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REVIEW

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Phytochemical drug candidates for the modulation of peroxisome proliferator-activated receptor γ in inflammatory bowel diseases

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Plant-based compounds or phytochemicals such as alkaloids, glycosides, flavonoids, volatile oils, tannins, resins, and polyphenols have been used extensively in traditional medicine for centuries and more recently in Western alternative medicine. Extensive evidence suggests that consumption of dietary polyphenolic compounds lowers the risk of inflammatory diseases. The anti-inflammatory properties of several phytochemicals are mediated through ligand-inducible peroxisome proliferator-activated receptors (PPARs), particularly the PPARγ transcription factor. Inflammatory bowel disease (IBD) is represented by ulcerative colitis, which occurs in the mucosa of the colon and rectum, and Crohn's disease (CD) that can involve any segment of gastrointestinal tract. Because of the lack of cost-effective pharmaceutical treatment options, many IBD patients seek and use alternative and unconventional therapies to alleviate their symptoms. PPARγ plays a role in the inhibition of inflammatory cytokine expression and activation of anti-inflammatory immune cells. The phytochemicals reported here are ligands that activate PPARγ, which in turn modulates inflammatory responses. PPARγ is highly expressed in the gut making it a potential therapeutic target for IBDs. This review summarizes the effects of the currently published phytochemicals that modulate the PPARγ pathway and reduce or eliminate colonic inflammation.

KEYWORDS
colitis, inflammatory bowel disease, phytochemicals, PPARγ

Abbreviations: AP-1, activating protein-1; CD, cluster of differentiation; COX-2, cyclooxygenase-2; DSS, dextran sodium sulfate; ERK, extracellular signal-regulated kinases; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSK, glycogen synthase kinase; HNE, hydroxynonenal; HO-1, heme oxygenase-1; IBD, inflammatory bowel diseases; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun *N*-terminal kinase; MAPK, mitogen-activated protein kinase; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response 88; NFκB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2–related factor 2; PGE2, prostaglandin E2; PPAR, peroxisome proliferator activated receptor; STAT, signal transducer and activator of transcription; Th1/2, helper T cell 1/2; TLR, toll-like receptor; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TNFα, tumor necrosis factor alpha; TRPV1, transient receptor potential cation channel subfamily V member 1; UC, ulcerative colitis; ZO-1, Zonula occludens-1.

1 | INTRODUCTION

Plant-based compounds or phytochemicals such as alkaloids, glycosides, flavonoids, volatile oils, tannins, resins, and polyphenols have been used extensively as bioactive compounds in commercial, industrial, and medicinal applications (Vikram, Chiruvella, Ripain, & Arifullah, 2014). One popular definition of phytochemicals (of the Kingdom *Plantae*) is "bioactive non-nutrient plant compounds in fruits, vegetables, grains, and other plant foods that have been linked to reducing the risk of major chronic diseases" (Liu, 2004).

Polyphenolic compounds are an important group of phytochemicals commonly found in plant-based food sources (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004). Numerous lines of evidence suggest that the consumption of polyphenolic-rich dietary foods is beneficial in lowering the risk of several diseases (Scalbert, Manach, Morand, Remesy, & Jimenez, 2005) such as neurodegenerative diseases (Bhullar & Rupasinghe, 2013; Ebrahimi & Schluesener, 2012), diabetes (Babu, Liu, & Gilbert, 2013), cancer (Nishiumi et al., 2011), and inflammatory disorders (Gonzalez et al., 2011; Lambert, Hong, Yang, Liao, & Yang, 2005). Studies using polyphenol derivatives have also been demonstrated to inhibit a variety of biochemical pathways, including phospholipase A2, cyclooxygenase, lipoxygenase, and nuclear factor-κB (NFκB) activation (Santangelo et al., 2007). These data suggest that the effect of polyphenols encompass more than just antioxidant activity. The anti-inflammatory effects of many polyphenols are mediated through activation of peroxisome proliferator activated receptors (PPARs), particularly PPARγ.

PPARs are members of the nuclear receptor superfamily that, acting as ligand-inducible transcription factors, play an important role in the control of expression of genes involved in various physiological processes. There are three different, highly homologous subtypes of PPAR: PPARα, PPARδ (also referred to as PPARβ), and PPARγ, each encoded by different genes and with different tissue expression and ligand selectivity (Tontonoz & Spiegelman, 2008). Of these three subtypes, PPARγ was the first to be identified and the most widely studied (Agostini et al., 2018; Monsalve, Pyarasani, Delgado-Lopez, & Moore-Carrasco, 2013; Yun, Han, & Park, 2018). A large number of genes are under the influence of PPARγ, several of them involved in energy, carbohydrate, and lipid metabolism. PPARγ is activated by ligand binding that induces conformational changes in the receptor molecule. The ligand-PPARγ complex activates retinoid X receptors, recruits co-activators containing histone acetylase activity, and binds to peroxisome proliferator response element gene promoters, leading to changes in gene transcription. PPARγ is activated by both synthetic, dietary, and polyphenol ligands (Kliewer et al., 1997; Nolte et al., 1998; Wang et al., 2014; Weidner et al., 2012), which inhibit inflammatory pathways by interacting with NFκB (Kelly et al., 2004) and activating protein-1 (AP-1) (Yamazaki et al., 2007), signal transducer and activator of transcription (STAT; Linard, Gremy, & Benderitter, 2008), and nuclear factor-activated T cell (Yang et al., 2000). PPARγ is expressed in various tissues in the body including liver, kidney, pancreas, and immune cells, but high amounts are found in adipose tissue and colon (Braissant, Foufelle, Scotto, Dauca, & Wahli, 1996; Dubuquoy et al., 2006). Thus, PPARγ plays a critical role in regulating intestinal inflammation. Studies have shown that both synthetic and natural PPARγ ligands have beneficial effects in experimental colitis models (Adachi et al., 2006; Bassaganya-Riera et al., 2004; Camuesco et al., 2005; Kohno, Suzuki, Sugie, & Tanaka, 2005; Su et al., 1999), thus making them plausible drug development targets for inflammatory bowel disease (IBD). Even though the effect of PPARγ ligands in treatment of diabetes and other diseases is positive, side effects such as weight gain, fluid retention, and increased risk of heart failure (Ciudin, Hernandez, & Simo, 2012) have prevented their long-term use (Home, 2011).

IBD is represented by ulcerative colitis (UC) that occurs in the inner lining of the colon (large intestine) and rectum and Crohn's disease (CD) that can involve any segment of gastrointestinal tract. IBD is characterized by chronic or relapsing immune activation and inflammation within the gastrointestinal tract (Rubin, Shaker, & Levin, 2012). The etiology of IBD remains unclear, but infectious, genetic susceptibility, immunological, and psychosomatic factors appear to contribute to the onset of disease and exacerbation of symptoms during relapse (Sun et al., 2019). The prevalence of IBD is increasing and currently affects about 150–250 persons per 100,000 of the populations in developed nations. It can greatly diminish quality of life because of pain, vomiting, and diarrhea and also increase the risk of colorectal cancer; the latter particularly in the case of UC (M'Koma, 2013). The current therapy for IBD relies on the use of sulfasalazine, corticosteroids, and immunosuppressive agents, such as azatriopine together with biological therapy using humanized anti-tumor necrosis factor alpha (TNFα) antibody administration as a mainstream treatment to downregulate aberrant immune responses and inflammatory cascades (Bots, Gecse, Barclay, & D'Haens, 2018). However, adverse effects of these drugs over prolonged treatment periods, and the high relapse rate of IBD, limit their use (Reinglas, Gonczi, Kurt, Bessissow, & Lakatos, 2018). Because of the lack of cost-effective pharmaceutical treatment options, many IBD patients seek and use unconventional therapies with the hope of increased beneficial effect. It is estimated that 40% of IBD patients use some form of herbal or dietary supplements (Head & Jurenka, 2004). Few studies have investigated the role of diet and polyphenols on IBD prevention and treatment (Lee et al., 2015; Shapiro, Singer, Halpern, & Bruck, 2007). With increased focus, it seems reasonable to assume that herbal medicines could provide alternative therapy as well as to become valuable sources for drug discovery and development targeted at inflammatory diseases. The majority of medicinal plant extracts used for inflammation primarily target the arachidonic acid pathway. However, recent reports suggest that some natural products exhibit shown anti-inflammatory effect through activation or modulation of PPARγ, and these may be valuable for a variety of inflammatory conditions (Ortuno Sahagun, Marquez-Aguirre, Quintero-Fabian, Lopez-Roa, & Rojas-Mayorquin, 2012).

