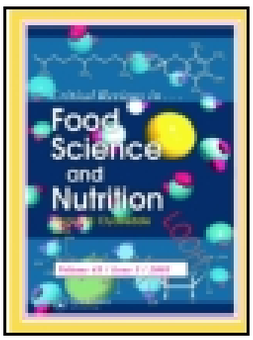

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REVIEW

Phytochemicals and inflammatory bowel disease: a review

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ABSTRACT

Gastrointestinal tract is the second largest organ in the body that mainly functions in nutrients and minerals intake through the intestinal barrier. Intestinal permeability maintains the circulation of minerals and nutrients from digested foods. Life and all the metabolic processes depend either directly or indirectly on proper functioning of GI tract. Compromised intestinal permeability and related disorders are common among all the patients with inflammatory bowel disease (IBD), which is a collective term of inflammatory diseases including Crohn's disease and ulcerative colitis. Many synthetic drugs are currently in use to treat IBD such as 5-aminosalicylic acid corticosteroids. However, they all have some drawbacks as long-term use result in many complications. These problems encourage us to look out for alternative medicine. Numerous in vitro and in vivo experiments showed that the plant-derived secondary metabolites including phenolic compounds, glucosinolates, alkaloids, terpenoids, oligosaccharides, and quinones could reduce permeability, ameliorate-related dysfunctions with promising results. In addition, many of them could modulate enzymatic activity, suppress the inflammatory transcriptional factors, ease oxidative stress, and reduce pro-inflammatory cytokines secretion. In this review, we summarized the phytochemicals, which were proven potent in treating increased intestinal permeability and related complication along with their mechanism of action.

KEYWORDS

Phytochemicals; Intestinal permeability; Inflammation; Colitis; Oxidative stress; Gut microbiota

Introduction

Gastrointestinal (GI) tract is an essential organ system, which has been considered to be the most overlooked part before this century. Since the beginning of this century, people started to realize the importance of GI tract for the proper functioning of life. As it is not only responsible for absorbing minerals and nutrients, but also removing the wastes as feces from the body. At the same time, it acts as a selective barrier that prevents pathogens and unwanted substances from harming the body. The GI tract is divided into four layers namely serosa, muscular mucosa, submucosa, and mucosa. Mucosa is the innermost layer which maintains a sealed barrier with the help of tight junction (TJ) proteins.

Mucosa is inhabited by approximately 100 trillion (10^{14}) microbes (Furusawa et al. 2013; Ley, Peterson, and Gordon 2006; Wells et al. 2011). Most of the microbes are from *Bifidobacterium*, *Bacteroides*, *Clostridium*, *Faecalibacterium*, and *Peptostreptococcus*, and 99% of them are anaerobic in nature (Willey, Sherwood, and Woolverton 2011). *Bifidobacterium* alone accounts for over 30% of all the bacteria present in the gut (Guarner and Malagelada 2003; Sears 2005; Beaugerie and Petit 2004). The modern lifestyle and food habit are very much altering the microbial balance and composition in the gut (Singh et al. 2017). People are taking high fat and sugar-rich food items, instead of fibrous balanced diets, which leads to dysfunction and dysbiosis. Improper food habit, stress condition, altered microorganisms, and infection influences gut homeostasis eventually, lead to barrier dysfunction (McGuckin et al. 2009).

Intestinal permeability is increased by mucosal damage which leads to bacterial translocation and inflammation (Swank and Deitch 1996). As a consequence of unhealthy food habit and lifestyle choice for long period, the intestinal mucosa along with TJ proteins damages and ultimately inflammatory cytokines come into the action. The presence of inflammatory cytokines in excessive amounts has exerted deleterious effects which leads to severe inflammation and finally to diseases (Scarpioni, Ricardi, and Albertazzi 2016). Inflammatory bowel disease (IBD) is, in fact, a collective term for a wide range of intestinal diseases which starts with inflammation and ends up in many complications such as diarrhea, rectal bleeding, and colon cancer. Compromised intestinal permeability is one of the prime causal factors of IBD including Crohn's disease (CD) and ulcerative colitis (UC) (McGuckin et al. 2009). Since the discovery of IBD, many drugs were developed to treat it. Most of the

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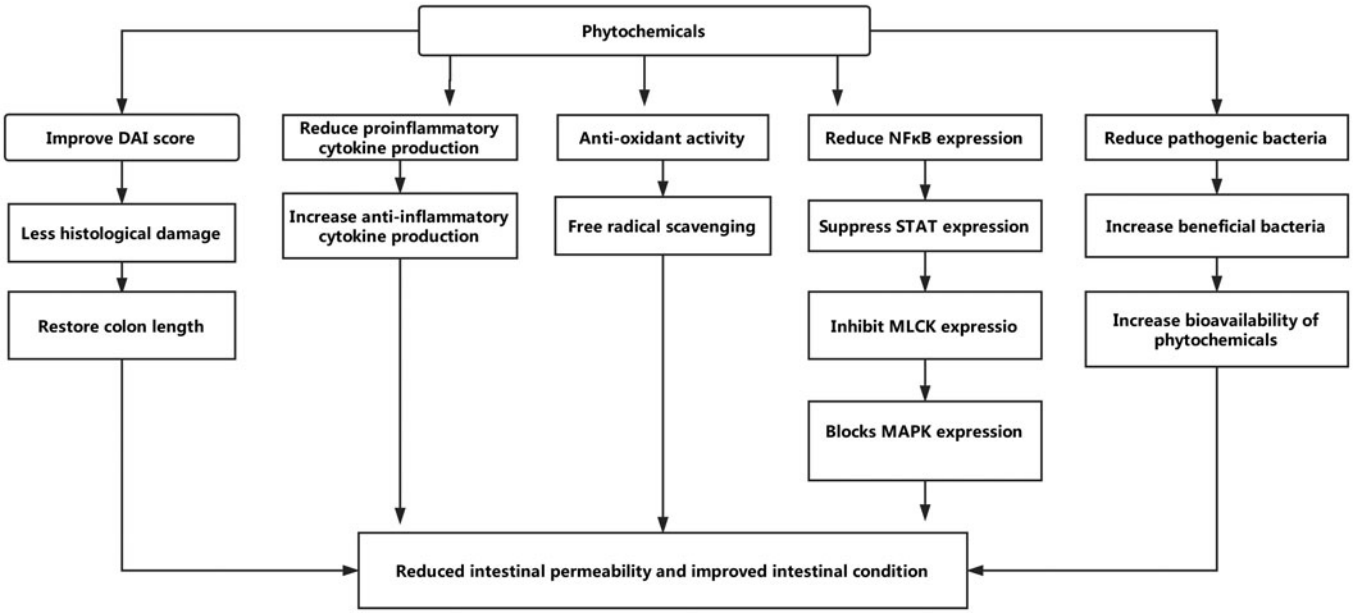

Figure 1. Effects of phytochemicals in modulation of intestinal permeability.

functional synthetic drugs have a wide range of side effects including nausea, vomiting, fatigue, diarrhea, abdominal pain, pulmonary fibrosis, etc (Rogler 2010). For centuries, traditional medicine, especially herbal treatments, have shown their potential to ameliorate countless diseases and disorders with no or fewer side effects. There are also plenty of studies suggesting an intake of fruits and vegetables rich in phytochemicals reduce the risk of many severe diseases including intestinal diseases (Liu 2003; Hung et al. 2004; Chen et al. 2007). Since we consume them on regular basis, the chances of their side effects will be very low or absent.

Phytochemicals are diverse groups of chemicals, which are metabolitic products of plants (Molyneux et al. 2007). Among them, most promising ones are polyphenols, lignans, terpenoids, alkaloids, saponins, and organosulfides (Heneman and Zidenberg-Cherr 2008). They possess numerous potential health benefits including antioxidant activities, antimicrobial activities, immune system stimulation, detoxifying enzyme modulation, etc. (Fig. 1) (Andre, Larondelle, and Evers 2010). *Ziziphus spina-christi* fruit extract (400 mg/kg) significantly reduced inflammation, oxidative stress, and apoptosis compared to mesalazine treatment (300 mg/kg) in 4% acetic acid-induced colitic Wistar rats (Almeer et al. 2018). Berberine administration attenuated intestinal barrier dysfunction in type 2 diabetic rats by upregulating TJ protein expression and by downregulating IL-1β and TNF-α expression significantly (Gong et al. 2017).

In this review article, we tried to present the investigations done in this field since the beginning of this century, mainly focusing on phytochemical compounds that exert beneficial effects in the intestinal barrier improvement and related properties along with their mechanism of actions. The following sections update the details about intestinal barrier and permeability, classification of phytochemicals, according to their chemical group, their mechanism of action, and the conclusion during the recent years.

Intestinal permeability

Comprehensive experimental and clinical data proved the importance of the intestinal barrier and intestinal permeability in health and disease. Intestinal barrier works as selective filter to regulate the vectorial transport of nutrients, water, and waste products; second, it limits the interaction between human body and the luminal contents, such as the intestinal microbiota and various allergens of food source (Groschwitz and Hogan 2009; Khan and Asif 2015; Odenwald and Turner 2017).

Intestinal epithelial cells, mucin layer above them and TJ between them control intestinal permeability. Columnar epithelial cells are located at the luminal surface of the GI tract. Stem cells residing in intestinal crypts are responsible to differentiate into different cells to construct and restore the intestinal epithelial layer. Those cells are enterocytes, enteroendocrine cells, goblet cells, Paneth cells, tuft cells, etc. Over 80% of all the barrier cells are enterocytes which function as absorption of nutrients, while enteroendocrine cells secrete gastrointestinal hormones (Van Der Flier and Clevers 2009; Sarmento 2015). Tuft cells work for defense and secrete interleukin 25, whereas goblet cells function as lubrication and protection of internal wall of the intestine (Johansson and Hansson 2013; Harris 2016). Goblet cells secrete high molecular weight glycoproteins called mucin, which helps in food digestion, defense, and provides a niche for gut microbes.

