Pharmacological Effects of Polyphenol Phytochemicals on the Intestinal Inflammation via Targeting TLR4/NF-κB Signaling Pathway

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Abstract: TLR4/NF-κB is a key inflammatory signaling transduction pathway, closely involved in cell differentiation, proliferation, apoptosis, and pro-inflammatory response. Toll like receptor 4 (TLR4), the first mammalian TLR to be characterized, is the innate immune receptor that plays a key role in inflammatory signal transductions. Nuclear factor kappa B (NF-κB), the TLR4 downstream, is the key to accounting for the expression of multiple genes involved in inflammatory responses, such as pro-inflammatory cytokines. Inflammatory bowel disease (IBD) in humans is a chronic inflammatory disease with high incidence and prevalence worldwide. Targeting the TLR4/NF-κB signaling pathway might be an effective strategy to alleviate intestinal inflammation. Polyphenol phytochemicals have shown noticeable alleviative effects by acting on the TLR4/NF-κB signaling pathway in intestinal inflammation. This review summarizes the pharmacological effects of more than 20 kinds of polyphenols on intestinal inflammation via targeting the TLR4/NF-κB signaling pathway. We expected that polyphenol phytochemicals targeting the TLR4/NF-κB signaling pathway might be an effective approach to treat IBD in future clinical research applications.

Keywords: polyphenols; TLR4/NF-κB signaling pathway; intestinal inflammation

1. Introduction

Inflammatory bowel disease (IBD), including mainly Crohn’s disease and ulcerative colitis (UC), is a chronic intestinal inflammation characterized by bellyache, malabsorption, diarrhea, general malaise, etc. [1]. The incidence areas of CD can occur throughout the gastrointestinal tract, whereas the main incidence area of UC is the colon and rectum [2]. Approximately 3 million adults in the United States were diagnosed with IBD in 2015, and the incidence rate in 2030 is predicted to increase to 4–6 times that [3]. The incidence rate of IBD in China is 3.44%, ranking the highest in Asia [4]. To date, preclinical models of IBD are widely established to explore the pathogenesis and therapy. Furthermore, 2,4,6-trinitrobenzene sulfonic acid (TNBS) and dextran sulfate sodium (DSS) models have been largely employed.

Inflammatory signaling pathways play a crucial role in the treatment of inflammatory disease. Several external stimuli can activate toll-like receptor 4 (TLR4) and downstream nuclear factor kappa B (NF-κB) pathway, also promoting the production of inflammatory cytokines, subsequently provoking the inflammatory response [5]. As shown, there is strong evidence of the upregulation of TLR4/NF-κB and MAPK signaling in IBD [6,7]. IBD patients are commonly treated with medicine therapy but this gives rise to a lot of side effects. Therefore, there are well recognized requirements for new and safe strategies.
for IBD treatment. On that basis, accumulating studies demonstrated the pharmaceutical effects of polyphenols on the IBD. Polyphenols are secondary metabolites of plants that normally contain at least one or more hydroxyl group-linked benzene rings [8]. In the past, accumulating evidences suggested that polyphenols are potential sources of alternative medications to treat the oxidative stress and inflammation associated with degenerative diseases, such as diabetes mellitus (DM), rheumatoid arthritis (RA), and cardiovascular disease [9]. More importantly, a recent study showed that polyphenol extract of *Moringa oleifera* containing astragalin, chlorogenic acid, isoquercitrin, kaempferitrin, luteolin, quercetin, and rutin could alleviate colonic inflammation in DSS-treated mice associated with the NF-κB signaling pathway [10], indicating the anti-inflammatory potential of polyphenols on intestinal diseases. The small intestine plays a key role in the digestion and absorption of nutrients, including carbohydrates, proteins, and lipids. To date, the gastrointestinal tract has been considered as a potential research hotspot that is associated with inflammation induced by pathogens, toxins, and external stimulus [11]. Increased attention has been paid to the link between the polyphenols and intestinal inflammation. Increased intestinal inflammation is largely driven by activation of the TLR4/NF-κB signaling pathway [6]. It is worth noting that numerous studies have been conducted to date on the anti-inflammatory effects of polyphenols, in both in vitro and in vivo multiple inflammatory models, but few studies have addressed the specific effect and mechanisms of polyphenols on intestinal inflammation. However, although various models of severe intestinal inflammation were used, these pathologies share common inflammatory processes and mechanisms. In this regard, the present review will focus on recent advances in the intestinal anti-inflammatory properties of polyphenols which link the TLR4/NF-κB-mediated signaling pathways in both in vitro and in vivo intestinal inflammatory models. Polyphenols could contribute, as adjuvant, or preventive approaches, to the treatment of chronic inflammatory diseases.

2. TLR4 Signaling Pathways

The innate immune system constitutes the first line of host defense against extraneous pathogen invasion, including bacteria, viruses, yeasts, and fungi. Transmembrane receptors designated toll-like receptors (TLRs) belonging to members of pattern recognition receptors (PRRs) play a key role in recognizing invading microbial pathogens and inducing innate immune responses for the host defense [12]. They are expressed on multiple immune cells, including B cells, dendritic cells, macrophages, specific types of T cells, and even on non-immune cells such as intestinal epithelial cells [13]. TLRs are type I transmembrane glycoproteins constituted by an extracellular N-terminal domain of leucine-rich repeats and an intracellular C-terminal domain similar to that of the interleukin 1 receptor (IL-1R), thus designated as toll/interleukin 1 receptor (TIR) domain, which is responsible for downstream signal transduction [13,14].

TLR4, one class of TLRs, is thought to play a crucial role in intestinal inflammatory diseases [6]. It can lead to the maturation of dendritic cells and differentiation of helper T cell (Th) 1 and Th2 [7]. Moreover, it can induce the differentiation of macrophages to an M1 phenotype, thereby producing pro-inflammatory cytokines [15]. Upon activation, TLR4 dimerizes and triggers two major signaling cascades, myeloid differential factor 88 (MyD88)-dependent and toll/interleukin 1 receptor domain-containing adaptor inducing interferon-beta (TRIF)-dependent pathways, which result in the downstream activation of NF-κB and mitogen-activated protein kinases (MAPKs) and induction of various pro-inflammatory gene products, including cytokines and inflammation related enzymes [14,16].

The MyD88-dependent pathway begins with the cytoplasmic TIR domain [17]. Upon MyD88 activation associated with TIR domain-containing adaptor protein (TIRAP), the autophosphorylation of IL-1 receptor-associated kinase (IRAK), namely, IRAK1, and IRAK4 was subsequently triggered, and it further temporarily interacts with tumor necrosis factor receptor-associated factor 6 (TRAF6). This activation of IRAK and TRAF6 eventually results in the phosphorylation and degradation of NF-kappa-B inhibitor alpha
(IkBa), and the following translocation of NF-κB into the nucleus [14,18]. In addition, TRAF6 can stimulate MAPKs, namely, p38, extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and the subsequent activation of the activator protein-1 (AP-1) [19]. Next, the activation of NF-κB and MAPK can induce inflammatory responses through the activation of inflammation related enzymes, such as inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), and pro-inflammatory cytokines secretion, such as interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor-α (TNF-α), and others [19]. On the other hand, the TRIF-dependent pathway is also confirmed to trigger after TLR4 activation. It primarily recruits TRIF and leads to the ubiquitination of TRAF6, which induces TANK-binding kinase 1 (TBK1) combining to I-kappa-B kinase epsilon (IKKe, the inhibitor of NF-κB). Later, the transcription factor interferon regulatory factor 3 (IRF3) is phosphorylated and activated by the TBK1-IKKe complex, finally driving the transcription of interferon-alpha (IFN-α) and IFN-β [20,21].

3. TLR4 and NF-κB in the Development of Inflammatory Bowel Disease

As mentioned earlier, IBD is a chronic, relapsing, and lifelong disease that has been a worldwide threat to healthcare with increasing incidence and prevalence. More importantly, there is strong evidence that TLRs, and TLR-activated signaling pathways, are involved in the pathogenesis of IBD [7,22]. TLRs not only play a crucial role in innate immunity, but also critically modulate adaptive immunity, such as T cell activation. There is disequilibrium between T regulatory cells (Tregs) and effector T cells in patients with IBD. This implies that when Tregs’ function of inhibiting effector T cells, such as Th1, Th2, Th17, and NKT cells, is suppressed due to TLR-induced over immune responses, IBD will become out of control [23,24]. In addition, TLRs act as the bridge between immune response to microbes in the gut, thus giving rise to IBD [7]. That is, the innate inflammatory response can result in dysbiosis of the intestinal microbiota, leading to host metabolic dysfunction. In this respect, TLRs can mediate the interactions between the host immunity and intestinal microbiota. Taken together, TLRs are a potential molecular mechanism in the development of IBD due to controlling the immune response and disordering the intestinal microbiome.

Among all TLRs, the TLR4 is the first verified TLR in the mammalian system and the receptor of lipopolysaccharide (LPS) in Gram-negative bacteria. Under normal physiological conditions, TLR4 is expressed at a low level in intestinal epithelial cells [25]. However, the TLR4 is expressed at high levels in the intestinal epithelium of patients with active UC, indicating that TLR4 might be involved in the development of UC. NF-κB is the final transcription factor of the TLR4 signaling pathway. The NF-κB signaling pathway plays a pivotal role in promoting the development of intestinal diseases via regulation of transcription and translation of inflammatory mediators, such as pro-inflammatory cytokines [26]. NF-κB is formed by five important proteins, including p65 (RelA), p50, p52, c-Rel, and RelB, which exist in cytoplasm as inactive heterodimeric complexes by binding to its inhibitory protein, I kappa B (IkB). P65 is the most representative protein for the regulation and function of NF-κB. Upon activation by various inflammatory stimuli, such as LPS, the activation of the IkB kinase (IkkB) triggers the phosphorylation and degradation of IkBα. Afterwards, nuclear translocation of NF-κB occurs after NF-κB phosphorylation. Upon entering the nucleus, NF-κB binds to DNA and activates the expression of pro-inflammatory genes including cytokines (IL and TNF-α), adhesion molecules, and inducible enzymes (iNOS and COX-2) [27]. Previous study has demonstrated that inflammatory cytokines can induce disturbances in intestinal barrier function, thereby causing intestinal mucosal barrier damage and inflammatory response [22,28]. On the other hand, the high expression of iNOS can lead to high NO production, which participates in the pathology of chronic IBD [29,30]. Cyclo-oxygenases are enzymes that influence many biological processes, ranging from homeostasis to inflammation [31]. There are two cyclo-oxygenases isoforms: the constitutive COX-1 isoform and the inducible COX-2 isoform. Among them, COX-2 induction can be reflected by increased prostaglandin E2 (PGE_2) levels at the site of inflammation [31,32].
Taken together, regulation of the TLR4/NF-κB-mediated signaling pathway could be novel potential therapeutic strategies against IBD.

4. Polyphenols Alleviate Intestinal Inflammation via Modulating the TLR4/NF-κB Signaling Pathway

Polyphenols, widely known as secondary metabolites, are plant-synthesized compounds possessing various biological activities [33,34]. Polyphenols can be classified into flavonoids and tannins, alkaloids, terpenoids, and phenylpropanoid [35]. The chemical structures of some of the polyphenolic compounds are depicted in Figure 1. There are enormous structural variations among these compounds. However, the anti-inflammatory effects of these compounds are consistent in both in vitro and in vivo inflammatory disease models. They become involved in multiple biological processes inside the body, such as radical scavenging and anti-inflammatory processes, as well as cell signaling [9,36,37]. Currently, numerous studies have indicated that phytochemicals may be promising candidates for the treatment of several inflammatory diseases. However, there is a gap in the knowledge of in vitro and in vivo effects although the pharmacokinetics of polyphenols have improved a lot in the last decade [38]. Interestingly, the predominant anti-inflammatory mechanism is attributed to an inhibition of TLR4/NF-κB-mediated signaling pathways and the downregulation of expression of pro-inflammatory mediators [38,39]. Another point worth noting is the evidence that many polyphenols, especially flavonoids, have been studied for their intestinal anti-inflammatory activity associated with inhibition of inflammatory signaling pathways, pro-inflammatory genes expression, and promotion of anti-inflammatory genes expression. In this section, we will discuss, in detail, how polyphenols exert their intestinal anti-inflammatory properties linked with TLR4/NF-κB-mediated signaling pathways in both in vitro and in vivo intestinal inflammatory models (Table 1, Figures 2 and 3).
Figure 1. Chemical structure of some of the flavonoids and other polyphenolic compounds featured in this review. Polyphenols can be classified into flavonoids and tannins, alkaloids, terpenoids, and phenylpropanoid. Substantial variation is intuitively observed by distinct chemical substitutions, especially hydroxylation and glycosylation.
Table 1. Summary of polyphenols’ effects on intestinal inflammatory diseases along the TLR4/NF-kB-mediated signaling pathway in vitro and in vivo.