The present detailed literature survey has uncovered extensive information on the effects of phytochemical PPARγ agonists on carbohydrate and fat metabolism (Goto, Takahashi, Hirai, & Kawada, 2010; Ortuno Sahagun et al., 2012) as well as computational approaches to the discovery of phytochemical ligands for PPARα and PPARγ, which shed more light on the PPAR pathway in general

(Lewis, Bassaganya-Riera, & Bevan, 2010). However, until now, there has been no extensive review focused on the effects of phytochemical agonists of PPARγ in the arena of IBDs. Bertin, Dubuquoy, Colombel, and Desreumaux (2013) reported that several PPAR modulators have promising effects both in vitro and in vivo inflammation models without toxicity. Some of these compounds are being evaluated in clinical trials. It is widely accepted that phytochemicals, acting as ligands for PPARγ, can modulate inflammatory responses and help to prevent inflammatory responses and pathologies (Hirai et al., 2010; Martin, 2010). It is conceivable that this novel approach to treatment of IBD may provide increased efficacy with reduced side effects.

2 | METHODOLOGY

2.1 | Search method

The organized searchable electronic collections of resources including PubMed, Scopus, Google, and Google scholar were used to search with the key words like "IBD," "colitis," "intestinal inflammation," "phytochemical," "plant," "natural product," "plant-based nutraceuticals," "bioactive molecules," "phytochemicals," and "PPARγ agonist." This review highlights studies carried out using in vivo and in vitro experimental IBD models, as well as clinical trials in IBD patients, involving phytochemical modulation of the PPARγ pathway, published between 1990–2019. This review also highlights the perceived merits of those phytochemicals for potential use in clinical settings for IBD in particular. The source of phytochemicals, the models used, and the effect/mechanisms reported are presented in Table 1, whereas the chemical structures of these phytochemicals are presented in Figure 1.

2.2 | Evaluation of compounds for "Lipinski rule of five" for distinguishing between drug-like and nondrug-like molecules

Molecular properties of each phytochemical were calculated on the basis of Lipinski's rule and its components. Lipinski rule of five (i.e., a molecule with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol–water partition coefficient log *P* not greater than 5). Theoretical values for miLogP and topological polar surface area (TPSA) were calculated using commercially available Molinspiration software. The calculated values are presented in Table 2.

3 | PHYTOCHEMICALS INVOLVED WITH PPARγ ACTIVITY IN IBD

3.1 | 2,3,5,4′-Tetrahydroxystilbene-2-O-beta-D-glucoside

2,3,5,4′-tetrahydroxystilbene-2-O-beta-D-glucoside (THSG), extracted from rhizome of *Polygonum multiflorum* Thunb, is a traditional Chinese medicinal herb that has been used for thousands of years as a tonic and to treat skin depigmentation diseases, inflammatory diseases, and age-related disease (Ling & Xu, 2016). Wang, Zhao, Han, Chen, and Wang (2008) showed that THSG could ameliorate colon damage and with a reduced damage score and improved free radical scavenging effects in experimental colitis models. Zeng, Xiao, Chang, and Wang (2011) have reported that THSG could attenuate acetic acid-induced colon lesions and reduced NFκB-induced inflammatory mediators such as TNFα, interleukin (IL)-6, and cyclooxygenase-2 (COX-2) dose dependently.

3.2 | 2-Hydroxyethyl-5-chloro-4,5-didehydrojasmonate

2-Hydroxyethyl-5-chloro-4,5-didehydrojasmonate is a stability-improved analog of methyl jasmonate—a natural cyclopentanone lipid belonging to the jasmonates family of plant oxylipin stress hormones (oxygenated fatty acids; Cesari et al., 2014). 2-Hydroxyethyl-5-chloro-4,5-didehydrojasmonate was shown to increase the production of anti-inflammatory cytokines including IL-2 and IL-4 as well as the proliferative factor, granulocyte-macrophage colony-stimulating factor (GM-CSF); inhibit the activation of mitogen-activated protein kinases (MAPKs) and NFκB; and thereby reduce intestinal inflammation by increasing the transcriptional activity of PPARγ (Choo et al., 2015).

3.3 | Abscisic acid

Abscisic acid (ABA; a 15-C weak acid) is one of the "classical" ubiquitious plant hormones. It is also produced by certain phytopathogenic fungi, bacteria, and metazoans ranging from sea sponges to humans (Finkelstein, 2013). ABA was found to ameliorate colitis and to reduce colonic leukocyte infiltration and inflammation. These improvements were associated with downregulation in vascular cell adhesion marker-1, E-selectin, and mucosal addressin adhesion marker-1 expressions (Guri, Hontecillas, & Bassaganya-Riera, 2010). Further, ABA was shown to improve colonic histopathology and upregulate expression of epithelial lanthionine synthetase C-like protein 2 expression (a novel therapeutic target) which is an upstream target of the PPARγ pathway (Hontecillas & Bassaganya-Riera, 2012).

3.4 | Alliin

Alliin (S-allyl cysteine sulfoxide) is an organosulfur compound from garlic with potent antioxidant, cardioprotective, and neuroprotective effects (Martins, Petropoulos, & Ferreira, 2016). Alliin suppresses expression of malondialdehyde, myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), and inflammatory factors such as MAPK and inhibits the phosphorylation of PPARγ (Shi et al., 2017).

TABLE 1 The list of phytochemicals, the experimental models used, and the effect/mechanisms mediated by each phytochemical is highlighted

Name of the phytochemicals	Dose, duration, and model	PPAR activity	IBD parameter	Reference
2,3,5,4′-tetrahydroxystilbene-2-O-beta-D-glucoside (THSG)	10–60 mg kg^{-1} intragastrically (IG), once a day for 7 days, Acetic acid (5%)-induced colitis in male Kunming mice	↑ mRNA and protein	↓ colitis damage ↓ histological score ↓ MDA ↓ TNFα, IL-6, COX-2 and NFκB	(Zeng et al., 2011)
2-Hydroxyethyl-5-chloro-4,5-didehydrojasmonate	50 mg kg^{-1} in diet for 11 days, DSS (3%)-induced colitis in male C57BL/6J mice	↑ PPARγ transcription	↑ IL-2 and IL-4 ↓ MAPKs and NFκB activation	(Choo et al., 2015)
Abscisic acid	100 mg kg^{-1} in diet for 35 days, DSS (2.5%)-induced colitis in C57BL/6J mice	No change	↓ disease activity and colonic inflammation ↓ VCAM-1, MAdCAM-1, E-selectin ↓ IL-6, iNOS, and MMP-9	(Guri et al., 2010)
		↑ PPARγ	↓ colonic inflammation, colitis severity ↑ LANCL2	(Hontecillas & Bassaganya-Riera, 2012)
Alliin	500 mg kg^{-1} day^{-1} P.O for 7 days, 2% DSS-induced colitis in ICR background male mice	↓ phosphorylation of PPARγ	↓ NO, MDA, MPO, iNOS, MAPK	(Shi et al., 2017)
Amorfrutins	1 and 10 μM, (TNFα, 50 ng/ml induced on HT-29 cells)	↑ PPARγ	↓ NFκB target genes	(Fuhr et al., 2015)
Andrographolide	(AL-1) 5, 15 and 45 mg kg^{-1} day^{-1} P.O for 3–7 days, trinitrobenzene sulfonic acid (TNBS) (intrarectally [I.R])-induced colitis in C57BL/6J mice	—	↓Th1/Th17	(W. Liu et al., 2014)
		↑ PPARγ	↓ Colon mucosa damage index (CMDI) ↓ p-p^{65}, p-IκBα and COX-2	(Y. Yang et al., 2016)
Bergenin	20 and 50 mg kg^{-1} day^{-1} P.O for 7 days, 2.5% DSS-induced colitis in female C57BL/6J mice	↑ PPARγ	↓ IL-6 and TNFα	(Wang et al., 2017)
Cannabidiol	10 mg kg^{-1} day^{-1} I.P two doses, LPS (*Escherichia coli* 055:B5; 20 mg/kg)-induced intestinal inflammation in male Swiss OF1 mice	—	↑ iNOS and NO when administered with PPARγ antagonist	(De Filippis et al., 2011)
Conjugated linoleic acid	1.33/100 g diet for 49 days, *Brachyspira hyodysenteriae*-induced colitis in pigs	↑ PPARγ	↓ mucosal damage ↓ IFN-γ and IL-10	(Hontecillas et al., 2002)
	1/100 g diet for 49 days, 2.5% DSS-induced colitis in C57BL6/J mice	↑ PPARγ &-δ	↑ UCP1, UCP3, CD36, PGC-1α; Keratin 20 ↑ NFκB-p^{65} activation ↓ Gob-4 and TNFα	(Bassaganya-Riera et al., 2004)
	2.21% CLA-supplemented diets for 49 days, 4% DSS-induced colitis in pigs	↑ PPARγ, PGC1-α, UCP3	↓ TNFα	(Bassaganya-Riera & Hontecillas, 2006)
	1% CLA-supplemented diets for 24 days, 2.5% DSS-induced colitis in C57BL6/J mice	PPARγ dependent protection	↓ disease activity, gross and histopathology	(Bassaganya-Riera, Viladomiu, Pedragosa, De Simone, Carbo, et al., 2012)
	100 mg kg^{-1} day^{-1} in diet for 7 days, 2% DSS-induced colitis in female BALB/c mice	↑ PPARγ	↓ iNOS, NFκB ↓ trefoil peptides- TFF	(Borniquel et al., 2012)
Curcumin	25–300 mg kg^{-1} day^{-1} I.G for 7 days, TNBS (30–100 mg/ml)-induced colitis in female BALB/c mice and SD rats	↑ PPARγ	↓ MPO, MDA ↓ IL-1, IL-12, IFN-γ, TNFα, iNOS ↓ TLR-4, MyD88, p38 MAPK activation ↑ IL-4, IL-10, PGE2	(Camacho-Barquero et al., 2007; Jiang et al., 2006; Lubbad et al., 2009; Ukil et al., 2003; Zeng et al., 2013; Zhang et al., 2006)
Geniposide	50, 100, and 200 mg kg^{-1} day^{-1} P.O for 8 days, 2.5% DSS-induced colitis in female C57BL/6J mice	↑ PPARγ	↓ TNFα, IL-6, and IL-1β	(Shan et al., 2017)

