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Dietary Agents and Phytochemicals in the Prevention and Treatment of Experimental Ulcerative Colitis

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ABSTRACT

Inflammatory bowel diseases (IBDs), consisting mainly of ulcerative colitis (UC) and Crohn's disease (CD), are important immune-mediated diseases of the gastrointestinal tract. The etiology of the disease includes environmental and genetic factors. Its management presents a constant challenge for gastroenterologists and conventional surgeon. 5-Amninosalicylates, antibiotics, steroids, and immune modulators have been used to reduce the symptoms and for maintenance of remission. Unfortunately, long-term usage of these agents has been found to lead to severe toxicities, which are deterrent to the users. Pre-clinical studies carried out in the recent past have shown that certain dietary agents, spices, oils, and dietary phytochemicals that are consumed regularly possess beneficial effects in preventing/ameliorating UC. For the first time, this review addresses the use of these dietary agents and spices in the treatment and prevention of IBD and also emphasizes on the mechanisms responsible for their effects.

Key words: Cancer, Colitis, Colon, Inflammation, Phytochemicals

INTRODUCTION

Inflammatory bowel disease (IBD), manifested clinically by bloody diarrhea, abdominal cramps, and pain, is an immunologically mediated relapsing and chronic disease that affects the intestinal mucosa.[1] Patients with IBD are also at a higher risk to develop colorectal cancer, when compared to the average population.[2] Crohn's disease (CD) and ulcerative colitis (UC) represent the two most common forms of IBD.[1,2] These diseases mimic each other in symptoms and some mucosal pathology, but differ sufficiently to be considered as independent ailments.[1] The etiology and the exact disease mechanisms remain unknown despite much effort and research.[2] It is well known that the incidence of IBD is high in the countries of North America, and northern and western Europe, while it is low in Africa, eastern Europe, South America, Asia, and the Pacific region. Conversely, recent studies indicate that the incidence has stabilized or slightly increased in countries with a high prevalence previously, while it is on the rise in countries with a low incidence previously. Jointly, these reports indicate that IBD could be a global health problem in the future and understanding its pathogenesis and developing affordable safe treatment is important.[3]

CURRENT STATUS OF KNOWLEDGE

Molecular events responsible for UC

From a clinical perspective, the central sign of UC is inflammation of the mucosal lining of the colon and mechanistically,

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this end event is a result of interplay between various molecular constituents of the cells. The inflammatory pathway in UC involves ubiquitous expression of proinflammatory eukaryotic transcription factors [activator protein (AP)-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)],[4,5] which leads to the production of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, with T-helper (Th)-17 cytokines such as IL-23 and IL-17 predominating, and a concomitant decrease in the anti-inflammatory cytokines and proteins.[6,7] This surge in pro-inflammatory cytokines is followed by an increase in the production of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), myeloperoxidase,[8] and signal transducer and activator of transcription[9] -3,[5,6] which further increases inflammation and leads to oxidative stress[10] and a concomitant decrease in the level of antioxidants.[10,11] All these events lead to an increase in cell inflammation, infiltration of the immune cells, especially the neutrophils, and culminate into epithelial cell damage and colonic barrier dysfunction. UC is also an established risk for colon cancer, which is caused due to the repeated cycle of inflammation leading to spontaneous mutation in the DNA repair mechanism, oncogenes, and tumor suppressor genes like p53.[4,5] Another factor responsible for the development of UC is the change in the constituent, number, and activity of the colon microflora, as studies with germ-free mice have conclusively shown less or no inflammation developing in chemical and genetic models of colitis.

Conventional treatments in UC

Chemotherapy has been the mainstay of treatment of UC; in the event of a mild disease, anti-inflammatory drugs such as sulfasalazine and 5-aminosalicylic acid are given, while in severe and chronic cases, treatment with rectal and systemic corticosteroid and immunosuppressant is administered.[12] In most cases, the benefits are restricted to the reduction of inflammation and its complications.[1] However, in extreme conditions, surgery is the last solution to the patient's condition. Conversely, regular intake of these medications is unsafe as they may have severe side effects such as gastric ulcers, Cushing's habitus, hyperglycemia, muscle weakness, fragile skin, purple striae, flaring up of latent infections, delayed wound healing, cataract, osteoporosis, glaucoma and hypothalamic pituitary axis suppression with corticosteroids, and an increased risk of opportunistic infections and development of lymphomas.[1] In addition, some refractory condition can lead to severe morbidity and decrease in the quality of life.[1]