Mucins act as the key structural element of the mucus layer. They are of two types, secreted mucin, and membrane-bound mucin. So far, in humans 21 mucin genes have been identified (Dharmani et al. 2009). Among them, MUC2 is the most important mucin-producing gene and is the first one identified from humans. The mucus layer formed by mucin serves to establish beneficial microbes, prevents invasion and colonization of pathogenic bacteria,

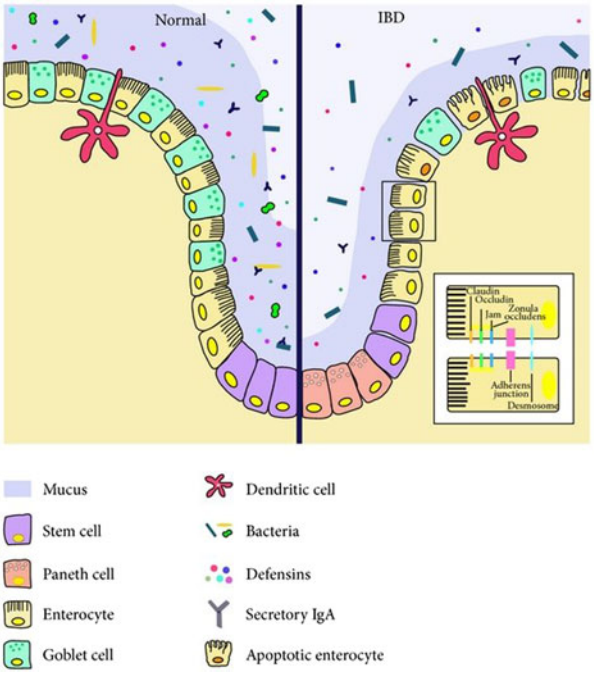

Figure 2. Graphical presentation of healthy and diseased intestinal barrier. Adopted from Michielan and D'Incà (2015).

and blocks noxious substances to get inside the body (Kim and Ho 2010).

As the main physical barrier between the lumen and mucosal tissues, the intestinal epithelial layer is sealed by intercellular junctions complex. There are four types of junctions namely tight junctions (TJ), gap junctions, adherens junctions (Turner 2006; Khan and Asif 2015; Farquhar and Palade 1963). They not only seal the paracellular space to maintain the stability of the epithelial layer, but also regulate the flow of water ions and small molecules from the lumen, and function. They also act as a multifunctional complex to coordinate various cellular activities including signaling, cell proliferation, and differentiation (Marcelino and Anderson 2001; Tsukita, Furuse, and Itoh 2001; Schneeberger and Lynch 2004; Matter et al. 2005).

Transcellular permeability and paracellular permeability are the two major means of selective permeability (Groschwitz and Hogan 2009). TJ proteins regulate the movement of nutrients and ions from the gut lumen to the body by creating a diffusion barrier and paracellular pathway (Rao and Wang 2011; Balda and Matter 2008). Over 50 TJ proteins construct TJ structure, and among them, most important ones are Claudin and Occludin (Ulluwishewa et al. 2011). Many genes regulate the expression and interaction of TJ proteins. Occludin (OCLN) gene, Claudin 1 (CLDN1) gene, Claudin 5 (CLDN5) gene, Claudin 9 (CLDN9) gene, and TJ associated protein 1 (TJAP1) gene are among all those important genes which are the key players in the expression of TJ proteins (Ando-Akatsuka et al. 1996; Halford et al. 2000; Peacock, Jeffrey Keen, and Inglehearn 1997; Meertens et al. 2008; Kawabe et al. 2001).

Countless factors are responsible for altered intestinal permeability including modulation of gut microbes, an altered mucus layer, food, lifestyle, inflammation, stress, infection, and so on (Bischoff et al. 2014; Wang et al. 2008). When the intestinal epithelial layer loses integrity, it results in increased intestinal permeability and barrier dysfunction (Fig. 2). Compromised intestinal permeability and barrier dysfunction leads to many diseases and disorders including IBD, irritable bowel syndrome (IBS), Celiac disease, nonalcoholic fatty liver disease (NAFLD), obesity, type 2 diabetes, food allergies, septic shock, etc. (Bischoff et al. 2014; Viggiano et al. 2015; Teixeira et al. 2012; Sánchez de Medina et al. 2014). It is not universal that intestinal permeability will show up in the case of all the diseases. Nevertheless, for most of the cases, increased intestinal permeability will be visible before disease appearance (Fasano 2011). Therefore, if we can prevent the damage or alteration in the intestinal epithelial layer and the inhabiting microorganisms, we will be able to prevent the diseases and may also develop a new and more effective way to treat all the related diseases and disorders (Teshima and Meddings 2008).

Phytochemicals modulating intestinal permeability

Phytochemicals are nonnutrients produced by plants through primary and secondary metabolism for their defense and survival from herbivorous animals, insects, etc. (Ajuru, Williams, and Ajuru 2017; Molyneux et al. 2007). Even though the scientific community discovered around 12,000 phytochemicals, of them more than 8000 compounds are polyphenols. However, estimation is that these are just 10% of all the phytochemicals present in plants (Cheynier 2005; Tapsell et al. 2006). Based on their origin, chemical structure, and function, phytochemicals are classified into polyphenols, alkaloids, polysaccharides, terpenes, glucosinolates, carotenoids, lectins, polyacetylenes, capsaicinoids, betalains, chlorophyl, and allium compounds (Campos-Vega and Oomah 2013). Except these, there are many compounds which are also present in the plants and can be regarded as phytochemicals, like saponins (Garcia et al. 2006), quinones (El-Dakhakhny 1963), amino acids, hormones, and fatty acids.

Phenolic compounds

Phenolic compounds are a vast group of chemicals including flavonoids, phenolic acids, stilbenes, lignans, curcuminoids, tannins, which are widely distributed in the fruits or vegetables like apples, grapes, strawberries, celery, carrot, etc. (Han, Shen, and Lou 2007). These possess countless medicinal properties including anti-inflammatory, anticarcinogenic, antioxidant, antimicrobial, and antiatherosclerotic activities (Huang, Cai, and Zhang 2009). So far, more than 8000 phenolics are identified and are divided into several classes based on the number of phenolic rings and side chains (Fresco et al. 2006).

Flavonoids

Flavonoids are the biggest family of phenolic compounds with over 4000 compounds that have a low molecular weight (Ren et al. 2003; Nyamai et al. 2015). Fifteen-carbon skeleton is their basic structure and further divided into flavanols, flavones, flavanones, anthocyanins, isoflavonoids, neoflavonoids, and bioflavonoids (Huang, Cai, and Zhang 2009; Birt and Jeffery 2013). An earlier study conducted by Hämäläinen et al. (2007) on the bioactivities of flavonoids showed their potential as anti-inflammants, antioxidants, and as a modulator of inflammation-related gene expression. Genistein (100 µM) suppressed activation of nuclear factor kappa B (NF-κB) up to 57% and pelargonidin (100 µM) reduced 80% NF-κB activity induced by lipopolysaccharide (LPS) (100 ng/ml) in murine J774 macrophages cells. Consequently, iNOS expression reduced drastically as NF-κB is a precursor to it and so as inflammation (Hämäläinen et al. 2007). Wu et al. (2018) studied apple procyanidin extract (100 µg/ml), which increased ZO-1 expression that was reduced by LPS (50 µg/ml) treatment in Caco-2 cells. Apple procyanidin (150 µg/ml) reduced IL-6 expression significantly after 12 and 24 h of incubation compared to LPS treated groups. By oxidative stress modulation, apple procyanidin exerted the beneficial effects and reduced inflammation (Wu et al. 2018).

Phenolic acids

Phenolic acids, also known as aromatic acids, are classified into hydroxybenzoic acids and hydroxycinnamic acids (Cai et al. 2006). The shikimate pathway produces phenolic acids, and they possess tremendous potential health benefits. Saibabu et al. (2015) wrote a detailed review about the therapeutic potentials of phenolic acids including tissue damage and oxidative stress reduction, cytokine expression modulation, and suppression of inflammation-related gene expression. Sadar, Vyawahare, and Bodhankar (2016) studied ferulic acid (40 mg/Kg), a phenolic acid, reduces colonic myeloperoxidase (MPO) activity from 18.78 U/mg to 9.78 U/mg after treatment in 2,4,6-trinitrobenzenesulfonic acid (TNBS) (100 mg/Kg) induced colitic Sprague Dawley rats. It also reduced oxidative stress and mediated inflammatory cytokines. In this way, it prevents cellular apoptosis, which reduced intestinal permeability (Sadar, Vyawahare, and Bodhankar 2016). Another study by Lee (2018) on sinapic acid showed it reduced colonic malondialdehyde (MDA) levels from over 0.9 mU/mg to less than 0.4 mU/mg in TNBS (100 mg/kg) induced female BALB/c colitic mice (Lee 2018). Zhang et al. (2016) found that caffeic acid (1 µM) reduced TNF-α expression by almost 100% in 2.5% dextran sodium sulfate (DSS) induced C57BL/6 colitic mice. It also improved relative abundance of *Akkermansia* in the gut. Both of these data points to the fact that caffeic acid prevents epithelial cell and mucin layer damage and reduces intestinal permeability (Zhang et al. 2016).

Stilbenes

Stilbenes are phenolic compounds derived from the phenylpropanoid pathway and presence of aromatic rings connected with an ethane bridge, which is one of their key features (Fresco et al. 2006). Their number and occurrence are not as many as other polyphenols, yet they possess broad spectrum of prophylactic activities. Stilbenes exert their bioactive properties by downregulating inflammatory cytokine expression, suppressing oxidative stress, and inflammation-related gene expression (Reinisalo et al. 2015). Pterostilbene, a stilbene, completely inhibits the induction of iNOS and cyclooxygenase-2 (COX-2) in HT-29 cell line induced with several cytokine mixtures at the dose of 100 µmol/L. Reduced oxidative stress aids to reduce permeability (Paul et al. 2009). 4′-Methoxyresveratrol (5 µM), a monomethylated analog of resveratrol, reduced IL-6 expression from over 8-folds to almost 4-folds. It also downregulated TNF-α expression from 4- to 2-folds in LPS (0.1 µg/ml) induced RAW 264.7 macrophage cells for 24 h. Reduction of these cytokines expression is a sign of less inflammation, which indirectly suggested to be beneficial for permeability reduction (Yao et al. 2018).