| Polyphenol | Cell Type or Animal Model | Induction of Intestinal Inflammation | Anti-Inflammatory Mechanism | References |
|------------|---------------------------|-------------------------------------|----------------------------|------------|
| Apigenin   | Swiss albino mice         | Radiation-induced gastrointestinal damages | It inhibited NF-κB expression | Begum et al. [40] |
|            | HCT-116 human colonic epithelial cancer cells | 5 µg/mL LPS | It downregulated NF-κB and STAT3 expression, as well as IL-6 and IL-10 secretion in a dose dependent manner | Ai et al. [41] |
|            | C57BL/6J mice              | Oral administration of 1% DSS for 21 d | It reduced the severity of colitis by decreasing TNF-α, IL-1β, IL-6, and COX-2 levels | Ai et al. [41] |
| Luteolin   | Human Caco-2 cells         | 5 µmol/L decabromodiphenyl ether (BDE-209) for 12 h | It inhibited ERK and NF-κB p50 expression and IκBα phosphorylation, as well as secretion of TNF-α, IL-6, IL-1β | Yuan et al. [42] |
|            | C57BL/6J mice              | Drinking water containing 3.0% DSS | It decreased the levels of IL-6, IL-1β, and TNF-α in the serum and colon, and the protein levels of TLR4, MyD88, and NF-κB p65, and phosphorylation of NF-κB p65 | Zuo et al. [43] |
|            | Caco-2/RAW264.7 co-culture model | LPS stimulation | It suppressed NF-κB nuclear translocation, and mRNA expression of IL-8 and TNF-α | Nishitani et al. [44] |
| Baicalein  | Female Balb/c mice         | 2 mg of TNBS | It reduced TNF-α and IL-1β, and phosphorylation of NF-κB p65 and IκBα, and protein expression of TLR4 and MyD88 | Luo et al. [45] |
| Sprague-Dawley rats | Ulcerative colitis | It inhibited NF-κB and MAPK expression, as well as IL-1β, IL-6, and IL-17 | Liang et al. [46] |
| Quercetin  | IEC-6 cells                | 300 µmol/L indomethacin for 24 h | It suppressed calcium-mediated JNK and Src activation Pretreatment with it reduced the IL-8 secretion and NF-κB translocation into the nucleus | Fan et al. [47] |
|            | Human intestinal epithelial cell line Int407 | Vibrio cholerae | | Das et al. [48] |
|            | Male Sprague-Dawley rats | Acute necrotizing pancreatitis induced by 3.5% sodium taurocholate solution | It downregulated intestinal protein expression of TLR4 and MyD88, and phosphorylation of p38 MAPK | Zheng et al. [49] |
|            | Sprague-Dawley rats | Indomethacin dissolved in 5% NaHCO3, at 40 mg/kg body weight | Its oxidation metabolite prevented NF-κB activation and IL-8 secretion | Fuentes et al. [50] |
| Kaempferol | Rat intestinal microvascular endothelial cells | 10 µg/mL LPS for 12 h | It inhibited LPS-induced NF-κB, IκBα and STAT phosphorylation, decreased TLR4 overexpression, and LPS-induced IL-1β, IL-6 and TNF-α upregulation | Bian et al. [51] |
|            | C57BL/6J male mice         | High fat diet | It reduced the protein expression of TLR4, MyD88 and NF-κB, and mRNA expression of TNF-α in the colon | Bian et al. [52] |
| Rutin      | Rag1−/− mice               | CD4+ CD62L+ T cells transfer model of colitis | It inhibited STAT4 and IκB phosphorylation, as well as IL-1β and IFN-γ expression in CD4+ spleen cells of the mice | Mascaraque et al. [1] |
|            | Female Wistar rats          | 10 mg of TNBS induced ileitis and colitis | Intragastric rutin resulted in reduced IL-1β and IL-17 mRNA expression in the treatment of ileitis rats, while just tended to decrease levels of IL-17 and IFN-γ in the colitis rats | Mascaraque et al. [53] |
| Myricetin  | IEC-6 cells                | 300 µmol/L indomethacin for 24 h | It increased the expression of tight junction proteins, and reduced JNK/Src phosphorylation | Fan et al. [47] |
|            | Male Kunming mice           | Oral administration of 3% DSS solution for 2 weeks | It suppressed TNF-α, NF-κB and COX-2 expression, and increased tight junction proteins expression | Li et al. [54] |
| Polyphenol | Cell Type or Animal Model | Induction of Intestinal Inflammation | Anti-Inflammatory Mechanism | References |
|------------|--------------------------|------------------------------------|----------------------------|------------|
| Myricetin-3-O-\-b-D-lactose sodium salt | Male C57BL/6 mice | Oral water containing 1.0% DSS | It reduced the protein expression of IL-6, and the phosphorylation of JAK2, STAT3 and NF-κB, as well as TNF-α pathway, increased IL-4 and IL-10 secretion | Zhou et al. [55] |
| Hesperidin | Wistar albino male rats | TNBS-induced colitis | It reduced the colonic levels of NF-κB, TNF-α and IL-6 | Polat et al. [56] |
| Hesperidin methyl chalcone | Male Swiss mice | Acetic acid-induced colitis | It reduced acetic acid-induced NF-κB, IL-6, IL-1β, and IL-33 production and inhibited NF-κB activation by blocking Ser276 | Guazelli et al. [57] |
| Naringin | Mice | Cecal ligation and puncture-induced intestinal sepsis | It inhibited the release of TNF-α and IL-6, increased IL-10, inhibited NF-κB expression | Li et al. [58] |
| | RAW 264.7 macrophages | LPS (1 μg/mL) stimulation for 24 h | It reduced NF-κB translocation and phosphorylation of p38, ERK, and JNK, as well as the expressions of COX-2, IL-1β and TNF-α | Ha et al. [59] |
| EGCG | Male C57BL/6J mice | High fat diet | It protected against gut barrier dysfunction, and decreased ileal and colonic mRNA expression of TNF-α | Dey et al. [60] |
| | Rat intestinal epithelial cells | LPS (1 μg/mL) stimulation for 24 h | It blocked NF-κB signaling via degradation of IκBα and inhibition of NF-κB nuclear translocation, thereby suppressed the expression of adhesion molecules ICAM-1 and VCAM-1 | Myung et al. [61] |
| | Bone marrow-derived macrophages | LPS (1 μg/mL) incubation for 0–1 h | It prevented LPS-induced inflammation through inhibiting IκBα phosphorylation/degradation, NF-κB RelA nuclear translocation, and phosphorylation of ERK1/2, JNK and p38 expression | Joo et al. [62] |
| Genistein | Male Arbor Acre broilers | *Escherichia coli* O78 | It improves intestinal mucosa barrier function by modulating apoptosis and secretion of TNF-α and IL-6 | Zhang et al. [63] |
| | Caco-2 cells | 3% DSS for 7 d | It reduced nuclear NF-κB p65 and upstream TLR4 expression | Zhang et al. [64] |
| | RAW 264.7 macrophage cells | LPS stimulation | It down-regulated TLR4 and NF-κB expression, IκBα degradation and phosphorylation of ERK1/2 and p38, as well as COX-2, TNF-α, IL-6 and IL-1β expression | Byun et al. [65] |
| Cyanidin-3-glucoside | Caco-2 cells | Exposed for 3 h to 50 ng/mL TNF-α | It inhibited NF-κB translocation into the nucleus, and IκBα degradation, as well as IL-6 and COX-2 expression | Ferrari et al. [66] |
| | Caco-2-HUVECs coculture model | Exposed for 1 h to 50 ng/mL TNF-α | It prevented translocation of NF-κB into the nucleus and inhibited leukocyte adhesion in a dose dependent manner | Ferrari et al. [67] |
| | Balbc mice | Drinking water containing 2.5% DSS | It suppressed NF-κB phosphorylation, thereby inhibited IL-1β, IL-6, IL-8, COX-2 and TNF-α mRNA expression | Tan et al. [68] |
| Malvidin 3-glucoside | HUVECs | TNF-α (10 μg/L) stimulation for 6 h | It suppressed IκBα degradation and blocked the nuclear translocation of NF-κB p65 | Huang et al. [69] |
| | Male Wistar rats | TNBS-induced colitis | It reduced leukocyte infiltration, downregulated iNOS and COX-2 expression | Pereira et al. [70] |
| | Caco-2-HUVECs coculture model | TNF-α (1 ng/mL) stimulation for 3 h | It reduced NF-κB mRNA expression, and IL-8 and IL-6 secretion | Kuntz et al. [71] |
| Polyphenol                  | Cell Type or Animal Model          | Induction of Intestinal Inflammation | Anti-Inflammatory Mechanism                                                                 | References                               |
|----------------------------|-----------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------|
| Pelargonidin               | Balb/c mice                       | TNBS-induced colitis                | It decreased the colonic expression of IL-6, TNF-α, IL-1β, and IFN-γ, and increased IL-10 expression | Biagioli et al. [72]                      |
|                            | Female C57BL/6 mice               | Drinking water containing 2.5% DSS for 8 d | It inhibited the activation of NF-κB p65 and IκBα degradation, as well as reduced the serum level of IL-6, IFN-γ and TNF-α | Zhang et al. [73]                         |
|                            | Myofibroblasts-like cell line     | 1 ng/mL IL-1β stimulation for 24 h  | It reduced the IL-8 and COX-2 expression                                                  | Zielinska et al. [74]                    |
| Pelargonidin-3-O-glucoside | RAW 264.7 Macrophages              | 1 µg/mL LPS stimulation for 24 h    | It inhibited nuclear translocation of NF-κB p65, phosphorylation and degradation of IκBα, as well as phosphorylation of JNK, thereby reduced the expression of pro-inflammatory cytokines, including IL-1α, TNF-α, IL-27, and IL-6, and enzymes related to inflammation, such as COX-2 and iNOS | Zhang et al. [75]                         |
|                            | RAW 264.7 Macrophages              | 1 µg/mL LPS stimulation for 24 h    | It suppressed phosphorylation of JNK, p38 MAPK, IκBα and NF-κB p65, and reduced TNF-α and IL-6 production | Duarte et al. [76]                        |
| Caffeic acid phenethyl ester | Male Sprague-Dawley rats          | X-ray irradiation (9 Gy)            | It reduced the plasma level of TNF-α, and phosphorylation of p38 MAPK and suppressed TNF-α, and IL-1β and IL-6 production | Jin et al. [77]                           |
|                            | Male Balb/c mice                  | Drinking water containing 3.5% DSS for 7 d | It inhibited the phosphorylation of NF-κB p65 and IκBα, and blocked nuclear translocation of NF-κB p65, and suppressed TNF-α, IL-1β and IL-6 production | Pandurangan et al. [78]                  |
| Chlorogenic acid           | IPEC-J2 cells                     | 50 ng/mL TNF-α for 3 h             | It inhibited the phosphorylation of NF-κB p65 and IκBα, and blocked nuclear translocation of NF-κB p65, and suppressed TNF-α, IL-1β and IL-6 production | Chen et al. [79]                          |
|                            | Caco-2 cells                      | LPS (0.1 mg/mL) stimulation for 24 h | It inhibited the phosphorylation of NF-κB p65 and IκBα, and blocked nuclear translocation of NF-κB p65, and suppressed TNF-α, IL-1β and IL-6 production | Yu et al. [80]                           |
| Ellagic acid               | C57BL/6 mice                      | Drinking water containing 5% DSS for 7 d | It reduced the protein expression and phosphorylation of ERK1/2, p38, and JNK | Gao et al. [81]                          |
|                            | Wistar Albino rats                | 3% acetic acid (2 ml intrarectal) induced colitis | It decreased the protein levels of TNF-α, COX-2, and NF-κB | Yipel et al. [82]                        |
|                            | Female Balb/C mice                | Drinking water containing 5% DSS for 7 d | It reduced the production of IL-6, TNF-α, and IFN-γ | Marin et al. [83]                         |
|                            | Female C57BL/6 mice               | Four week-long cycles of DSS (1% and 2%) | It inhibited p38 MAPK and STAT3 phosphorylation, IκBα degradation, NF-κB p65 activation, as well as IL-6, COX-2 and iNOS expression | Marin et al. [83]                         |
|                            | Four-week-old male Wistar rats    | TNBS-induced colitis                | It decreased the expression of TNF-α, COX-2, and iNOS, and p38 MAPK, p-JNK and p-ERK1/2, as well as the nuclear translocation of NF-κB p65 | Rosillo et al. [84]                      |
| Resveratrol                | Black-boned chickens              | Circular heat stress               | It reduced the jejunal protein expression of NF-κB | Liu et al. [85]                          |
|                            | Weaned piglets                    | Weaning stress                     | It downregulated MAPK pathway and reduced the levels of intestinal pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α | Meng et al. [86]                          |
|                            | 50 eligible patients              | Ulcerative colitis                 | It reduced plasma levels of TNF-α and activity of NF-κB in peripheral blood mononuclear cells (PBMC) | Samsami-kor et al. [87]                  |
Table 1. Cont.

| Polyphenol | Cell Type or Animal Model | Induction of Intestinal Inflammation | Anti-Inflammatory Mechanism | References |
|------------|--------------------------|-------------------------------------|-----------------------------|------------|
| Curcumin   | Male Sprague-Dawley rats | Diarrhea and constipation induced by intracolonic acetic acid instillation or cold water gavage | It inhibited IκBα degradation and NF-κB phosphorylation, as well as IL-1β and TNF-α | Yao et al. [88] |
|            | Male Sprague-Dawley rats | Experimental colitis induced by intra-rectal administration of TNBS | It Inhibited TLR4, MyD88 and NF-κB protein expression | Lubbad et al. [89] |
| Emodin     | IEC-6 cells              | TNF-α (50 ng/mL) stimulation        | It inhibited the expression of TLR4, NF-κB and NLRP3, also the production of IL-1β and IL-6 | Zhuang et al. [90] |
|            | HT-29 cells              | Flagellin (500 mg/L) stimulation for 24 h | It increased the expression of IκB, but inhibited the expression of TLR5 and MyD88, nuclear translocation of NF-κB p65, as well as the IL-8 production in flagellin-stimulated HT-29 cells | Luo et al. [91] |
|            | Male Wistar rats         | Cecal ligation and puncture induced jejunal sepsis | It decreased the levels of IL-6 and TNF-α, and increased the phosphorylated levels of JAK1 and STAT3 | Chen et al. [92] |