Recently, biologics such as anti–TNF-α, anti–alpha-4 integrin, as well as Peroxisome proliferator-activated receptor gamma (PPARγ) ligand and probiotic therapy are being used, but their long-term benefits are unknown.[1] Importantly, reports suggest that the long-term use of biologics, especially infliximab, adalimumab, and certolizumab, may increase the risk of infections and malignancies, especially non-Hodgkin's lymphoma.[13] Drugs that block leukocyte adhesion such as natalizumab, those that target cytokines, like IL- 12/23, and antibodies inhibiting T-cell signaling, such as IL-6 receptor antibodies, are also being studied. However, these drugs also have a number of contraindications and side effects, especially when used in combination with classical immunosuppressive drugs. The major effects are opportunistic infections, malignancies, and diverse complications like injection/infusion reactions and autoimmunity, and contraindications such as heart failure and acute infectious diseases.[14]

The repeated relapses, surgery phobia, severe morbidity, and derisory response to conventional drugs make the patient to resort to unconventional treatments with a hope to decrease the symptoms of the disease and concomitantly perk up the quality of life.[15] Recent reports indicate that at least 40% of IBD patients have used complementary and alternative medicines, and that the botanicals constitute a major share of all these alternatives.[15]

Results from preclinical studies suggest the beneficial effect of medicinal plants including *Aloe vera* gel (蘆薈 Lú Huì), *Boswellia serrata* (乳香 Rǔ Xiāng), *Cassia fistula, Lepidium sativum, Bunium persicum, Plantago ovata, Pistacia lentiscus, Bunium persicum, Solanum nigrum, Commiphora mukul, Commiphora myrrha, Ocimum basilicum* (羅勒 Luó Lè), *Linum usitatissimum, Dracaena cinnabari, Plantago major, Lallemantia royleana,* and *Allium porrum*, which have been used since time immemorial in the various systems of traditional and folk medicine.[16,17]

From human perspective, it is always desirable to consume dietary agents that also possess medicinal value as their regular use can be achieved easily and regularly. This aspect was very well recognized by Hippocrates, the Father of Medicine, who proclaimed almost 25 centuries ago, "*Let food be thy medicine and medicine be thy food.*" To further substantiate the importance and relevance of this adage, observations from around the world clearly indicate that the incidence of diet-related diseases is progressively increasing due to greater availability of hypercaloric food and a sedentary lifestyle, which cause low-grade inflammation in the individual.[18]

Recent reports also suggest that the functional foods and nutraceuticals rich in polyphenols and antioxidants are beneficial due to their intrinsic ability to scavenge free radicals, induce anti-inflammatory responses, maintaining a homeostatic regulation of the gut microbiota, and activate the intestinal T regulatory cells.[18] All these properties are extremely beneficial in the prevention and mitigation of the IBD. Studies have shown that the dietary agents like apple, bilberry, black raspberry, cocoa, bael, green tea (綠茶 Lǜ Chá); spices like garlic (大蒜 Dà Suàn), Malabar tamarind, saffron (番紅花 Fān Hóng Huā), fenugreek, ginger (生薑 Shēng Jiāng), turmeric (薑黃 Jiāng Huáng); oil of olive; nutraceuticals like grape seed polyphenols; and the dietary phytochemicals like resveratrol, ellagic acid, zerumbone, quercetin, kaempferol, rutoside, and rutin are consumed regularly and are commonly used. They will be addressed in detail by emphasizing on the mechanism of action.

DIETARY AGENTS WITH ANTI-IBD EFFECTS

Apple

Apple, known as *Malus malus*, belongs to the family Rosaceae and is an important dietary agent.[19-21] It has occupied a prime position in the dietary and nutritional requirements of humans and epidemiological studies have linked its consumption with reduced risk of certain cancers, cardiovascular diseases, asthma, and diabetes.[21] Apple is a good source of several flavonoids and certain phy-

tochemicals including quercetin glycosides, catechin, epicatechin, procyanidin, cyanidin-3-galactoside, coumaric acid, chlorogenic acid, gallic acid, and phloridzin.[22] Recently, D'Argenio *et al*. found that rectal administration of apple polyphenols protected rats from 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis by decreasing the transcription and protein levels of COX-2, TNF-α, calpain, as well as tissue transglutaminase. Thus, polyphenolic compounds obtained from apple may serve as potential therapeutic agents for UC patients.[23]

Bilberry

Bilberry, also known as blaeberry (a Scottish name meaning blueberry), mountain bilberry, whinberry, whortleberry, whortles, myrtle whortleberry, tracleberry, and huckleberry, is a plant indigenous to Europe and has long been consumed in jams, pies, cobblers, and cakes.[24,25] Its scientific name is *Vaccinium myrtillus* L. and it belongs to the family Ericaceae. Phytochemical studies have shown it to contain the flavonoids like hyperoside, isoquercitrin, quercitrin, and astragaline and the anthocyanins like myrtillin, malvidin, cyanidin, delphinidin, and tannins.[26]