Lignans

Lignans are phenolic compounds formed of phenylpropanoid moieties (Aehle et al. 2011). They occur in free form in plants and major constituents of lignans are lignanolides, cyclolignaolides, neolignans, and bisepoxylignans (Fresco et al. 2006; Surveswaran et al. 2007). Besides their parent forms, intestinal bacteria metabolizes lignans and form mammalian lignans known as enterolignans (Peterson et al. 2010). They suppress inflammatory cytokine expression, reduces oxidative stress, and inhibits inflammatory gene expression (Delmas et al. 2006; Durazzo et al. 2013). Pinoresinol (100 µmol/L), a lignan, reduced 75% NF-κB activity induced by IL-1β application in Caco-2 cells. It also reduced IL-1β-induced IL-6 secretion by 65%. These data indicated a possible role of pinoresinol in inflammation reduction and intestinal permeability reduction (During et al. 2012). Magnolol (15 mg/Kg), another lignan, reduced colonic MPO activity and pro-inflammatory cytokine significantly in DSS-induced colitic mice. As it improved colonic health, it certainly reduced intestinal permeability increased by DSS treatment (Zhao et al. 2017).

Tannins and curcuminoids

Besides the above, there are many other types of phenolics including condensed tannins, hydrolyzable tannins, curcuminoids, coumarins, etc. Ellagic acid possesses antioxidant and anticancer activities (Seeram et al. 2005). Ellagic acid (2% w/w) reduced IL-6 expression from 108.92 to 59.04 pg/mg in DSS-induced colitic BALB/c mice. It also reduced the expression of COX-2 by 78%, which suggested ellagic acid could play a vital role in oxidative stress amelioration and permeability reduction (Marín et al. 2013a). Curcumin (2% w/w) reduced colonic histopathological score by 50% and MPO activity more than 50%. It prevented mucosal damage

to the intestinal epithelial layer and reduced neutrophil infiltration, possibly by antioxidative effects and blocking NF-κB activation (Deguchi et al. 2007).

Glucosinolates

Glucosinolates are secondary metabolites produced by Cruciferous plants and are divided into three classes based on the structure of their amino acid precursors, i.e. aliphatic glucosinolates, aromatic glucosinolates, and indole glucosinolates (Ishida et al. 2014). They remain inactive upon ingestion, but after degradation due to enzyme activity, they form numerous active products including isothiocyanates (Traka 2016). Glucosinolates are of great medicinal importance, as they possess anticarcinogenic, anti-inflammatory, and antioxidative properties (Jeffery and Araya 2009). Allicin (25 µg/ml) markedly blocked the activation of p-38 and JNK pathway stimulated by 1 ng/ml IL-1β treatment in Caco-2 cells. At 30 mg/kg treatment dose in Wistar rats, it reduced IL-1β and TNF-α by about 60% and 33%, respectively. Oral administration of allicin also improved the colonic histopathological score. All of these linked to inflammation mediation and intestinal permeability reduction (Li et al. 2015).

Terpenoids

Terpenoids are a major group of chemicals produced mainly by flowering plants and so far, around thousand terpenoids have been isolated (Pichersky and Raguso 2018). Based on their number of isoprene units, they are classified into hemiterpenoids, monoterpenoids, sesquiterpenoids, etc. (Zwenger and Basu 2008). Terpenoids act as antioxidants, reduce tissue damage, and downregulate cytokine expression. Salminen et al. (2008) described the mechanism of terpenoids in the inhibition of inflammation and cancer by downregulating NF-κB expression. Lutein (10 µM) reduced the expression of iNOS almost 72.5% on an average in Raw 264.7 macrophage cells induced with LPS (1 µg/ml) followed by 18 h incubation period (Rafi and Shafaie 2007). Crocetin (100 mg/kg) reduced colonic erosion scale from 2.80 to 1.30 and reduced MDA concentration by more than 66%. These two suggested the influence of terpenoids in ameliorating experimental colitis by lessening colonic damage, inflammation, and possibly by reducing permeability (Kazi and Qian 2009).

Alkaloids

Alkaloids are a vast group of chemicals characterized by the presence of nitrogen in their structure (Cushnie, Cushnie, and Lamb 2014). Based on the chemical structure, they are classified into heterocyclic alkaloids and nonheterocyclic alkaloids. Alkaloids reduce oxidative stress, downregulate inflammatory cytokine production, and suppress NF-κB levels. Sophoridine, a natural alkaloid, reduced histological score from 13.47 to 7.92 in DSS-induced repeated colitis model in C57BL/6 mice. Reduced histopathological score is related to improved intestinal structure and barrier function, which led to reduced permeability (Zhao, Song, and Deng 2010). Oxymatrine (63 mg/Kg), another alkaloid, restored colonic damages induced by CCl_4 and downregulated the NF-κB levels around 50%. By preventing NF-κB p-65 activation, it reduced inflammation and possibly restored intestinal barrier function (Wen et al. 2014). Piperine (10 mg/kg) reduced colonic NO levels from 71.5 to 41.24 (µg/mg) after colitis was induced by 5% acetic acid (w/v) treatment. It also reduced TNF-α level from 200 to 110.3 pg/mg and microscopic score more than 60%. All this leads us toward the fact that their potential role in reducing inflammation and intestinal permeability (Gupta et al. 2015).

Quinones

Quinones are resultant of plants secondary metabolism (Monks and Jones 2002). Quinones are of four types, namely anthraquinone, naphthoquinone, benzoquinone, and phenanthrenequinone, based on their number of benzene rings (Gong et al. 2014). Quinones reduce inflammation, downregulate cytokine expression, suppress oxidation, and inhibit activation of inflammatory mediators including NF-κB. Thymoquinone (10 mg/kg) reduced both microscopic and macroscopic score by 50% compared to DSS-treated colitic mice alone. Thymoquinone reduced colonic MDA and MPO levels significantly in the same experiment. These findings proved the anti-inflammatory and antioxidative properties of thymoquinone, which led to restoring colonic permeability (Lei et al. 2012). El-Sheikh experimented with thymoquinone (10 mg/kg) in methotrexate (20 mg/kg) induced colitic rats. They found thymoquinone increased catalase and glutathione peroxidase from 4.9 U/g to 9.4 U/g and 2.6 U/g to 5.1 U/g, respectively (El-Sheikh, Morsy, and Hamouda 2016).

Amino acids, hormones, and fatty acids

Amino acids, hormones, and fatty acids possess therapeutic properties too. Threonine, an amino acid, is essential for the synthesis of mucin in the intestine (Mao et al. 2011). Alpha-linoleic acid (450 mg/kg/d) treatment in the Sprague Dawley rats induced with TNBS markedly suppressed intercellular adhesion molecule-1 (ICAM-1) expression. ICAM-1 was directly associated with leukocyte infiltration and barrier damage. As α-linoleic acid reduced ICAM-1 expression, it might exert this effect by reducing inflammation and by restoring intestinal barrier integrity (Ibrahim et al. 2012).

Polysaccharides

Polysaccharides, are a great source of dietary fibers, especially non-starchy ones, exhibit many biological properties, and are potential in treating many diseases including intestinal diseases. They already proved effective in the treatment of cardiovascular diseases, diabetes, and intestinal diseases (Nie, Lin, and Luo 2017). Pectins from wild jujube (80 mg/kg) reduced DAI score from 4.5 to 2 and histopathological

Table 1. Scoring system to calculate the Disease Activity Index (DAI)

Score	Weight loss (% of initial weight)	Stool consistency	Rectal bleeding	Inflammatory score
0	< 1	Normal	Normal pellets	Normal
1	1–4.99	Slightly bloody	Slightly loose faces	Slight inflammation
2	5–10	Bloody	Loose faces	Moderate inflammation
3	>10	Gross blood	Diarrhea	Heavy inflammation

Adopted from Sánchez-Fidalgo et al. (2010).

score from over 3 to around 1 in TNBS induced colitic rats. Pectins (80 mg/Kg) significantly upregulated the expression of ZO-1 and occludin in the same experiment. DAI indirectly confirmed the intestinal barrier integrity. It also reduced colonic MPO activity from 200 U/mg to almost 120 U/mg. As pectins reduced DAI score, it was clear that it increased the intestinal health and barrier integrity including permeability (Yue et al. 2015).

Effects of phytochemicals on intestinal permeability

Like their types, the action of phytochemicals is also diverse in the body. In the case of intestinal permeability, they are administered orally. Intestinal permeability is a feature of the intestinal mucosal barrier, which not only regulates the infiltration of macromolecules and pathogens but also ascertains the mutual habitation of microbial symbionts necessary for our normal life (Hooper, Littman, and Macpherson 2012). There are several biomarkers used to assess intestinal permeability. Lactulose–mannitol (L/M) is a very popular test to measure intestinal permeability. By measuring the ratio of L/M in the urine, the permeability is determined. Another important test is chromium-ethylenediaminetetraacetic acid (CrEDTA), which assesses urinary release of CrEDTA. The greater the release, the higher the permeability. Fluorescein isothiocyanate-labeled dextran (FITC dextran) is another biomarker used to determine intestinal permeability. It permeates paracellular pathway of intestinal cells and excellent marker for TJ integrity.

Increased intestinal permeability is one of the main drivers of intestinal diseases including CD and UC. For decades, scientists tried to figure out the ways to define the disease severity in some universal ways. In this way, disease activity index (DAI) assessment was designed. Probably the earliest example of such effort is by Truelove and Witts (1955). The current assessment method of DAI is a somewhat modified form of the method proposed by Sutherland et al. (1987).

DAI score is measured by combining the scores of different sets of parameters, but these parameters are not the same in all the approaches taken by the researchers. In general, DAI score is the total average of the percentage of body weight change, stool consistency, rectal bleeding, and rectal prolapse (Table 1) as per Sánchez-Fidalgo et al. (2010).

This review covers 64 phytochemicals from different chemical classes and among them, 34 gave a positive result to the DAI assessment as shown in Table 2. Among those 34 phytochemicals, 19 belongs to the phenolic group. It is not surprising because of the fact that two-thirds of all the phytochemicals belong to the phenolic group (Cheynier 2005). The DAI score difference among the colitic group and the treated groups varies from 1 to 5 in general, but some gave even better results. Oroxyloside, a flavonoid, reduces DAI score from 12 to 2 in C57BL/6 mice treated at the dose of 80 mg/kg dose (Wang et al. 2016). Many of the phenolic compounds gave such results proving their potential value.

