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Meta-analyses

Exploring the effects of phenolic compounds to reduce intestinal damage and improve the intestinal barrier integrity: A systematic review of *in vivo* animal studies

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SUMMARY

Background & aims: The integrity of the intestinal barrier in the diseased is key to prevent further complications and disease such as sepsis and death, whereas, the role of food bioactive molecules (i. e. phenolic compounds (PCs) on the intestinal barrier, is still unknown. The current aim was to explore the benefits of the oral PC administration on the intestinal barrier integrity in animals.
Methods: The effects of PCs on the intestinal barrier integrity in *in vivo* animal models of intestinal inflammation were assessed up-to August 2020 from the PubMed, SCOPUS, and Cochrane Library databases under the PRISMA methodology. The risk of bias was assessed from ARRAY and SCYRCLE tools.
Results: From 1241 articles, 14 studies were included. In animals, oral resveratrol (n = 6) improves the intestinal barrier integrity and reduces intestinal damage. Additionally, grape seed extract (n = 2), curcumin (n = 1), genistein (n = 1), chlorogenic acid (n = 1), grape pomace (n = 1), olive leaf (n = 1) or cranberry extract (n = 1) improve the intestinal barrier integrity downregulating various inflammatory molecules (TNF-α, and other interleukins), and increasing the antioxidant enzymes in animals. Furthermore, resveratrol, quercetin, epigallocatechin, and other PCs improve the epithelial barrier integrity and pro-inflammatory molecule expression in the intestinal epithelia.
Conclusions: The oral PC administration in animals improves the intestinal barrier integrity and function from three main mechanisms: 1) The reduction of pro-inflammatory molecules, 2) the improvement in tight-junction protein expression, and 3) the improvement of the antioxidant intracellular activity suggesting the potential use of PCs in the management of intestinal injury in humans, particularly for resveratrol, the most studied PC.

1. Introduction

The gastrointestinal tract is a key player in the pathogenesis of the multiorgan dysfunction found in critically ill patients which is secondary to the breakdown of the intestinal barrier, consequently impairing its protective role. The loss of the intestinal barrier integrity is common amongst critically ill patients causing higher mortality rates when compared against individuals with a preserved intestinal barrier integrity [1].

On the other hand, during a life-threatening intestinal disease such as necrotizing enterocolitis (NEC) in preterm infants [2], the gastrointestinal tract epithelia is characterized for because of increased permeability and inflammation secondary to an augmented rate of apoptosis [3,4]. NEC is characterized by the patchy necrosis of the small intestine with variable effects on the colon that might progress to systemic sepsis, multisystem organ failure, and finally death [2]. The increase in the intestinal permeability, evidenced as an increased plasmatic lipopolysaccharide

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(LPS) levels, is caused by the overexpression of different proteins such as the toll-like receptor 4 (TLR4) [2].

Moreover, in humans, the intestinal gut integrity is disrupted during critical illness [5,6]. The disruption is caused by an increased intestinal permeability during critical illness from the down-regulation of the B-cell lymphoma 2 (Bcl-2) protein expression [7,8]. As has been demonstrated, the downregulation of Bcl-2 is significantly associated with the necrosis and loss of function in the intestines of septic transgenic mice, while the Bcl-2 overexpression was associated with the inhibition of intestinal epithelial apoptosis and the improvement of survival in septic mice [7,8]. Finally, in animal models of critical illness the expression tight junction (TJ) proteins such as claudin-2, claudin-5, and zonula occludens (ZO)-1 all decrease, further evidencing the loss of the intestinal barrier integrity [9–11], thus demonstrating the importance of the TJ proteins in the development of sepsis [12,13].

Consequently, new therapeutic approaches for improving the intestinal integrity and barrier function are currently needed [14].

In that sense, the phenolic compounds (PCs) are a large group of natural bioactive molecules or phytochemicals present in plants, PCs including different sub-classes such as flavonoids, stilbenes, phenolic acids, and lignans [15], with promising potential for the treatment and prevention of diverse chronic diseases with an inflammatory component such as type 2 diabetes mellitus (T2DM), cancer and cardiovascular disease (CVD) [16–18].

PCs are considered to be safe for human consumption due to their low rates of adverse effects, even when consumed at high doses [15,19–21], and their tissue bioavailability has been confirmed after oral intake in diverse animals, suggesting that their presence in diverse target tissues leads to their associated health benefits [18].

From previous reviews, it has been demonstrated that in *in vivo* animal studies, PCs and PC extracts can lower the severity of colitis by modifying various intracellular signaling cascades in the intestinal epithelium and showing anti-inflammatory effects [22]. Additionally, a clinical trial using pomegranate extract as a PC source demonstrated to significantly reduce the plasmatic concentrations of the LPS-binding protein in humans, decreasing endotoxemia in overweight-obese individuals who were suffering from intestinal inflammation [23]. Furthermore, the supplementation with curcumin, a PC, has demonstrated to improve the intestinal disease activity in patients suffering from ulcerative colitis partially from the reduction of oxidative stress in a randomized, double-blinded, placebo-controlled pilot study [24]. In other studies where healthy humans consumed wine with 1758 mg/L of total polyphenols improved the expression of diverse pro-inflammatory cytokines improving the intestinal barrier integrity was demonstrated [25].

Due to the lack of a model able to precisely recreate the changes occurring in human intestines during critical illness [26], diverse animal models of induced intestinal damage and intestinal inflammation were used to assess the potential benefits of PCs on the intestinal barrier integrity during critical illness [3,27,28].

The present systematic review aims to explore the potential effects of the oral PC administration on the intestinal barrier integrity from *in vivo* animal models of induced intestinal damage.

2. Materials and methods

2.1. Literature search

This systematic review is structured following the general principles published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. The PRISMA flowchart (Fig. 1) and PRISMA checklist (Supplementary Table 1) for the present systematic review are presented.

2.1.1. Information sources and search strategy

The scientific web libraries Scopus (https://www.scopus.com), Cochrane Library (https://www.cochranelibrary.com/), and PubMed (https://pubmed.ncbi.nlm.nih.gov/Error! Hyperlink reference not valid.) were explored. For the present systematic review articles regarding the experimental use of PCs on human or *in vivo* animal research was searched through the following terms: "(phenolic compound OR polyphenol) AND (intestinal OR intestine OR bowel OR jejunum OR duodenum OR colon) AND (barrier OR disease OR inflammation OR inflammatory OR sepsis OR permeability) AND (human OR *in vivo*) NOT (review)".

2.1.2. Article's selection criteria

Our group identified the articles from the database search, duplicates were removed, and 3 additional articles were found by hand-search. Published articles were screened based on their titles, abstracts, and full texts according to the following inclusion criteria:

1) *in vivo* animal studies regarding the effects of at least one PC on the intestinal barrier integrity.
2) Studies where the effects of PCs were compared against both positive and negative controls in *in vivo* animal models.
3) Studies published in the last 20 years, from January 1st 2000 up to August 1st 2020.

The exclusion criteria were the following: 1) Non-English articles; 2) Low-quality after the risk of bias assessment for *in vivo* animal studies; 2) incomplete data publication; 3) Review articles; 4) studies assessing the effects from the metabolization of phenolic compounds by the intestinal microbiome, and 5) not fulfilling the inclusion criteria. After full-text analysis, the following information was extracted from the included articles: title, author information, type of study performed, assessed outcome/s, intervention target (animal used), administered dose, length of study, administration route, doses administered, and main conclusions. Whenever possible, the dose administered to animals was converted into its human equivalent dose (HED) defined as the conversion of the animal dose into its HED and expressed as the 24 h dose for an average human being weighting 70.0 kg [30].

Under the PRISMA methodology, two independent authors (B.A.S.-R. and U.C.) analyzed the titles, abstracts, and full-text articles for inclusion while a third reviewer (R.S.) resolved all differences if present.

2.1.3. Quality assessment

The reporting quality of the included animal study articles was assessed and interpreted following the Animal Research Reporting of In Vivo Experiments (ARRIVE) guidelines [31], while the risk of bias for the included animal studies was assessed using the SCYRCLE's tool for assessing the risk of bias in animal studies [32].