Figure 2. The intestinal anti-inflammatory mediated effects of polyphenols along the TLR4 signaling pathway. EGCG, epigallocatechin-3-gallate; C3G, cyanidin-3-glucoside; MV3G, malvidin 3-glucoside; P3G, pelargonidin-3-O-glucoside; CAPE, caffeic acid phenethyl ester; CGA, chlorogenic acid; EA, ellagic acid. Inhibition; Promotion; Promotion.
Flavonoids are bioactive substances belonging to a family of polyphenolic compounds which exist in natural plants, vegetables, and fruits and consumed in significant amounts as part of the human diet [38]. Flavonoids are recognized as compounds consisting of 3-ring core connected with phenolic hydroxyl groups through three central carbon atoms (Figure 1). According to the connection position of the B-ring (2- or 3-position) and the level of oxidation of the C-ring, flavonoids can be divided into the following six categories: flavonols, flavones, flavanones, anthocyanidins, flavanols, and isoflavones [93]. In addition, there are some flavonoids with unique molecular structure, such as dihydroflavonol and biflavones. The flavone, flavanol, flavanone, and flavanone families were identified depending on the presence of a 3-OH group and a double bond at 2-position. Compounds with a B ring in the 3-position instead of 2 are isoflavones, of which genistein is the most known substance. Anthocyanidins have a fully aromatized C ring while chalcones are related aryl kenotic compounds with a C opening ring [38,94]. Flavonoids are found in natural plants mainly in glycosylated form. As exhibited in Figure 1, there are substantial structural variations in these compounds, which must affect their biological profile. However, numerous studies provided evidence that there is consistency in the anti-inflammatory effects of these compounds in spite of the structure variations [38]. It has become a research hotspot due to their widely reported bioactive functions and low toxicity, thus they have also become potential therapeutic drugs. González et al. [38] summarized recent advances in the favorable effects of these flavonoids on the treatment of inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, asthma, atherosclerosis, ischaemia-reperfusion, and so on, indicating their outstanding pharmaceutical value with multiple bioactivities. It should be noted that flavonoids have exhibited favorable effects on intestinal tight junction proteins [95,96]. In this regard, accumulating studies have indicated that flavonoids can alleviate intestinal inflammation through inhibiting the activation of the TLR4/NF-κB signaling pathway.
4.1.1. Flavones

Apigenin (4′,5,7-trihydroxyflavone) is found in many fruits, herbs, and vegetables, such as celery, parsley, thyme, basil, coriander, and licorice [97]. This flavone has attracted more and more attention due to its anti-inflammatory activities [98–100]. Apigenin pretreatment can ameliorate intestinal damages and restore intestinal barrier integrity in radiation-induced Swiss albino mice, and prevent activation of NF-κB and NF-κB-mediated apoptotic signaling [40]. Apigenin downregulated NF-κB and signal transducer and activator of transcription 3 (STAT3) expression in the LPS-induced colonic epithelial cancer cell [41]. Going downstream, apigenin supplementation exerted protective effects in DSS-induced chronic colitis in mice associated with downregulation of colonic COX-2 and iNOS expression, and IL-1β and TNF-α proinflammatory cytokine [101]. In addition, the intestinal anti-inflammatory effects of apigenin in the treatment of colitis were widely reported [97,102,103].

Luteolin (3′,4′,5,7-tetrahydroxy flavonoids) is present in vegetables (carrots, celery, bell peppers), fruits (apple), and herbs (honeysuckle, chrysanthemum, perilla), which has favorable effects on intestinal barrier function. More specifically, luteolin can attenuate ulcerative colitis, suppress rectal cancer, and prevent irinotecan-induced mucositis [104–107]. From another perspective, luteolin had a notably alleviative effect on intestinal barrier damage induced by decabromodiphenyl ether (BDE-209) in a Caco-2 cell monolayer model through suppressing the phosphorylation of IκBα and the accumulation of NF-κB p50 and ERK expression [42]. Luteolin also relieved DSS-induced colitis in mice, and the mechanism by which is due to the suppression of high mobility group box chromosomal 1 (HMGB1), TLR4, and NF-κB p65 protein levels in the colon [43]. In a co-culture model consisting of intestinal epithelial Caco-2 and macrophage RAW264.7 cells, stimulated with LPS, the addition of luteolin suppressed NF-κB nuclear translocation, followed by reduction of TNF-α and IL-8 mRNA expression, indicating the positive effects of luteolin on gut inflammation [44].

Baicalein (5,6,7-trihydroxyflavonoid) is a flavonoid isolated from Scutellaria baicalensis Georgi with a variety of pharmacological effects, such as anti-inflammation, anti-oxidative stress, anti-infection, and so on [108]. Radiation-induced enteritis may be an ideal model of gastrointestinal inflammation. Some research revealed that baicalein has a therapeutic effect on radiation-induced intestinal inflammation by accelerating crypt regeneration, attenuating endothelial damage, rebalancing gut microbiota, and inhibiting apoptosis [108,109]. In addition, baicalein administration remarkably suppressed the phosphorylation of NF-κB p65 and IκBα in the colon of TNBS-colitis mice, which was in accordance with the inhibitory effects on the protein expression of TLR4 and MyD88 [45]. In a UC rat model, baicalein can suppress the NF-κB and MAPK pathways to achieve anti-inflammatory effects [46].

4.1.2. Flavonols

Quercetin

A plant flavonol, quercetin (3,3′,4′,5,7-pentahydroxyflvanone), present in tea, onions, apples, and red wine, has approved antioxidant, anti-inflammatory, anti-allergic, and anti-virus properties [110], indicating its potential therapeutic application. It was reported that intestinal epithelial (IEC-6) cells pretreated with 5 μmol/L quercetin could resist intestinal barrier dysfunction injury by indomethacin via reducing the JNK phosphorylation and subsequent activation [47]. Pretreatment of quercetin decreased the expression of IL-8 and suppressed the translocation of the p50 subunit of NF-κB into the nucleus in Vibrio cholerae induced intestinal epithelial cells [48]. In acute necrotizing pancreatitis disease induced by sodium taurocholate in rats, quercetin blocked intestinal TLR4/MyD88/p38 MAPK pathway and inhibited endoplasmic reticulum stress, thereby ameliorating intestinal
barrier disruption and inflammation [49]. A quercetin oxidation metabolite present in onion peel showed protective effects against indomethacin-induced intestinal epithelial barrier dysfunction accompanied by an inhibitory effect on the NF-κB activation and IL-8 secretion [50]. Interestingly, quercetin exhibited a protective effect on mitochondrial dysfunction in intestinal Caco-2 cells [111]. Furthermore, it attenuated intestinal mucosal damage from ischemia-reperfusion injury by inhibiting COX-2 and myeloperoxidase (MPO) expression [112]. Moreover, quercetin was found to be the main active ingredient in a traditional Chinese medicine widely used for UC treatment [113].

Kaempferol

Kaempferol, a natural flavonol component isolated from *Cudrania tricuspidata*, is known to have multiple bioactivities, such as anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-cancer effects [114]. Pharmacologically, increasing evidences suggest that kaempferol is an anti-inflammatory compound with activity inhibiting NF-κB, AP-1, and Janus kinase (JAK)/STAT pathways in vitro [115,116]. Lee et al. [115] and Fan et al. [117] revealed that kaempferol can improve barrier function in rat intestinal epithelial cells. A later study also demonstrated that kaempferol can attenuate diquat-induced intestinal dysfunction in intestinal porcine epithelial cells, indicating a functional role of kaempferol in the intestinal barrier [118]. More specifically, kaempferol may be an effective therapeutic agent for IBD treatment reflected by its inhibitory activity on multiple inflammatory pathways and evidenced by blocking NF-κB, I-κB, and STAT phosphorylation, and reducing TLR4 expression, as well as IL-1β, IL-6 and TNF-α secretion induced by LPS in rat intestinal microvascular endothelial cells [51]. Afterwards, the author further demonstrated that kaempferol protected mice from high-fat diet-induced obesity and intestinal inflammation by reducing the activation of the TLR4/NF-κB pathway [52].

Rutin

Rutin, quercetin-3-rhamnosyl glucoside, possess a variety of pharmacological effects, such as antioxidant, anti-inflammatory, antibacterial, and radioresistant effects [119]. More importantly, rutin has long been elucidated as the intestinal anti-inflammatory property in acetic acid [120], TNBS [121], and DSS induced rat colitis [122]. Profoundly, rutin inhibited the STAT4-IFN-γ pathway in splenic CD4+ cells of mice with CD4+CD62L+T cells transfer colitis [1]. Afterwards, the author conducted a profound trial to explore whether rutin and its closely related flavonol quercetin can protect against TNBS-induced ileitis and colitis. The results found that intragastric rutin could protect mice against TNBS-induced ileitis, as evidenced by amelioration of anorexia, damage score, body weight loss, and reduction of IL-1β and IL-17 mRNA levels. Colitis induced by TNBS was also ameliorated by rutin which was evidenced by reducing colon thickening, damage score, and the expression of IL-17 and IFN-γ [53].

Myricetin and Myricetin-3-O-b-D-Lactose Sodium Salt

Myricetin can be found in many edible plants, such as medicinal herbs, teas, and many fruits, possessing antioxidative, anticarcinogenic, and anti-inflammatory properties [123–125]. Myricetin has been proven to improve the intestinal barrier-promoting efficiency in rat IEC-6 cells evidenced by enhanced transepithelial electrical resistance and anti-bacterial effect [126]. Based on that, myricetin further exhibited protective effects on the IEC-6 cells against indomethacin-induced injury by increasing the expression of the tight junction proteins, and reducing JNK/Src phosphorylation [47]. Not surprisingly, it was reported that myricetin could alleviate DSS induced colitis via suppressing the TNF-α/NF-κB pathway, thereby increasing tight junction protein expression compared to colitis mice [54]. In addition, oral administration of myricetin-3-O-b-D-lactose sodium salt (M10), a derivative of myricetin, also exhibited preventive effect against ulcerative colitis through inhibiting the activation of IL-6 and TNF-α pathway, and phosphorylation of JAK2, STAT3, and NF-κB [55]. Herein, the results also indicated that M10 had higher efficacy than myricetin
in the treatment of DSS-induced ulcerative colitis. Prior to that, Zhu et al. [127] also revealed similar results that M10 showed higher activities in preventing UC than myricetin.

4.1.3. Flavanones

Hesperidin

Hesperidin (5,7,3′-trihydroxy-4′-methoxy-flavanone-7-rhamnoglucoside), belonging to the flavanone family, exists widely in citrus fruits and juices [128]. It was demonstrated that hesperidin had favorable effects on the intestine due to its antioxidant and anti-inflammatory activities [56,129,130]. For instance, hesperidin treatment ameliorates DSS-induced colitis and protects against intestinal inflammation through activating the nuclear factor E2-related factor 2 (Nrf2) antioxidant pathway and restoring intestinal barrier function [131]. A study conducted by Polat et al. [56] demonstrated that hesperetin administration significantly reduced colonic levels of NF-κB, TNF-α, and IL-6, thereby protecting the mice against TNBS-induced colitis. Alternatively, hesperidin methyl chalcone, the methylation process of hesperidin with higher water solubility, significantly reduced TNF-α, IL-6, IL-1β, and IL-33 production and inhibited NF-κB activation as observed by an increase in the total p65/phosphorylated-p65 ratio in a mouse model of acetic acid-induced colitis [57].

Naringenin

Naringin (4′,5,7-trihydroxyflavanone) extracted from citrus peels and grapefruit has been reported to exhibit various biological effects. Therein, some pieces of evidence show that naringin had beneficial effects on the intestinal barrier and amelioration of colitis [132–134]. In detail, naringin improved impaired intestinal permeability, inhibited the release of TNF-α and IL-6, and the expression of NF-κB, and thereby alleviated sepsis-induced intestinal mucosal injury [58]. Naringin supplementation reduced the development of colitis induced by DSS in mice through suppression of epithelial TNF-α production [133]. Moreover, a study performed by Ha et al. [59] also demonstrated that naringin inhibited the LPS-mediated activation of NF-κB and MAPKs pathways, and downstream COX-2, IL-1β, and TNF-α expression in macrophages.

4.1.4. Flavanols

Epigallocatechin-3-Gallate (EGCG)

Tea, derived from the leaves of *Camellia sinensis*, is one of the most widely consumed beverages worldwide. EGCG, a predominant component of green tea polyphenols, is indicated to be primarily responsible for the anti-inflammatory and antioxidant effects of green tea [135]. Previously, a study conducted by Navarro-Perán et al. [136] demonstrated that EGCG could suppress TNF-α-induced NF-κB activation in colon cancer cells. In a high-fat diet-induced nonalcoholic steatohepatitis model in mice, EGCG significantly attenuated intestinal inflammation by decreasing ileal and colonic TNF-α expression and preventing the loss in expression of intestinal tight junction proteins [60]. EGCG inhibited LPS-induced IκBα degradation and NF-κB nuclear translocation in rat intestinal epithelial cells, thus suppressing adhesion molecules expression, indicating the therapeutic potential of EGCG on intestinal inflammatory diseases [61]. Moreover, EGCG prevented LPS-induced pro-inflammatory gene expression through blocking NF-κB and MAPK signaling pathways in bone marrow-derived macrophages [62].