Bilberry has been used to treat ocular disorders and is believed to be useful in improving night vision, prevent the development and progression of cataracts, treat diabetic retinopathy and macular degeneration, and prevent glaucoma.[26,27] With respect to its use in UC, an open pilot trial by Biedermann and coworkers with 13 individuals with UC has shown that the daily intake of a standardized bilberry preparation caused 63.4% remission and 90.9% response in the volunteers. Intake of the bilberry preparation decreased the total Mayo score and the histologic Riley index.[28] However, an increase in disease activity was observed after cessation of bilberry intake, clearly indicating the beneficial effects of bilberries in UC, but only when taken regularly.

Black raspberry

The fruits of the perennial shrub *Rubus coreanus* Miquel, colloquially known as black raspberry, have been an important dietary and medicinal agent in traditional medicine.[29-31] The plants grow in Far East Asian countries, namely South Korea, Japan, and China.[32] The anthocyanin fraction of black raspberry has been found to be protective against esophageal and colorectal cancer.[31] Montrose and coworkers investigated the protective effects of freeze-dried black raspberry powder on dextran sodium sulfate (DSS)–induced UC in C57BL/6J mice and observed it to be effective in ameliorating the clinical conditions.[33] The mice fed with black raspberry powder showed better maintenance of body mass and reduction in colonic shortening and ulceration. They had reduced levels of plasma prostaglandin E2 (PGE2), while the levels of nitric oxide (NO) were unaltered.[33] Feeding black raspberry powder suppressed the tissue levels of COX-2 and key pro-inflammatory cytokines like TNF-α and IL-1β.[33] Mechanistic studies within the colonic tissue showed decreased levels of phospho-IκBα indicating that black raspberry powder modulated the NF-κB, supporting its possible therapeutic or preventive role in the pathogenesis of UC and related neoplastic events. With respect to phytochemicals, experiments have also shown that ellagic acid [Figure 1], which is present in raspberries and other berries like blackberries, cranberries, strawberries, and wolfberries, possesses concentration-dependent protective effects against the DSS-induced colitis in rats.[34]

Cocoa

Cocoa, known as *Theobroma cacao*, is a small evergreen tree native to South America.[35,36] Its seeds are used to make cocoa powder and chocolate, and are widely used in confectionery industry.[37] Furthermore, the seeds also contain polyphenols and flavonoids that possess several health benefits.[38] Andújar *et al*. found the polyphenol-enriched cocoa extract containing epicatechin, procyanidin B2, catechin, and procyanidin B1 to possess anti-inflammatory properties against DSS-induced colitis in mice. This effect was manifested by reduction in inflammation, crypt damage, and leukocyte infiltration in the mucosa due to decrease in the production of NO, COX-2, phospho-STAT-3 (pSTAT-3), pSTAT1α, and NF-κB p65. Similar results have been found *in vitro* using RAW 264.7 cells, indicating that cocoa extract is effective in ameliorating DSS-induced colitis and the effect may be mediated by the inhibition of transcription factor NF-κB in intestinal cells.[39] A clinical trial by Monagas *et al*.[40] concluded that cocoa polyphenol intake modulated inflammatory mediators in patients with a high risk of cardiovascular disease and could be beneficial against atherosclerosis.[40] These anti-inflammatory effects may contribute to the overall benefits of cocoa consumption against atherosclerosis. However, a study by Pérez-Berezo *et al*. showed that cocoa may be effective in reducing oxidative stress by downregulating serum TNF-α and iNOS activity in the colon or by increasing reduced glutathione (GSH), but this is not enough to reverse the DSS-induced colitis in the mice model. They concluded that cocoa intake may decrease colon cell infiltration and inflammation to a certain extent, but not completely.[41] Therefore, it becomes imperative to perform more experimental and clinical studies to get a verdict for the use of cocoa in the treatment of colitis before its usage as a complimentary medicine.

Bael

Aegle marmelos, commonly known as holy fruit, Bengal quince, Indian quince, golden bael, or bilva, is arguably one of the most important plants in ancient India.[42] The plants are indigenous to India, and contain tannins, some essential oils like caryophyllene, citral, sterols, and/or triterpenoids, flavonoids like rutin and coumarins, including aegeline, marmesin, phlobatannins, flavon-3-ols, leucoanthocyanins, and anthocyanins[42,43] [Figure 1]. In Ayurveda, the Indian traditional system of medicine, bael is utilized for its ability in the treatment of various diseases including diarrhea, dysentery, and dyspeptic symptoms.[44] With regard to IBD, recent studies by Behera *et al*. have shown bael to be effective in ameliorating acetic acid-induced UC and indomethacin-induced enterocolitis in Wistar albino rats. The investigators observed that oral administration of the Bael fruit extract caused a significant decrease in disease activity index, macroscopic score, and microscopic scores. Mechanistic studies showed that administering Bael caused reduction in mast cell degranulation and malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) activity.[45]