3. Results

3.1. Literature search, study selection, and characteristics

From our initial database screening, 1241 articles published from January 1st, 2000 up to August 1st, 2020 were retrieved from all databases. All titles and abstracts were assessed; as a result, 1183 articles were excluded after the initial screening, 7 articles were excluded as duplicates, 16 articles were excluded as *in vitro* studies, 5 publications were excluded for being reviews, 13 publications

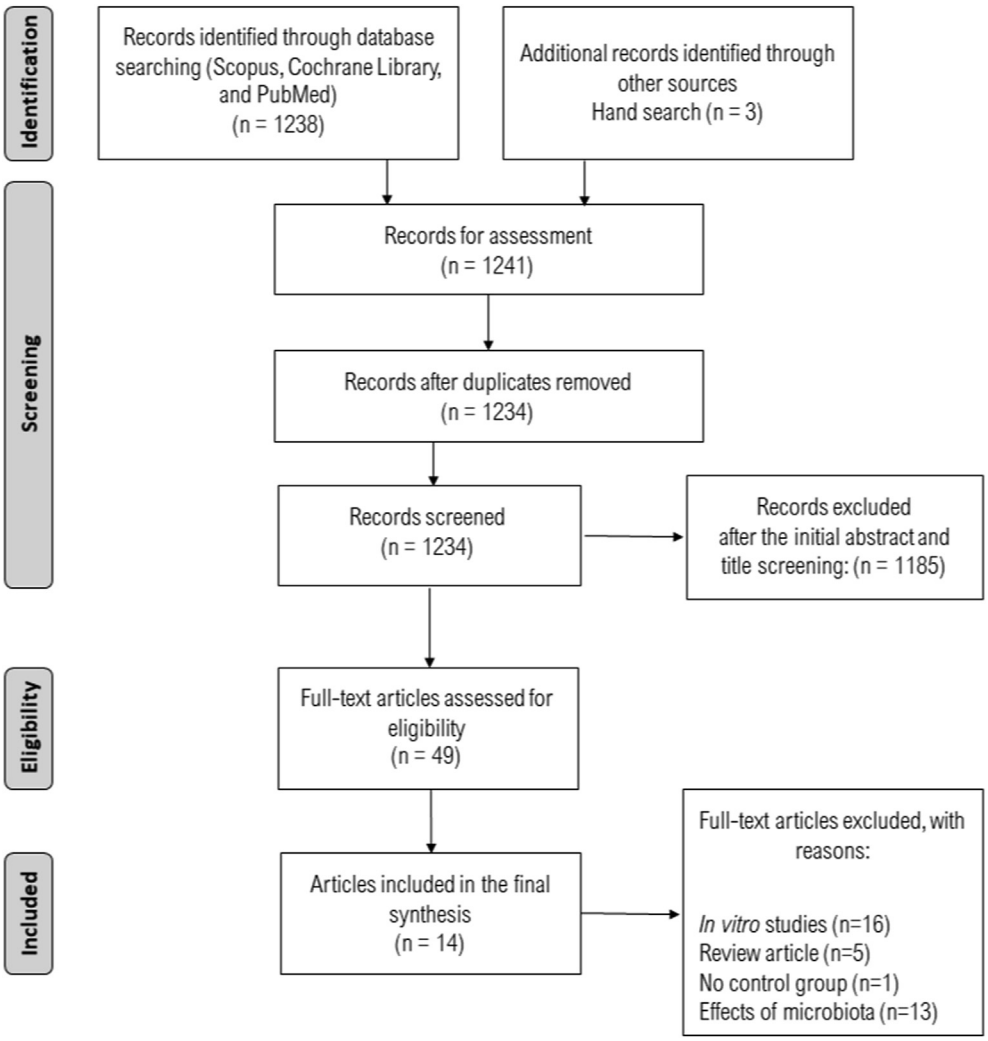

Fig. 1. PRISMA flow diagram for the included studies.

were excluded for assessing the effects of the intestinal metabolization of PCs, and 1 experiment was excluded for not having a control group leaving a total of 14 articles for final inclusion [33–46].

The complete PRISMA statement flow diagram for the included studies is presented in Fig. 1. No studies performed on humans were found regarding the effects of the PC supplementation on the intestinal health and barrier integrity of critically ill humans.

The following information was retrieved from the included studies:

Regarding the animal models used in the 14 included *in vivo* animal studies: Wistar rats (n = 4) [31,34,36,40], C57BL/10 SnSn mice (n = 1) [35], C57BL/6J mice (n = 1) [37], both C57BL/6 and IL-deficient mice (n = 1) [38], both C57BL/6 and CD1 mice (n = 1) [41], C57BL/6 mice alone (n = 1) [43], weaned pigs (n = 2) [33,44], Sprague–Dawley rats (n = 1) [32], IL-10 deficient mice (n = 1) [39], and BALB/C mice (n = 1) [45]. The current animal models used to assess intestinal inflammation are summarized in Table 1.

Most of the included studies assessed different PCs individually, with the exception of two studies where resveratrol and curcumin were evaluated separately in the same experiment [35,46]. In *in vivo* animal studies, resveratrol as an extract was the most commonly used source of PCs (n = 6) [31,32,34,35,44,45]; after its oral (n = 5) [31,34,35,44,45], or intravenous administration (n = 1) [32]. Other PC sources used in *in vivo* animal studies were: oral grape seed extract (GSE) (n = 2) [38,39], oral grape pomace extract (n = 1) [40], oral cranberry extract (n = 1) [37], oral curcumin (n = 1) [35], oral hesperidin (n = 1) [43], oral Olive (*Olea europaea*) leaves extract (n = 1) [41], genistein by intestinal injection (n = 1) [36], and oral chlorogenic acid (n = 1) [33]. Complete information on the included animal studies is reported in Table 2.

3.1.1. Quality assessment

The reporting quality of the 14 included animal studies was assessed through the ARRIVE guidelines. As a result it was determined that the included animal articles adequately reported their results. Moreover, the risk of bias of the 14 included animal studies was assessed using the SCYRCLE's tool; as a result, all the included articles were of moderate quality. Nonetheless, after a thorough assessment of the included animal articles, it was determined that despite their moderate score, there is a low risk of bias in the included publications. The complete results on the ARRIVE guidelines and SCYRCLE's tool for risk of bias assessment are reported on Supplementary Tables 2 and 3, respectively.

Table 1
Summary of the current models used to assess intestinal inflammation.