(Continues)

TABLE 1 (Continued)

Name of the phytochemicals	Dose, duration, and model	PPAR activity	IBD parameter	Reference
Geraniol	250 mg kg^{-1} day^{-1} P.O for 11 days, TNBS (30 mg/ml)-induced colitis in male Wistar rats	↑ PPARγ	↓ Wnt/β-catenin, p38MAPK, NFκB, and caspase-3	(Soubh et al., 2015)
Glycyrrhizin	100 mg kg^{-1} day^{-1} P.O for 7 days, 3% DSS-induced colitis in female Wistar rats	↑ PPARγ	↓ TNFα	(Sethuraman et al., 2015)
Isoquiritigenin	3, 15, and 75 mg.Kg^{-1}.Day^{-1} P.O for 12 days, AOM/2% DSS-induced colitis in male BALB/c mice	↑ PPARδ	↓ PGE2 and IL-6	(Zhao et al., 2014)
Lentinus edodes β-glucans	500–1,000 mg kg^{-1} day^{-1} I.G for 6 days, 2% DSS-induced colitis in male ICR mice	↓ p-PPARγ ^{Ser112}	↓ MDA, MPO ↓ TNFα, IL-1β and IL-6, and JNK/ $ERK^{1/2}$	(Shi et al., 2016)
Magnolol	25, 50, and 100 mg kg^{-1} day^{-1} I.G for 8 days, 2.5% DSS-induced colitis in male C57BL/6J mice	↑ PPARγ	↓ TNFα, IL-1β, and IL-12 ↑ ZO-1	(Shen et al., 2018)
Oroxyloside	20–80 mg kg^{-1} day^{-1} I.G for 10 days, 5% DSS-induced colitis in female C57BL/6J mice	↑ PPARγ	↓ MPO, iNOS	(Wang et al., 2016)
Oxylipins	25, 50, and 100 μM, (TNFα, 50 ng/ml induced on HT-29 cells)	↑ PPARγ	↓ IL-1β, IL-6, IL-8, iNOS, and COX-2	(Avila-Roman et al., 2018)
Punicic acid	45–80 mg day^{-1} in diet for 7 days, 2.5% DSS-induced colitis in female C57BL/6J mice	↑ PPARγ and δ	↓ TNFα, NFκB ↑ TGF-β1	(Bassaganya-Riera et al., 2011)
Resveratrol	25 μM for 1 hr, HT-29 cells treated with 10 ng/ml IL-1α, 20 ng/ml TNFα, and 60 ng/ml IFN-γ.	↑ PPARγ	↑ GSH/GSSG ratio ↑ Nrf2 activation	(Serra et al., 2016)
Tetramethylpyrazine	80 mg kg^{-1} day^{-1} I.P for 4 days, 3%oxazolone (I.R)-induced colitis in male Kun Ming mice.	↑ PPARγ	↓ MPO, TNFα, iNOS, NFκB-p^{65}, COX-2	(He et al., 2012)
Verbascoside and acteoside	2 mg day^{-1} P.O for 3 days, DNBS (4 mg/ml)-induced colitis in mice	↑ PPAR-α	↓ PMN infiltration ↓ intestinal permeability and colon injury	(Esposito et al., 2010)
α-Eleostearic acid	1 g/100 g diet for 7 days, 2.5% DSS-induced colitis in C57BL/6J mice	↑ PPARγ	↓ IL-6 and VCAM-1	(Lewis et al., 2011)
β-Caryophyllene	12.5–50 mg kg^{-1} day^{-1} P.O for 7 days, 3% DSS-induced colitis in male CD1 mice / 3% (I.R) oxazolone-induced colitis in male CD1 mice	↑ PPARγ	↓ N-acetylglucosaminidase ↓ TNFα, IL-1β, IFN-γ, and keratinocyte-derived chemokine ↓ $ERK^{-1/2}$, NFκB, IκB-kinase α/β, CREB, caspase-3, and Ki-67	(Bento et al., 2011)
Plant products regulated PPAR activity				
Portulaca extract	100 mg kg^{-1} day^{-1} P.O for 7 days, 2.5% DSS-induced colitis in female C57BL/6J mice	↑ PPARγ	↓NFκB phosphorylation	(Kong et al., 2018)
Zanthoxylum bungeanum essential oil	20–80 mg kg^{-1} day^{-1} P.O for 7 days, 3% DSS-induced colitis in male C57BL/6J mice	↑ PPARγ	↓NFκB, IκB ↓NLRP3, ASC, and caspase-1	(Zhang et al., 2017)

Abbreviations: CLA, conjugated linoleic acid; COX-2, cyclooxygenase-2; DSS, dextran sodium sulfate; DNBS, 2,4,6-dinitrobenzene sulfonic acid; GSH, glutathione; GSSH, oxidized glutathione; IBD, inflammatory bowel disease; IFN-γ, interferon gamma; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IL, interleukin; iNOS, inducible nitric oxide synthase; LANCL2, lanthionine synthetase C-like protein 2; MadCAM-1, mucosal addressin adhesion marker-1; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, metalloproteinase; MPO, myeloperoxidase; NFκB, nuclear factor-κB; PGE2, prostaglandin E2; PGC1-α, PPARγ-coactivator-1α; PMN, polymorphonuclear neutrophil; PPAR, peroxisome proliferator activated receptor; TGF-β1, transforming growth factor β1; Th, helper T cell; TLR, toll-like receptor; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion marker-1.