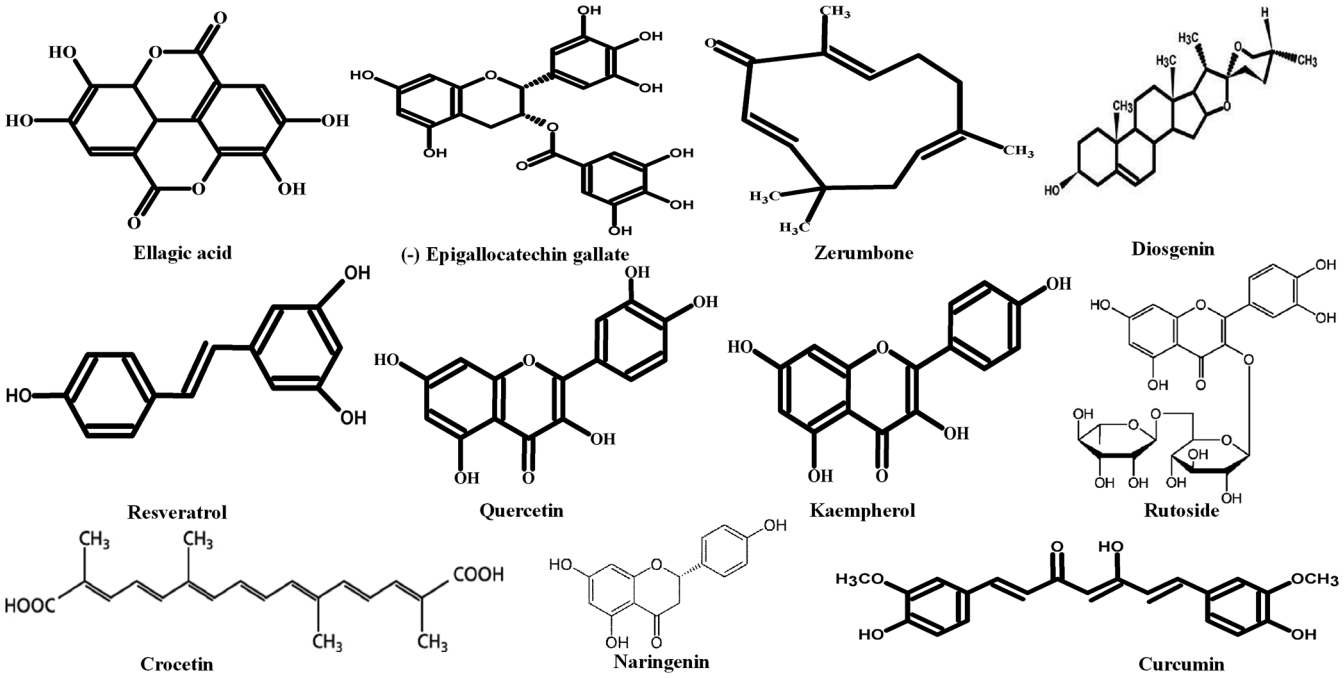

Figure 1. Chemical structures of some phytochemicals effective against UC

Green tea (綠茶 Lǜ Chá)

Tea (*Camellia sinensis*), a plant native to China and Southeast Asia, is today the most commonly used botanical globally.[46,47] It is the second most widely consumed beverage after water, and may be consumed as green tea (unfermented), oolong tea (partially fermented), and black tea (fully fermented). Many studies carried out in the past three decades have shown that green tea possesses myriad benefits owing to its polyphenol content.[48-50] The active compounds of green tea are the catechins [(–)-epicatechin (EC), (–)-epigallocatechin (EGC), (–)-epicatechin-3-gallate (ECG), and (–)-epigallocatechin-3-gallate (EGCG)] [Figure 1], proanthocyanidins, flavonols (kaempferol, quercetin, and myricitin in the form of glycosides), gallic acids, and theanine.[51]

Animal studies have proved that use of green tea polyphenol (GrTP) ameliorated the symptoms associated with colitis induced by DSS,[52] dinitrobenzene sulfonic acid (DNBS),[53] and in IL-2 deficient mice.[54] These include bloody diarrhea, weight loss, wet colon weights,[55] colonic damage, hemorrhage, ulcers, edema, and neutrophil infiltration.[55] Experiments also revealed that GrTP prevented acute colitis and inflammation-associated colon carcinogenesis in male ICR mice.[56] Furthermore, the phytochemical EGCG reduced DSS-[57] and TNBS-induced colitis in rats[58] and mice.[55] Moreover, treatment with green tea had significantly less impact on the hematocrit,[52,54] serum amyloid A,[52,54] and blood GSH[52] in animals after colitis induction, indicating an improvement in the animal health with the antioxidant administration.