Another problem of intestinal diseases is that the colon length shortens drastically. Subsequently, many abnormalities appear, and the efficiency of food digestion reduces exponentially. The stem cells inhabiting the intestinal crypt are responsible for the production of different cells of the intestinal epithelial layer and continuous maintenance of the layer as well. In the normal case, the epithelial layer regenerates in a couple of days with the aid of stem cells (Barker, van de Wetering, and Clevers 2008). However, when the normal process is hampered, the whole cycle disrupts and brings about numerous abnormalities and diseases. It results in loss and complete destruction of intestinal villi and sometimes the crypt along with the stem cells. Hence, goblet cells, paneth cells are lost and along with them the mucus layer. The stability of the complete intestinal structure depends on these, and when their function fails, it brings many diseases and disorders with it (Umar 2010; Pieter and Laukens 2012; Al-Hussaini, Machida, and Butzner 2003).

Numerous phytochemicals ameliorate this disorder and, in this review, among the reviewed phytochemicals, 41 of them helps to restore colon length as shown in Table 2. More than half the phytochemicals belong to phenolic groups proving their medicinal value. Phenolic compounds, rutin and curcumin, both restored the colon length to an almost normal value, which was decreased 50% by DSS treatment (Kwon et al. 2005; Deguchi et al. 2007). Berberine, an alkaloid, at the dose of 100 mg/kKg and shikonin, a quinone, at the dose of 25 mg/Kg also showed similar results (Andújar et al. 2012; Li et al. 2015).

Colonic injury hinders the process of absorption of minerals, nutrients, and water. Therefore, the health condition of the individual deteriorates dramatically. Increased intestinal permeability has been found in the epithelium of inflamed and damaged intestinal mucosa, which proves that it is connected to the inflammation and subsequent complications (Capaldo and Nusrat 2009). Thus, microbial products and other antigens from the intestinal lumen translocate to lamina propria, lead to inflammation, and end up in intestinal diseases (Hu et al. 2015). Without proper treatment, the situation worsens and leads to other severe complications that lead to cancer (Viennois, Chen, and Merlin 2013).

Among the reviewed phytochemicals, 59 showed positive results to attenuate colonic injury to a significant extent and the majority of them are phenolics, as mentioned in Table

2. Allicin, a glucosinolate, reduced the histological score from 20 to 8 at the dose of 10 mg/kg (Pandurangan et al. 2015), whereas luteolin, a flavonoid, reduced the histological score from 10 to 5.5 at the dose of 50 mg/kg (Li, Shen, and Luo 2016). Crocetin, a terpenoid, reduced histological score from 2.8 to 1.3 and boldine, an alkaloid, reduced score from 8 to 5 after treatment (Kazi and Qian 2009; Pandurangan et al. 2016).

Transepithelial electrical resistance (TEER) measures the integrity of the intestinal epithelial layer in cell culture experiments. It is an effective method to determine the status of the monolayer, yet it is noninvasive and facilitates to examine the different stages of growth and differentiation (Srinivasan et al. 2015). With compromised permeability, the resistance of the epithelial monolayer reduces dramatically (Zucco et al. 2005). However, the application of phytochemicals increases the expression of junction proteins, hence increases the TEER.

Among the phytochemicals reviewed in this article, five are tested and found to give a positive result in TEER test. These are kaempferol, berberine, quercetin, and theaflavins (Suzuki and Hara 2009; Suzuki, Tanabe, and Hara 2011; Shin et al. 2015; Sun et al. 2013; Park et al. 2015; Cao et al. 2013). Among them, berberine reduced permeability from 500% to 200% compared to the control group while trachelogenin increased TEER from 100% to 350% after treatment (Cao et al. 2013; Shin et al. 2015).

Mechanism of intestinal permeability restoration by phytochemicals

Cytokine regulation

Cytokines are small proteins produced in a cascade in response to the stimuli, and they serve as a specific purpose in the body. In normal cases, anti-inflammatory cytokines like interleukin (IL)-4, IL-10, IL-11, and IL-13 maintain the normal cytological condition and sustain the intestinal permeability. However, when the function of anti-inflammatory cytokines is suppressed and the production of pro-inflammatory cytokines e.g. tumor necrosis factor-α (TNF-α), IL-1β, IL-6 and interferon gamma (IFN-γ) boosts, the normal physiological condition fails. This situation initiates inflammation, depending on the severity of the condition; the extent of inflammation varies as well (Capaldo and Nusrat 2009). Phytochemicals, upon administration, suppress the production of pro-inflammatory cytokines and increase the production and effects of anti-inflammatory cytokines.

Total 48 phytochemicals in this review mediate the inflammation effectively and among them, many are from the phenolic group as presented in Table 2. Asiatic acid, a terpenoids, reduced the mRNA expression of TNF-α from (3- to 1-fold) at the dose of 30 mg/kg whereas mangiferin, a phenolic compound, inhibited the mRNA expression of IL-6 by 88% at the dose of 20 mg/kg (Guo et al. 2015; Jeong et al. 2014). Norisoboldine, at the dose of 40 mg/kg and curcumin, at the dose of 100 mg/kg upregulated the expression of IL-10 more than 100% (Lv et al. 2015; Song et al. 2010).

Oxidative stress amelioration

The gastrointestinal tract is very susceptible to oxidative stress as it is constantly experiencing harsh conditions like aerobic metabolism, gastric acid, nonsteroidal anti-inflammatory drugs, luminal oxidants, etc. Oxidative stress is the result of an imbalance in the production of reactive oxygen (ROS) and nitrogen (RNS) species and their eliminating process (Hussain et al. 2016). Stress condition leads to many complications including pro-inflammatory response, cell transformation, apoptosis, and even DNA damage (Valko et al. 2007; Denis et al. 2015).

At low concentrations, ROS regulate many cellular functions including cell proliferation, cell adhesion, and apoptosis (Maeda et al. 2010). Under stress conditions, due to excess concentration of the free radicals namely superoxide anion ($O_2\bullet^-$) and nitric oxide radical (NO•), a harmful oxidative agent is formed which is called peroxynitrite ($ONOO^-$). All of these create an imbalance in the intestinal environment and disturbs the normal physiological processes by changing the concentration of several enzymes and other related molecules (Piechota-Polanczyk and Fichna 2014). These, on one hand, increase the concentration of nitric oxide (NO), prostaglandin E2 (PGE2) and MDA, and the activity of myeloperoxidase (MPO), COX-2, catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), and heme oxygenase-1 (HO-1). The imbalance in those enzymes and free radical is a marker of colonic tissue damage and leukocyte infiltration.

Phenolic compounds like flavonoids exert antioxidative effect because of the presence of phenolic hydroxyl groups in their structure. The greater the number of phenolic hydroxyl groups, the higher their effect (Heim, Tagliaferro, and Bobilya 2002). Catechin is a flavanol that exerts both direct and indirect antioxidative effects. In case of direct effects, they donate electron from the hydroxyl group and the aromatic structure of them sustains the unrest caused by oxidative stress. For indirect effects, they interfere with the production of enzymes, which are responsible for the production of oxidants by blocking the binding of ligands with receptors like TNF-α (Fan, Sang, and Jiang 2017).

Among the reviewed articles, 50 phytochemicals mediate these processes and most of them are phenolic compounds (data presented in Table 2). Increased MPO activity is an important marker of oxidative stress. Crocetin (50 mg/kg), a terpenoid, reduced MPO activity from 36.7 U/g to 16 U/g whereas soyasaponin I (20 mg/kg) reduced it from 33 U/g to 6.9 U/g (Kazi and Qian 2009; Lee, Hyun, and Kim 2010). Similarly, reduced CAT activity is a sign of stress. Mangiferin (60 mg/kg) increased CAT activity from 1.8 U/mg to 3.5 U/mg whereas berberine (20 mg/kg) increased it from 1.49 to 4.77 mol/min/mg (Somani, Zambad, and Modi 2016; Lee, Hyun, and Kim 2010).

Gene expression and signaling modulation

Intestinal inflammation and the subsequent complications are not just the results of some simple processes. On the contrary, they are the consequence of multiple biochemical

Table 2. Phytochemicals, sources, dosages and their effects in cell and animal models.

Class of phytochemical	Compound name	Optimal doses (mg/kg, uM)	Source	Experimental model	Morphological aspects	Cytokine expression	Oxidative stress alleviation	Mechanism of action	Reference
Alkaloid	Berberine	20 mg/kg	*Coptis chinensis*	1DSS induced colitis model with C57BL/6 mice	[2]DAI ↓, Colon shortening ↓, Colonic injury ↓	[3]TNF-α ↓, [4]IL-6 ↓, [5]IL-23 ↓	–	Decrease [6]p-STAT3 expression	Li, Shen, and Luo (2016)
		100 mg/kg	*Coptis chinensis*	[7]TNBS induced colitis model with BALB/c mice	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, [8]IL-1β ↓, IL-6 ↓,[9] IL-22 ↑	1[0]MPO ↓	Decrease [11]p-STAT1, p-STAT3 expression and phosphorylation of1[2]NF-κB p65	Li et al. (2015)
		100 μM	*Coptidis rhizoma*	1[3]IFN-γ and TNF-α induced Caco-2 cells	1[4]TEER ↑	–	–	Inhibits1[5]MLCK and1[6]pMLC expression	Cao et al. (2013)
		100 mg/kg	*Coptidis rhizoma*	DSS induced colitis model with BALB/c mice	Colon shortening ↓, Colonic injury ↓	INF-γ ↓,1[7]IL-12 ↓,1[8]IL-4 ↑,1[9]IL-10 ↑	MPO ↓, [20]MDA ↓	——	Hong et al. (2012)
		20 mg/kg	*Coptidis japonica*	TNBS induced colitis model with C3H/HeN and C3H/HeJ mice and LPS stimulated peritoneal macrophages	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓, IL-10 ↑	MPO ↓, MDA ↓, [21]GSH ↑, [22]SOD ↑, [23]CAT ↑	Inhibits phosphorylation of IκBα and phosphorylation and nuclear translocation of NF-κB. Suppress [24]JNK, [25]ERK 1/2 and [26]p38 MAPK activation in the macrophages.	Lee, Hyun, and Kim (2010)
		150μM	*Coptidis rhizoma*	Ethanol induced disruption of intestinal epithelial TJ with Caco-2 cells	TEER ↑	TNF-α ↓, INF-γ ↓	–	Inhibits MLCK activation	Sun et al. (2013)
		100 mg/kg	*Coptis chinensis*	DSS induced colitis model with C57BL/6 mice	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, SOD ↑, CAT ↑	Decrease p-STAT3 expression	Zhang et al. (2017)
	Oxymatrine	200 mg/kg	*Sophora flavescens*	DSS induced colitis model with C57BL/6- WT mice and [27]LPS induced [28]IECs	Colon shortening ↓, Colonic injury ↓	IL-6 ↓, IL-1β ↓	–	Reduce nuclear accumulation of NF-κB p65	Guzman et al. (2013)
		63 mg/kg	*Sophora flavescens*	CCl_4 induced cirrhotic model with Sprague-Dawley rats	Colonic injury ↓	TNF-α ↓, IL-6 ↓	–	Inhibits activation and translocation of NF-κB p65	Wen et al. (2014)
	Boldine	50 mg/Kg	*Peumus boldus*	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓, [29]IL-17 ↓	MPO ↓, MDA ↓	Suppressed IκBα phosphorylation/degradation and reduces nuclear accumulation of NF-κB p65 and [30]p-STAT3^{Y705}	Pandurangan et al. (2016)
	Sanguinarine	10 mg/Kg	*rgemone mexicana*	Acetic acid induced colitis with Kunming mice	DAI ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	MPO ↓	Reduce NF-κB p65 expression	Niu et al. (2013)
	Norisoboldine	40 mg/Kg	*Radix linderae*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, [31]IL-17A ↓, IFN-γ ↓, IL-10 ↑	MPO ↓	Suppress the phosphorylation of p38 MAPK, ERK and NF-κB p65. Also reduces nuclear	Lv et al. (2015)