4.1.5. Isoflavones

Genistein

Genistein (4′,5,7-trihydroxyisoflavone) is a kind of natural phytoestrogens and isoflavones richly found in soybeans. Numerous in vitro and in vivo studies provided evidence that genistein plays an important role in the prevention and treatment of intestinal inflammation [63,137–139]. A study performed by Lv et al. [140] demonstrated that adding genistein into the diet of chicks can ameliorate LPS-induced intestinal injury via altering the
RNA expression profile. More specifically, genistein inhibited I-κB kinase/NF-κB signaling, MAPK cascade, and JAK-STAT pathway, thereby improving the growth performance of chicks. Not surprisingly, genistein reduced DSS-induced inflammation response via suppressing the activation of TLR4/NF-κB signaling in Caco-2 cells [64]. In addition, in LPS-induced macrophages, gamma-irradiated genistein exerted an anti-inflammatory property associated with inhibition of TLR4-mediated NF-κB and MAPK pathways [65].

4.1.6. Anthocyanins

**Cyanidin-3-glucoside (C3G)**

Anthocyanin-rich extracts have exhibited anti-inflammatory activity in mouse colitis models [141]. Cyanidin-3-glucoside (C3G) is a kind of natural anthocyanin originated from *Aronia melanocarpa* berries belonging to the Rosaceae family, Queen Garnet plums (*Prunus salicina* Lindl.), and purple carrots, which has been proven to provide anti-inflammatory potential in TNBS-induced colitis mice, LPS-stimulated Caco-2 cellular monolayer inflammation [141], and DSS-induced inflammatory bowel disease in rats [142]. Tan et al. [143] summarized the potential mechanism of C3G against intestinal injury, indicating its important role in the TLR4/NF-κB mediated pathway. More specifically, pretreatment with C3G dose-dependently prevented TNF-α-induced NF-κB pathway activation, thereby inhibiting IL-6 and COX-2 expression [66]. Moreover, in TNF-α-induced Caco-2 and human umbilical endothelial cells (HUVECs) coculture model, C3G prevented the translocation of NF-κB into the nucleus and inhibited leukocyte adhesion in a dose-dependent manner, which suggested that anthocyanins may contribute to the treatment of chronic gut inflammatory diseases [67]. Not surprisingly, C3G inhibited NF-κB phosphorylation, reduced mRNA expression of pro-inflammatory cytokines including IL-1β, IL-6, IL-8, COX-2, and TNF-α, and protein levels of apoptosis related genes in DSS-induced colitis mice, providing new ideas for using C3G as adjuvant agent for treating UC [68].

**Malvidin 3-glucoside (MV3G)**

Malvidin 3-glucoside, one of the major anthocyanins present in blueberries, has been proven to possess antioxidant and anti-inflammatory function [69,144]. A study conducted by Liu et al. [145] demonstrated the favorable effects and mechanism of malvidin 3-glucoside (MV3G) in alleviating gut dysfunction using a murine colitis model induced by DSS, and the results showed that MV3G could attenuate intestinal inflammation through increasing IL-10 expression, and modulating gut microbiome and metabolome, indicating the beneficial effects of MV3G in promoting intestinal homeostasis and health. In a TNF-α-induced inflammatory model in HUVECs, MV3G suppressed IκBα degradation and blocked the nuclear translocation of NF-κB p65 [69]. Furthermore, MV3G downregulated the expression of iNOS and COX-2 in a TNBS-induced colitis rat model [70]. Moreover, in an in vitro epithelial-endothelial co-culture model, MV3G suppressed TNF-α stimulated expression of adhesion molecules, leukocyte adhesion, NF-κB mRNA expression, and secretion of IL-8 and IL-6, indicating the potential anti-inflammatory activity for the management of chronic intestinal diseases [71].

**Pelargonidin and Pelargonidin-3-O-glucoside (P3G)**

Pelargonidin-3-O-glucoside (P3G) is a major anthocyanin isolated from raspberries and strawberries, thought to be beneficial for human health [146,147]. Some pieces of evidence indicated that administration of pelargonidin attenuated TNBS-induced colitis in a dose-dependent manner [72]. To be specific, treating mice with TNBS increased the colonic expression of IL-6, TNF-α, IL-1β, and IFN-γ, colitis score, and intestinal permeability; this was fully reversed by pelargonidin administration [72]. In the study performed by [75], LPS stimulation for 1 h markedly promoted phosphorylation and degradation of IkBα, nuclear translocation of NF-κB p65, and phosphorylation of JNK, but this pattern was suppressed when macrophages were pretreated with P3G. Pretreatment with P3G also reduced 11 pro-inflammatory cytokines’ secretion, including IL-1α, TNF-α, IL-27, and IL-6, and enzymes...
(COX-2 and iNOS) related to inflammation in LPS-induced macrophages [75]. Similarly, P3G exhibited anti-inflammatory effects in LPS induced macrophages on account of arrest of the IκBα and NF-κB activation and reduction in JNK and p38 MAPK phosphorylation [76].

4.2. Phenolic Acids

4.2.1. Caffeic Acid and Caffeic acid Phenethyl Ester (CAPE)

Caffeic acid is one of the most abundant hydroxycinnamic acids widely distributed in vegetables, fruits, and some beverages, such as potatoes, gooseberries, artichokes, and coffee [148]. It was indicated that caffeic acid can reach appropriate concentration in the colon where it could act on the intestinal cells and achieve its anti-inflammatory effects [74]. More than a decade ago, mice consuming caffeic-acid-enriched diets exhibited attenuation of DSS-induced colitis [149]. Correspondingly, caffeic acid exerted anti-inflammatory effects in DSS colitis mice associated with the inhibition of the NF-κB signaling pathway and suppression of the secretion of IL-6, TNF-α, and IFN-γ [73], which is similar with the results of [150]. In the study conducted by Zielińska et al. [74], IL-1β-stimulated myofibroblasts of the colon were employed as a human intestinal inflammation model. The results found that caffeic acid could reduce the expression of COX-2 and IL-8. In addition, CAPE, a biologically active ingredient of honeybee propolis, showed protective effects in treatment of DSS-induced colonic fibrosis [151] and intestinal ischemia-reperfusion injury [152]. In an ionized radiation-induced intestinal injury model in rats, pretreatment of CAPE reduced intestinal epithelial cell apoptosis, plasma TNF-α level, and phosphorylation of p38MAPK [77]. Recently, in a DSS-induced UC in a mouse model, administration of CAPE protected against colon damage by decreasing the expression of NF-κB and production of key cytokines [78].

4.2.2. Chlorogenic Acid (CGA)

Chlorogenic acid (CGA) is a polyphenol compound present in various fruits, vegetables, and plants, such as honeysuckle, Eucommia ulmoides, coffee, and tea [153,154]. CGA has shown many biological effects including antioxidation, anti-inflammatory, anti-cancer, and antibacterial action [155,156]. Many in vitro and in vivo investigations reported that CGA can alleviate intestinal injury and inflammation [157–159]. For instance, CGA was shown to attenuate DSS-induced colitis in mice through the MAPK/ERK/JNK pathway [81]. Moreover, Vukelić et al. [160] also found that CGA can suppress the expression of ERK1/2, JNK1/2, STAT3, and nuclear translocation of NF-κB p65 for the purpose of ameliorating DSS-induced colitis. A study performed by Chen et al. [79] revealed that chlorogenic acid attenuated diquat-induced intestinal injury in weaned pigs associated with reduction in inflammatory cytokine secretion, and suppressed TNF-α-induced inflammation in IPEC-J2 cells via decreasing the phosphorylation of NF-κB and IκBα. CGA blocked the NF-κB pathway by preventing phospho-p65 translocation into cell nuclei, and suppressed TNF-α, IL-1β, and IL-6 production, and thereby restored intestinal epithelial tight-junction integrity [80]. It was also demonstrated that CGA could attenuate colonic barrier damage and promote dynamic distribution of tight junction proteins in TNBS-induced colitic rats [161]. CGA could be a promising medical countermeasure for the alleviation of intestinal inflammation.

4.2.3. Ellagic Acid (EA)

Ellagic acid (EA), found in pomegranate (Punica granatum L.), has shown to exert anti-inflammatory and antioxidant properties. In this context, EA-enriched pomegranate extract markedly decreased COX-2 and iNOS overexpression, reduced MAPKs phosphorylation, and prevented nuclear NF-κB translocation, thereby attenuated chronic colonic inflammation [84]. In an ulcerative colitis model induced by acetic acid in rats, EA administration decreased the protein levels of TNF-α, COX-2, and NF-κB, and thereby exerted protective effects on colonic inflammation [82]. In the acute DSS-induced mice colitis model, EA attenuated colitis severity slightly through the reduction of inflammatory mediators
(IL-6, TNF-α, and IFN-γ) [83]. Moreover, EA inhibited the NF-κB, p38 MAPK, and STAT3 signaling pathway, and enzymes related to inflammation, such as COX-2 and iNOS [83]. This pattern provides evidences that EA could be used in the dietary prevention of intestinal inflammation. Furthermore, urolithins, which are microbial metabolites of ellagic acid, have been widely reported in intestinal anti-inflammatory activity. In the DSS-induced rat colitis model, the author reported that urolithin-A decreased inflammation markers (iNOS and COX-2) and positively modulated the gut microbiota [162]. A study conducted by González-Sarrias et al. [163] revealed that urolithin-A is the main compound responsible for the EA anti-inflammatory properties, which is evidenced by its inhibitory effects on the activation of NF-κB and MAPK, and COX-2 expression in IL-1β-treated human colonic fibroblasts. Similarly, urolithin-A ameliorated cytokine-induced inflammation in human colon fibroblasts via downregulation of the levels of IL-8 and phenyl glycidyl ether E2 (PGE2), as well as cell migration and adhesion [164]. Some studies also revealed the protective effects of urolithin-A on gut barrier integrity [165,166]. Taken together, whether the intestinal inflammatory effects of EA are due to its microbiota-derived urolithins requires further characterization.

4.3. Stilbenes

Resveratrol

Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a polyphenolic compound found in peanuts, grape skins, and red wine [167]. Due to its multiple pharmacological activities, such as anti-inflammatory, antioxidant, and antitumor properties, it has been proven to be effective in a variety of inflammatory diseases, such as arthritis [168], pancreatitis [169], and UC [170,171]. Multiple lines of evidence indicate that resveratrol could alleviate intestinal injury and inflammation [85–87]. Additionally, an earlier study demonstrated that resveratrol could inhibit TLR4-mediated NF-κB activation through inhibiting TRAF6, and thus inhibiting JNK and p38 MAPK activation [172]. With our current knowledge, resveratrol could inhibit NF-κB activation and COX-2 expression in RAW264.7 cells following TLR4 stimulation [173]. Under circular heat stress, resveratrol reduced the protein expression of NF-κB and heat shock proteins (HSPs) in the jejunal villi, thereby alleviating jejunum mucosa injuries [174]. Resveratrol also reduced intestinal pro-inflammatory cytokine production including IL-1β, IL-6, and TNF-α, and downregulated the MAPK signaling pathway in post-weaning piglets [175]. More importantly, 6 weeks supplementation with 500 mg resveratrol can alleviate UC in patients associated with reduction in plasma levels of TNF-α and activity of NF-κB in peripheral blood mononuclear cells (PBMC) [176].

4.4. Other Polyphenols

4.4.1. Curcumin

Curcumin, a natural active component extracted from the root of turmeric, a rhizomatous herbaceous perennial plant of the ginger family, is widely known to possess anti-inflammatory and antioxidant effects [88]. Previously, numerous studies in both animals and cell lines have demonstrated the inhibitory activity of curcumin on TLR4/MyD88/NF-κB signaling [89,90,177,178]. In intracolonic acetic acid-induced intestinal diarrhea and cold water induced constipation rat models, curcumin showed inhibitory effects on the NF-κB pathway by suppressing IκBα degradation and NF-κB phosphorylation [91]. IκBα inhibits NF-κB activation via forming an inactive NF-κB/IκBα complex [92]. It also attenuated experimental colitis induced by intra-rectal administration of TNBS through inhibition of TLR4 receptor, MyD88, and NF-κB protein expression [179].

4.4.2. Emodin/Rhein

Emodin/rhein (1,3,8-trihydroxy-6-methyl-9,10-anthraquinone) is a natural anthraquinone compound that derives from many Polygonaceae plants, such as Rheum officinale Baill. There has been growing evidence showing that emodin with multiple pharmacological effects may be a promising agent for UC treatment [180–182]. Chen et al. [183]
conducted a trial to investigate whether emodin can protect the jejunum against sepsis injury by inhibiting inflammation. As expected, the results found that emodin alleviated jejunum injury and inflammation via activating the JAK1/STAT3 signaling pathway, and decreasing the levels of IL-6 and TNF-α in septic rats. After that, it was observed that emodin markedly downregulated the expression of TLR5 and NF-κB p65 in the colon of DSS-induced colitis mice [182]. Besides, it also increased the expression of IκB, but inhibited the expression of TLR5 and MyD88, nuclear translocation of NF-κB p65, as well as the IL-8 production in flagellin-stimulated HT-29 cells [182]. In vitro, emodin led to inactivation of TLR4, NF-κB, and NLRP3, and also inhibition of IL-1β and IL-6 production, thereby exerting protective effects against barrier disruption and inflammation in an IEC-6 cell model with TNF-α stimulation, indicating potential therapeutic effects against intestinal diseases [181].