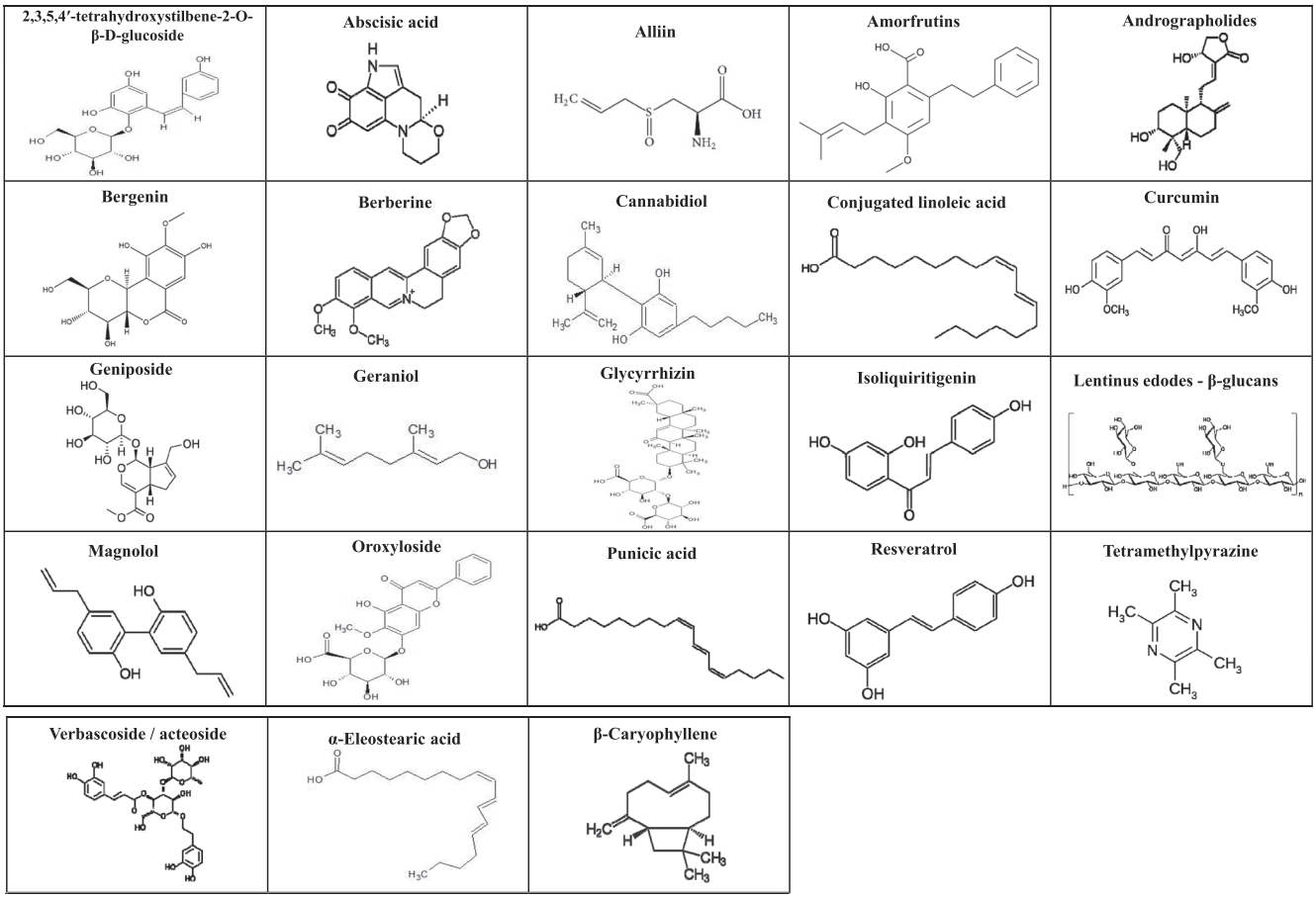

FIGURE 1 Chemical structures of phytochemicals that are involved in PPARγ activation

3.5 | Amorfrutins

Amorfrutins are isoprenoids isolated from the fruits of *Amorpha fruticosa* and edible roots of *Glycyrrhiza foetida* (licorice). They are used as traditional medicine and show potent antidiabetic properties by binding to PPARγ and thereby activating its downstream pathways (Weidner et al., 2012). Amorfrutins A attenuate expression of inflammatory marker genes macrophage inflammatory protein 3α, IL-8, and growth-regulated oncogene-α through binding to PPARγ in HT-29 cells (Fuhr, Rousseau, Plauth, Schroeder, & Sauer, 2015), and thus, in vivo studies in IBD are warranted.

3.6 | Andrographolide

Andrographolide, a diterpenoid lactone, isolated as a major bioactive constituent of *Andrographis paniculata*, has shown potent anti-inflammatory and anticancer effects (Shi et al., 2017). Andrographolide sulfonate inhibits helper T cell (Th)1/Th17 response and reduces activation of p38 MAPK and NFκB in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis (Liu et al., 2014). The inhibitory effects on Th1/Th17 responses and the promoting effects on Th2 responses of andrographolide were confirmed in peripheral blood mononuclear cells from UC patients (Zhu et al., 2018). Furthermore, the andrographolide-lipoic acid conjugate, AL-1 alleviated colon injury by decreasing expression of p-p^{65}, p-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha, and COX-2 and increasing expression of PPARγ (Yang et al., 2016). Another derivative, 3,14,19-triacetyl andrographolide, down-regulated the phosphorylation of p38 MAPK, extracellular signal-regulated kinases (ERK), and c-Jun *N*-terminal kinase (JNK; Gao et al., 2018). These promising data support a role for andrographolide in the prevention of UC.

3.7 | Bergenin

Bergenin (also known as cuscutin), a trihydroxybenzoic acid glycoside, is the C-glucoside of 4-O-methyl gallic acid isolated from plants such as *Bergenial crassifolia*, *Corylopsis spicata*, *Caesalpinia digyna*, *Mallotus japonicus*, and *Sacoglottis gabonensis* (Bajracharya, 2015). Bergenin alleviates TNBS-induced colitis damage by reducing expression of pro-inflammatory proteins and cytokines via regulation of pSTAT3 and NFκB signaling, and by inhibiting the (nucleotide-binding domain, leucine-rich repeat family) pyrin domain containing 3/ASC inflammasome pathways (Lopes de Oliveira et al., 2019). Additionally,

TABLE 2 Evaluation of compounds for "Lipinski rule of five" to distinguishing between drug-like and nondrug-like molecules

Compound	Molecular mass	Hydrogen bond donor	Hydrogen bond acceptor	miLogP	TPSA	Number of violation of Lipinski rule
2,3,5,4′-Tetrahydroxy-stilbene-2-O-β-D-glucoside	404	7	8	1.26	**150.83**	—
Abscisic acid	250	2	4	1.55	74.60	—
Alliin	192	3	4	−2.42	80.39	—
Amorfrutin A	340	4	2	4.97	66.76	—
Andrographolide	250	3	5	1.05	86.99	—
Bergenin	334	5	9	−2.09	**145.91**	—
Cannabidiol	314	2	2	**7.14**	40.46	1
Conjugated linoleic acid	280	1	2	**7.09**	37.20	1
Curcumin	368	2	6	2.30	93.07	—
Geniposide	384	5	8	−0.39	**136.68**	—
Geraniol	154	1	1	3.20	20.23	—
Isoliquiritigenin	256	3	4	2.77	77.75	—
Magnolol	266	2	2	4.80	40.46	—
Oroxyloside	468	5	**11**	0.82	**176.12**	1
Glycyrrhizin	**822**	**8**	**15**	2.65	**257.81**	3
Oxylipins	296	1	3	**5.92**	49.83	1
Punicic acid	278	1	2	**6.60**	37.30	1
Resveratrol	228	3	3	2.99	60.68	—
Tetramethylpyrazine	136	0	2	1.12	25.78	—
Verbascoside and acteoside	**624**	**9**	**15**	−0.45	**245.29**	3
α-Eleostearic acid	278	1	2	**6.60**	37.30	1
β-Caryophyllene	204	0	0	**5.17**	0.00	1

Bold Values: Molecules with a topological polar surface area (TPSA) of greater than 140 $Å^2$ tend to be poor at permeating cell membranes.
Note: Lipinski's rule of five is used to evaluate the drug-likeness. An orally active drug has no more than one violation of Lipinski's rule of five. Molecules with a topological polar surface area (TPSA) of greater than 140 $Å^2$ tend to be poor at permeating cell membranes and tend to exhibit less bioavailability.

bergenin activates PPARγ, upregulates SIRT1, inhibits NFκB-p^{65} acetylation and nuclear translocation, thereby suppressing the release of pro-inflammatory cytokines (Wang et al., 2017). These reports indicate a promising role in the prevention of IBD.

3.8 | Cannabidiol

Cannabidiol (CBD) is a nonpsychotropic phytocannabinoid component of industrial hemp and *cannabis cultivars* that exerts a wide range of pharmacological effects through interactions with endocannabinoid receptors in mammals. (Burstein, 2015). CBD prevents reactive enteric gliosis induced by lipopolysaccharide (LPS) in mice and that induced by LPS + interferon gamma (IFN-γ) in cultured biopsies from UC patients, through the massive reduction of astroglial signaling neurotrophin (S100B) and reduced TNFα expression. But these effects were reversed when CBD was administered with GW9662, a potent PPARγ antagonist, indicating direct interaction of CBD with the PPARγ receptor (De Filippis et al., 2011).