								translocation and [32]DNA binding activity of NF-κB p65.	
Phenolic compound	Oroxyloside	80 mg/Kg	*Scutellaria*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, [33]iNOS↓	Increase expression of [34]PPAR-γ and inhibits nuclear translocation of NF-κB	Wang et al. (2016)
	Mangiferin	60 mg/Kg	*Mangifera indica*	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓	MPO ↓, MDA ↓, CAT ↑, GSH ↑, SOD ↑	Reduce [35]MMP-9 expression	Somani, Zambad, and Modi (2016)
		20 mg/Kg	*Mangifera indica*	TNBS induced colitis model with C57BL/6 mice and LPS & peptidoglycan induced peritoneal macrophage	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓, IL-10 ↑	[36]NO ↓, [37]COX-2 ↓, iNOS ↓, [38]PGE2 ↓,	Inhibited phosphorylation and degradation of [39]IRAK1, [40]IKKβ, [41]IκBα. Also suppressed phosphorylation and translocation of NF-κB p65, MAPKs p38, ERK and JNK.	Jeong et al. (2014)
		50 mg/Kg	*Mangifera indica*	DSS induced colitis model with C57BL/6 mice	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, iNOS↓	Downregulates IκBα degradation and phosphorylation of NF-κB p65. Also, suppress JNK, ERK 1/2 and p38 MAPK activation in the colon.	Dou et al. (2014)
	Glabridin	50 mg/Kg	Liquorice	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	MPO ↓, NO ↓, PGE2 ↓	–	Kwon, Oh, and Kim (2008)
	Naringenin	100 mg/Kg	Tomatoes	Acetic acid induced colitis model with Wister albino rats	Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	NO ↓, PGE2 ↓, SOD ↑, CAT ↑	–	Al-Rejaie et al. (2013)
		30 mg/Kg	Citrus fruits	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓	IL-6 ↓, IL-17A ↓	–	–	Azuma et al. (2013)
	Apocynin	500 μM	*Picrorhiza kurroa*	Inflammatory response analysis with LPS induced Raw 264.7 cells	–	TNF-α ↓	NO ↓, PGE 2 ↓, iNOS ↓, COX-2 ↓	Inhibits degradation of IκB and suppress JNK, ERK 1/2 and p38 MAPK activation.	Hwang et al. (2016)
		20 mg/Kg	*Picrorhiza kurroa*	DSS induced colitis model with BALB/c mice	Colon shortening ↓, Colonic injury ↓	–	NO ↓, PGE 2 ↓, iNOS ↓, COX-2 ↓	Blocks the activation of NF-κB p65 as well as [42]STAT3	Marín et al. (2013a)
	Hydroxytyrosyl acetate	190 mg/Kg	Olive	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	–	MPO ↓, COX-2 ↓, iNOS ↓	Downregulated JNK phosphorylation and prevented translocation of NF-κB p65	Sánchez-Fidalgo et al. (2015)
	Curcumin	100 mg/Kg	*Curcuma longa*	MTX induced enteritis with SD rats and LPS induced IEC-6 cells	DAI ↓	TNF-α ↓, IL-1β ↓, IL-10 ↑	MPO ↓, SOD ↑	Reduced p38 phosphorylation in vivo and suppressed nuclear translocation of NF-κB p65	Song et al. (2010)
		50 mg/Kg	*Curcuma longa*			TNF-α ↓, IL-1β ↓	MPO ↓		Liu et al. (2013)

(*continued*)

Table 2. Continued.

Class of phytochemical	Compound name	Optimal doses (mg/kg, uM)	Source	Experimental model	Morphological aspects	Cytokine expression	Oxidative stress alleviation	Mechanism of action	Reference
		20 mg/Kg	*Curcuma longa*	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic shortening ↓, Colonic injury ↓	–	MPO ↓	Blocks activation and expression of STAT3 and NF-κB	Deguchi et al. (2007)
		20 mg/Kg	*Curcuma longa*	TNBS induced colitis model with C57BL/6 mice	Colonic injury ↓	TNF-α ↓, INF-γ ↓, [43]IL-1 ↓, IL-12 ↓	——	Inhibits both degradation of IκB and nuclear translocation of NF-κB p65	Sugimoto et al. (2002)
		100 mg/Kg	*Curcuma longa*	TNBS induced colitis model with Wistar rats	Colonic injury ↓	TNF-α ↓, IL-10 ↑	MPO ↓, iNOS ↓, COX-2 ↓,	Diminishes the activation of MAPK p38	Camacho-Barquero et al. (2007)
		60 mg/Kg	*Curcuma longa*	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	TNF-α ↓	MPO ↓	Reduce p38 MAPK and p-p38MAPK expression	Li et al. (2015)
		92 mg/Kg	*Curcuma longa*	DSS induced colitis with [44]ICR mice	–	TNF-α ↓, IL-1β ↓	–	Blocked DNA binding of STAT3 and inhibits expression of p53	Yang et al. (2013)
		100 mg/Kg	*Curcuma longa*	TNBS induced colitis model with BALB/c mice	Colonic injury ↓	–	NO ↓, MPO ↓, MDA ↓	Suppress DNA binding activity of NF-κB.	Ukil et al. (2003)
		30 mg/Kg	*Curcuma longa*	TNBS induced colitis model with Sprague Dawley rats	Colonic injury ↓	TNF-α ↓, INF-γ ↓, IL-1 ↓, IL-12 ↓, IL-4 ↑, IL-10 ↑	–	–	Zhang et al. (2006)
	Resveratrol	10 mg/Kg	Blue berries	TNBS induced colitis model with Wistar albino rats	Colonic injury ↓	——	MPO ↓, MDA ↓, iNOS ↓, COX-2 ↓, GSH ↑, NO ↑	–	Abdallah and Ismael, (2011)
		300 mg/Kg	Red grapes	DSS induced colitis model with C57BL/6 mice	Colon shortening ↓	TNF-α ↓, IFN-γ ↓	iNOS ↓, COX-2 ↓,	Reduces p53 and p53-phospho-serine 15 levels	Cui et al. (2010)
		20 mg/Kg	Red grapes	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-10 ↑	iNOS ↓, COX-2 ↓, [45]PGES-1 ↓	Diminishes the activation of MAPK p38	Sánchez-Fidalgo et al. (2010)
		10 mg/Kg	Red grapes	TNBS induced colitis model with Wistar rats	Colonic injury ↓	TNF-α ↓	MPO ↓, PGE 2 ↑, COX-2 ↓,	Reduces nuclear translocation of NF-κB p65	Martín et al. (2006)
	Gallic acid	10 mg/Kg	Green tea	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	[46]IL-21 ↓, IL-23 ↓	MDA ↓, SOD ↑, CAT ↑, GR ↑, [47]GPx ↑	Upregulates the expression of [48]Nrf2	Pandurangan et al. (2015)
	Chlorogenic acid	50 mg/Kg	Peaches	Intestinal permeability assessment of Sprague Dawley rats challenged with LPS	Colonic injury ↓	TNF-α ↓, IFN-γ ↓	–	–	Ruan et al. (2014)
	Arctigenin	50 mg/Kg	*Arctium lappa*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	MPO ↓, MDA ↓, SOD ↓, GSH ↓	Suppress JNK, ERK and p38 MAPK activation. Also suppressed phosphorylation of IκBα and NF-κB p65.	Wu et al. (2014)
	Avicularin	300 μM	*Psidium guajava*	LPS induced Raw 264.7 macrophage cells	–	IL-1β ↓	NO ↓, PGE 2 ↓, iNOS ↓, COX-2 ↓	Inhibits degradation of IκB, suppresses ERK phosphorylation and blocks	Vo et al. (2012)

