1173–1182.

158 A. P. Femia, C. Luceri, F. Bianchini, M. Salvadori, F. Salvianti, P. Pinzani, P. Dolara, L. Calorini and G. Caderni, Marie Ménard apples with high polyphenol content and a low-fat diet reduce 1,2-dimethylhydrazine-induced colon carcinogenesis in rats: effects on inflammation and apoptosis, *Mol. Nutr. Food Res.*, 2012, **56**, 1353–1357.

159 S. Bibi, Y. Kang, M. Du and M.-J. Zhu, Dietary red raspberries attenuate dextran sulfate sodium-induced acute colitis, *J. Nutr. Biochem.*, 2018, **51**, 40–46.

160 P. Dey, B. D. Olmstead, G. Y. Sasaki, Y. Vodovotz, Z. Yu and R. S. Bruno, Epigallocatechin gallate but not catechin prevents nonalcoholic steatohepatitis in mice similar to green tea extract while differentially affecting the gut microbiota, *J. Nutr. Biochem.*, 2020, **84**, 108455.

161 À. Casanova-Martí, N. González-Abuín, J. Serrano, M. T. Blay, X. Terra, G. Frost, M. Pinent and A. Ardévol, Long Term Exposure to a Grape Seed Proanthocyanidin Extract Enhances L–Cell Differentiation in Intestinal Organoids, *Mol. Nutr. Food Res.*, 2020, **64**, 2000303.

162 F. Lu, Y. Li, X. Wang, X. Hu, X. Liao and Y. Zhang, Early-life polyphenol intake promotes Akkermansia growth and increase of host goblet cells in association with the potential synergistic effect of Lactobacillus, *Food Res. Int.*, 2021, **149**, 110648.

163 C. González-Quilen, C. Grau-Bové, R. Jorba-Martín, A. Caro-Tarragó, M. Pinent, A. Ardévol, R. Beltrán-Debón, X. Terra and M. T. Blay, Protective properties of grape-seed proanthocyanidins in human ex vivo acute colonic dysfunction induced by dextran sodium sulfate, *Eur. J. Nutr.*, 2021, **60**, 79–88.

164 C. Carrasco-Pozo, P. Morales and M. Gotteland, Polyphenols Protect the Epithelial Barrier Function of Caco-2 Cells Exposed to Indomethacin through the Modulation of Occludin and Zonula Occludens-1 Expression, *J. Agric. Food Chem.*, 2013, **61**, 5291–5297.

165 B. Diwan and R. Sharma, Green tea EGCG effectively alleviates experimental colitis in middle-aged male mice by attenuating multiple aspects of oxi-inflammatory stress and cell cycle deregulation, *Biogerontology*, 2022, **23**, 789–807.

166 Q. Wu, Y. Chen, Y. Ouyang, Y. He, J. Xiao, L. Zhang and N. Feng, Effect of catechin on dietary AGEs absorption and cytotoxicity in Caco-2 cells, *Food Chem.*, 2021, **355**, 129574.

167 T. Zhang, S. Bai, X. Ding, Q. Zeng, K. Zhang, L. Lv, J. Li, H. Peng, Y. Xuan and J. Wang, Dietary Theabrownin

Supplementation Improves Production Performance and Egg Quality by Promoting Intestinal Health and Antioxidant Capacity in Laying Hens, *Animals*, 2022, **12**, 2856.

168 F. Yan, W. Chen, L. Zhao, Q. Lu, C. Wang and R. Liu, Procyanidin A_1 and its digestive products prevent acrylamide-induced intestinal barrier dysfunction *via* the MAPK-mediated MLCK pathway, *Food Funct.*, 2021, **12**, 11956–11965.

169 M. Amasheh, S. Andres, S. Amasheh, M. Fromm and J. Schulzke, Barrier Effects of Nutritional Factors, *Ann. N. Y. Acad. Sci.*, 2009, **1165**, 267–273.

170 R. Hu, S. Wu, B. Li, J. Tan, J. Yan, Y. Wang, Z. Tang, M. Liu, C. Fu, H. Zhang and J. He, Dietary ferulic acid and vanillic acid on inflammation, gut barrier function and growth performance in lipopolysaccharide-challenged piglets, *Anim. Nutr.*, 2022, **8**, 144–152.