Further, GrTP decreased spontaneous interferon-gamma (IFN-γ) and TNF-α secretion from the colon explant in IL-2 deficient animals when compared to their control counterparts,[54] and reduced the levels of TNF-α,[52,53,55] IL-6, IL-10, and the keratinocyte-derived chemokine,[55] which further reflects reduction of inflammation by GrTP administration. Administration of the polyphenol EGCG also led to a decrease in the levels of COX-2,[58] myeloperoxidase,[8,53,55] and intercellular adhesion molecule-1 (ICAM)-1,[53] and rectified the distorted actin cytoskeleton in the colonic tissue.[52] These beneficial effects of EGCG were associated with a significant reduction of NF-κB and AP-1 activation.[55] The phytochemicals EGCG and Polyphenon E also attenuated inflammation-induced colon cancer caused by DSS and azoxymethane (AOM) and the protective effects were mediated by reducing COX-2 and the mRNA expression levels of TNF-α, IFN-γ, IL-6, IL-12, and IL-18 in the colonic mucosa.[59] Further, treatment with a combination of EGCG and piperine reduced body weight loss, improved the clinical course, and increased the overall survival, when compared to untreated groups.[57] The attenuated colitis was associated with lower histological damage and colon insult, reduction in lipid peroxidation, decreased levels of MPO, and a concomitant increase in the levels of antioxidant enzymes [SOD and glutathione peroxidase (GPx)] in the colonic tissue.[57] A recent study by Oz *et al*.[60] has shown the protective effect of different dosages of GrTP (0.25%, 0.5%, and 1%), EGCG (0.12%, 0.25%, and 0.5%), and a single dosage of sulfasalazine (50 mg/kg) in experimental colitis model. They found that GrTP and EGCG improved hematocrit values, as compared to sulfasalazine which caused anemia. Also, low dose of EGCG reduced colonic pathological lesions and normalized global antioxidant ratio, but was least beneficial in inhibiting reduction of leptin levels. However, GrTP partially protected animals against weight loss and elevated TNF-α. This study concluded that low-dose EGCG and GrTP may become potential therapeutic or additive agents in the treatment of IBD; however, clinical trials are warranted to prove this.[60]

However, seminal studies by Inoue *et al*.[61] have provided evidence that oral treatment of 1% GrTP to both normal and colitic

animals induced nephrotoxicity in the ICR mice. The investigators observed that 1% GrTP given to colitic mice significantly increased their kidney weight and increased the levels of serum creatinine and thiobarbituric acid reactive substances (TBARS), but decreased the expression of heme oxygenase-1 (HO-1), NAD (P) H: Quinone oxidoreductase 1 (NQO1), and heat-shock protein (HSP) 90 in both kidney and liver, as compared to the colitic mice treated with the standard diet.[61] Antioxidant enzymes' mRNA expression and HSPs, such as HO-1, HSP27, and HSP90, were significantly down-regulated in the colitic mice receiving 1% GrTPs.[61] It is noteworthy that these results clearly indicate that high-dose GrTP diet disrupts kidney functions through the reduction of antioxidant enzymes and HSP expression in both treated and untreated control ICR mice.[61] In clinical studies, green tea has been shown to provide antioxidant protection in metabolic syndrome[62] and has shown a positive effect on blood pressure, insulin resistance, inflammation, and oxidative stress in patients with obesity-related hypertension.[63]

Grapes

In the history of mankind, grapes (*Vitis vinifera*) have been one of the most important fruits due to their importance in winery.[64] The major constituents of grape are epicatechin gallate; procyanidin dimers, trimers, tetramers; catechin; epicatechin; gallic acid; procyanidin pentamers, hexamers, and heptamers and their gallates; resveratrol; phenolics; flavonoids; and anthocyanins [Figure 2].[65] Grapes possess anti-inflammatory, anti-aging, potent antioxidant, antimutagenic, antidiabetic, hepatoprotective, cardioprotective, nephroprotective, neuroprotective, and anti-carcinogenic properties.[65] Pre-clinical studies provided evidence that polyphenols from grape seed are effective in reducing TNBS-[66,67] and DSS-induced colitis in rats,[68] with the protective effects being equal to those of the clinically used drug.[66]