3.9 | Conjugated linoleic acid

Conjugated linoleic acid (CLA) is a family of isomers of linoleic acid found mostly in meat and dairy products derived from ruminants. In a porcine bacterial colitis model, CLA decreases mucosal damage and maintains cytokine profiles (IFN-γ and IL-10) and lymphocyte subset distributions (i.e., cluster of differentiation (CD4)+ and CD8+; Hontecillas et al., 2002). In the dextran sodium sulfate model in mice, CLA ameliorates colitis through a PPARγ-dependent mechanism. (Bassaganya-Riera et al., 2004). In the porcine bacterial colitis model, inhibition of colitis correlated with induction of colonic PPARγ and its responsive gene PPARγ-coactivator-1α and downregulation of TNFα (Bassaganya-Riera & Hontecillas, 2006). Probiotic bacteria produced CLA in the gut targets macrophage PPARγ to suppress colitis (Bassaganya-Riera et al., 2012) and also decreases COX-2 levels (Bassaganya-Riera, Viladomiu, Pedragosa, De Simone, & Hontecillas, 2012). Furthermore, a CLA-enriched diet prevents the colon shortening, reduces expression of iNOS and NFκB, and increases expression of PPARγ and trefoil factor 3 (a stable secretory protein expressed in

gastrointestinal mucosa that appears to play a protective role in the mucosa) in the colon (Borniquel, Jadert, & Lundberg, 2012). Collectively, these results show that CLA recruits PPARγ-associated anti-inflammatory pathways to counteract colitis damage.

3.10 | Curcumin

Curcumin is a polyphenol derived from *Curcuma longa* plant that has been used extensively in complementary and alternative medicine (Keihanian, Saeidinia, Bagheri, Johnston, & Sahebkar, 2017). Curcumin prevents and improves the wasting and histopathologic signs of TNBS-induced colonic inflammation, respectively (Jian et al., 2005; Jian, Wang, Mai, Zhang, & Lai, 2004; Sugimoto et al., 2002). In addition, curcumin reduces neutrophil infiltration and lipid peroxidation and decreases serine protease activity in colon. Curcumin also reduces the levels of nitric oxide, COX-2, and $O_{(2)}^{(-)}$ associated with the favorable expression of iNOS and Th1 (IL-1, IL-12, IFN-γ, and TNFα) and Th2 (IL-4 and IL-10) cytokines and increases PPARγ and prostaglandin E2 (PGE2) levels (Jiang, Deng, Zhang, & Xia, 2006; Ukil et al., 2003; M. Zhang, Deng, Zheng, Xia, & Sheng, 2006). Curcumin attenuates the activation of toll-like receptor (TLR)-4, MyD88, p38 MAPK, and NFκB and the inhibition of p38 MAPK signaling (Camacho-Barquero et al., 2007; Lubbad, Oriowo, & Khan, 2009; Salh et al., 2003) and reduces carbachol-induced contraction (Lubbad et al., 2009). Curcumin inhibits IL-27 expression via the TLR-4/NFκB signaling pathway (Zeng, Zhan, Liao, Chen, & Lv, 2013). Furthermore, curcumin reduces TNFα, IL-2, IL-12 p40, IL-17, and IL-21 levels (Zhao et al., 2016) and exhibits anti-inflammatory effects by enhancing suppressor of cytokine signaling 1 expression and inhibiting Janus kinase/STAT pathway (Zhang et al., 2016). By modulating the Janus kinase/STAT/suppressor of cytokine signaling pathway, curcumin suppresses the activation of dendritic cells and restores immunologic balance to effectively treat experimental colitis (Zhao et al., 2016). Curcumin decreases the density CD8 + CD11c + cells in spleen and Peyer's patches (gut-associated lymphoid tissue usually found in the lowest portion of small intestine) and the expression of major histocompatibility complex II, CD205, CD40, and CD40L, whereas intercellular adhesion molecule-1 was also inhibited (Zhao et al., 2017).

Curcumin reduces histological signs of colonic inflammation in $Mdr1a^{-/-}$ mice—a spontaneously develop intestinal inflammation, predominantly in colon, with pathology similar to IBD (Nones et al., 2009). In addition, key transcription factors and other regulatory molecules (ERK, FN1, TNFSF12, and PI_3K complex) activated in inflammation were downregulated by dietary intervention with curcumin (Cooney et al., 2016). Curcumin was able to attenuate 2,4,6-dinitrobenzene sulfonic acid-induced colitis in mice, by acting as a transient receptor potential cation channel subfamily V member 1 (TRPV1) agonist with reductions in both the macroscopic and histological damage scores (Martelli et al., 2007). In IL-10 gene-deficient mice (another murine model for IBD), curcumin was shown to have anti-inflammatory effects mediated through a reduced production of potent pro-inflammatory mucosal cytokines (Ung et al., 2010).

In dextran sodium sulfate (DSS)-induced colitis model, curcumin reduces disease activity index, histological colitis score, MPO activity, and NFκB activation (Deguchi et al., 2007; Jia et al., 2011) and decreases TNFα, NO levels & cyclin dependent kinase 4, cylinD1 levels as well as STAT3 signaling (Arafa, Hemeida, El-Bahrawy, & Hamada, 2009; Liu et al., 2013; Yang et al., 2013). Curcumin inhibits the p38MAPK signaling pathway, thereby reducing the release of TNFα (Li, Li, He, Chen, & Shi, 2015). Additionally, curcumin maintains S-nitrosylation levels and inhibits the activity of inhibitor of nuclear factor kappa-B kinase subunit beta (Kao, Hu, Wu, & Kong, 2016). Curcumin has been shown to alleviate the hyperalgesia associated with experimental colitis (Yang et al., 2017). At least in part this effect is mediated by reducing the colonic expression of TRPV1 and partly by inhibiting the phosphorylation of TRPV1 in nociceptive neurons projecting from the dorsal root ganglia (Yang et al., 2017). Essential turmeric oils of curcumin were shown to upregulate the anti-inflammatory cytokines including IL-10 and IL-11 as well as forkhead box P3 in the colon (Toden, Theiss, Wang, & Goel, 2017).

TNFα-colitis is characterized by hemorrhagic edema and crypt abscesses massively infiltrated by inflammatory cells, namely neutrophils. Curcumin attenuates the hallmarks of oxidative stress, neutrophils influx, and reactive oxygen species-related cellular and histological damages (Mouzaoui, Rahim, & Djerdjouri, 2012). In the acetic acid-induced colitis model, curcumin decreases colonic injury, and this is associated with decreased inflammatory reactions, lipid peroxidation, and apoptotic cell death, as well as suppression of the p38- and JNK-MAPK signaling pathways (Topcu-Tarladacalisir et al., 2013). Curcumin also increases colonic PGE2 and IL-10 concentrations (Gopu et al., 2015). The colitis in 2,4,6-trinitrobenzene sulfonic acid-treated BALB/c mice is believed to be a mixed Th1/Th2-derived cytokine response. In contrast in SJL/J mice, which lack natural killer T cells, the colitis is Th1-mediated. Interestingly, curcumin has no protective effect against TNBS-induced colitis in SJL/J mice (Billerey-Larmonier et al., 2008). Similarly, curcumin demonstrates only limited effectiveness on Th-1-mediated colitis in $IL\text{-}10^{(-/-)}$ mice, with moderately improved colonic morphology (Larmonier et al., 2008).

Curcumin has been reported as a promising and safe medication for maintaining remission in randomized, multicenter, double-blind, placebo-controlled trial in UC patients (Hanai et al., 2006). In another study, curcumin showed a significantly better outcome in terms of clinical response, clinical remission, and improvement on endoscopy in a single-center pilot trial (Singla et al., 2014). In combination with mesalamine (5-aminosalicylic acid), curcumin showed beneficial effects inducing both clinical and endoscopic remission in patients with mild-to-moderate active UC, with no apparent adverse effects (Lang et al., 2015). In contrast, however, a low dose oral curcumin (450 mg/day) was not effective in inducing remission in mild-to-moderate cases of UC (Kedia et al., 2017). Considering the efficacy of curcumin in human subjects, it would be reasonable to speculate that this common spice could have excellent prospects for further pharmaceutical and/or nutraceutical development as a drug or efficacious supplement for colitis.