5. Conclusions and Future Perspectives

Polyphenols are a huge and various group of natural compounds of which only a few have been investigated regarding their alleviative effect on intestinal inflammation. This review summarized the intestinal anti-inflammatory properties of more than 20 kinds of polyphenols associated with modulation of the TLR4/NF-κB-mediated signaling pathway. It should be noted that the mechanisms for ameliorating intestinal inflammation are pleiotropic and usually target multiple sites of action in the TLR4/NF-κB signaling pathway, some of them are common between different polyphenols. In this regard, the listed polyphenols, collectively, inhibit the TLR4 receptor activation, and block the nuclear translocation of NF-κB, thereby reducing the production of downstream pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α, and IFN-γ, and inflammation related enzymes, such as COX-2 and iNOS. Moreover, besides their inhibitory effect on TLR4/NF-κB cascade, these mentioned polyphenols also inhibit MAPK and JAK/STAT signaling pathways, which further confirmed their intestinal anti-inflammatory properties. This review provides evidence that polyphenols targeting the TLR4/NF-κB signaling pathway might be an effective approach or adjuvant agent to treat IBD in future clinical research implications.

Alterations in chromatin play a vital role in pathological processes via regulating gene transcription [184]. Epigenetic processes with no changes to the DNA sequences mainly include DNA modifications, histone post-translational modifications (PTMs), microRNAs (miRNAs), and chromatin remodeling [185]. A recent review has summarized how polyphenols ameliorate various inflammatory diseases via epigenetic modification [186]. Although this review covered multiple polyphenols applied in various in vitro and in vivo inflammatory models for investigating their epigenetic regulatory mechanisms, few studies have focused on the epigenetic-mediated actions of these polyphenols to intestinal inflammatory models. Hence, in-depth investigations to reveal these polyphenols attenuating IBD associated with epigenetic alterations may help in finding new therapeutic targets for treating IBD. To the best of our knowledge, post-transcriptional modifications in RNA may have regulatory effects on different signal transductions [184]. In this respect, it will be of great benefit if further research is directed towards revealing how these polyphenols differentially regulate inflammatory-related miRNAs, and how they finally ameliorate the development of IBD. Furthermore, no studies report the effect of polyphenols on histone acylation. This lack of information highlighted the necessity of investigating the mechanisms by which polyphenols intervene in epigenetic modification. In addition to epigenetic regulations, most of the polyphenols containing a number of phenolic hydroxyl groups present low water solubility and are poorly absorbed in the small intestine, which may result in a great deal of differences in the results of in vivo and in vitro models. Therefore, the poor bioavailability of multiple polyphenols is another problem to be solved in further investigations. In this context, exploring nano-emulsion and nanoparticles formulations for polyphenols would be beneficial to improve the bioavailability of polyphenols [187]. More importantly, the anti-inflammatory effects of polyphenols must depend greatly on pharmacokinetics and cell access [38]. A substantial body of evidence has elucidated the pharmacokinetic
profile of polyphenols. For example, quercetin glycosides are substrates of the intestinal glucose transporter (SGLT-1) in the rat, which may promote their absorption in the small intestine [188]. It was reported that flavanones, such as hesperidin and naringenin, can be taken up by epithelial cells through a H^+—linked transporter and transcellular passive diffusion, thereby absorbed from the gastrointestinal tract [189–191]. Investigating pharmacokinetic variations between different polyphenols could help to further explore various combinations of polyphenols with similar absorption rates and distribution sites, and examine any potentiation of intestinal anti-inflammatory effects resulting from such combinations. On the other hand, it should be noted that polyphenols may exert anti-inflammatory effects in a dose-dependent manner. That is, increasing evidences indicate that polyphenols may show toxicity when used at higher concentrations [41,67,118]. Therefore, it is inevitable to explore effective technologies for enhancing bioavailability of several polyphenols at lower doses, such as solubilizers, targeted drug-delivery systems [192], and aforementioned nanotechnology. Furthermore, the anti-inflammatory effects of polyphenols are also dependent on the catabolites derived from the microbiota. From this perspective, the fermentation of phenolic compounds is an important issue that might be taken into consideration when investigating their beneficial effects. As stated in this review, numerous studies reported the intestinal anti-inflammatory effects of a single phytochemical substance; few studies investigated the interactions occurring between polyphenols [193]. Further work should therefore be conducted to investigate the polyphenol-polyphenol interactions and the combined effects of these interactions during intestinal inflammation. It has to be mentioned that pharmacokinetics of polyphenols should be taken into account when addressing the interactions due to the discrepancies in absorption, distribution, metabolism, and excretion inside the body [194,195].

Author Contributions: Conceptualization and writing—original draft preparation, C.Y.; writing—review and editing, D.W.; supervision, Z.Y.; funding acquisition, T.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Tian Wang, grant number 2018YFD0501101.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: This work was supported by the National Key Research and Development Program of China (No. 2018YFD0501101).

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Mascaraque, C.; Aranda, C.; Ocón, B.; Monte, M.J.; Suárez, M.D.; Zarzuelo, A.; Marín, J.G.; Martínez-Augustin, O.; de Medina, F.S. Rutin has intestinal antiinflammatory effects in the CD4+ CD62L+ T cell transfer model of colitis. Pharmacol. Res. 2014, 90, 48–57. [CrossRef] [PubMed]
2. Xavier, R.J.; Podolsky, D.K. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007, 448, 427–434. [CrossRef] [PubMed]
3. Yin, F.; Huang, X.; Lin, X.; Chan, T.F.; Lai, K.P.; Li, R. Analyzing the synergistic adverse effects of BPA and its substitute, BHPF, on ulcerative colitis through comparative metabolomics. Chemosphere 2022, 287, 132160. [CrossRef] [PubMed]
4. Liu, M.L.; Yuan, W.; Park, S.M. Association between IL-10 rs3024505 and susceptibility to inflammatory bowel disease: A systematic review and meta-analysis. Cytokine 2022, 149, 155721. [CrossRef]
5. Wang, N.; Wang, H.G.; Yao, H.; Wei, Q.; Mao, X.-M.; Jiang, T.; Xiang, J.; Dila, N. Expression and activity of the TLR4/NF-κB signaling pathway in mouse intestine following administration of a short-term high-fat diet. Exp. Ther. Med. 2013, 6, 635–640. [CrossRef]
6. Burge, K.; Gunasekaran, A.; Eckert, J.; Chaaban, H. Curcumin and intestinal inflammatory diseases: Molecular mechanisms of protection. Int. J. Mol. Sci. 2019, 20, 1912. [CrossRef]
7. Lu, Y.; Li, X.R.; Liu, S.S.; Zhang, Y.F.; Zhang, D.K. Toll-like receptors and inflammatory bowel disease. Front. Immunol. 2018, 9, 72. [CrossRef]
8. Zhang, W.W.; Qi, S.Z.; Xue, X.F.; Al Naggar, Y.; Wu, L.M.; Wang, K. Understanding the gastrointestinal protective effects of polyphenols using foodomics-based approaches. Front. Immunol. 2021, 12, 671150. [CrossRef]
9. Islam, M.A.; Alam, F.; Solayman, M.; Khalil, M.I.; Kamal, M.A.; Gan, S.H. Dietary phytochemicals: Natural swords combating inflammation and oxidation-mediated degenerative diseases. *Oxid. Med. Cell. Longev.* 2016, 2016, 5137431. [CrossRef]

10. Zhang, Y.J.; Peng, L.; Li, W.Y.; Dai, T.Y.; Nie, L.; Xie, J.; Ai, Y.; Li, L.F.; Tian, Y.; Sheng, J. Polyphenol extract of *moringa oleifera* leaves alleviates colonic inflammation in dextran sulfate sodium-treated mice. *Evid.-Based Complementary Altern.* 2020, 2020, 6295402. [CrossRef]

11. Ding, S.; Chi, M.; Scull, B.; Rigby, R.; Schwerbrock, N.; Magness, S.; Jobin, C.; Lund, P. High-fat diet: Bacteria interactions promote inflammatory inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS ONE* 2010, 5, e12191. [CrossRef] [PubMed]

12. Frantz, S.; Falcao-Pires, I.; Balligand, J.; Bauersachs, J.; Brutsaert, D.; Ciccarelli, M.; Dawson, D.; de Windt, L.J.; Giacca, M.; Hamdani, N.; et al. The innate immune system in chronic cardiomyopathy: A European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. *Eur. J. Heart Fail.* 2018, 20, 445–459. [CrossRef] [PubMed]

13. Islam, M.A.; Alam, F.; Solayman, M.; Khalil, M.I.; Kamal, M.A.; Gan, S.H. Dietary phytochemicals: Natural swords combating inflammation and oxidation-mediated degenerative diseases. *Oxid. Med. Cell. Longev.* 2016, 2016, 5137431. [CrossRef]

14. Akira, S. Toll-like receptors in innate immunity. *Adv. Immunol.* 2001, 78, 1–56. [CrossRef] [PubMed]

15. Gohda, J.; Matsumura, T.; Inoue, J. Cutting edge: TNFR-associated factor (TRIF) 6 is essential for MyD88-dependent pathway but not toll/IL-1 receptor domain-containing adaptor-inducing IFN-β (TRIF)-dependent pathway in TLR signaling. *J. Immunol.* 2004, 173, 2913–2917. [CrossRef] [PubMed]

16. Newton, K.; Dixit, V.M. Signaling in innate immunity and inflammation. *Cold Spring Harb. Perspect. Biol.* 2012, 4, a6049. [CrossRef] [PubMed]

17. Guven-Maiorov, E.; Keskin, O.; Gursoy, A.; Nussinov, R. A structural view of negative regulation of the toll-like receptor-mediated immunity pathway. *Biophys. J.* 2015, 109, 1214–1226. [CrossRef]

18. Keating, S.E.; Maloney, G.M.; Moran, E.M.; Bowie, A.G. IRAK-2 participates in multiple toll-like receptor signaling pathways to new insights into transcriptional regulations in innate immunity. *Biochem. Pharmacol.* 2006, 72, 1102–1113. [CrossRef] [PubMed]

19. Doyle, S.L.; O’Neill, L.A. Toll-like receptors: From the discovery of NF-κB to new insights into transcriptional regulations in innate immunity. *Biochem. Pharmacol.* 2006, 72, 1102–1113. [CrossRef] [PubMed]

20. Häcker, H.; Redecke, V.; Blagojev, B.; Kratchmarova, I.; Hsu, L.; Wang, G.G.; Kamps, M.P.; Raz, E.; Wagner, H.; Häcker, G.; et al. Specificity in toll-like receptor signaling through distinct effector functions of TRAF3 and TRAF6. *Nature 2006*, 439, 204–207. [CrossRef]

21. Sato, S.; Sugiyama, M.; Yamamoto, M.; Watanabe, Y.; Kawai, T.; Takeda, K.; Akira, S.Z. Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF)-dependent pathway in TLR signaling. *J. Immunol.* 2003, 171, 4304–4310. [CrossRef] [PubMed]

22. Coussens, L.M.; Sepulveda, A.; Bladé, C.; Fernandez-Larrea, J.; Pujadas, G.; Salvadó, M.; et al. Grape-seed procyanidins act as antiinflammatory agents in endotoxin-stimulated RAW 264.7 macrophages by inhibiting NFκB signaling pathway. *J. Agric. Food Chem.* 2007, 55, 4357–4365. [CrossRef]

23. Baumgart, D.C.; Carding, S.R. Gastroenterology 1 Inflammatory bowel disease: Cause and immunobiology. *Lancet 2007*, 369, 1627–1640. [CrossRef]

24. de Souza, H.S.P.; Fiocchi, C. Immunopathogenesis of IBD: Current state of the art. *Nat. Rev. Gastroenterol. Hepatol.* 2016, 13, 13–27. [CrossRef] [PubMed]

25. Toiyama, Y.; Araki, T.; Yoshiyama, S.; Hiro, J.; Miki, C.; Kusunoki, M. The expression patterns of toll-like receptors in the ileal pouch mucosa of postoperative ulcerative colitis patients. *Surg. Today 2006*, 36, 287–290. [CrossRef] [PubMed]

26. Chen, C.Y.; Kao, C.L.; Liu, C.M. The cancer prevention, anti-inflammatory and anti-oxidation of bioactive phytochemicals attenuate inflammation in dextran sulfate sodium-induced experimental colitis in mice. *Int. J. Immunopathol. Pharmacol.* 2014, 27, 615–627. [CrossRef]

27. Wang, W.P.; Xia, T.S.; Yu, X.P. Wogonin suppresses inflammatory response and maintains intestinal barrier function via TLR4-MyD88-TAK1-mediated NF-κB pathway in vitro. *Inflamm. Res.* 2015, 64, 423–431. [CrossRef]

28. Martinez-Micaelo, N.; González-Abuin, N.; Terra, X.; Picard, C.; Ardevol, A.; Bladé, C.; Fernandez-Larrea, J.; Pujadas, G.; Salvadó, M.; et al. Specificity in toll-like receptor signaling through distinct effector functions of TRAF3 and TRAF6. *Nature 2006*, 439, 204–207. [CrossRef] [PubMed]

29. Toumi, R.; Souifi, I.; Rafa, H.; Belkhelfa, M.; Biad, A.; Touil-Boukoffa, C. Probiotic bacteria *Lactobacillus* and *Bifidobacterium* attenuate inflammation in dextran sulfate sodium-induced experimental colitis in mice. *Int. J. Immunopathol. Pharmacol.* 2014, 27, 615–627. [CrossRef]

30. Do, J.H.; Chang, S.K. Expression of cyclooxygenase-2 and inducible nitric oxide synthase in colorectal cancer cell lines related to microsatellite instability. *Gastroenterology 2003*, 124, A365–A366. [CrossRef]

31. Yoo, S.Y.; Kim, K.; Nam, H.J.; Lee, D. Discovering health benefits of phytochemicals with integrated analysis of the molecular network, chemical properties and ethnopharmacological evidence. *Nutrients 2018*, 10, 1042. [CrossRef] [PubMed]
34. Middleton, E., Jr; Kandaswami, C.; Theoharides, T.C. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease and cancer. Pharmacol. Rev. 2000, 52, 673–751.