Model type	Model sub-type	Model used	Description
Animal model			
	Knockout mice		
		IL-10	Involved in anti-inflammatory pathways
		IL-23R	Involved in T-cell differentiation
		CD4+ CD25+	Involved in the T-cell glycoprotein adaptation
		NOD2/CARD15	Peptidoglycan involved in apoptosis
		TGF-β1	Involved in T-cell development and immune response regulation
		RAG	Involved in lymphocyte maturation
		ATG16L1	Involved in pathogen regulation
		$APC^{MIN/+}$	Used for intestinal tumorogenesis
		IL-2	Involved in the inflammatory process
		TNF-α	Involved in the activation of apoptosis
		STAT3	Involved in intestinal mucosa regeneration
		NFκβ	Involved in inflammation and cell survival
		MUC2	Involved in the production of mucin
		IFN-γ	Involved in the inflammatory process
		MYD88	Involved in the signaling process for toll-like receptors and NFκβ
		TLR	Involved in the microbial surface identification
	Rats		Frequently employed along with the use of chemical agents to induce inflammation. Furthermore, HLA-B27 models spontaneously develop intestinal inflammation
	Nematodes and insects		
		Caenorhabditis elegans	*Caenorhabditis elegans* has been used to examine host–microbiome interactions in apical surface of intestinal epithelia cells.
		Drosophila melanogaster	Models have been used to explore the alterations in the innate immune response related to chronic inflammation and cancer development
	Fish		
		Zebrafish (*Danio rerio*)	Zebrafish have been used to test adaptative and immune responses due to intestinal cell similarities with mammalians such as the enterocytes, goblet cells and microvilli. Especially useful for motility and peristaltic studies.
	Pigs		Pigs have been used because of their anatomical similarities with the human intestines, particularly for the stomach and small intestine. However, several differences in the expression of IFN-γ, IL-12 and IL-10 production must be taken into consideration when compared against humans.
	Non-human primates		
		Macaques	Non-human primate animal models are considered the gold standard for the study of the mechanisms involved in chronic and acute inflammation due to the similarities in physiology, immunology, anatomy, and the intestinal microbiome.
Surgical procedures			
		Xenograft	The procedure involves the transplantation of fetal intestinal segments from one species into another.
		Cannulation	Commonly applied to obtain gastrointestinal samples and to examine nutritional metrics.
		Intestinal loops	Are complex procedures useful to study host–pathogen interactions with an added advantage of replicating the normal intestinal characteristics by creating intestinal segments partitioned into “loops"
Chemical agents		Dextran sulphate sodium	Causes basal crypt and epithelial cell damage after long term administration with an increase in the production of pro-inflammatory cytokines
		Trinitrobenzene sulfonic acid	Causes a Th1 mediated immune response with an increase in the production of pro-inflammatory cytokines
		Oxazolone	Causes a Th2 mediated immune response with an increase of interleukins 4, 5, and 13.
		Azoxymethane	Commonly used in conjunction with dextran sulphate sodium to induce an increased production of IL-21, IL-17α, and IL-6.
Biological agents			
	Bacteria	*Citrobacter rodentium*	Used to cause acute inflammation in the colon, producing ulcerative and proliferative intestinal lesions
		Helicobacter pylori	Has been used for its ability to occupy the gastric and intestinal epithelia causing damage after cytotoxin release in the presence of urease
		Salmonella enterica	Used to induce chronic models of intestinal inflammation in mice causing deep injury in the intestinal layers
		Mycobacterium avium	Used to cause intestinal changes like the ones found in humans with Crohn's disease
	Helminths	*Trichuris muris*	The most used nematode for intestinal inflammation in murine models, characterized for the loss in barrier function of the colon
	Protozoa	*Toxoplasma gondii*	Commonly used to cause a robust Th1 immune response in the small intestine resulting in an increased expression of IL-12 and IFN-γ

Note: IL, interleukin; IFN-γ, interferon gamma; HLA, human leucocitary antigen; NFκβ, nuclear factor kappa beta; NOD2, nucleotide-binding oligomerization domain-containing protein 2; CARD15, caspase recruitment domain-containing protein 15; TGF-β1, tumor growth factor beta 1; RAG, recombinant activation gene; ATG16L1, autophagy related 16 like 1; TNF-α, tumor necrosis factor alpha; STAT3, signal transducer and activator of transcription 3; MUC2, mucin 2; MYD88, myeloid differentiation primary response 88; TLR, toll like receptor.

3.2. In vivo animal studies

3.2.1. Resveratrol

The effects of resveratrol on the intestinal barrier were assessed on seven different animal studies [33–35,41,45,53,55]. The animal models used were BALB/C mice (n = 1) [32], Wistar rats (n = 2) [33,41], C57BL/6/10ScSn mice (n = 1) [35], piglets (n = 2) [45,55], and Sprague–Dawley rats (n = 1) [34].

In a dextran sodium sulfate (DSS) colitis model induced for 14 days to 21 male BALB/C mice, the oral dietary supplementation

Table 2
General information of the included studies assessing the effects of polyphenols on the intestinal barrier integrity and intestinal health in diverse animal (*in vivo*) studies.

Title	Author	Year	Outcome	Intervention target	N (m/f)	Phenolic compound used	Animal dose	Human equivalent dose (70 kg human)	Length of study	Administration route	PC treatment	Doses administered (N)	Main conclusions
Enteral resveratrol supplementation attenuates intestinal epithelial inducible nitric oxide synthase activity and mucosal damage in experimental necrotizing enterocolitis.	Ergün, O. et al.	2007	Nitric oxide synthase activity and musocal wall integrity	Newborn Wistar rats	27 (NR)	Resveratrol	15 mg/kg/BID	85 mg/day	4 days	Oral	Oral PC treatment started on day 0 and continued for 4 days until animal sacrifice. Necrotizing enterocolitis was provoked on day 0 using a chemical agent and from hypoxia with a 5% oxygen room air until sacrifice in day 4.	8	The resveratrol treated group showed no changes in the macroscopic intestinal appearance (intestinal edema, pneumatosis intestinalis and ileal necrosis). The Western blot analysis revealed that resveratrol caused a marked decrease in the elevation of the NO synthase protein expression (0.6 ± 5.1; $p < 0.01$), when compared against the NEC group (3.7 ± 2.9). When compared against the NEC group (191.4 ± 4.1 μmol/L·g), resveratrol significantly reduced the ileal nitrate/nitrite levels (181 ± 3.6 μmol/L·g; $p < 0.01$) in a significant manner.
The protective effect of resveratrol on the intestinal mucosal barrier in rats with severe acute pancreatitis.	Jha, R.K. et al.	2008	Intestinal mucosal barrier	Sprague −Dawley rats	54 (m)	Resveratrol	10 mg/kg	1.61 mg/day	12 h	Intravenous	One single PC dose was administered on minute 0 after a bile duct clipping surgery to induce pancreatitis and intestinal inflammation.	1	The resveratrol treated animals showed lower endotoxin levels at 3, 6, and 12 h when compared against the pancreatitis group ($p < 0.05$). At 12 h, resveratrol significantly reduced the endotoxin levels in ≈51% ($p < 0.05$), as well as the pancreatic and intestinal mucosal congestion, edema, inflammatory cell infiltration, when compared against the pancreatitis group ($p < 0.05$). The intravenous administration of resveratrol significantly lowered the apoptotic cell index of the mucosal cells ($p < 0.05$), decreased the expression of the Bax protein ($p < 0.05$), and increased the expression of the Bcl-2 protein.
Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation.	Bereswill, S. et al.	2010	Intestinal inflammation	C57BL/10ScSn mice	NR	Resveratrol Curcumin	20 mg/day 100 mg/day	1.62 mg/day 8.13 mg/day	10 days	Oral	Oral PCs were administered on day 0 until animal sacrifice in day 10. The intestinal inflammation (ileitis) was induced in day 2 from a Toxoplasma *gondii* inoculation.	10	After 19 days, the resveratrol group showed higher survival rates (40% survival; $p < 0.005$), when compared against the control group (0% survival; $p < 0.005$). Resveratrol significantly decreased the animal weight loss in 9% (11%; $p < 0.005$) when compared against the control group (20%; $p < 0.005$). The animals treated either with resveratrol or curcumin presented only mild signs of inflammation (edema and cell-free exudate) in the visual exploration of the ileal mucosa, while maintaining an intact epithelium ($p < 0.0001$). Both treatments reported a lower increase in T lymphocytes ($p < 0.05$), a 20−30% increase in the FOXP3+ cell numbers ($p < 0.05$), and 25−50% fewer MPO-7+ cells ($p < 0.05$), while significantly reducing the total bacterial load in 1−2 orders of magnitude when compared against the placebo control ($p < 0.05$).
Protective effect of soy isoflavone genistein on ischemia-reperfusion in the rat small intestine.	Sato, Y. et al.	2011	Ischemmia-reperfusion intestinal injury	Male Wistar rats	NR (m)	Genistenin	500 μL	NA	NA	Intestinal injection	One single PC dose was directly administered into the intestinal lumen 30 min after the induction of intestinal ischemia from mesenteric artery clamping.	1	Genistein significantly reduced the damage and loss of villi to the intestinal crypts ($p < 0.05$), mainly inhibiting the intestinal xanthine oxidase activity, and enhancing the reactive oxygen species scavenging activity.