3.11 | Geniposide

Geniposide, an iridoid glycosideextracted from the fruit of *Gardenia jasminoides* Ellis, is present in nearly 40 species belonging to various families, especially the *Rubiaceae*, which is known to have anti-inflammatory, antioxidative, antidiabetic, neuroprotective, hepatoprotective, and cholagogic effects (Shan et al., 2017). Geniposide reduces the DSS-induced increase of the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor and NFκB-p^{65} protein phosphorylation and attenuates DSS-induced reduction of PPARγ (Shan et al., 2017). In addition, geniposide downregulates COX-2, iNOS, and myosin light-chain kinase (– a serine/threonine-specific protein kinase that phosphorylates myosin light chain kinase expression and increases expression of the tight junction proteins (occludin and ZO-1), and expedites adenosine 5′ monophosphate-activated protein kinase phosphorylation (Xu et al., 2017).

3.12 | Geraniol

Geraniol is a terpene occurring in the essential oils of several aromatic plants like palmarosa, ninde, rose, and citronella oils (Cho, So, Chun, & Jeon, 2016). Geraniol appears to exert its antioxidant, anti-inflammatory, and immunosuppressive effects by modulating the Wnt/GSK-3β/β-catenin, p38MAPK, NFκB, and PPARγ signaling pathways (Soubh, Abdallah, & El-Abhar, 2015). Furthermore, geraniol inhibits NFκB-p^{65}-DNA binding as well as nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha phosphorylation, degradation, and subsequent increase in nuclear translocation (Medicherla et al., 2015). In addition, geraniol was shown to have multi-target effects that simultaneously targeted dysbiosis, local, and systemic inflammation and mucosal damage via suppression of COX-2 and inflammatory cytokines (De Fazio et al., 2016). The effects and molecular mechanisms that mediate the anti-inflammatory activity of geraniol warrant further exploration.

3.13 | Glycyrrhizin

Glycyrrhizin (triterpenoid glycoside or saponin) is the primary sweet-tasting constituent found in licorice root, *Glycyrrhiza glabra* L (Spinks & Fenwick, 1990). The glycyrrhizin derivative, diammonium glycyrrhizinate, reduces inflammatory injury via inhibition of NFκB, TNFα, and intercellular adhesion molecule-1 in the colon (Yuan et al., 2006). Glycyrrhizic acid suppresses lipid peroxidation and expression of TNFα and IL-1β in the TNBS-induced colitis model (Liu et al., 2011). Topical application of glycyrrhizin ameliorates the production of pro-inflammatory cytokines and chemokines, such as IL-1β, TNFα, IL-6, cytokine-induced neutrophil chemoattractant-2 and -3, monocyte chemoattractant protein 1, macrophage inflammatory protein 3α, tissue inhibitor of metalloproteinases-1, fractalkine, ciliary neurotrophic factor, leptin, and GM-CSF (Kudo, Okamura, Zhang, Masuo, & Mori, 2011). In another study, glycyrrhizin-inhibited inflammatory mediators, including IL-6 and cytokine-induced neutrophil chemoattractant-3 and MPO activity (Lee et al., 2013). Dipottasium glycyrrhizate, another glycyrrhizin derivative, inhibits high mobility group box 1 protein activity (secreted by immune cells like macrophages and monocytes), thereby reducing intestinal inflammation. Glycyrrhizate also decreases iNOS and COX-2, as well as NO and PGE2 levels in the DSS–colitis models (Vitali et al., 2013; Vitali et al., 2015). Furthermore, glycyrrhizin reduces macroscopic and microscopic lesions and reduces expressions of PPARγ and TNFα (Sethuraman et al., 2015). It is interesting to speculate that glycyrrhizin could be developed for pharmaceutical and/or nutraceutical therapeutic use in the treatment of colitis.

3.14 | Isoquiritigenin

Isoliquiritigenin (ISL) is a bioactive ingredient isolated from the roots of plants belonging to licorice, including *Glycyrrhiza uralensis*, Mongolian glycyrrhiza, *G. glabra*, and other family members (Peng et al., 2015). ISL inhibits PGE2 and IL-6 signaling in colitis-associated tumorigenesis via obstruction of M2 macrophage polarization (Zhao et al., 2014). ISL suppresses the phosphorylation of $ERK^{1/2}$ and p38 and the activation of NKκB (Choi et al., 2016). In addition, ISL increases the levels of probiotics, particularly butyrate-producing bacteria (*Butyricicoccus*, *Clostridium*, and *Ruminococcus*; Wu et al., 2016). ISL is an attractive nutraceutical candidate for prevention of colitis.

3.15 | β-Glucans

The β-glucans are a family of β-D-glucose polysaccharides found in the cell walls of cereals, bacteria and fungi. A study of the β-glucans from Shiitake mushrooms (*Lentinus edodes*) in the DSS-induced colitis model in mice revealed that it suppressed the inflammatory response, reduced expression of iNOS, TNFα, IL-1β, and IL-6 and production of NO, and blocked the phosphorylation of $JNK/ERK^{1/2}$ and p38 and Elk-1 and PPARγ at $serine^{112}$ (Shi et al., 2016).

3.16 | Magnolol

Magnolol (5,5′-di-2-propen-1-yl-2,2′-Bichavicol) is a hydroxylated biphenyl lignan found in the bark of *Magnolia officinalis* or in *Magnolia grandiflora* (Ranaware et al., 2018). Magnolol reduces expression of colonic pro-inflammatory cytokines (TNFα, IL-1β, and IL-12) by increasing the expression of PPARγ (Shen et al., 2018). Magnolol also downregulates NFκB-p^{65} mRNA and TLR-4 protein expression in the TNBS–colitis model (Zhang, Fu, & Tang, 2018).

3.17 | Oroxyloside

Oroxyloside is a metabolite of oroxylin A from the root of *Scutellaria baicalensisis* (H. B. Li & Chen, 2005). Oroxyloside attenuates inflammation in the DSS-induced colitis model. It reduces the body weight loss,

colon length shortening, and colonic pathological damage, inhibits inflammatory cell infiltration and decreases MPO and iNOS activities. Oroxyloside inhibits NFκB pathway activation through PPARγ (X. Wang et al., 2016). However, additional mechanistic studies are warranted to elucidate the pronounced in-vivo effects of oroxyloside.

3.18 | Oxylipins

Oxylipins are a family of oxygenated products formed from polyunsaturated fatty acids by cyclooxygenases and lipoxygenases which are widely distributed in animals, plants, mosses, algae, bacteria and fungi (Avila-Roman, Talero, Rodriguez-Luna, Garcia-Maurino, & Motilva, 2016). Oxylipins down-regulate COX-2 and iNOS by inhibition of the NFκB signaling pathway (Avila-Roman et al., 2014). (Avila-Roman et al., 2014). Oxylipins are agonists of PPARγ and activation results in NFκB/PPARγ co-localization in the cytoplasm, interfering with the nuclear translocation of NFκB, thereby reducing the transcription of pro-inflammatory genes (Avila-Roman, Talero, de Los Reyes, Garcia-Maurino, & Motilva, 2018).

3.19 | Punicic acid

Punicic acid is a bioactive compound of pomegranate seed oil that has gained wide attention for its therapeutic potential (Shabbir et al., 2017). Punicic acid is potent inhibitor of TNFα-induced priming of reactive oxygen species production and MPO release by neutrophils (Boussetta et al., 2009). Punicic acid ameliorates colitis in IL-$10^{-/-}$ mice and in DSS-induced colitis in mice by suppressing TNFα and NFκB activation while inducing the immunoregulatory cytokine transforming growth factor β1. Macrophage-specific deletion of PPARγ caused a complete abrogation of the protective effect of punicic acid, indicating direct activation of PPARγ (Bassaganya-Riera et al., 2011). Because of these potent effects, investigation of the effectiveness of this compound in human IBD is warranted.

3.20 | Resveratrol

Resveratrol is a natural polyphenol found in grapes, red wine, grape juice, and several species of berries (Nunes, Danesi, Del Rio, & Silva, 2018). Resveratrol activates PPARα and PPARγ in a number of cell-based reporter assays (Inoue et al., 2003). Resveratrol was shown to upregulate HO-1 and germ cell-less mRNA levels in cytokine-stimulated HT-29 cells. Further, resveratrol increased nuclear levels of PPARγ in cytokine-stimulated cells (Serra, Almeida, & Dinis, 2016). These novel findings suggest the further development of resveratrol as a natural drug candidate for the treatment of IBD.