Administering grape seed proanthocyanidin extract (GSPE) reduced the macroscopic and microscopic damage scores and changes in weight/length ratio (mg/mm) of colon segments, when compared with standard diet in rats.[66,67] Studies have also shown that when compared to DSS-treated controls, GSPE significantly decreased ileal villus height and mucosal thickness toward the values of normal controls.[68] In addition, GSPE significantly reduced the histological severity score only in the proximal colon and failed to prevent crypt damage of both proximal and distal colonic regions of the DSS-treated rats.[68]

Mechanistic studies revealed that the levels of MDO[66,67] and NO,[67] activities of MPO[66,67] and iNOS,[67] and the levels of inflammatory cytokines like IL-1β[66] were reduced in the colon tissues and serum of the GSPE-treated rats as compared to colitis control group.[66] Furthermore, grape seed polyphenol treatment was associated with notably increased SOD and GPx activities and also the glutathione level[67,69] of colon tissues and serum of rats. The levels of IL-2 and IL-4[66] were also found to be significantly increased. GSPE significantly reduced the expression levels of TNF-α, phospho-Inhibitor of nuclear factor kappa-B kinase subunit alpha/beta (p-IKKα/β), and 9phospho-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (p-IκBα), and the translocation of NF-κB in the colon mucosa. Administration of GSPE did not negatively impact metabolic parameters, nor did it induce any deleterious gastrointestinal side effects in healthy animals.[68] Thus, it can be concluded that GSPE exerts a protective effect on colitic rats by modulating the inflammatory response locally and systemically, and promotes tissue repair to improve colonic oxidative stress, at least in part by modulating the NF-κB signaling pathway.[69]

Olive oil

The oil extracted from the fruits of the olive tree (*Olea europaea*) is one of the highly investigated dietary agents in recent times, and studies suggest that it possesses a wide range of therapeutic applications.[70-72] The trees are native to the Mediterranean basin and parts of Asia Minor, and are mentioned in the ancient literature from Biblical and Roman times to Greek mythology. Olive oil is a major component of the Mediterranean diet and many beneficial effects of this diet have been attributed to the ample use of the oil. The chief active components of olive oil include oleic acid, phenolic constituents, and squalene. The main phenolics include hydroxytyrosol, tyrosol, and oleuropein, which occur in highest levels in virgin olive oil and have demonstrated antioxidant activity.[72]

Seminal studies by Sánchez-Fidalgo and coworkers have shown that the olive oil attenuates DSS-induced acute UC[73-75] and DSS-colitis-associated colon carcinogenesis in mice.[76] The active phytochemical hydroxytyrosol was also shown to be effective in reducing the DSS-induced damage.[74] The investigators observed that administering diets enriched with extra virgin olive oil (EVOO) significantly reduced the DSS-induced mortality by nearly 50%, attenuated the clinical and histological signs of damage, and improved the disease activity index.[74]

Mechanistic studies have shown that administering EVOO reduces the damage in acute colitis model by alleviating the oxidative stress. It prevents the degradation of IκBα, deactivates PPARγ, down-regulates the expression of iNOS, COX-2, monocyte chemoattractant protein-1 (MCP-1), and TNF-α, and activates p38 mitogen-activated protein kinases (MAPKs) in the colonic mucosa.[73,74] Observations from the DSS-colitis–associated carcinogenesis experiments also suggest that the feeding EVOO reduced the incidence and multiplicity of dysplastic lesions due to reduced β-catenin and decreased levels of COX-2, iNOS, and other proinflammatory cytokines.[76]

Agaricus blazei

Agaricus blazei Murill, an edible mushroom indigenous to Brazil, is a rich source of a variety of β-glucans, proteoglucans, glycoproteins, saponins, tannins, cerebrosides, polysaccharides, and steroids. It is one of the most important edible and culinary medicinal species.[77,78] It is cultivated commercially for the health food market and is shown to possess a range of medicinal properties against diseases like cancer[79,80] and chronic hepatitis.[81] Preclinical studies have shown it to possess anti-inflammatory effects against a range of ulcerogens.[78] With respect to its beneficial effects in the treatment of IBD, a recent clinical study has shown that consumption of 60 ml/day of immunomodulatory extract (AndoSan™) at a concentra-