Naringin	15.8 mg/Kg	Grapefruit	DSS induced colitis with CD-1 mice	–	–	MDA ↓, NO ↓, iNOS ↓	– nuclear translocation of NF-κB.	Amaro et al. (2009)
Paeonol	100 mg/Kg	*Paeonia moutan*	TNBS induced colitis model with BALB/c mice and TNF-α & IFN-γ stimulated CW-2 cells and Jurkat cells	Colon shortening ↓, Colonic injury ↓	–	MPO ↓, iNOS ↓	Reduces activation of NF-κB and [49]STAT-1 expression	Ishiguro et al. (2006)
Diapocynin	100 mg/Kg	*Picrorhiza kurroa*	DSS induced colitis model with BALB/c mice and LPS induced Raw 264.7 macrophages	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, NO ↓, PGE2 ↓, COX-2 ↓, iNOS ↓	Reduce translocation of both NF-κB p65 and IκBα.	Marín et al. (2017)
Oxyresveratrol	80 mg/Kg	*Morus alba* L	DSS induced colitis model with C57BL/6 mice and LPS induced Raw 264.7 macrophages	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	COX-2 ↓, PGE 2 ↓, iNOS ↓, NO ↓,	Upregulates [50]TFF3 mRNA expression	Hwang et al. (2017)
Magnolol	10 mg/Kg	*Magnolia officinalis*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓	–	Zhao et al. (2017)
Guggulsterone	100 mg/Kg	*Commiphora mukul*	DSS induced colitis model with C57BL/6 mice and IL-1β/LPS stimulated Caco-2 & IEC-18 cells	DAI ↓, Colon shortening ↓, Colonic injury ↓	–	–	Inhibits NF-κB transcriptional activity, NF-κB DNA binding activity, phosphorylation/degradation of IκB and IKK activity	Cheon et al. (2006)
Piceatannol	10 mg/Kg	Grapes	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, NO ↓, PGE2 ↓	Decrease nuclear translocation of phosphor-STAT3 and NF-κB p65.	Kim et al. (2008)
Hesperidin	80 mg/Kg	Citrus fruit	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	IL-6 ↓	MPO ↓, MDA ↓	–	Xu et al. (2009)
Theaflavins	20 μM	Black tea	Caco-2 cell monolayers	TEER ↑	–	–	Increases [51]AMPK expression	Park et al. (2015)
Kaempferol	30 mg/Kg	Broccoli	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, NO ↓, PGE2 ↓, COX-2 ↓, iNOS ↓	Upregulates TFF3 mRNA expression	Park, Ji, and Sung (2012)
	100 μM	Tea	TJ expression analysis with Caco-2 cells	TEER ↑	–	–	–	Suzuki, Tanabe, and Hara (2011)
Rutin	10 mg/Kg	Tomatoes	DSS induced colitis model with ICR mice	Colon shortening ↓, Colonic injury ↓	IL-1β ↓, IL-6 ↓	NO ↓, PGE 2↓, MPO ↓	–	Kwon et al. (2005)
EGCG	50 mg/Kg	Green tea	Acetic acid induced colitis with Sprague Dawley rats	DAI ↓, Colonic injury ↓	TNF-α ↓, IFN-γ ↓	MDA ↓, NO ↓, SOD ↑	Reduce NF-κB p65 expression	Ran, Chen, and Xiao (2008)
	100 mg/Kg	Green tea	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	IL-6 ↓, IL-10 ↓, IL-17 ↓	–	Reduce STAT3 expression	Xu et al. (2015)
	6.9 mg/Kg	Green tea	DSS induced colitis model with C57BL/6 mice	Colon shortening ↓, Colonic injury ↓	–	MDA ↓, SOD ↑, GPx ↑	–	Brückner et al. (2012)
Luteolin	50 mg/Kg	Celery	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	MDA ↓, iNOS ↓, SOD ↑, CAT ↑, [52]HO-1 ↑	Increases Nrf2 expression	Li, Shen, and Luo (2016)
Thearubigin	100 mg/Kg	Black tea	TNBS induced colitis model with BALB/c mice	Colonic injury ↓	–	MPO ↓, MDA ↓, NO ↓	Suppresses DNA binding activity of NF-κB	Maity et al. (2003)

(*continued*)

Table 2. Continued.

Class of phytochemical	Compound name	Optimal doses (mg/kg, uM)	Source	Experimental model	Morphological aspects	Cytokine expression	Oxidative stress alleviation	Mechanism of action	Reference
	γ-oryzanol	50 mg/kg	Rice bran	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, COX-2 ↓	Reduces nuclear translocation of NF-κB p65 and increases IκBα levels.	Islam et al. (2009)
	Trachelogenin	25 mg/Kg	*Trachelospermi caulis*	Caco-2 cell monolayer study	TEER ↑	–	–	——	Shin et al. (2015)
	Quercetin	100 μM	Red onion	Intestinal barrier assessment with Caco-2 cells	TEER ↑	———	–	Inhibits PKCδ expression	Suzuki and Hara, (2009)
		100 mg/Kg	Red onion	Acetic acid induced colitis model with Swiss albino mice	Colonic injury ↓	IL-1β ↓, [53]IL-33 ↓, IL-10 ↑	MPO ↓, GSH ↑	– ————	Guazelli et al. (2013)
	Isoquercitrin	10 mg/Kg	Apple	DSS induced colitis model with Wistar albino rats	DAI ↓, Colon shortening ↓, Colonic injury ↓	–	COX-2 ↓, iNOS ↓, MPO ↓	–	Cibiček et al. (2016)
	Chrysin	10 mg/Kg	Propolis	DSS induced colitis model with BALB/c mice and TNF-α induced [54]IEC-6 cells	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓, IL-6↓	MPO ↓, NO ↓, PGE2 ↓	Inhibits Iκ-Bα and nuclear translocation of NF-κB p65	Shin et al. (2009)
	Tannic acid	375 mg/kg	Grapes	Antibiotic induced intestinal epithelial barrier damage with Wistar rats	Colonic injury ↓	–	–	–	van Ampting et al. (2010)
Glucosinolates	Allicin	10 mg/Kg	Garlic	DSS induced colitis model with BALB/c mice	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓, IL-17 ↓	MPO ↓, MDA ↓, SOD ↑, CAT ↑, GPx ↑, [55]GR ↑	Blocks nuclear translocation of NF-κB and inhibits phosphorylation and translocation of STAT-3 into the nucleus	Pandurangan et al. (2015)
		40 μM	Garlic	TNF-α induced HT-29 and Caco-2 cells	–	IL- 1β ↓, [56]IL-8 ↓	–	Inhibits the degradation of IκBα.	Lang et al. (2004)
	Phenethyl isothiocyanate	75 mg/Kg	*Barbara verna*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	IL-1β ↓	–	Reduce STAT1 and pSTAT1 expression	Dey et al. (2010)
	Sulforaphane	25 mg/Kg	Broccoli	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IFN-γ ↓, IL-6 ↓	HO-1↑	Increases Nrf2 dependent gene expression	Wagner et al. (2013)
		600 mg/Kg	Broccoli	Indomethacin induced intestinal injury model with ddy mice and aspirin induced IEC6 cells	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	MPO ↓	–	Yanaka, Sato, and Ohmori (2013)
	Diallyl trisulfide	17.8 mg/Kg	Garlic	DSS induced colitis with ICR mice	DAI ↓, Colonic injury ↓	–	COX-2↓, iNOS ↓	Inhibits DNA binding of NF-κB, STAT3 activation and phosphorylation of IκBα.	Lee et al. (2013)
	Isothiocyanate	150 mg/kg	*Moringa oleifera*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1 ↓, IL-6 ↓	MPO ↓	–	Kim et al. (2017)
	Alliin	500 mg/Kg	Garlic	DSS induced colitis with ICR mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, MDA ↓, NO ↓, iNOS ↓	Suppress JNK, ERK 1/2 and p38 MAPK activation in the colon. Also reduced the	Shi et al. (2017)

								phosphorylation of PPARγ and activation of NF-κB and STAT-1.	
Terpenoids	Lycopene	200 μg/ml	Tomatoes	Spontaneous colitis model with IL-10$^{-/-}$ mice. DSS induced colitis with NF-κB ^{EGFP} mice, and LPS induced IEC-18 cells	Colon shortening ↓, Colonic injury ↓	–	–	Inhibits IκBα degradation and NF-κB transcriptional activity	Joo et al. (2008)
	Lupeol	30 mg/Kg	Olive	DSS induced colitis model with C57BL/6 mice, IL deficient C57BL/6 mice, LPS induced IECs COLO 205 and Raw 264.7 macrophage	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓, IL-8 ↓, IL-12 ↓	–	Inhibits IκBα phosphorylation/degradation and DNA binding activity of NF-κB.	Lee et al. (2016)
	Crocetin	50 mg/Kg	Saffron	TNBS induced colitis model with BALB/c mice	Colonic injury ↓	INF-γ ↓, IL-12 ↓	NO↓, MPO ↓, MDA ↓	Suppresses DNA binding activity of NF-κB	Kazi and Qian, (2009)
	β-Caryophyllene	300 mg/Kg	*Syzygium*	DSS induced colitis model with BALB/c mice	DAI ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓	MPO ↓	Inhibits phosphorylation of NF-κB and IκB	Cho et al. (2015)
	Triptolide	0.07 mg/kg	*Tripterygium wilfordii* Hook.	C3H.IL-10$^{-/-}$ mice	Colonic injury ↓	IL-17 ↓	MPO ↓	Decrease p-STAT3 expression	Li et al. (2010)
	Ursolic acid	20 mg/Kg	Apple	DSS induced colitis model with C57BL/6- WT mice and, LPS & TNF-α induced IECs COLO 205	DAI ↓, Colon shortening ↓, Colonic injury ↓	–	–	Suppressed IκBα phosphorylation/degradation	Chun et al. (2014)
	Monotropein	200 mg/Kg	*Morinda officinalis*	DSS induced colitis model with ICR mice and LPS induced Raw 264.7 macrophages	DAI ↓	TNF-α ↓, IL-1β ↓	MPO ↓, COX-2 ↓, iNOS ↓	Inhibits translocation of NF-κB p65 & NF-κB p50 and suppresses phosphorylation and degradation of IKKβ & IκBα.	Shin et al. (2013)
	Soyasaponin I	20 mg/Kg	Soybeans	TNBS induced colitis model with ICR mice and LPS induced peritoneal macrophage	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓	MPO ↓, PGE2 ↓, iNOS ↓, NO ↓„ COX-2 ↓, GSH ↑, CAT ↑, SOD ↑	Inhibits phosphorylation and degradation of IκBα & prevents nuclear translocation of NF-κB p65.	Lee, Hyun, and Kim (2010)
	Saponin	60 mg/Kg	*Panax japonicus*	Study of epithelial TJ of Sprague Dawley rats	Colonic injury ↓	TNF-α ↓, IL-1β ↓	–	Decreased the levels of NF-κB p65 and reduce JNK, ERK 1/2 and p38 MAPK activation in the colon.	Dun et al. (2018)
	Asiatic acid	30 mg/Kg	*Centella asiatica*	DSS induced colitis model with C57BL/6 mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓, IFN-γ ↓, IL-1β ↓	MPO ↓	–	Guo et al. (2015)
Quinones	Thymoquinone	10 mg/Kg	*Nigella sativa* seeds	Acetic acid induced colitis with Wistar albino rats	Colonic injury ↓	–	MPO ↓, GSH ↑	–	Mahgoub (2003)
		25 mg/Kg	*Nigella sativa* seeds	DSS induced colitis model with C57BL/6 mice	Colon shortening ↓, Colonic injury ↓	–	MPO ↓, MDA ↓, GSH ↑	–	Lei et al. (2012)
	Embelin	50 mg/Kg	False black pepper	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-1β ↓, IL-6 ↓	MPO ↓, NO ↓, iNOS ↓,	–	Kumar et al. (2011)

(*continued*)

Table 2. Continued.