3.21 | Tetramethylpyrazine

Tetramethylpyrazine (ligustrazine) is a compound isolated from *Ligusticum wallichii*, which has been extensively used for Chinese herbal medicine for centuries (Zhao, Liu, & Chen, 2016). Tetramethylpyrazine decreases MPO activity and expression of TNFα, iNOS, NFκB-p^{65}, and COX-2, as well as increasing in PPARγ production (He et al., 2012). Tetramethylpyrazine also suppresses colitis through inhibition of NFκB translocation, with subsequent inhibition of pro-inflammatory factor production (Lu et al., 2014). In addition, it was shown to inhibit transcription factors such as transcription factor-AP-1 and nuclear factor of activated T cells (Zhao, Liu, & Chen, 2016). Considering these findings, tetramethylpyrazine has significant potential for future therapeutic utility in the amelioration of colitis.

3.22 | Verbascoside (also known as acteoside)

Verbascoside is a member of a large family of phenylpropanoid glycosides that are widespread in the plant kingdom. Phenylethanoid verbascoside, isolated from *Plantago lanceolata* L. decreases IL-10, TNFα, IFN-γ, and GM-CSF secretion in acute colitis animal models (Hausmann et al., 2007). Verbascoside reduces the progression of colon injury and microscopic and macroscopic indications of colitis brought about by the suppression of NFκB and activation of the pro-active form of metalloproteinase (MMP)-2 and pro-MMP-9 (Mazzon et al., 2009). In addition, verbascoside weakens the anti-inflammatory activity in PPARα knockout mice and inhibits neutrophil infiltration, intestinal permeability, and colon injury (Esposito et al., 2010). Verbascoside ameliorates these inflammatory pathways, thus substantiating its putative preventive effect in colitis.

3.23 | α-Eleostearic acid

α-Eleostearic acid is isolated from tung and bitter gourd seed oils. Several health benefits have been attributed to this compound (Yuan, Chen, & Li, 2014). α-Eleostearic acid was shown to decrease macrophage infiltration and initiate both PPARγ-dependent and -independent pathways that significantly impedes the progression of disease activity index and lesions of intestine (Lewis et al., 2011).

3.24 | β-Caryophyllene

β-Caryophyllene (BCP) is a natural bicyclic sesquiterpene present in significant amounts in natural products for example, clove oil, cinnamon leaves, and copaiba balsam and has marked anti-inflammatory activity (Meeran et al., 2019). Cho et al. (2007) have shown that BCP reduces colon inflammation and prevents the increases in MPO activity and IL-6 expression in a mouse model of DSS-colitis. BCP exhibits anti-inflammatory effects involving cannabinoid type-2 and the PPARγ pathways (Bento et al., 2011). Furthermore, BCP reduces the expression in colon tissue of inflammation-related genes, including cytokines and chemokines (Ccl2, Ccl7, Ccl11, Ifitm3, IL-1β, and IL-28); TNF receptor superfamily member 1B or 12A and TNF receptor 2; acute-phase proteins (S100a8, Saa3, and Hp); adhesion molecules (Cd14, Cd55, Cd68, Mmp3, Mmp10, Sema6b, Sema7a, and Anax13);

and signal regulatory proteins (Cho et al., 2015). Collectively, these results suggest that BCP has multiple anti-inflammatory effects targeting pathways that contribute to experimental colitis.

4 | PLANT PRODUCTS INVOLVED WITH PPARγ ACTIVITY IN IBD

4.1 | Portulaca extract

Portulaca oleracea L. (POL) is a traditional Chinese herb praised for its rich multi-minerals, proteins, α-amyrin, β-carotene, terpenoids, vitamins, and fatty acids (Uddin, Juraimi, Ali, & Ismail, 2012). In addition to its use as an edible plant, it is also considered valuable for alleviating a wide spectrum of diseases (Iranshahy et al., 2017). Yang et al. (2016) have demonstrated that POL decreases oxidative stress and the colonic expression of pro-inflammatory cytokines and TNFα and NFκB-p^{65} in the murine model of DSS colitis. POL alleviates DSS-colitis through regulation of inflammatory reaction, apoptosis, and PPARγ level (Kong et al., 2018). In addition, POL extract was more effective than sulfasalazine in preventing the increase concentrations of TNFα, IL-6, and IL-1β in the mouse model DSS colitis. Similarly, the POL extract was more effective than sulfasalazine in decreasing NO production in cultured macrophages (Kim et al., 2018).

4.2 | Zanthoxylum bungeanum pericarp

Zanthoxylum bungeanum Maxim. (Rutaceae) is a popular food additive and traditional Chinese herbal medicine commonly referred to as HuaJiao and widely distributed in Asian countries. It has been used in the treatment of abdominal pain, toothache, dyspepsia, vomiting, diarrhea, ascariasis, and eczema (Xiang et al., 2016). The essential oil obtained from pericarp of Zanthoxylum bungeanum alleviates colitis through regulation of suppression of pro-inflammatory mediators and regulation of the NFκB and PPARγ pathways. The extract also inhibited (nucleotide-binding domain, leucine-rich repeat family) pyrin domain containing 3, ASC, and caspase-1 production in a dose-dependent manner, resulted in reduction in IL-1β release into the colon in murine experimental colitis (Zhang et al., 2017).

5 | DISCUSSION

UC, a subtype of IBD characterized by colonic mucosal inflammation, causes significant morbidity in the affected individuals (Harbord et al., 2017). UC is commonly considered to be severe than Crohn's disease because it is less frequently associated with development of fistulas and abscesses. However, UC causes a similar deterioration in quality of life. Though the cause of UC is not fully understood, it is widely accepted that there is an interaction between diverse factors, such as an immune system disturbance, genetic predisposition, and environmental factors, that activate a damaging immune response in the intestine (Salaritabar et al., 2017). Current treatment options for UC include the use of 5-aminosalycilates, corticosteroids, thiopurines, TNFα inhibitors, and α4β7 integrin blockers. (Panes & Alfaro, 2017). Unfortunately, long-term usage of these drugs has been found to lead to severe toxicities (Saxena et al., 2014). As mentioned earlier, because the etiology of UC has not been fully identified, no standard treatment protocol has been established thus far, based on the reported biological effects. In this context, phytochemicals reviewed here may indeed, have promising utility as supplements, drugs, and even topical agents and that deserve increased attention from the medical community.

The gut microbiota contains many types of bacteria, viruses, and fungi that normally coexist in a balanced microenvironment (Dieterich, Schink, & Zopf, 2018). Imbalance of that milieu and gut dysbiosis in general has been associated with various health problems, including IBD (Hasan & Yang, 2019; Kho & Lal, 2018). When dextran sodium sulfate-induced colitis mice are treated with *Lactobacillus paracasei*, PPARγ activity is upregulated, and intestinal integrity is restored (Simeoli et al., 2015). *Bifidobacteria* produce short-chain fatty acids, such as butyrate, which are ligands for PPARs. In turn, PPARγ supports maintenance of commensal bacteria such as *Candida albicans* and *Bacteroides fragilis* (Hasan, Rahman, & Kobori, 2019). Consequently, PPARγ activates β-defensin-1-mediated immunity, which constitutes another intestinal anti-inflammatory mechanism (Peyrin-Biroulet et al., 2010). Microbiota-activated PPARγ-signaling also prevents dysbiotic expansion of pathogenic *Escherichia* and *Salmonella* by reducing the bioavailability of respiratory electron acceptors to Enterobacteriaceae in the lumen of the colon (Byndloss et al., 2017). These studies suggest that the normal gut microbiota activates the intestinal PPARγ in the maintenance of intestinal mucosal homeostasis.