35. Salih, M.; Osman, W.; Garelnabi, E.; Osman, Z.; Osman, B.; Khalid, H.; Mohamed, M. Secondary metabolites as anti-inflammatory agents. J. Phytopharmacol. 2014, 3, 275–285. [CrossRef]

36. Egert, S.; Bosy-Westphal, A.; Seibler, J.; Kürbitz, C.; Settler, U.; Plachta-Danielzik, S.; Wagner, A.E.; Frank, J.; Schrezenmeir, J.; Rimbach, G.; et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: A double-blinded, placebo-controlled cross-over study. Br. J. Nutr. 2009, 102, 1065–1107. [CrossRef]

37. Perez-Gregorio, R.; Simal-Gandara, J. A critical review of bioactive food components, and of their functional mechanisms, biological effects and health outcomes. Curr. Pharm. Des. 2017, 23, 2731–2741. [CrossRef]

38. González, R.; Ballester, I.; López-Posadas, R.; Suárez, M.D.; Zarzuelo, A.; Martínez-Augustin, O.; Medina, F.S.D. Effects of flavonoids and other polyphenols on inflammation. Crit. Rev. Food Sci. 2011, 51, 331–362. [CrossRef]

39. Schink, A.; Neumann, J.; Leifke, A.L.; Ziegler, K.; Fröhlich-Nowoisky, J.; Cremer, C.; Thines, E.; Weber, B.; Pöschl, U.; Schuppan, D.; et al. Screening of herbal extracts for TLR2- and TLR4-dependent anti-inflammatory effects. PLoS ONE 2018, 13, e0203907. [CrossRef]

40. Begum, N.; Rajendra, P.N.; Kanimozhi, G.; Agilan, B. Apigenin prevents gamma radiation-induced gastrointestinal damages by modulating inflammatory and apoptotic signalling mediators. Nat. Prod. Res. 2021, 36, 1631–1635. [CrossRef]

41. Ai, X.; Qin, Y.; Liu, H.; Cui, Z.; Li, M.; Yang, J.; Zhong, W.; Liu, Y.; Chen, S.; Sun, T.; et al. Apigenin inhibits colonic inflammation and tumorigenesis by suppressing STAT3-NF-κB signaling. Oncotarget 2017, 8, 100216–100226. [CrossRef] [PubMed]

42. Yuan, J.W.; Che, S.Y.; Ruan, Z.; Song, L.Q.; Tang, R.X.; Zhang, L. Regulatory effects of flavonoids luteolin on BDE-209-induced intestinal epithelial barrier damage in Caco-2 cell monolayer model. Food Chem. Toxicol. 2021, 150, 112098. [CrossRef] [PubMed]

43. Zuo, T.; Yue, Y.Z.; Wang, X.H.; Li, H.; Yan, S. Luteolin relieved DSS-induced colitis in mice via HMGB1-TLR-NF-κB pathway. Inflammation 2021, 44, 570–579. [CrossRef] [PubMed]

44. Nishitani, Y.; Yamamoto, K.; Yoshida, M.; Azuma, T.; Kanazawa, K.; Hashimoto, T.; Mizuno, M. Intestinal anti-inflammatory activity of luteolin: Role of the aglycone in NF-κB inactivation in macrophages co-cultured with intestinal epithelial cells. Biofactors 2013, 39, 522–533. [CrossRef] [PubMed]

45. Luo, X.P.; Yu, Z.L.; Deng, C.; Zhang, J.J.; Ren, G.Y.; Sun, A.; Mani, S.; Wang, Z.T.; Dou, W. Baicalin ameliorates TNBS-induced colitis by suppressing TLR4/MyD88 signaling cascade and NLRP3 inflammasome activation in mice. Sci. Rep. 2017, 7, 16374. [CrossRef] [PubMed]

46. Liang, S.; Deng, X.; Lei, L.; Zheng, Y.; Ai, J.; Chen, L.; Xiong, H.; Mei, Z.; Cheng, Y.; Ren, Y. The comparative study of the therapeutic effects and mechanism of baicalin, baicalein, and their combination on ulcerative colitis rat. Front. Pharmacol. 2019, 10, 01466. [CrossRef] [PubMed]

47. Fan, J.; Li, B.R.; Zhang, Q.; Zhao, X.H.; Wang, L. Pretreatment of IEC-6 cells with quercetin and myricetin resists the indomethacin-induced loss of intestinal epithelial barrier function by a quercetin oxidation metabolite present in onion peel: In vitro and in vivo studies. J. Nutr. Biochem. 2022, 100, 108886. [CrossRef]

48. Das, T.; Mukherjee, S.; Chaudhuri, K. Effect of quercetin on Vibrio cholerae induced nuclear factor-κB activation and interleukin-8 expression in intestinal epithelial cells. Microbes Infect. 2012, 14, 690–695. [CrossRef]

49. Zheng, J.Y.; Hui, X.; Huang, C.L.; Fan, J.J.; Mei, Q.X.; Lu, Y.Y.; Lou, L.H.; Wang, X.P.; Yue, Z. Quercetin protects against intestinal barrier disruption and inflammation in acute necrotizing pancreatitis through TLR4/MyD88/p38 MAPK and ERS inhibition. Pancreatology 2018, 18, 742–752. [CrossRef]

50. Fuentes, J.; Brunser, O.; Atala, E.; Herranz, J.; de Camargo, A.C.; Zbinden-Foncea, H.; Speisky, H. Protection against indomethacin-induced loss of intestinal epithelial barrier function by a quercetin oxidation metabolite present in onion peel: In vitro and in vivo studies. J. Nutr. Biochem. 2022, 100, 108886. [CrossRef]

51. Bian, Y.F.; Liu, P.; Zhong, J.; Hu, Y.S.; Fan, Y.S.; Zhuang, S.; Liu, Z.J. Kaempferol inhibits multiple pathways involved in the secretion of inflammatory mediators from LPS-induced rat intestinal microvascular endothelial cells. Mol. Med. Rep. 2019, 19, 1598–1604. [CrossRef] [PubMed]

52. Bian, Y.F.; Lei, J.Q.; Zhong, J.; Wang, B.; Wan, Y.; Li, J.X.; Liao, C.Y.; He, Y.; Liu, J.Z.; Ito, K.; et al. Kaempferol reduces oxytosis, prevents intestinal inflammation, and modulates gut microbiota in high-fat diet mice. J. Nutr. Biochem. 2022, 99, 108840. [CrossRef] [PubMed]

53. Mascaraque, C.; López-Posadas, R.; Monte, M.J.; Romero-Calvo, I.; Daddaoua, A.; González, M.; Martínez-Plata, E.; Suárez, M.D.; González, R.; Marin, J.J.G.; et al. The small intestinal mucosa acts as a rutin reservoir to extend flavonoid anti-inflammatory activity in experimental ileitis and colitis. J. Funct. Foods 2015, 13, 117–125. [CrossRef]

54. Li, E.Y.; Wang, T.; Zhou, R.; Zhou, Z.W.; Zhang, C.Y.; Wu, W.H.; He, K. Myricetin and myricetin alleviate liver and colon damage in a chronic colitis mice model: Effects on tight junction and intestinal microbiota. J. Funct. Foods 2021, 87, 104790. [CrossRef]

55. Zhou, X.L.; Yang, J.; Qu, X.J.; Meng, J.; Miao, R.R.; Cui, S.X. M10, a Myricetin-3-O-b-D-Lactose Sodium salt, prevents ulcerative colitis through inhibiting necroptosis in mice. Front. Pharmacol. 2020, 11, 557312. [CrossRef]

56. Polat, F.R.; Karaboga, I.; Polat, M.S.; Erboga, Z.; Yılmaz, A.; Güzel, S. Effect of hesperetin on inflammatory and oxidative status in trinitrobenzene sulfonic acid-induced experimental colitis model. Cell Mol. Biol. 2018, 64, 58–65. [CrossRef]
57. Guazelli, C.F.S.; Fattori, V.; Ferraz, C.R.; Borghi, S.M.; Casagrande, R.; Baracat, M.M.; Verri, W.A. Antioxidant and anti-inflammatory effects of hesperidin methyl chalcone in experimental ulcerative colitis. *Chem. Biol. Interact.* 2021, 333, 109315. [CrossRef]

58. Li, Z.L.; Gao, M.; Yang, B.C.; Zhang, H.L.; Wang, K.K.; Liu, Z.L.; Xiao, X.Z.; Yang, M.S. Naringin attenuates MLC phosphorylation and NF-κB activation to protect sepsis-induced intestinal injury via RhoA/ROCK pathway. *Biomed. Pharmacother.* 2018, 103, 50–58. [CrossRef]

59. Ha, S.K.; Park, H.; Eom, H.; Kim, Y.; Choi, I. Narirutin fraction from citrus peels attenuates LPS-stimulated inflammatory response through inhibition of NF-κB and MAPKs activation. *Food Chem. Toxicol.* 2012, 50, 3498–3504. [CrossRef]

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

61. Myung, D.; Park, Y.; Joo, S.; Myung, E.; Chung, C.; Park, H.; Kim, J.; Cho, S.; Lee, W.; Kim, H.; et al. Epigallocatechin-3-gallate inhibits the expression of adhesion molecules by blocking nuclear factor kappa B signaling in intestinal epithelial cells. *Infect. Res.* 2013, 11, 261. [CrossRef]

62. Joo, S.; Song, Y.; Park, Y.; Myung, E.; Chung, C.; Park, K.; Cho, S.; Lee, W.; Kim, H.; Rew, J.; et al. Epigallocatechin-3-gallate inhibits LPS-induced NF-κB and MAPK signaling pathways in bone marrow-derived macrophages. *Gut Liver* 2012, 6, 188–196. [CrossRef] [PubMed]

63. Zhang, M.; Kou, J.; Wu, Y.J.; Wang, M.M.; Zhou, X.M.; Yang, Y.; Wu, Z.L. Dietary genistein supplementation improves intestinal mucosal barrier function in *Escherichia coli* O78-challenged broilers. *J. Nutr. Biochem.* 2020, 77, 108267. [CrossRef] [PubMed]

64. Zhang, R.; Xu, J.; Zhao, J.; Chen, Y.Z. Genistein improves inflammatory response and colonic function through NF-κB signal in DSS-induced colonic injury. *Onco target* 2017, 8, 61385–61392. [CrossRef] [PubMed]

65. Byun, E.; Sung, N.; Yang, M.; Lee, B.; Song, D.; Park, J.; Kim, J.; Jang, B.; Choi, D.; Park, S.; et al. Anti-inflammatory effect of gamma-irradiated genistein through inhibition of NF-κB and MAPK signaling pathway in lipopolysaccharide-induced macrophages. *Food Chem. Toxicol.* 2014, 74, 255–264. [CrossRef]

66. Ferrari, D.; Speciale, A.; Cristiani, M.; Fratantonio, D.; Molonia, M.S.; Ranaldi, G.; Saija, A.; Cimino, F. Cyanidin-3-O-glucoside inhibits NF-κB signaling in intestinal epithelial cells exposed to TNF-α and exerts protective effects via Nrf2 pathway activation. *Toxicol. Lett.* 2016, 264, 51–58. [CrossRef]

67. Ferrari, D.; Cimino, F.; Fratantonio, D.; Molonia, M.S.; Bashillari, R.; Busà, R.; Saija, A.; Speciale, A. Cyanidin-3-O-glucoside modulates the in vitro inflammatory crosstalk between intestinal epithelial and endothelial cells. *Mediat. Inflamm.* 2017, 2017, 3454023. [CrossRef]

68. Tan, C.; Wang, M.Y.; Kong, Y.W.; Wan, M.Z.; Deng, H.T.; Tong, Y.Q.; Lyu, C.M.; Meng, X.J. Anti-inflammatory and intestinal microbiota modulation properties of high hydrostatic pressure treated cyanidin-3-glucoside and blueberry pectin complexes on dextran sodium sulfate-induced ulcerative colitis mice. *Food Funct.* 2022, 13, 4384. [CrossRef]