Class of phytochemical	Compound name	Optimal doses (mg/kg, uM)	Source	Experimental model	Morphological aspects	Cytokine expression	Oxidative stress alleviation	Mechanism of action	Reference
	Shikonin	25 mg/Kg	*Lithospermum erythrorhizon*	DSS induced colitis model with BALB/c mice	DAI ↓, Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IFN-γ ↓, IL-1 ↓, IL-6 ↓	MPO ↓, COX-2 ↓	Inhibits translocation of NF-κB p65 and reduces p-STAT3 expression	Andujar et al. (2012)
Amino acid	Arginine	10 mg/Kg	Nuts	Intestinal mucosal disruption induced by LPS with weaned pigs	Colonic injury ↓	TNF-α ↓, IL-6 ↓	–	Upregulates PPARγ expression	Liu et al. (2008)
	N-acetylcysteine	500 mg/Kg	Potatoes	Acetic acid induced porcine model with weaned piglets	Colonic injury ↓	TNF-α ↓, IL-6 ↓	MPO ↓, MDA ↓, PGE 2↓	–	Wang et al. (2013)
Hormone	Melatonin	10 mg/Kg	Tart cherries	Acetic acid induced colitis with Wistar rats	Colonic injury ↓	–	MPO ↓, GSH ↑	–	Nosál'ová et al. (2007)
Fatty acid	Docosahexaenoic acid	30 mg/Kg	*Schizochytrium sp.*	DSS induced colitis model with BALB/c mice	Colon shortening ↓, Colonic injury ↓	–	MPO ↓	–	Cho, Chi, and Chun (2011)
Storage protein	Prolamin	0.2% diet	Rice	LPS induced IECs and macrophages & DSS induced colitis with C57BL/6 mice	Colon shortening ↓, Colonic injury ↓	TNF-α ↓, IL-6 ↓	–	Blocks IκBα phosphorylation/degradation and phosphorylation of NF-κB p65	Chung et al. (2014)
Polysaccharide	Apple polysaccharide	100 mg/Kg	Apple	Chronic inflammation and gut permeability analysis with HFD-fed Sprague Dawley rats	Colonic injury ↓	TNF-α ↓, IL-1β ↓	–	–	Wang et al. (2017)
	Acidic polysaccharide of *Panax ginseng*	10 mg/Kg	*Panax ginseng*	Small intestinal damage assessment by whole body irradiation with C57BL/6 mice	Colonic injury ↓	–	–	Inhibits expression of p53	Park et al. (2011)
	Rheum tanguticum polysaccharide	10 mg/Kg	*Rheum tanguticum*	Radiation induced Intestinal Mucosal Injury assessment in IEC-6 cells and Sprague Dawley rats	Colonic injury ↓	–	–	–	Liu et al. (2015)
		200 mg/Kg	*Rheum tanguticum*	TNBS induced colitis model with Sprague Dawley rats	Colon shortening ↓, Colonic injury ↓	IFN-γ ↓, IL-4 ↑	MPO ↓	–	Liu et al. (2008)
		300 μg/ml	*Rheum tanguticum*	Hydrogen peroxide induced intestinal epithelial cell injury with [57]HIEC cell	–	–	MDA ↓, SOD ↑	–	Liu et al. (2005)
		200 mg/Kg	*Rheum tanguticum*	TNBS induced colitis model with Sprague Dawley rats	Colonic injury ↓	–	MPO ↓, SOD ↑	–	Liu et al. (2003)

↓: Decrease/Downregulate/Reduce, ↑: Increase/Upregulate, ——: Not assessed.

[1]DSS: Dextran sodium sulfate, [2]DAI: Disease activity index, [3]TNF-α: Tumor necrosis factor alpha, [4]IL-6: Interleukin 6, [5]IL-23: Interleukin 23, [6]p-STAT3: phospho-Signal transducer and activator of transcription 3, [7]TNBS: 2,4,6-trinitrobenzene sulfonic acid, [8]IL-1β: Interleukin-1 beta, [9]IL-22: Interleukin 22, [10]MPO: Myoperoxidase, [11]p-STAT 1: phospho-Signal transducer and activator of transcription 1, [12]NF-κB-p65:nuclear factor kappa-light-chain-enhancer of activated B cells-p65 subunit, [13]IFN-γ: Interferon gamma, [14]TEER: Transepithelial electrical resistance, [15]MLCK: Myosin light chain kinase, [16]pMLC: phosphorylated myosin light chain, [17]IL-12: Interleukin 12, [18]IL-4: Interleukin 4, [19]IL-10: Interleukin 10, [20]MDA: Malondialdehyde, [21]GSH: Glutathione, [22]SOD: Superoxide dismutase, [23]CAT: Catalase, [24]JNK: c-Jun N-terminal kinases, [25]ERK 1/2: Extracellular signal–regulated kinases 1/2, [26]p38- MAPK: P38 mitogen-activated protein kinases, [27]LPS: Lipopolysaccharide, [28]IECs: Intestinal epithelial cells, [29]IL-17 A: Interleukin 17 A, [30]p-STAT 3^{Y705}: phospho-Signal transducer and activator of transcription 3 Y705, [31]IL-17 A: Interleukin 17 A, [32]DNA: Deoxyribonucleic acid, [33]iNOS: Inducible nitric oxide synthase, [34]PPAR-γ: Peroxisome proliferator-activated receptor gamma, [35]MMP-9: Matrix metallopeptidase 9, [36]NO: Nitric oxide, [37]COX-2: Cyclooxygenase 2, [38]PGE-2: Prostaglandin e 2, [39]IRAK-1: Interleukin-1 receptor-associated kinase 1, [40]IKK-β: Inhibitor of nuclear factor kappa-B kinase subunit beta, [41]IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, [42]STAT 3: Signal transducer and activator of transcription 3, [43]IL-1: Interleukin 1, [44]ICR mice: Institute of Cancer research mice, [45]PGES-1: Prostaglandin e synthase 1, [46]IL-21: Interleukin 21, [47]GPx: Glutathione peroxidase, [48]Nrf-2: Nuclear factor (erythroid-derived 2)-like 2, [49]STAT 1: Signal transducer and activator of transcription 1, [50]TFF-3: Trefoil factor 3, [51]AMPK: AMP activated protein kinase, [52]HO-1: Heme oxygenase 1, [53]IL-33: Interleukin 33, [54]IEC-6: Intestinal epithelial cell line 6, [55]GR: Glutathione reductase, [56]IL-8: Interleukin 8, [57]HIEC: Human intestinal epithelial cells.

signaling pathways. These pathways are interdependent on each other, and several proteins and other compounds are associated with it. Among signaling pathways, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling comes first, because they are crucial in the dysregulation of intestinal barrier and upregulation of inflammation and the following complications (He et al. 2015).

In normal homeostatic condition, the five members of NF-κB remains inactive in the cytoplasm with small inhibitory proteins namely IκBs (inhibitor of κB). These are responsible for the masking of stimulating effects that leads to the activation of IκB kinase (IKK) complex and ends up in nuclear translocation of NF-κB (Li and Verma 2002; Siebenlist, Brown, and Claudio 2005). Nuclear translocation of NF-κB is the result of phosphorylation of IκBs which is intervened by a subunit of IKK namely IKKβ that ensures proteosomal degradation of IκB (Bonizzi and Karin 2004). Because of increases in NF-κB expression, the related cells release proinflammatory cytokines like TNF-α, IL-6, IL-1β and ends up in inflammation and subsequent abnormalities (Schneider, Abdel-Aziz, and Efferth 2014). The patients of IBD showed an elevated level of NF-κB in the epithelial cells, macrophages, and fibroblasts, which leads straight to the production of pro-inflammatory cytokines TNF-α, IL-1, and IL-6 (Neurath et al. 1996).

Among the 64 reviewed phytochemicals, 30 suppresses NF-κB signaling (Table 2). Treatment of TNBS induced colitic mice with thearubigin (100 mg/kg) significantly reduced NF-κB activation, whereas LPS-induced IEC-18 cells treated with lycopene (200 μg/ml) reduced NF-κB transcriptional activity from 8- to 0.5-folds (Maity et al. 2003; Joo et al. 2009). DSS induced colitic mice treated with monotropein (200 mg/kg) markedly suppressed nuclear translocation of p50 and p65 subunits of NF-κB whereas treatment of LPS-stimulated RAW 264.7 cells with avicularin (30 μM) significantly attenuated IκB degradation (Shin et al. 2013; Vo et al. 2012).

MAPKs are a crucial signaling pathway, which is present only in eukaryotic cells, and so far, 14 MAPKs is present in mammals. Extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino (N)-terminal kinases 1/2/3 (JNK1/2/3), p38-MAPK, and extracellular signal-regulated kinase 5 (ERK5) are the four signaling cascades comprising MAPK signaling pathway (Cargnello and Roux 2011; Pearson 2001). Usually, three sequentially specific acting kinases form MAPKs, which are a MAPK, a MAPK kinase (MAPKK), and a MAPKK kinase (MAPKKK). Because of MAPKKK activation phosphorylation initiates and MAPKK activates which arouses MAPK activity (Robbins et al. 1993). MAPKs upon stimulation and activation initiates the vicious cycles of inflammation and along with it the production of several inflammatory cytokines like TNF-α, IL-1, IL-2, and IL-6. Moreover, because of these, intestinal disorders and diseases occur including IBD (Broom et al. 2009).

Eleven phytochemicals in this review influence MAPK pathway as shown in Table 2. Treatment of DSS colitic mice with mangiferin (50 mg/kg) reduced p-JNK and p-ERK 1/2–50%, whereas alliin (500 mg/kg) treatment with markedly reduced their expression (Dou et al. 2014; Shi et al. 2017).