Further detailed studies are required to elucidate the precise interactions of PPARs and the regulation of microbiota in the maintenance of gut mucosal integrity (Hasan et al., 2019). Gut microbiota-driven PPARγ-mediated activation may provide better treatment for IBD. Indeed, microbiota-based therapeutic concepts are gradually changing from a focus on altering dietary habits to a focus on modulating microbiota (Borody & Khoruts, 2011) and ingesting probiotic strains to produce helpful short-chain fatty acids (Koh, De Vadder, Kovatcheva-Datchary, & Backhed, 2016). Antibiotics affect the balance of the gut microbiota but co-administration of plant products can normalize the microbial imbalance by reduced intrusion of pathogens and increased probiotics such as *Lactococcus*, *Lactobacillus*, *Bacillus*, and *Pseudomonas* (Wu & Tan, 2019). Resveratrol reduces levels of *Enterobacteria* while improving the availability of *Bifidobacteria* and *Lactobacilli* in the DSS-induced colitis rat model (Larrosa et al., 2009). Another phytochemical, quercetin restores the gut host-microbe relationship, that in turn results in alleviating colitis through rebalancing the anti-inflammatory effects and bactericidal capacity of macrophages (Ju et al., 2018). Curcumin is also efficacious in influencing the composition of our gut microbiota and intestinal permeability with suppression of inflammation and oxidative stress (Lopresti, 2018). Complex beneficial phytochemical and gut interactions reflect the

microbial conversion of plant products into potently bioactive molecules that are better absorbed than the native compounds in many disease conditions (Espin, Gonzalez-Sarrias, & Tomas-Barberan, 2017; Guo et al., 2015; Kim, 2015; Wu & Tan, 2019). In this context, phytochemicals and their positive influence on gut microbiota highlighted in this review will pave way for different approaches in treating IBD and perhaps other inflammatory conditions.

Understanding the role of PPARγ in the intestine will give better insight about its function. PPARγ is an important member of the nuclear receptor family and can be found in a variety of cells. PPARγ is highly expressed in the colon, adipose tissue, and to a lesser degree in macrophages. It participates in regulation of inflammation and mucosal damage in UC lesions (Vetuschi, Pompili, Gaudio, Latella, & Sferra, 2018) and also in the regulation of intestinal inflammation induced by bacteria (Lefebvre et al., 1998). PPARγ is a member of a family of ligand activated nuclear receptors, and for its activation, PPARγ binds with another nuclear receptor, retinoid X receptor, and this heterodimer then binds to specific DNA sequences called peroxisome proliferator response elements, located in the gene promoter region (Kliewer, Umesono, Noonan, Heyman, & Evans, 1992). These two nuclear factors play an important role in the regulation of inflammatory signaling by altering expression of kinases and blocking transcriptional activation by NFκB and thus inhibit production of inflammatory cytokines such as IL-6 & TNFα, chemokines, and adhesion molecules as well as proliferation of inflammatory cells (Desreumaux et al., 2001).

PPARγ has been extensively shown to decrease the expression of TNFα. TNFα is an important cytokine in regulating immune cell function and also acting as a macrophage and neutrophil chemoattractant. Although this cytokine has an important role in the killing of bacteria, excessive expression unfortunately promotes chronic inflammation results in other poor health effects, such as rapid weight loss. In human neutrophils, TNFα actually increases PPARγ mRNA and protein expression, likely as a compensatory mechanism or a feedback loop (Reddy et al., 2008). THSG, berberine, CAPE, cavidine, CLA, and punicic acid have all shown potential for interfering with TNFα activity and production.

Macrophages can transform to pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes in response to invading pathogen. But these deviations are not fully understood (Atri, Guerfali, & Laouini, 2018). It is well documented that infective products such as LPS or TH1 cytokines, such as TNFα and IL-6, can polarize macrophages into the pro-inflammatory (M1) pathway, leading to further pro-inflammatory cytokine release which is responsible for the inflammatory cascade that disperses attacking microbes (Atri et al., 2018; Shapouri-Moghaddam et al., 2018). In contrast, TH2 cytokines such as IL-4 and IL-13 channel the macrophage release towards the M2 pathway, which releases anti-inflammatory cytokines involved in tissue repair and remodeling (Biswas & Mantovani, 2010; Mosser & Edwards, 2008).

Along with TNFα, several ILs are produced in response to inflammatory stimuli. IL-6 is a component of the acute inflammatory response. PPAR agonists were reported to decrease local production of IL-6 in the intestine (Celinski et al., 2011; Zingarelli et al., 2003) as well as IL-8 production (Yin, Hou, Li, Wang, & Kang, 2014). IL-8 is a key chemokine for neutrophil trafficking and broadly expressed by a multitude of cell types, including macrophages, and induced by a variety of inflammatory stimuli (Croasdell et al., 2015). IL-1β is also produced to promote acute inflammation and is reduced by PPAR agonists in a PPARγ-dependent manner (Heming et al., 2018). The broad-ranging effects of PPARγ ligands on pro-inflammatory cytokines may be due to PPARγ effects on the NFκB pathway, as PPARγ has been shown to decrease NFκB expression. Most of the phytochemicals listed in this review have been shown to suppress pro-inflammatory cytokines and modulate intracellular transduction in inflammatory pathways.

In addition to its effects on NFκB, PPARγ activation also inhibits expression of other transcription factors, such as AP-1, activator of transcription (STAT-1), and the expression of adhesion molecules, such as intercellular adhesion molecule 1, as well as the matrix metalloproteinase, MMP-9 (Vetuschi et al., 2018). During inflammation in UC, PPARγ directly regulates expression of pro-inflammatory genes in a ligand-dependent manner, by antagonizing the activities of other transcription factors such as families of NFκB and AP-1 (Bertin et al., 2013). The efficacy and mechanisms of recently reported phytochemicals in experimental UC are reviewed and highlighted here. However, it is important to note that phytochemical bioavailability is a major limiting factor to achieve desired concentration in the target tissues. The gut microbiota plays a major role in transforming ingested phytochemicals, but other critical factors such as hydrophilicity and lipophilicity also influence the bioavailability (Carrera-Quintanar et al., 2018). A few phytochemicals highlighted in this review such as andrographolide (45 mg/kg), geraniol (50 mg/kg), glycyrrhizin (300 mg/kg) and β-caryophyllene (100 mg/kg), curcumin (300 mg/kg), and resveratrol (240 mg/kg) have been reported to reach effective concentrations on target tissues when used a different doses (Chen et al., 2014; He et al., 2018; Hou et al., 2005; Pavan et al., 2018; Scalbert et al., 2005; Walle, 2011). Before investigating a phytochemical for its efficacy, the bioavailability cannot be accurately predicted. However, analysis by "Lipinski's rule of five" provides some insight in as much as; it helps distinguish between drug-like and nondrug-like molecules to evaluate drug-likeliness (Lipinski, Lombardo, Dominy, & Feeney, 2001). Molecules with a topological polar surface area of greater than 140 $Å^2$ tend to be poor at permeating cell membranes. Phytochemicals listed in this review such as 2,3,5,4-tetrahydroxy-stilbene-2-O-β-D-glucoside, bergenin, cyaniding-3-glucoside, geniposide, glycyrrhizin, and verbascoside showed TPSA score of greater than 140 $Å^2$ thus, these phytochemicals are likely to exhibit low bioavailability (Table 2). To overcome the bioavailability issue, employing drug delivery system using nanoparticles, cyclodextrins, niosomes, liposomes, and implants may be helpful before undertaking any in-depth mechanistic studies.

6 | CONCLUSIONS

IBDs are a major health problem worldwide, characterized by markedly diminished quality of life because of pain, vomiting, diarrhea, fatigue, and

increased the risk of colorectal cancer. The incidence of IBD is increasing. Because of inadequate efficacy and serious side effects of current therapies, many patients with IBD turn to alternative medicine sources to alleviate their symptoms with some degree of success. It is clear from recent studies that phytochemicals that modulate PPARγ expression or activity may be valuable in mitigating inflammatory diseases with less side effects than currently used drugs. Several of these compounds warrant further investigation. It should be noted that although bioavailability may be a problem in treating systemic inflammatory diseases, being localized to the intestinal mucosa, IBD represents a rather unique situation where local concentrations of ingested compounds may be adequate to produce a therapeutic response even when general bioavailability is compromised. As such, animal models of IBD are particularly useful in development of therapeutics that may have good topical properties. These natural compounds might also represent the blueprints for molecular modeling that may result in development of synthetic compounds with increased anti-inflammatory efficacy combined with reduced unwanted side-effects. Randomized controlled trials are urgently needed in finding better phytochemical compounds or combinations of such compounds to treat and prevent IBD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

SBS and SO conceptualized the study. BV and SBS wrote the first draft of the manuscript. PDB and BB carried out chemical structure and technical input, BB conducted the evaluation of Lipinski's rule of five. SBS, TEA, SO, and PC edited the manuscript.

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