(*continued on next page*)

Table 2 (*continued*)

Title	Author	Year	Outcome	Intervention target	N (m/f)	Phenolic compound used	Animal dose	Human equivalent dose (70 kg human)	Length of study	Administration route	PC treatment	Doses administered (N)	Main conclusions
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	Anhê, F. et al.	2014	diet-induced intestinal inflammation and metabolic endotoxemia	C57Bl/6J mice	36 (m)	Crandberry extract (phenolic acids, flavonols, anthocyanins, proanthocyanidins)	200 mg/kg	1120 mg/day	8 weeks	Oral	Oral PC administration started after a 2-week acclimation period along with a high fat and high sucrose diet to induce intestinal inflammation.	56	The oral administration of crandberry extract completely prevented a twofold increase in circulating levels LPS levels after 8 weeks of a high fat/high sucrose diet in
Grape seed extract improves epithelial structure and suppresses inflammation in ileum of IL-10-deficient mice.	Yang, G. et al.	2014	Ileal inflammation	C57BL/6 mice and IL-deficient mice	NR (f)	GSE	1% w/w supplemented diet	NA	16 weeks	Oral	Oral PC administration started on day 0 until week 16. Intestinal inflammation was provoqued by the genetic IL-10 deficiency.	112	The GSE decreased the intestinal crypt depth ($p < 0.05$) and increased the ratio of villus vs. crypt length in the terminal ileum ($p < 0.05$). GSE significantly decreased the proliferation and enhanced the differentiation of the intestinal epithelial cells ($p < 0.05$), suppressing the NF-kβ in activated B-cells ($p < 0.05$). Finally, GSE significantly reduced the intestinal cell autophagy by decreasing the expression of beclin-1 ($p < 0.05$).
Favorable effects of grape seed extract on intestinal epithelial differentiation and barrier function in IL10-deficient mice.	Yang, G. et al.	2015	Intestinal epithelial differentiation and barrier function	IL10-deficient female mice	NR (f)	GSE	140 mg/kg/day 160 mg/kg/day	798 mg/day 910 mg/day	12 weeks	Oral	Oral PC administration started on day 0 until the end of week 12 when animals were sacrificed. Intestinal inflammation was provoqued by IL-10 deficiency	84	After 12 weeks of oral GSE supplementation with 140 or 160 mg/kg/day in mice, the *in vivo* intestinal permeability significantly decreased with additional reductions in the fecal total antioxidant capacity, and serum TNF-α levels ($p < 0.01$). In addition, the GSE significantly reduced the number of proliferating nuclear antigen-positive cells per crypt ($p < 0.01$), and downregulated the MAP kinase's growth signaling in the colon ($p < 0.01$).
Dietary Supplementation with a Low Dose of Polyphenol-Rich Grape Pomace Extract Prevents Dextran Sulfate Sodium-Induced Colitis in Rats	Boussena, A. et al.	2016	dextran sulfate sodium (DSS)-induced colitis in rats	Wistar rats	40	Grape pomace extract (GPE)	0.1%, 0.5% and 1%	NA	21	Oral	Oral PCs were administered from day 0 until day 21, colitis was induced on day 14 from DSS oral administration.	21	The GPE 0.1% diet significantly delayed the onset of colitis symptoms, prevented the decrease in food intake, weight loss, the colon shortening, and the polimorphonuclear infiltration of the intestinal wall when compared against the positive control group. 0.5% and 1% GPE doses did not show significant effects.
Resveratrol Protects Oxidative Stress-Induced Intestinal Epithelial Barrier Dysfunction by Upregulating Heme Oxygenase-1 Expression.	Wang, N. et al.	2016	Epithelial barrier disfunction and oxidative stress	Male Wistar rats	60 (m)	Resveratrol	10 mg/kg 20 mg/kg	112 mg/day 225 mg/day	7 days	Oral	One single PC dose was administered orally after bile duct ligation to cause intestinal inflammation	1	When compared against the control group (3.19 ± 0.90), both resveratrol treatments significantly decreased the intestinal permeability as evidenced in the decrease of the lactulose/mannitol ratio in 70.5% by the 10 mg/kg dose (0.94 ± 0.43; $p < 0.05$), and in 86.8% by the 20 mg/kg dose (0.42 ± 0.25; $p < 0.05$). Resveratrol upregulated the hemeoxygenase-1 protein expression ameliorating the TJ protein disruption ($p < 0.05$).
Immunomodulatory properties of *Olea europaea* leaf extract in intestinal inflammation	Vezza, T. et al.	2017	dextran sulfate sodium-induced intestinal inflammation	C57BL/6J	NR (m)	Olive (*Olea europaea*) leaves extract	0.5, 1, and 10 mg/kg	2.8, 5.6, and 56 mg/day	11	Oral	PC doses started at day 0 and were administered until animal sacrifice on day 11. Intestinal inflammation was induced on day 0 until sacrifice on day 11 using DSS.	11	The olive leaf extract at 1 and 10 mg/kg doses significantly improved the evolution of the colitis severity, enhanced the intestinal functionality from the improvement of intestinal permeability assessed by FITC-dextran permeability. Additionally, the olive leaf extract improved epithelial regeneration, reduced the inflammatory cell infiltration and edema in the intestinal mucosa.

			dinitrobenzenesulfonic acid-induced intestinal inflammation	CD1 mice	NR (m)	Olive (*Olea europaea*) leaves extract	1, 10, and 25 mg/kg	5.6, 56, and 140 mg/day	6	Oral	PC doses started on day 0 and were administered until animal sacrifice on day 6. Intestinal inflammation was induced using dinitrobenzene sulfonic acid on day 2 and continued until sacrifice on day 6.	6	The olive leaf extract 1 mg/kg dose significantly improved inflammation in the colon of treated mice, reduced the expression of IL-1β, TNF-a, IL-6, IL-17, and MIP-2. Additionally, the olive leaf extract significantly upregulated the ICAM-1, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in the intestines of treated animals.
Resveratrol Ameliorates Intestinal Barrier Defects and Inflammation in Colitic Mice and Intestinal Cells.	Mayangsari, Y. et al.	2018	Intestinal barrier defects and inflammation	BALB/C mice	21 (m)	Resveratrol	0.1% w/w supplemented diet	NA	14 days	Oral	Oral PC administration started at day 0 and continued until day 14 when animals were sacrificed	14	When compared against the control, resveratrol significantly prevented the body weight loss in 28% (100 ± 1%; $p < 0.05$), the shortening of the colon length in 0.8 cm (4.6 ± 0.1 cm; $p < 0.05$). Additionally, resveratrol reduced the plasmatic levels of IL-1β in 89.9% (5.9 ± 1.8 AU; $p < 0.05$) and of IL-6 in 96% (10 ± 3 AU; $p < 0.05$). Resveratrol reduced the expression of the CXCL-2 (14 ± 7 AU; $p < 0.05$), increased the expression of occludin (0.76 ± 0.06 AU; $p < 0.05$), and reduced the neutrophil infiltration (9.3 ± 0.7 cells; $p < 0.05$).
Chlorogenic acid improves intestinal barrier functions by suppressing mucosa inflammation and improving antioxidant capacity in weaned pigs.	Chen, J. et al.	2018	Intestinal barrier function	Weaned pig	24 (NR)	Chlorogenic acid	1000 mg/kg/day	38.85 g/day	2 weeks	Oral	Oral PC administration started at 24 days of age when pigs were weaned and continued for 2 weeks until animal sacrifice.	14	Chlorogenic acid significantly decreased the serum D-lactic acid content and diaminooxidase activity ($p < 0.05$). Chlorogenic acid showed a tendency for lower endotoxin levels ($p < 0.10$), however, no significant differences in the levels of cortisol and corticotrophin-releasing hormone were observed between the two groups. Chlorogenic acid reduced the histamine contents in the jejunum and ileum ($p < 0.05$), while reducing the tryptase levels only in the jejunum ($p < 0.05$). Significant decreases in the counts of tryptase-positive mast cells in the duodenum and jejunum of pigs were noted after the chlorogenic acid supplementation ($p < 0.05$). Moreover, chlorogenic acid also downregulated the expression of IL-1β and TNF-α in the small intestine of pigs ($p < 0.05$), of the IL-6 and TNF-α levels in the ileum ($p < 0.05$), and up-regulated the jejunal and ileal expression of claudin-1. Finally chlorogenic acid downregulated the expression of diverse inflammatory proteins such as IL-23p19 ($p < 0.001$), and TNF-α ($p < 0.01$).
Resveratrol improves intestinal barrier function, alleviates mitochondrial dysfunction and induces mitophagy in diquat challenged piglets	Cao, S. et al.	2019	Intestinal injury induced by diquat (herbicide)	Piglets	24	Resveratrol	100 mg/kg/day	4.97 g/day	14 days	Oral	Oral PC administration started on day 0 until day 13 along with diquat to induce intestinal inflammation and compared against a diquat-free control group.	13	Resveratrol significantly increased the total intestinal antioxidant capacity in treated piglets. Additionally, oral resveratrol reversed the increase in the mucosal concentration of hydrogen peroxide and malondialdehyde in the jejunum. The oral resveratrol administration also improved the intestinal barrier function evidenced as an improvement in the TEER reduction provoqued by the herbicide. Moreover, resveratrol prevented reduction of occludin, claudin-1 and ZO-1 levels in the jejunal mucosa.