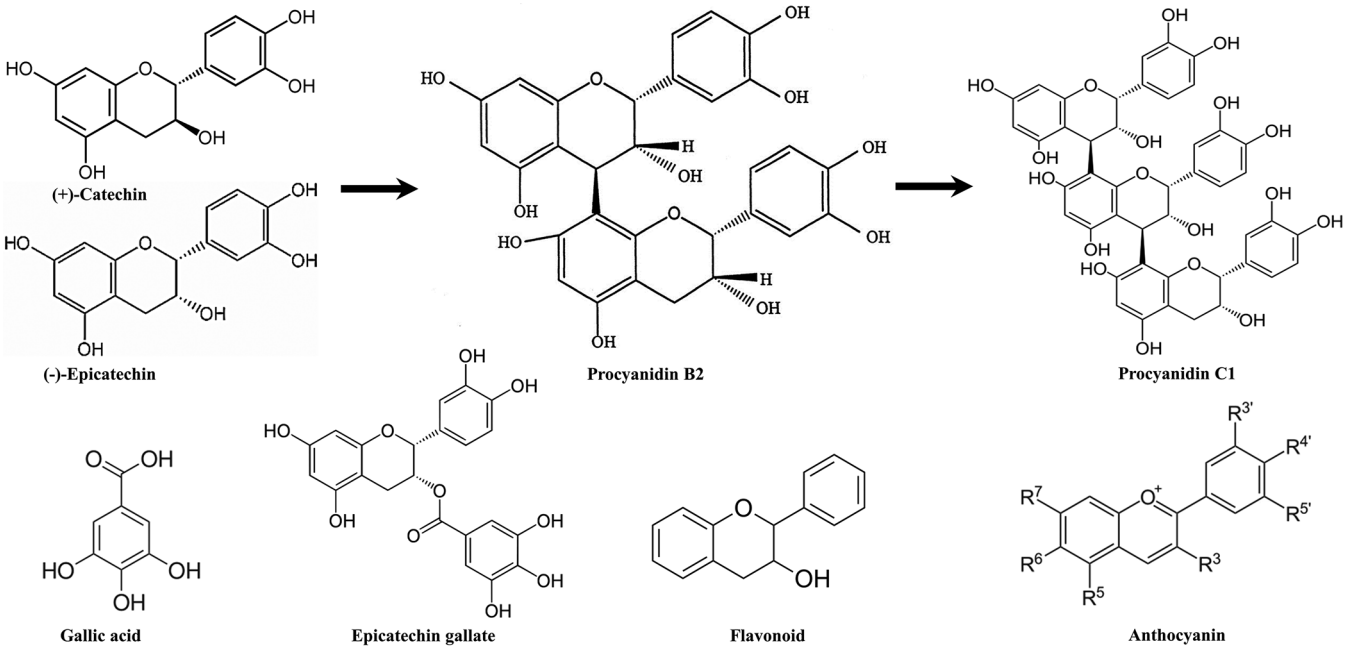

Figure 2. Some phytochemicals present in grape seed

tion of 340 g/l or 20.4 g/day for 12 days caused reduction in the levels of pro-inflammatory cytokines like IL-1β and IL-6 and chemokines like IL-8, Macrophage inflammatory protein (MIP-1β), Monocyte chemoattractant protein-1 (MCP-1), Granulocyte macrophage colony-stimulating factor (GM-CSF), and Granulocyte colony-stimulating factor (G-CSF) in UC and CD patients, indicating a reduction in inflammation. Levels of fecal calprotectin were also reduced in UC patients, with an overall reduction in IBD pathology.[82]

Indian gooseberry

Indian gooseberry or amla, scientifically known as *Emblica officinalis* Gaertn. or *Phyllanthus emblica* Linn., is an indigenous plant of India.[83] The fruits are a rich source of ascorbic acid and the juice prepared from the ripe fruits is an excellent coolant in the hot summer season.[84] The fruits also contain gallic acid, ellagic acid, chebulinic acid, chebulagic acid, emblicanin-A, emblicanin-B, punigluconin, pedunculagin, ellagitannin, trigalloyl glucose, chebulagic acid, corilagin, quercetin, kaempferol 3-*O*-α-l (6'' methyl) rhamnopyranoside, and kaempferol 3-*O*-α-l (6'' ethyl) rhamnopyranoside.[84]

Amla is arguably the most important medicinal botanic in the traditional Indian system of medicine, the Ayurveda. Studies have shown it to possess antibacterial, antifungal, antiviral, free radical scavenging, anti-mutagenic, anti-inflammatory, cardioprotective, gastroprotective, hepatoprotective, nephroprotective, neuroprotective, and anticancer properties.[84] A recent study by Deshmukh *et al*.[93] has shown that the methanolic extract of *E. officinalis* (200 mg/kg) was effective in ameliorating the severity of acetic acid–induced colitis in rats.[85] It reduced colon weight/length ratio, colon insult, and macroscopic scores for inflammation, in addition to lactate dehydrogenase (LDH), indicating that amla protected against the inflammogen and possessed cytoprotective effects.[85]

SPICES WITH ANTI-IBD EFFECTS

Spices, which are termed as aromatic vegetable substances, in the whole, broken, or ground form, and whose significant function in food is seasoning rather than nutrition, are an important constituent of the Indian curries.[86,87] In addition to their organoleptic properties, spices are also useful in prolonging the shelf life of foods by preventing rancidity through their free radical scavenging effects and also by imparting antimicrobial activities.[86,87] Historical reports also support the fact that ancient physicians like Charaka, Sushrutha, Hippocrates, and Dioscorides used spices extensively in their practice.[87] Additionally, most of the spices also possess medicinal benefits and are extensively used to treat various gastrointestinal ailments.[86, 87] In the following section, the beneficial effects of spices like garlic, saffron, Malabar tamarind, fenugreek, ginger, and turmeric [Figure 3] will be addressed in detail.