69. Huang, W.Y.; Liu, Y.M.; Wang, J.; Wang, X.; Li, C.Y. Anti-inflammatory effect of the blueberry anthocyanins Malvidin-3-Glucoside and Malvidin-3-Galactoside in endothelial cells. *Molecules* 2014, 19, 12827–12841. [CrossRef]

70. Pereira, S.R.; Pereira, R.; Figueiredo, I.; Freitas, V.; Dinis, T.C.P.; Almeida, L.M. Comparison of anti-inflammatory activities of an anthocyanin-rich fraction from Portuguese blueberries (*Vaccinium corymbosum L.*) and 5-amino salicylic acid in a TNBS-induced colitis rat model. *PLoS ONE* 2017, 12, e0174116. [CrossRef]

71. Kunz, S.; Asseburg, H.; Dold, S.; Römpp, A.; Fröhling, B.; Kunz, C.; Rudloff, S. Inhibition of low-grade inflammation by anthocyanins from grape extract in an in vitro epithelial-endothelial co-culture model. *Food Funct.* 2015, 6, 1136–1149. [CrossRef] [PubMed]

72. Biagioli, M.; Carino, A.; Fiorucci, C.; Annunziato, G.; Marchiano, S.; Bordoni, M.; Roselli, R.; Giorgio, C.D.; Castiglione, F.; Ricci, P.; et al. The aryl hydrocarbon receptor (AhR) mediates the counter-regulatory effects of pelargonidins in models of inflammation and metabolic dysfunctions. *Nutrients* 2019, 11, 1820. [CrossRef] [PubMed]

73. Zhang, Z.; Wu, X.Y.; Cao, S.Y.; Wang, L.; Wang, D.; Yang, H.; Feng, Y.M.; Wang, S.L.; Li, L. Caffeic acid ameliorates colitis in association with increased Akkermansia population in the gut microbiota of mice. *Onco target* 2016, 7, 31790–31799. [CrossRef] [PubMed]

74. Zielinski, D.; Zielinski, H.; Laparra-Llopis, J.M.; Szawara-Nowak, D.; Honke, J.; Giménez-Bastida, J.A. Caffeic acid modulates processes associated with intestinal inflammation. *Nutrients* 2021, 13, 554. [CrossRef]

75. Zhang, Q.Z.; Luna-Vital, D.; de Mejia, E.G. Anthocyanins from colored maize ameliorated the inflammatory paracrine interplay between macrophages and adipocytes through regulation of NF-kB and JNK-dependent MAPK pathways. *J. Funct. Foods* 2019, 54, 175–186. [CrossRef]

76. Duarte, L.J.; Chaves, V.C.; Nascimento, M.M.P.D.; Calvete, E.; Li, M.; Ciraolo, E.; Ghigo, A.; Hirsch, E.; Simões, C.M.O.; Reginatto, F.H.; et al. Molecular mechanism of action of Pelargonidin-3-O-glucoside, the main anthocyanin responsible for the anti-inflammatory effect of strawberry fruits. *Food Chem.* 2018, 247, 56–65. [CrossRef]

77. Jin, L.G.; Chu, J.J.; Pang, Q.F.; Zhang, F.Z.; Wu, G.; Zhou, L.Y.; Zhang, X.J.; Xing, C.G. Caffeic acid phenethyl ester attenuates ionize radiation-induced intestinal injury through modulation of oxidative stress, apoptosis and p38MAPK in rats. *Environ. Toxicol. Pharmacol.* 2015, 40, 156–163. [CrossRef]
Jäger, A.; Saaby, L. Flavonoids and the CNS. *Molecules* 2011, 16, 9503–9520. [CrossRef] [PubMed]
99. Mafuvadze, B.; Cook, M.; Xu, Z.; Besch-Williford, C.; Hyder, S. Effects of dietary apigenin on tumor latency, incidence and multiplicity in a medroxyprogesterone acetate-accelerated 7,12-Dimethylbenz(a)anthracene-induced breast cancer model. *Br. J. Nutr.* 2016, 116, 376–383. [CrossRef] [PubMed]
100. Wang, Y.; Xu, Y.S.; Yin, L.H.; Xu, L.N.; Peng, J.Y.; Zhou, H.; Kang, W. Synergistic anti-glioma effect of Hydroxygenkwanin and Apigenin in vitro. *Chem. Biol. Interact.* 2013, 206, 401–408. [CrossRef]
101. Mascaraque, C.; Gonzalez, R.; Suarez, M.D.; Zarzuelo, A.; Sanchez, D.M.F.; Martinez-Augustin, O. Intestinal anti-inflammatory activity of ellagic acid in the prevention and treatment of ulcerative colitis: Preclinical and clinical observations. *J. Agri. Food Chem.* 2013, 61, 618–626. [CrossRef] [PubMed]
102. Ganjare, A.B.; Nirmal, S.A.; Patil, A.N. Use of apigenin from *Cordia dichotoma* in the treatment of colitis. *Fitoterapia* 2011, 82, 1052–1056. [CrossRef] [PubMed]
103. Gentile, D.; Fornai, M.; Colucci, R.; Pellegrini, C.; Tirotta, E.; Benvenuti, L.; Segnani, C.; Ippolito, C.; Duranti, E.; Virdis, A.; et al. The flavonoid compound apigenin prevents colonic inflammation and motor dysfunctions associated with high fat diet-induced obesity. PLoS ONE 2018, 13, e0195502. [CrossRef] [PubMed]

104. Boeijing, T.; Souza, P.; Specia, S.; Somensi, L.B.; Mariano, L.N.B.; Cury, B.J.; Ferreira Dos Anjos, M.; Quintâo, N.L.M.; Dubuqoy, L.; Desreumax, P.; et al. Luteolin prevents irinotecan-induced intestinal mucositis in mice through antioxidant and anti-inflammatory properties. Br. J. Pharmacol. 2020, 177, 2393–2408. [CrossRef] [PubMed]

105. Liu, D.M.; Yu, X.; Sun, H.Y.; Zhang, W.; Liu, G.; Zhu, L. Flos Ilicivae flavonoids attenuate experimental ulcerative colitis in rats via suppression of NF-κB signaling pathway. Naunyn-Schmiedeberg's Arch. Pharmacol. 2020, 393, 2481–2494. [CrossRef]

106. Jiang, R.; Poschet, G.; Owen, R.; Cekli, M.; Jansen, L.; Hell, R.; Hofmeister, M.; Brenner, H.; Chang-Claude, J. Serum concentration of genistein, luteolin and colorectal cancer prognosis. Nutrients 2019, 11, 600. [CrossRef]

107. Mizun, M.; Nishitani, Y. Luteolin ameliorates gut inflammation by inhibition of NF-κB activation in in vivo and in vitro inflammation models. Free Radic. Biol. Med. 2012, 53, S77. [CrossRef]

108. Wang, M.F.; Dong, Y.P.; Wu, J.; Li, H.Y.; Zhang, Y.Y.; Fan, S.J.; Li, D.G. Baicalein ameliorates ionizing radiation-induced injuries by rebalancing gut microbiota and inhibiting apoptosis. Life Sci. 2020, 261, 118463. [CrossRef]

109. Jang, H.S.; Lee, J.; Park, S.; Kim, J.S.; Shim, S.; Lee, S.B.; Han, S.; Myung, H.; Kim, H.; Jang, W.; et al. Baicalein mitigates radiation-induced enteritis by improving endothelial dysfunction. Front. Pharmacol. 2019, 10, 00892. [CrossRef]

110. Rauf, A.; Imran, M.; Khan, I.A.; Ur-Rehman, M.; Gilani, S.A.; Mehmood, Z.; Mubarak, M.S. Anticancer potential of quercetin: A comprehensive review. Phytother. Res. 2018, 32, 2109–2130. [CrossRef]

111. Vissenaekens, H.; Smagghe, G.; Criel, H.; Grootaert, C.; Raes, K.; Rajkovic, A.; Goeminne, G.; Boon, N.; De Schutter, K.; Van Camp, B. J. Intracellular quercetin accumulation and its impact on mitochondrial dysfunction in intestinal Caco-2 cells. Food Res. Int. 2021, 145, 11043. [CrossRef] [PubMed]

112. Tóth, S.; Jonecová, Z.; Čurgali, K.; Mareta, M.; Šoltés, J.; Šváha, M.; Kalpadikis, T.; Caprnnda, M.; Adamek, M.; Rodrigo, L.; et al. Quercetin attenuates the ischemia reperfusion induced COX-2 and MPO expression in the small intestine mucosa. Biomed. Pharmacother. 2017, 95, 346–354. [CrossRef] [PubMed]

113. Xu, L.; Zhang, J.; Wang, Y.; Zhang, Z.; Fang, F.; Tang, X. Uncovering the mechanism of Ge-Gen-Qin-Lian decoction for treating ulcerative colitis based on network pharmacology and molecular docking verification. Biosci. Rep. 2021, 41, BSR20203565. [CrossRef] [PubMed]

114. Imran, M.; Rauf, A.; Shah, Z.; Saeed, F.; Imran, A.; Arshad, M.; Bawazeer, S.; Atif, M.; Peters, D.G.; et al. Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. Phytother. Res. 2019, 33, 263–275. [CrossRef]

115. Lee, S.; Shin, J.; Han, H.; Lee, H.; Park, J.C.; Lee, K. Kaempferol 7-O-β-D-glucoside isolated from the leaves of Cudrania tricuspisata inhibits LPS-induced expression of pro-inflammatory mediators through inactivation of NF-κB, AP-1, and JAK-STAT in RAW 264.7 macrophages. Chem. Biol. Interact. 2018, 284, 101–111. [CrossRef]

116. Kadioglu, O.; Jass, N.; Saeed, M.E.; Schuler, B.; Effrther, T. Kaempferol is an anti-inflammatory compound with activity towards NF-kappaB pathway proteins. Anticancer. Res. 2015, 35, 2645–2650. [CrossRef]

117. Fan, J.; Zhao, X.H.; Li, T.J. Heat treatment of galangin and kaempferol inhibits their benefits to improve barrier function in rat intestinal epithelial cells. J. Pharm. Pharmacol. 2021, 73, 110–117. [CrossRef]

118. Galvez, J.; Cruz, T.; Crespo, E.; Ocete, M.A.; Lorente, M.; Sánchez De Medina, F.; Zarzuelo, A. Rutoside as mucosal protective in acetic acid-induced rat colitis. Planta Med. 1997, 63, 409–414. [CrossRef]

119. Cruz, T.; Galvez, J.; Ocete, M.A.; Crespo, M.E.; Sánchez De Medina, F.; Zarzuelo, A. Oral administration of rutoside can ameliorate inflammatory bowel disease in rats. Life Sci. 1998, 62, 687–695. [CrossRef]

120. Kwon, K.; Murakami, A.; Tanaka, T.; Ohigashi, H. Dietary rutin, but not its aglycone quercetin, ameliorates dextran sulfate sodium-induced experimental colitis in mice: Attenuation of pro-inflammatory gene expression. Biochem. Pharmacol. 2005, 69, 395–406. [CrossRef] [PubMed]

121. Miean, K.; Mohamed, S. Flavonoid (Myricetin, Quercetin, Kaempferol, Luteolin, and Apigenin) content of edible tropical plants. J. Agric. Food Chem. 2001, 49, 3106–3112. [CrossRef] [PubMed]

122. Li, Y.; Cui, S.X.; Sun, S.Y.; Shi, W.N.; Song, Z.Y.; Wang, S.Q.; Yu, X.F.; Gao, Z.H.; Qu, X.J. Chemoprevention of intestinal tumorigenesis by the natural dietary flavonoid myricetin in APCMin/+ mice. Oncotarget 2016, 13, 60446–60460. [CrossRef]

123. Domitrovic, R.; Rashid, K.; Cvijanovic, V.; Vladimir-Knežević, S.; Škoda, M.; Višnić, A. Myricitrin exhibits antioxidant, anti-inflammatory and antifibrotic activity in carbon tetrachloride-intoxicated mice. Chem. Biol. Interact. 2015, 230, 21–29. [CrossRef]

124. Fan, J.; Li, T.J.; Zhao, X.H. Barrier-promoting efficiency of two bioactive flavonoids quercetin and myricetin on rat intestinal epithelial (IEC-6) cells via suppressing Rho activation. RSC Adv. 2020, 10, 27249–27258. [CrossRef]
127. Zhu, S.F.; Yang, C.; Zhang, L.; Wang, S.X.; Ma, M.X.; Zhao, J.C.; Song, Z.Y.; Wang, F.; Qu, X.J.; Li, F.; et al. Development of M10, myricetin-3-O-β-d-lactose sodium salt, a derivative of myricetin as a potent agent of anti-chronic colonic inflammation. *Eur. J. Med. Chem.* 2019, 174, 9–15. [CrossRef]

128. Ferraz, C.; Carvalho, T.; Manchope, M.; Artero, N.; Rasquel-Oliveira, F.; Fattori, V.; Casagrande, R.; Verri, W.A., Jr. Therapeutic potential of flavonoids in pain and inflammation: mechanisms of action, pre-clinical and clinical data, and pharmaceutical development. *Molecules* 2020, 25, 762. [CrossRef]

129. Wu, X.; Song, M.; Gao, Z.; Sun, Y.; Wang, M.; Li, F.; Zheng, J.; Xiao, H. Nobiletin and its colonic metabolites suppress colitis-associated colon carcinogenesis by down-regulating iNOSs, inducing antioxidative enzymes and arresting cell cycle progression. *J. Nutr. Biochem.* 2017, 42, 17–25. [CrossRef]

130. Guo, K.; Ren, J.N.; Gu, G.S.; Wang, G.F.; Gong, W.B.; Wu, X.W.; Ren, H.J.; Hong, Z.W.; Li, J.S. Hesperidin protects against intestinal inflammation by restoring intestinal barrier function and up-regulating Treg cells. *Mol. Nutr. Food Res.* 2019, 63, e1800975. [CrossRef] [PubMed]

131. Suzuki, T. *Naringenin Regulates the Intestinal Tight Junction Barrier and Inflammation*; Nova Science Publishers, Inc.: Haupage, NY, USA, 2015; pp. 137–149.