(*continued on next page*)

Table 2 (*continued*)

Title	Author	Year	Outcome	Intervention target	N (m/f)	Phenolic compound used	Animal dose	Human equivalent dose (70 kg human)	Length of study	Administration route	PC treatment	Doses administered (N)	Main conclusions
Hesperidin Protects Against Intestinal Inflammation by Restoring Intestinal Barrier Function and Up-Regulating Treg Cells	Guo, K. et al.	2019	dextran sulfate sodium (DSS)-induced colitis in mice	C57BL/6 mice	30	Hesperidin	10 mg/kg 20 mg/kg 40 mg/kg	56 mg/day 112 mg/day 224 mg/day	13 days	Oral	PC treatment started on day 0 and continued until animal sacrifice on day 13. Inflammation was induced from day 0 until day 7 using DSS.	13	Hesperidin significantly reduced the disease activity score, and pathological changes in the intestines such as edema, hyperema, inflammatory infiltration, and necrosis. Additionally, hesperidin significantly decreased TNF-α, IL-6 and increased Il-10 and IFN-α in the intestines of treated animals.

Note: GSE, grape seed extract; NF-kβ, nuclear factor kappa-light-chain-enhancer; BID, twice a day; MAP, mitogen-activated protein; AU, arbitrary units; CXCL2, chemokine motif ligand 2; TJ, tight junction; NO, nitric oxide; NEC, necrotizing enterocolitis; MP, myeloperoxidase; AhR, aryl hydrocarbon receptor; Nrf2, nuclear factor erythroid 2–related factor 2; IL, interleukin; NR, not reported; m, male; f, female; DSS, dextran sulfate sodium; PC, phenolic compound.

with resveratrol 0.1% (w/w) resulted in a 28% reduction of the animal's weight loss (100 ± 1%; $p < 0.05$), and prevented the colon shortening by 0.8 cm (4.6 ± 0.1 cm; $p < 0.05$) when compared against the untreated control group [53]. Additionally, oral resveratrol reduced the plasmatic interleukin (IL)-1β concentrations in 89.9% (5.9 ± 1.8 arbitrary units (AU); $p < 0.05$), and the plasmatic IL-6 concentrations in 96% (10 ± 3 AU; $p < 0.05$) [53].

Additionally, a single oral resveratrol dose of either 10 or 20 mg/kg (HED: 112 or 125 mg/day) of resveratrol on the intestinal barrier integrity was appraised 1 week after its administration to 60 male Wistar rats with severe intestinal damage induced by the bile duct ligation (BDL) [41]. As a result, the treatment with resveratrol 10 mg/kg significantly decreased the intestinal permeability in 6% (0.94 ± 0.43; $p < 0.05$) while the 20 mg/kg dose decreased the intestinal permeability of Wistar rats in 58% (0.42 ± 0.25; $p < 0.05$) when compared against the BDL control group (3.19 ± 0.90) [41]. Finally, a single oral resveratrol dose of 20 mg/kg dose, significantly upregulated the heme oxygenase (HO)-1 protein, improving the intestinal antioxidant capacity ($p < 0.05$) when compared against the BDL controls [41].

The effects of an oral 15 mg/kg resveratrol dose (HED: 85 mg/day) twice for 4 days were assessed in a necrotizing enterocolitis (NEC) model developed on 27 newborn Wistar rats [33]. As a result, the NEC Wistar rats treated with resveratrol showed no changes in their macroscopic intestinal appearance, whereas the rats on the non-treated NEC group presented different degrees of intestinal edema, pneumatosis intestinalis and ileal necrosis [33]. Additionally, the Western blot analysis revealed that resveratrol in NEC Wistar rats caused a marked decrease in the elevation of the nitric oxide (NO) synthase protein expression (0.6 ± 5.1; $p < 0.01$) when compared against the NEC control group (3.7 ± 2.9) [33]. Finally, when compared against the NEC Wistar rat group [191.4 ± 4.1 μmol/(L·g)], 15 mg oral resveratrol dose twice daily for 4 days significantly reduced the ileal nitrate/nitrite levels [181 ± 3.6 μmol/(L·g); $p < 0.01$] [33].

The intestinal effects of the oral supplementation with either resveratrol 20 mg/day (HED: 1.62 mg/day) or curcumin 100 mg/day (HED: 8.13 mg/day), and simvastatin for 10 days were assessed from the intestines of C57BL/10ScSn mice, an animal model commonly used to study inflammation [35]. As a result, on the 8th day after the induction of an acute ileitis with *Toxoplasma gondii*; the resveratrol, curcumin, and simvastatin treated C57BL/10ScSn mice showed lesser hyper-acute inflammation in the small intestine [35]. At 10 days, the end of the intervention, the resveratrol treated group showed higher survival rates (40% survival; $p < 0.005$), when compared against the control group (0% survival; $p < 0.005$) [35]. Additionally, in C57BL/10ScSn mice, resveratrol significantly decreased the weight loss by 9% (11%; $p < 0.005$) when compared against the control group (20%; $p < 0.005$) [35]. The C57BL/10ScSn mice treated either with resveratrol or curcumin presented only mild signs of inflammation (edema and cell-free exudate) in the visual exploration of the ileal mucosa while maintaining an intact epithelium ($p < 0.0001$) [35]. Both treatments, curcumin or resveratrol, reported a lower increase in T lymphocytes ($p < 0.05$), a 20–30% increase in the numbers of a T regulatory lymphocyte cell sub-type important for the immune system's tolerance and homeostasis called FOXP3+ cells ($p < 0.05$), and 25–50% fewer myeloperoxidase (MPO)-7+ cells ($p < 0.05$), while significantly reducing the total serum bacterial load in 1–2 orders of magnitude when compared against the placebo control C57BL/10ScSn mice ($p = 0.05$) [35].

The effects of a single 10 mg/kg (HED: 1.61 mg/kg) intravenous resveratrol dose on the intestinal barrier integrity were assessed in 54 male Sprague–Dawley rats after the induction of severe acute pancreatitis induced by the clipping of the bile and biliopancreatic

ducts [34]. As a result, the intravenous treatment of severe pancreatitis using resveratrol on Sprague–Dawley rats showed lower endotoxin levels at 3, 6, and 12 h when compared against the pancreatitis control group ($p < 0.05$) [34]. At 12 h of intravenous administration, resveratrol significantly reduced the endotoxin levels in ≈51% ($p < 0.05$) [34], as well as the pancreatic and intestinal mucosal congestion, edema, and the inflammatory cell infiltration, when compared against the pancreatitis control group ($p < 0.05$) [34]. The intravenous administration of resveratrol significantly lowered the apoptotic cell index of the mucosal cells ($p < 0.05$) [34], decreased the expression of the Bax protein ($p < 0.05$) [34], and increased the expression of the Bcl-2 protein compared with Sprague–Dawley rats with severe pancreatitis as a control [34].

The effects of a resveratrol 100 mg/kg/day (HED: 4.97 g/day) on the intestinal inflammation induced by diquat, a herbicide, were assessed on 24 piglets [45]. For the experiment, the oral resveratrol administration started on day 0 until day 13 along with diquat to induce intestinal inflammation, the effects were compared against a diquat-free control group [45]. As a result, resveratrol significantly increased the intestinal antioxidant capacity, in addition, resveratrol reversed the increased concentrations of hydrogen peroxide and malondialdehyde caused by diquat in the jejunum [45]. Moreover, resveratrol improved the intestinal barrier function, evidenced as an improvement in the TEER reduction secondary to diquat administration [45]. Finally, resveratrol prevented the reduction of various TJ proteins in the jejunal mucosa (occludin, claudin-1, ZO-1) [45].