Signaling pathway of signal transducer and activator of transcription (STAT), especially STAT3 leads to inflammation, mucosal damage, tumor initiation, progression, and apoptosis (Yu, Pardoll, and Jove 2009). Like NF-κB, STAT proteins remain inactive in the cytoplasm until stimulated by several factors including Janus kinases (JAK), cytokine, or growth factor receptors. After activation, they migrate to the nucleus and regulate the expression of genes involving in cell proliferation, cell cycle progression, tumor invasion, and colorectal cancer (Pandurangan and Esa 2014; Schreiber et al. 2002).

Thirteen phytochemicals in this review inhibit the activation of the STAT pathway as shown in Table 2. DSS-induced colitic mice treated with 25 mg/kg shikonin reduced the expression of p-STAT 3 to 50%, whereas IL-10 deficient mice treated with 0.07 mg/kg triptolide reduces p-STAT 3 expression to almost 70% (Li et al. 2010; Andújar et al. 2012).

TJ proteins literally control the exchange of nutrients and minerals from the digestive tract to the body. Myosin light chain kinase (MLCK) and protein kinase C (PKC) are among the signaling proteins, which regulate the TJ and their interaction among the transmembrane proteins. Phosphorylation of TJ also plays a vital role in the regulation of epithelial layer integrity (Ulluwishewa et al. 2011). PKCs are further divided into classic, novel, and atypical isoforms based on their structures and functions. Some isoforms protect the cells from damage while some cause serious damage (Farhadi et al. 2005). Patients with UC and CD have reduced composition and expression of TJ proteins (Vetrano et al. 2008; Schmitz et al. 1999). Berberine and quercetin significantly suppress MLCK activity (Cao et al. 2013; Sun et al. 2013; Suzuki and Hara 2009).

Different types of stress and stimuli, e.g. inflammatory cytokines, activates the related proteins to these pathways, leading to their activation (He et al. 2015; Karin and Greten 2005). If phosphorylation is checked, the entire inflammatory process and the consequent problems could be prevented (Tkach et al. 2013; Greten et al. 2007). Currently used immunosuppressive drugs, like corticosteroids, methotrexate, and sulfasalazine, mediate inflammation mainly by impeding transcriptional factors (Atreya, Atreya, and Neurath 2008). At this point, phytochemicals come into play. Many of the phytochemicals are very effective in fighting off the problem with the inflammatory pathway.

Phytochemicals and gut microbiota

Gut microbiota plays a substantial role in modulating intestinal structure and intestinal permeability. Phytochemicals, directly and indirectly, affect the structure of gut microbiota. In the case of IBS and IBD including CD and UC, abundance and diversity of gut microbiota show dramatic downfall in comparison to healthy individuals. In these cases, the number of pathogenic bacteria increases while *Firmicutes* to *Bacteroidetes* ratio decreases drastically (Jeffery et al. 2012;

Sokol et al. 2006). As the number of phenolics is highest among all phytochemicals, they are well studied and their mechanism of action with gut flora is clearly explained by many experiments (Tomás-Barberán, Selma, and Espín 2016). The intestine does not instantly absorb polyphenols upon ingestion; rather a very minute proportion gets absorbed. The major fraction goes through several biochemical processes including hydrolysis and cleavage. Gut microbiota comes into action in these reactions with their vast array of enzymes, and these tiny organisms are the actual controller of intestinal permeability and the gut health as well (Carrera-Quintanar et al. 2018).

The interaction between phytochemicals and intestinal microbes are two ways and because of their interaction, gut health and permeability change significantly. Therefore, this relationship can be seen as a triangle, but interconnected and reversible (Fig. 3). First, phytochemicals shape the gut microbes by their antimicrobial and antioxidative properties (McCarthy and O'Gara 2015). This is due to the bonding of polyphenols to the bacterial cell membrane and interrupting the normal bacterial functions. Some phytochemicals produce hydrogen peroxide, which in turn affects bacterial membrane and then sustains the gut. Some polyphenols bind with the lipid bilayer of the bacteria with their hydroxyl group (Cardona et al. 2013). Second, phytochemicals moderate the mucin layer, which in turn affects the microbial adhesion and colonization (Puupponen-Pimiä et al. 2005). Third, gut microbes themselves influence the bioavailability of the phenolic compounds by enzymatic activity and produce numerous aglycones, which affect intestinal permeability (Stevens and Maier 2016). For instance, curcumin is a very important phenolic compound, which transforms into tetrahydrocurcumin by the enzymatic activity of *Escherichia coli* (Hassaninasab et al. 2011).

Shortcomings

Indeed, the phytochemicals possess great medicinal properties but it is still not enough to replace all the existing synthetic medicine available in the market and to ameliorate the gastrointestinal diseases/abnormalities. First, even though phytochemicals exert potential therapeutic effects, but still is not convincingly better to switch to these. It is because the models of disease study and the approaches taken to conduct the experiment differ greatly from researcher to researcher. Second, all the experiments are in vitro cell experiments and in vivo animal experimental models. These results are not quite convincing enough to jump to conclusion that these phytochemicals are ready replace of the current drugs used, as without repeated clinical trials with humans it is very hard to tell the extent of influence they will exert upon administration or application. Third, there is no uniform method of extraction and the dose of administration. For the same phytochemical, researchers using different doses, a different animal and cell models and variable experimental period to perform the same experiment. These variations make it difficult to conclude about the methods, effects, and pathway of action of phytochemicals to fight off the intestinal disease and abnormalities.

Standard drugs namely sulfasalazine, infliximab, mesalazine reduce the complications of IBD significantly, but they also cause many complications including nausea, fatigue, diarrhea, and headache (Rogler 2010). This is why multidrug treatment is now gaining attention to check and confirm the usefulness of synergistic effects of phytochemicals and standard drugs. Li et al. (2015) worked on the synergistic effects of allicin (30 mg/kg)-mesalazine (30 mg/kg), and allicin (30 mg/kg)-sulfasalazine (100 mg/kg) on TNBS (50 mg/kg) induced Wistar rats. Allicin-mesalazine treatment reduced colonic histopathological score from 5.83 to 2.10 and allicin-sulfasalazine reduced it to 3.38. Interesting thing is the separate treatment of allicin, mesalazine, and sulfasalazine reduced histopathological score 4.29, 3.33 and 2.22. Apparently, combined treatment with allicin-mesalazine reduced the score least, other than mesalazine or sulfasalazine treatment only. Allicin-mesalazine treatment reduced TNF-α levels to 2.65 from 6 (pg/ml) whereas allicin or mesalazine treatment alone reduced it to around 3.8 (pg/ml). TNBS treatment lessened IL-4 concentration to below 4 (pg/ml), but the application of mesalazine-allicin upregulated their concentration to 5.76 (pg/ml), but the separate treatment of allicin or mesalazine could not increase their expression up to the synergistic levels. Another synergistic study of Li et al. (2015) on DSS (2%, w/v) induced C57BL/6 mice by berberine and 5-aminosalicylic acid (5-ASA) proved that combined effects are better than their individual treatment. 5-ASA (200 mg/kg) treatment reduced DAI score by 19%, whereas 5-ASA (200 mg/kg), and berberine (20 mg/kg) treatment reduced DAI score by 59%. Crypt loss, related to colonic injury, greatly prevented by 5-ASA and berberine treatment. 5-ASA (200 mg/kg) reduced crypt damage by 36%, but administration of berberine (20 mg/kg) and 5-ASA

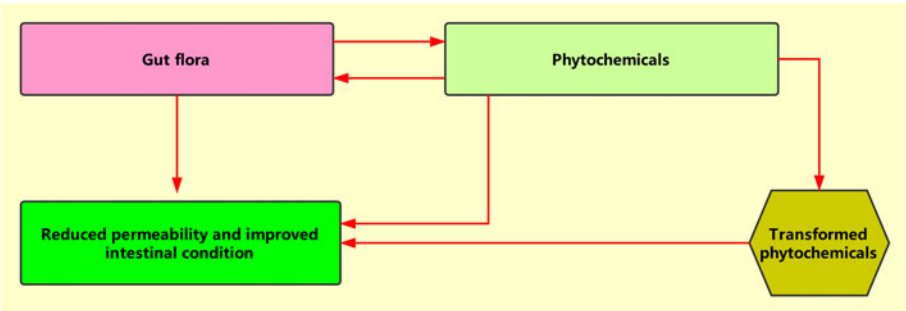

Figure 3. Interaction between phytochemicals and gut microbes.

(200 mg/kg) prevented crypt damage by 54%. Combined drug treatment looks promising than the individual treatment alone, and this field needs further extensive research. Hopefully, it will open a new dimension in the treatment of IBD.

Conclusion

As per civilization's progress, people's lifestyle and food habit are also changing greatly. The dietary pattern is changing to high fat and low fiber one, imposing a negative effect on the body, reducing the immunity and making us susceptible to diseases and pathogens. Earlier inflammatory bowel disease was confined to western countries; however with globalization and change of lifestyle especially food habit, the occurrence of these diseases is increasing in Asian countries including China (Prideaux et al. 2012). Because of consuming high fat and fewer fibrous foods, the digestive system along with the microbiome lose its efficiency and the mucus layer is being impaired. Consequently, pathogenic bacteria, pro-inflammatory cytokines, and other similar compounds entering the bloodstream and causing complications range from inflammation, ulceration, body weight reduction, and oxidative stress. For centuries, pharmaceutical companies are trying to find out the best medicine to treat intestinal diseases including IBD. There are many synthetic drugs, which are currently in play, but the problem with those drugs is that they have many side effects and sometimes rather than ameliorating the situation, the condition of the patient worsens. Therefore, light focuses on phytochemicals, as they have many potentials as therapeutic drugs. Additionally, many phytochemicals yet to be discovered and studied for the treatment of IBD and related disorders. The more they studied, the more information can be gathered about their specific mechanism of action and their signaling pathway. In the end, these will lead us to discover more specific target for the treatment. With any luck, a perfect therapeutic drug will be synthesized for the treatment of gastrointestinal diseases especially CD and UC, because the answer to all our questions is rooted in nature.

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Disclosure statement

There are no conflicts to declare.

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