132. Chaen, Y.; Yamamoto, Y.; Suzuki, T. Naringenin promotes recovery from colonic damage through suppression of epithelial tumor necrosis factor-α production and induction of M2-type macrophages in colitic mice. *Nutr. Res.* 2019, 64, 82–92. [CrossRef] [PubMed]

133. Jennings, A.; Welch, A.A.; Fairweather-Tait, S.J.; Kay, C.; Minihane, A.; Chowienczyk, P.; Jiang, B.; Cecelja, M.; Spector, T.; Macgregor, A.; et al. Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. *Am. J. Clin. Nutr.* 2012, 96, 781–788. [CrossRef]

134. Macgregor, A.; et al. Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. *Am. J. Clin. Nutr.* 2012, 96, 781–788. [CrossRef]

135. Jennings, A.; Welch, A.A.; Fairweather-Tait, S.J.; Kay, C.; Minihane, A.; Chowienczyk, P.; Jiang, B.; Cecelja, M.; Spector, T.; Macgregor, A.; et al. Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. *Am. J. Clin. Nutr.* 2012, 96, 781–788. [CrossRef]

136. Ortega-Santos, C.P.; Al-Nakkash, L.; Whisner, C.M. Exercise and/or genistein treatment impact gut microbiota and inflammation in rats. *Poult. Sci.* 2020, 99, 3411–3427. [CrossRef]

137. Bose, M.; Lambert, J.D.; Ju, J.; Reuhl, K.R.; Shapses, S.A.; Yang, C.S. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, and anti-inflammatory and anti-cancer properties of epigallocatechin-3-gallate are mediated by folate cycle disruption, adenosine release and NF-κB suppression. *Inflamm. Res.* 2008, 57, 472–478. [CrossRef]

138. Ortega-Santos, C.P.; Al-Nakkash, L.; Whisner, C.M. Exercise and/or genistein treatment impact gut microbiota and inflammation in rats. *Poult. Sci.* 2020, 99, 3411–3427. [CrossRef]

139. Ortega-Santos, C.P.; Al-Nakkash, L.; Whisner, C.M. Exercise and/or genistein treatment impact gut microbiota and inflammation in rats. *Poult. Sci.* 2020, 99, 3411–3427. [CrossRef]

140. Lv, Z.P.; Dai, H.J.; Wei, Q.W.; Jin, S.; Wang, J.; Wei, X.H.; Yuan, Y.W.; Yu, D.B.; Shi, F.X. Dietary genistein supplementation protects against lipopolysaccharide-induced intestinal injury through altering transcriptomic profile. *Poult. Sci.* 2020, 99, 3411–3427. [CrossRef]

141. Chen, Y.; Le, T.H.; Du, Q.M.; Zhao, Z.; Liu, Y.X.; Zou, J.J.; Hua, W.W.; Liu, C.; Zhu, Y.B. Genistein protects against DSS-induced colitis by inhibiting NLRP3 inflammasome via TGR5-cAMP signaling. *Int. Immunopharmacol.* 2019, 71, 144–154. [CrossRef]

142. Ghattamaneni, N.K.R.; Panchal, S.K.; Brown, L. Cyanidin 3-glucoside from queen garnet plums and purple carrots attenuates malvidin-3-glucoside modulated gut microbial dysbiosis and global properties in endothelial cells. *Oxid. Med. Cell. Longev.* 2016, 2016, 1591803. [CrossRef] [PubMed]

143. Ghattamaneni, N.K.R.; Panchal, S.K.; Brown, L. Cyanidin 3-glucoside from queen garnet plums and purple carrots attenuates malvidin-3-glucoside modulated gut microbial dysbiosis and global properties in endothelial cells. *Oxid. Med. Cell. Longev.* 2016, 2016, 1591803. [CrossRef] [PubMed]

144. Liu, F.; Wang, T.T.Y.; Tang, Q.; Xue, C.; Li, R.W.; Wu, V.C.H. Malvidin-3-glucoside modulated gut microbial dysbiosis and global properties in endothelial cells. *Oxid. Med. Cell. Longev.* 2016, 2016, 1591803. [CrossRef] [PubMed]

145. Liu, F.; Wang, T.T.Y.; Tang, Q.; Xue, C.; Li, R.W.; Wu, V.C.H. Malvidin-3-glucoside modulated gut microbial dysbiosis and global properties in endothelial cells. *Oxid. Med. Cell. Longev.* 2016, 2016, 1591803. [CrossRef] [PubMed]

146. Liu, F.; Wang, T.T.Y.; Tang, Q.; Xue, C.; Li, R.W.; Wu, V.C.H. Malvidin-3-glucoside modulated gut microbial dysbiosis and global properties in endothelial cells. *Oxid. Med. Cell. Longev.* 2016, 2016, 1591803. [CrossRef] [PubMed]

147. Zhu, S.F.; Yang, C.; Zhang, L.; Wang, S.X.; Ma, M.X.; Zhao, J.C.; Song, Z.Y.; Wang, F.; Qu, X.J.; Li, F.; et al. Development of M10, myricetin-3-O-β-d-lactose sodium salt, a derivative of myricetin as a potent agent of anti-chronic colonic inflammation. *Eur. J. Med. Chem.* 2019, 174, 9–15. [CrossRef]

148. Ferraz, C.; Carvalho, T.; Manchope, M.; Artero, N.; Rasquel-Oliveira, F.; Fattori, V.; Casagrande, R.; Verri, W.A., Jr. Therapeutic potential of flavonoids in pain and inflammation: mechanisms of action, pre-clinical and clinical data, and pharmaceutical development. *Molecules* 2020, 25, 762. [CrossRef]

149. Ye, Z.; Liu, Z.P.; Henderson, A.; Lee, K.; Hostetter, J.; Wannemuehler, M.; Hendrich, S. Increased CYPI4B1 mRNA is associated with the inhibition of dextran sulfate sodium-induced colitis by caffeic acid in mice. *Exp. Biol. Med.* 2009, 234, 605–616. [CrossRef]
174. Liu, L.L.; Fu, C.X.; Yan, M.L.; Xie, H.B.; Li, S.; Yu, Q.F.; He, S.P.; He, J.H. Resveratrol modulates intestinal morphology and HSP70/90, NF-κB and EGF expression in the jejunal mucosa of black-boned chickens on exposure to circular heat stress. *Food Funct.* 2016, 7, 1329–1338. [CrossRef] [PubMed]

175. Meng, Q.W.; Sun, S.S.; Luo, Z.; Shi, B.M.; Shan, A.S.; Cheng, B.J. Maternal dietary resveratrol alleviates weaning-associated diarrhea and intestinal inflammation in pig offspring by changing intestinal gene expression and microbiota. *Food Funct.* 2019, 10, 5626–5643. [CrossRef]

176. Samsami-kor, M.; Daryani, N.E.; Asl, P.R.; Hekmatdoost, A. Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: A randomized, double-blind, placebo-controlled pilot study. *Arch. Med. Res.* 2015, 46, 280–285. [CrossRef] [PubMed]

177. Moon, D.; Jin, C.Y.; Lee, J.D.; Choi, Y.H.; Ahn, S.C.; Lee, C.M.; Jeong, S.C.; Park, Y.M.; Kim, G.Y. Curcumin decreases binding of shiga-like toxin-1B on human intestinal epithelial cell line HT29 stimulated with TNF-alpha and IL-1beta: Suppression of p38, JNK and NF-kappaB p65 as potential targets. *Biol. Pharm. Bull.* 2006, 29, 1470–1475. [CrossRef]

178. Jobin, C.; Bradham, C.A.; Russo, M.P.; Juma, B.; Narula, A.S.; Brenner, D.A.; Sartor, R.B. Curcumin blocks cytokine-mediated NF-kappaB activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappaB kinase activity. *J. Immunol.* 1999, 163, 3474–3483.

179. Lubbad, A.; Oriowo, M.A.; Khan, I. Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. *Mol. Cell. Biochem.* 2009, 322, 127–135. [CrossRef]

180. Wang, D.; Sun, M.H.; Zhang, Y.; Chen, Z.H.; Zang, S.Y.; Li, G.Y.; Li, G.; Clark, A.R.; Huang, J.G.; Si, L.Q. Enhanced therapeutic efficacy of a novel colon-specific nanosystem loading emodin on DSS-induced experimental colitis. *Phytomedicine* 2020, 78, 153293. [CrossRef]

181. Zhuang, S.; Zhong, J.; Zhou, Q.L.; Zhong, Y.; Liu, P.; Liu, Z.J. Rhein protects against barrier disruption and inhibits inflammation in intestinal epithelial cells. *Int. Immunopharmac.* 2019, 71, 321–327. [CrossRef]

182. Luo, S.; Deng, X.L.; Liu, Q.; Fan, Z.F.; Zhao, Z.X.; Zhou, L.; Luo, X. Emodin ameliorates ulcerative colitis by the flagellin-TLR5 dependent pathway in mice. *Int. Immunopharmac.* 2018, 59, 269–275. [CrossRef] [PubMed]

183. Chen, Y.K.; Xu, Y.K.; Zhang, H.; Yin, J.T.; Fan, X.; Liu, D.D.; Fu, H.Y.; Wan, B. Emodin alleviates jejunal injury in rats with sepsis by inhibiting inflammation response. *Biomed. Pharmacother.* 2016, 84, 1001–1007. [CrossRef] [PubMed]

184. Zhang, Q.; Cao, X.T. Epigenetic regulation of the innate immune response to infection. *Nat. Rev. Immunol.* 2019, 19, 417–432. [CrossRef] [PubMed]

185. Handy, D.E.; Castro, R.; Loscalzo, J. Epigenetic modifications: Basic mechanisms and role in cardiovascular disease. *Circulation* 2011, 123, 2145–2156. [CrossRef] [PubMed]

186. Saleh, H.A.; Youssef, M.H.; Abdennaser, A. The anti-Inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF-κB-mediated inflammation. *Front. Immunol.* 2021, 12, 606699. [CrossRef] [PubMed]

187. Lotfi, M.; Kazemi, S.; Shirafkan, F.; Hosseinzadeh, R.; Barary, M.; Sio, T.T.; Hosseini, S.M.; Moghadamnia, A.A. The protective effects of quercetin nano-emulsion on intestinal mucositis induced by 5-fluorouracil in mice. *Biochem. Biophys. Res. Commun.* 2021, 585, 75–81. [CrossRef]

188. Gee, J.M.; DuPont, M.S.; Rhodes, M.J.; Johnson, I.T. Quercetin glucosides interact with the intestinal glucose transport pathway. *Free Radic Biol Med* 1998, 25, 19–25. [CrossRef]

189. Kobayashi, S.; Konishi, Y. Transepithelial transport of flavanone in intestinal Caco-2 cell monolayers. *Biochem. Biophys. Res. Co.* 2008, 368, 23–29. [CrossRef]

190. Kanaze, F.I.; Bounartzi, M.I.; Georgarakis, M.; Niopas, I. Pharmacokinetics of the citrus flavanone aglycones hesperetin and naringenin after single oral administration in human subjects. *Eur. J. Clin. Nutur.* 2007, 61, 472–477. [CrossRef]

191. Gardana, C.; Guarnieri, S.; Riso, P.; Simonetti, P.; Porrini, M. Flavonan plasma pharmacokinetics from blood orange juice in human subjects. *Brit. J. Nutr.* 2007, 98, 165–172. [CrossRef]

192. Allijin, I.E.; Vaessen, S.F.C.; Quarles Van Ufford, L.C.; Beukelman, K.J.; de Winther, M.P.J.; Storm, G.; Schiffelers, R.M. Head-to-head comparison of anti-inflammatory performance of known natural products in vitro. *PLoS ONE* 2016, 11, e0155325. [CrossRef] [PubMed]

193. Evans, L.W.; Stratton, M.S.; Ferguson, B.S. Dietary natural products as epigenetic modifiers in aging-associated inflammation and disease. *Nat. Prod. Rep.* 2020, 37, 653–676. [CrossRef] [PubMed]

194. Lampe, J.W.; Chang, J.L. Interindividual differences in phytochemical metabolism and disposition. *Semin. Cancer Biol.* 2007, 17, 347–353. [CrossRef] [PubMed]

195. Lin, S.P.; Chu, P.M.; Tsai, S.Y.; Wu, M.H.; Hou, Y.C. Pharmacokinetics and tissue distribution of resveratrol, emodin and their metabolites after intake of *Polygonum cuspidatum* in rats. *J. Ethnopharmacol* 2012, 144, 671–676. [CrossRef] [PubMed]