3.2.2. Grape seed extract (GSE) and grape pomace extract (GPE)

The effects of GSE on the intestinal health were assessed from 2 animal interventions [38,39]. In mice, after 12 weeks of oral GSE supplementation with 140 or 160 mg/kg/day (HED: 798 or 910 mg/day respectively), the *in vivo* intestinal permeability significantly decreased while additionally increasing the fecal total antioxidant capacity, and serum TNF-α levels ($p < 0.01$) compared with the untreated group as a control [39]. Also, the GSE significantly reduced the number of proliferating nuclear antigen-positive cells per crypt ($p < 0.01$) and downregulated the mitogen-activated protein (MAP) kinase's growth signaling evidenced the reduced phosphorylation of the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the colon ($p < 0.01$) compared with the control mice [39].

In another mice experiment, interleukin (IL)-10-deficient and C57BL/6 wild type female mice as a multi-hit model where a colitogenic trigger initiates the inflammatory process [56], were used to test the effects of the oral water supplementation with GSE at 0.1% w/w on the ileal inflammation [38]. As a result in IL-10-deficient mice, GSE significantly decreased the intestinal crypt depth ($p < 0.05$) and increased the villus vs. crypt length ratio in the terminal ileum of animals ($p < 0.05$) when compared against wild type mice used as controls [38]. Furthermore, in separate IL10-deficient mice, the oral GSE administration significantly decreased the proliferation and enhanced the differentiation of the intestinal epithelial cells ($p < 0.05$), suppressing the nuclear factor kappa-light-chain-enhancer (NF-kβ) in activated B-cells ($p < 0.05$) compared against the GSE free control group [38]. Finally, oral GSE significantly reduced the intestinal cell autophagy by decreasing the expression of beclin-1 ($p < 0.05$) when compared against C57BL/6 wild type mice as a control [38]. Thus, oral GSE exerts protective effects on the ileal epithelial structure in IL-10-deficient mice, possibly through the suppression of the intestinal inflammatory response.

The effects from the oral administration of various GPE doses (0.1%, 0.5%, and 1%) on the intestinal inflammation secondary to the DSS oral administration were assessed on 40 Wistar rats, for the experiment GPE was administered from day 0 until day 21, on day 14 colitis was induced from the DSS oral administration [40]. As a result, GPE 0.1% significantly delayed the onset of colitis symptoms, prevented the decrease in food intake, animal weight loss, colon shortening, and the polymorphonuclear infiltration of the intestinal wall when compared against the positive control group [40]. The other GPE doses (0.5% and 1%) did not show the same effects [40].

3.2.3. Other phenolic compounds

The effects of oral chlorogenic acid on the intestinal barrier integrity were assessed in an experiment where a dose of 1000 mg/kg/day (HED: 38.85 g/day) of chlorogenic acid, a natural polyphenol present in human diet and plants, was orally administered to 24 weaned pigs for 14 days, as weaning is considered a cause of intestinal inflammation [44]. As a result, oral chlorogenic acid decreased the serum D-lactic acid content and diamine oxidase activity ($p < 0.05$), while showing a tendency for lower endotoxin levels ($p < 0.10$) when compared with the control group without oral chlorogenic acid [44]. No significant differences in the levels of cortisol and corticotrophin-releasing hormone were observed between the two weaned pig groups [44]. Moreover, oral chlorogenic acid reduced the histamine contents in the jejunum and ileum of weaned pigs ($p < 0.05$), while reducing the tryptase levels only in the jejunum of the treated animals ($p < 0.05$) when compared against the control group [44]. After chlorogenic the acid intake, significant decreases in the counts of tryptase-positive mast cells in the duodenum and jejunum of the weaned pigs were noted when compared against the control group ($p < 0.05$) [44]. Moreover, the chlorogenic acid consumption also downregulated the expression of IL-1β and TNF-α in the small intestine of the treated weaned pigs ($p < 0.05$), the IL-6 and TNF-α levels in the ileum of treated pigs ($p < 0.05$) [44], and upregulated the jejunal and ileal expression of claudin-1 in the supplemented animals [44]. However, the expression of inflammation repressors (suppressor of cytokine signaling 1 and toll-interacting protein) was up-regulated by the chlorogenic acid administration whereas chlorogenic acid downregulated the expression of diverse inflammatory proteins such as IL-23p19 ($p < 0.001$), and TNF-α ($p < 0.01$) compared against the weaned pig control [44]. The results suggest that oral chlorogenic acid ameliorates the intestinal barrier disruption in weaned pigs mediated by the suppression of the toll-like receptor (TLR)4/NF-κβ and the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/HO-1 signaling pathways [44].

Urolithin A, a major gut microbial PC metabolite derived from the transformation of the ellagitannins in berries and pomegranate fruits showing anti-inflammatory, anti-oxidative, and anti-aging activities in *Caenorhabditis elegans* [57] was also studied. The effects of urolithin A on the intestinal barrier function were assessed in one experiment where five urolithin A doses of 20 mg/kg (HEA: 1.62 mg/kg) were administered at 0 h, 6 h, 12 h, 18 h, and 24 h while LPS was administered intraperitoneally to induce inflammation at hour 24 in C57BL/6 wild type, Nrf2−/−, and AhR−/− mice [54]. As a result, urolithin A significantly modified the expression of 437 different genes ($p < 0.05$), mainly in the eukaryotic initiation factor 2 (eIF2), mammalian target of rapamycin (mTOR), and mitochondrial dysfunction pathways in C57BL/6 mice [54]. Moreover, urolithin A significantly upregulated the expression of claudin-4 ($p < 0.05$), Cyp1A1 ($p < 0.05$), and HO-1 ($p < 0.05$) in all mice when compared against baseline values. Finally, urolithin A significantly improved the intestinal TJ health through the activation of the aryl hydrocarbon receptor (AhR) - nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent pathways [54], and attenuated colitis in wild type, Nrf2−/−, and AhR−/− mice by

remedying the barrier dysfunction in addition to different anti-inflammatory activities [54].

The effects of genistein, a phytoestrogen part of the isoflavonone family, on the intestinal barrier integrity were assessed in an intestinal injury model on Wistar rats [36]. For this experiment, the Wistar rats were divided into two groups; one of them was pre-treated with a single intestinal injection of 500 μL of genistein, while the second group received a placebo treatment with saline solution [36]. After the single intestinal injection, an ischemia-reperfusion injury was induced in both groups, then the animals were euthanized and the oxidative status and epithelial integrity were assessed [36]. As a result, the single intestinal genistein injection significantly reduced the damage and loss of villi to the intestinal crypts ($p < 0.05$) [36], mainly inhibiting the intestinal xanthine oxidase activity, and enhancing the reactive oxygen species scavenging activity [36].

The effects of an olive leaf extract (OLE) were assessed on two models of intestinal inflammation [42]. For the first model an OLE dose of 0.5, 1 or 10 mg/kg (HED: 0.04, 0.08 or 0.8 mg/kg) was administered on a colitis model induced by DSS in C57BL/6J mice starting at day 0 until animal sacrifice in day 11 [42]. As a result, OLE at 1 and 10 mg/kg doses significantly improved the colitis severity, and enhanced the intestinal functionality from an improvement in the intestinal permeability [42]. Additionally, OLE improved epithelial regeneration, reduced inflammatory cell infiltration, and edema in the intestinal mucosa of the treated animals [42]. In the second model, OLE doses of 1, 10 or 25 mg/kg (HED: 0.08, 0.8, or 2 mg/kg) starting at day 0 until animal sacrifice were used. OLE was administered daily to CD1 mice with induced colitis from the oral administration of dinitrobenzene sulfonic acid at day 2 and was continued until animal sacrifice on day 6 [42]. As a result, 1 mg/kg dose significantly improved the intestinal inflammation of treated mice, reduced the intestinal expression of IL-1β, TNF-α, IL-6, IL-17, and the macrophage inflammatory protein (MIP)-2. Additionally, the OLE significantly upregulated intracellular adhesion molecule (ICAM)-1 expression, the inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX) 2 in the intestines of the treated animals [42].

The effects of the oral administration of a daily 10, 20, or 40 mg/kg hesperidin doses (HED: 0.8, 1.6, or 3.2 mg/kg) on a DSS-induced intestinal inflammation were assessed on 30 C57BL/6 mice [46]. For the treatment, the hesperidin doses were administered from day 0 until day 13, while the intestinal inflammation was induced from day 0 until day 7 from the oral DSS administration [46]. As a result, hesperidin was able to significantly reduce the disease activity score and the pathological changes provoked by DSS in the intestines of untreated animals such as edema, hyperemia, inflammatory cell infiltration, and necrosis [46]. In addition, hesperidin significantly decreased the TNF-α, IL-6, and increased IL-10 and IFN-α concentrations in the intestines of treated animals [46].

Finally, the effects of the oral administration of a 200 mg/kg (HED: 16 mg/kg/day) dose of a cranberry extract on the diet-induced intestinal inflammation and metabolic endotoxemia provoked by a high-fat high sucrose diet in 36 C57BL/6J mice were assessed [37]. For the experiment, the cranberry extract was administered along with a high fat and high sucrose diet for 8 weeks [37]. As a result, the cranberry completely prevented the two-fold increase in the circulating LPS levels after 8 weeks of the high fat/high sucrose diet in the treated animals when compared against the control group [37].

Notably, no side effects were observed for any of the PCs administered in all the included articles even when the PCs were given at doses only achievable from the PC extract administration [33–40,42–46,54,55].

The effects of the oral administration of resveratrol and other PCs on the intestinal barrier integrity are summarized in Fig. 2.

4. Discussion

The nutrition of patients is a vital necessity that should be treated as such [58]. In that sense, early enteral nutrition (EN) is

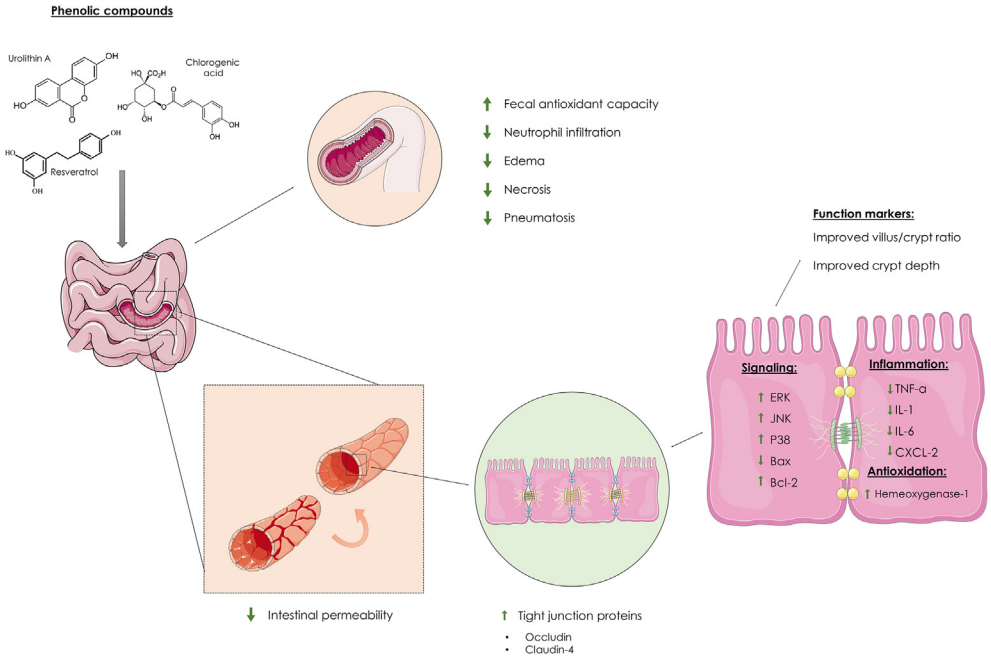

Fig. 2. The main effects of phenolic compounds (PCs) on the intestinal health and barrier function. The ingestion of various different PCs has demonstrated to significantly reduce the intestinal permeability, increasing the expression of different tight junction proteins and modulating the expression of various pro-inflammatory or antioxidant proteins resulting in the reduction of intestinal tissue damage, healthier cytological characteristics, lesser neutrophil infiltration, and an improved antioxidant capacity. *Abbreviations*: ERK, extracellular signal-regulated kinase; JNK, Janus kinase; Bax; Bcl-2, B-cell lymphoma 2; TNF-α, tumor necrosis factor alpha; IL; CXCL-2, Macrophage Inflammatory Protein 2.

recommended in current guidelines as it has demonstrated to reduce the mortality rates in intensive care units, helping to maintain the integrity of the intestinal barrier, leading to fewer gastrointestinal hemorrhages, infectious complications, the subsequent organ failure, and finally death in critically ill patients [59,60]; suggesting that composition of EN formulae is one area of medical interest.

As evidenced by the present systematic review, various PCs seem to have promising beneficial effects on the intestinal inflammation. For instance, it has been demonstrated that in animal models, the oral administration of various PCs at different doses significantly decreases various macroscopic signs of intestinal inflammation [33–36,38,39,53]. For instance, oral resveratrol significantly improves the intestinal edema, *pneumatosis intestinalis*, and ileal necrosis in newborn rats with necrotizing enterocolitis [33], the mucosal congestion, edema, and inflammatory cell infiltration in adult rats with intestinal inflammation secondary to acute pancreatitis [34], and also in C57BL/10ScSn mice with acute intestinal inflammation [35].

Additionally, resveratrol, genistein, and the oral GSE demonstrated to improve various characteristics of the intestinal epithelium such as the villus/crypt ratio, and crypt depth, in IL-10 deficient mice, Wistar rats and BALB/C mice [36,38,39,53] suggesting the improvement of the intestinal functionality and structure in diverse animal models. Thus, PCs might promote various beneficial effects to treat the decrease of the intestinal crypt proliferation and crypt/callus axis that occurs in critical patients secondary to systemic inflammation that leads to the reduction of the intestinal villus length which, in turn, causes nutrient malabsorption [2,12,13].

From all comments, the improvements in the intestinal function and structure after the oral PC administration seem to be caused by three main mechanisms in accordance with the information obtained from this review:

First, PCs improve the expression of various pro-inflammatory molecules as has been evidenced for resveratrol which improves the expression of pro-inflammatory proteins such as TNF-α, IL-1β, IL-6, and CXCL-2 in a dose-dependent manner [53]. Similar improvements on the intestinal cell expression of pro-inflammatory molecules have been observed for other PCs, for instance, GSE demonstrated to therapeutically improve the intestinal concentrations of TNF-α after 12 weeks of supplementation to IL-10 deficient mice [39]. Additionally, the oral administration of an olive leaf extract improved the expression of IL-1β, TNF-a, IL-6, and IL-17 in mice when administered in conjunction with the induction of colitis for 6 days [42]. Finally chlorogenic acid significantly improved the expression of endotoxin, histamine, tryptase, IL-1β, TNF-α, and IL-6 concentrations in the duodenum, jejunum, or ileum in various segments of the intestines of weaned pigs [44].

The reduced secretion of pro-inflammatory molecules in the intestinal epithelium of animals treated with PCs is evidenced as a smaller neutrophil infiltration rate in Wistar rats with intestinal inflammation secondary to bile duct ligation [41], lower T lymphocytes and MPO-7+ cells counts, as well as additional increases in the FOXP3+ cell numbers in the intestinal epithelium of C57BL/10ScSn mice treated with curcumin or resveratrol [35].

It must be noted that further benefits from oral PCs on the intestinal inflammatory profile might come from the improvement in the activity of proteins related to the inflammatory process as demonstrated after the olive leaf extract administration which significantly upregulated the expression of ICAM-1, iNOS, and COX-2 in the intestines of C57BL/6J and CD1 mice [42]. Such anti-inflammatory properties of PCs might constitute one of the most important mechanism of action for the improvement of intestinal health observed in IL-10 deficient mice [39], weaned pigs [44], Wistar rats [41], and C57BL/6J and CD1 mice [42].

Second, PCs improve the expression or prevent the reduction of different TJ proteins in the intestinal epithelium as demonstrated for resveratrol which significantly improved the protein expression of occludin in BALB/c mice [53], ameliorated the TJ protein disruption by upregulating the expression of antioxidant enzymes such as HO-1 in rats with intestinal inflammation secondary to bile duct ligation [41], and prevented the reduction of occludin, claudin-1 and zonula occludens (ZO)-1 levels in the jejunal mucosa of piglets with herbicide-induced intestinal inflammation [45]. Additionally, the prevention of the reduction of occludin, claudin-1 and ZO-1 levels in the jejunal mucosa is the mechanism that counteracts the alterations in the expression of various TJ proteins causes by inflammation such as the increase in the expression of claudin-2, and the decrease of claudin-5 and the ZO-1 proteins, possibly preventing the loss in the intestinal barrier function that characterizes critically ill patients [9–11] and in consequence possibly improving the intestinal permeability.

Third, PCs decrease the concentration of reactive oxygen species by increasing the activity of antioxidant enzymes such as HO-1 and xanthine oxidase as demonstrated in Wistar rats with intestinal inflammation and treated with resveratrol [41] or genistein [36] respectively, suggesting that the antioxidant benefits observed from the oral PC administration do not come only from their chemical structure but also from their metabolic regulatory activities.

Noticeably, the intestinal beneficial effects of PCs can also be attained from the intravenous administration of resveratrol which significantly lowered the endotoxin levels in plasma, as well as the intestinal edema, the inflammatory cell infiltration, and the apoptotic index of intestinal cells by improving the expression of pro-apoptotic proteins such as Bax and Bcl-2 in intestinal damage secondary to severe pancreatitis in Sprague–Dawley rats [34]. This might be of human benefit for the treatment of the increase in the intestinal apoptosis in critically ill patients where the intestinal disfunction has demonstrated to be regulated by a decreased expression of the Bcl-2 protein, causing intestinal necrosis and loss of function [7,8].

In accordance with the animal results, the *in vitro* evidence for resveratrol demonstrates that their oral administration significantly reduces the trans epithelial electrical resistance (TEER) provoked by different noxious agents in induced pluripotent cells (IPC)-J2 and caco-2 cells [51], counteracting their deleterious effects on diverse signaling proteins such as ERK, JNK, and p38 [51]. Similar cell effects were observed for other PCs [48,52].

Moreover, several *in vitro* studies provide other evidence suggesting that PCs improve the intestinal barrier integrity. For instance, a 20 μg/mL concentration of a proanthocyanin-rich purple potato extract significantly increased the expression of occludin, claudin-1, and the ZO-1 TJ proteins in caco-2 colon cancer cells [47]. Moreover, the same proanthocyanin-rich purple potato extract significantly increased the production of different intestinal transcription factors such as Elf3, and Hes1, demonstrating that different PCs can enhance the epithelial barrier integrity by increasing epithelial cell differentiation in caco-2 cells [47]. Finally, the extracts from three different passion fruits [48], routin extract [49], quercetin extract [49], epigallocatechin extract [49], and resveratrol extract [50,51], all demonstrated to be capable of increasing the TEER values, reflecting a better intestinal barrier integrity in *in vitro* models of intestinal damage [48–51].

The reduction of apoptosis, the increase of the villus length, and an increased expression of different TJ proteins coming from the early oral administration of PCs might counteract the increase in gut permeability that starts within the 1st hour of critical illness

and lasts for at least 48 h in humans [3,61]. Preventing the increase of the intestinal permeability might lead to lesser bacterial translocation, which in turn would reduce the subsequent systemic infection and distant organ damage [62], thus, the animal results suggest that the PC administration, through an oral or intravenous pathway might improve the intestinal integrity and barrier function of critically ill patients and possibly other patients suffering from intestinal inflammation [14].

From the above mentioned comments, the oral PC administration seems to exert beneficial effects directly from their interaction with diverse intracellular proteins in the intestinal epithelium [33–46]. However, it must be noted that the intestinal metabolization of PCs might also be of paramount importance for the intestinal barrier integrity since many of the PC's beneficial effects on the intestines might be caused by the first- or second-pass metabolization by the intestinal microbiota resulting in a more varied PC profile in the intestinal lumen of animals [63]. For instance, urolithin A, a PC resulting from the ellagitannin transformation by gut microbiota [64], significantly improved the intestinal barrier integrity, upregulating the expression of the TJ protein, claudin-4, and also the antioxidant enzyme HO-1, from the activation of the AhR-Nrf2 dependent pathway in mice with intestinal inflammation secondary to LPS injection [54].

Additionally, similar results on the improvement of TJ proteins were reported for curcumin and resveratrol when tested in combination with an antibiotic to assess the role of the intestinal microbiota in the alleviation of intestinal inflammation in 180 hybrids weaned piglets [55]. As a result of the intervention, curcumin and resveratrol at 300 mg/kg doses were able to significantly regulate the gut microbiota and reduced the intestinal inflammation from the decrease in the expression of the TLR4 signaling pathway in the jejunum and ileum of weaned piglets [55].

In same study, curcumin and resveratrol at all doses significantly reduced the IL-1β, TNF-α, while improving the IL-10, IgG, and IgA ($p < 0.05$) concentrations in the intestines of weaned pigs, thus, demonstrating not only that PCs might play a beneficial role for intestinal health but also the important role of the intestinal microbiota on the intestinal barrier health and function [55].

Therefore, as a result of the present systematic review of animal studies, it has become ostensible that the oral PC administration has the potential for improving the intestinal barrier integrity during severe inflammation, from an improvement in the inflammatory profile in intestinal epithelial cells, increasing the TJ protein expression thus reducing the intestinal permeability, and improving antioxidation in the intestinal epithelia. In consequence, the translation of PC animal results into human health problems suggests a possible improvement in the intestinal barrier function, possibly reducing further complications such as sepsis and death in some patients, such as critically ill patients and other patients suffering from intestinal inflammation from the improvement of the intestinal integrity.

5. Limitations

The current systematic review summarizes the results from various animal interventions to determine the possible beneficial effects of the PC supplementation on human nutrition to improve the intestinal inflammation, however, the animal results must be validated in a randomized control trial on humans to determine the effects of PCs on human intestinal health. A major limitation of the present review is that because of the complexity and extent of the information on the effects from the intestinal PC metabolization by the intestinal microbiota, and their possible effects over the intestinal health have only been briefly mentioned as a part of our work. However, the authors consider this as a major topic of increasing interest amongst the scientific community and it is worthy of study in future reviews focusing both on the microbiota and intestinal barrier.

6. Conclusions

From the present systematic review, in animals, the oral administration of various PCs improves the intestinal barrier integrity and function from three main mechanisms: 1) The reduction of several pro-inflammatory molecules, 2) the improvement in the expression of TJ proteins, and 3) the improvement of the antioxidant intracellular activity from chemical interactions and the increased expression of antioxidant enzymes. Furthermore, resveratrol, the most studied PC in different animal models of intestinal damage, improves the intestinal barrier integrity through an increase in the expression of various anti-inflammatory and antioxidant proteins in animals. Thus, suggesting the possible use of resveratrol or other PCs in the management of the intestinal injury associated with various intestinal and systemic pathologies in humans. However, the precise dose and time for the oral administration of resveratrol or other PCs in humans are still undetermined.

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Contributions

Study conception and design: B.A.S-R., ÚC, RS.
Acquisition of data: B.A.S-R., and Ú.C.
Analysis and interpretation of data: B.A.S-R., Ú.C., AP, RMV, LR, and R.S.
Drafting of the manuscript: B.A.S-R, and Ú.C.
Critical revision: Ú.C., MJM, and R.S.

Conflict of interest

The authors have declared no conflicts of interest. Complete Declaration of Interest forms for each author has been uploaded at the time of manuscript submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.09.027.

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