Garlic (大蒜 Dà Suàn)

Garlic, scientifically known as *Allium sativum* and a member of the Liliaceae family, is highly regarded throughout the world for both its medicinal and culinary value.[88] The plant is indigenous to Asia and historical documents suggest that the early men of medicine such as Hippocrates, Pliny, and Aristotle used this botanical for its numerous therapeutic uses, and it is regularly used in various traditional and folk medicines.[88] In traditional medicines, garlic, both raw and aged, is used as a natural antiviral, antibacterial, and antifungal agent, to suppress common cough,[89] to treat gastrointestinal disorders,[90] and to act as a cardioprotective agent.[91,92] Different types of antioxidants are present in different garlic preparations, including water- and lipid-soluble organosulfur compounds like *S*-allylcysteine and *S*-allylmercaptocysteine[93] and non-metals like selenium and phytoalexin-like

allixin, which are responsible for the protective effect of garlic in several disease models.[94,95] Rats fed garlic (0.25 g/kg b. wt.) orally for 4 weeks and 3 days during acetic acid–induced colitis showed a significant reduction in colon weight. Garlic administration restored the levels of GSH and antioxidant enzymes with a concomitant decrease in lipid peroxidation levels, as compared to placebo-treated colitis groups. Also, garlic treatment in the presence of the amino acid l-arginine (625 mg/kg b. wt.) mitigated the changes in both colon weight and colon tissue contents of lipid peroxidation and GSH.[92]

Ginger (生薑 Shēng Jiāng)

Ginger, a plant native to the northeast region of India, is one of the world's most important culinary and medicinal agents in various alternative systems of medicines.[96-98] Some of the important bioactive components of ginger extract include 10-gingerol, 8-gingerol, 6-gingerol, and 6-shogaol, with 6-gingerol being antiproliferative.[99] It has been documented to treat cold, headaches, nausea, stomach upset, diarrhea, and helps digestion, treats arthritis, rheumatological conditions, and muscular discomfort, and acts as a carminative and antiflatulent.[100] Scientific studies have shown that ginger possesses antimicrobial, antischistosomal, anti-inflammatory, antipyretic, antioxidative, hypoglycemic, hepatoprotective, diuretic, and hypocholesterolemic effects.[101]

Preclinical studies have shown that pretreatment with ginger extract ameliorated the acetic acid–induced edematous inflammation in the colon by significantly attenuating the extent and severity of edema, necrosis, and inflammatory cell infiltration in the mucosa.[102] The activity of colonic MPO and levels of lipid peroxides, protein carbonyl content, TNF-α, and PGE2 were also decreased. Administering ginger restored the levels of GSH, catalase (CAT), and SOD. The protective effect of highest doses of ginger was comparable to that of the standard sulfasalazine.[102]

In addition, studies have also shown that zerumbone (a sesquiterpenoid) [Figure 1], a minor constituent of *Zingiber officinale* but a major component of *Zingiber zerumbet*, mitigated the DSS-induced acute colitis in ICR mice.[103] Oral feeding of zerumbone reduced the inflammatory biomarkers (IL-1α, IL-1β, TNF-α, PGE2, and PGF2α) in the colonic mucosa and suppressed DSS-induced colitis. Nimesulide, a selective COX-2 inhibitor, suppressed the histological changes induced by DSS without affecting inflammatory biomarkers; but when combined with zerumbone, it enhanced the protective effects.[103]

Saffron (番紅花 Fān Hóng Huā)

Saffron, scientifically known as Crocus sativus L. and belonging to the family Iridaceae, is a perennial stemless herb widely cultivated in Iran, Pakistan, India, and Greece.[104-106] The stigmas are the most important plant part and are dried and sold as saffron.[106] Saffron has been used to treat depression, cancer, and cardiac ailments. It is used in various traditional and folk systems of medicine in the Arabian countries and in the Indian subcontinent.[106-109] Phytochemical studies have shown that the medicinal and organoleptic properties are due to the presence of crocetin [Figure 1], crocin, picrocrocin, and safranal.[106-109] Crocetin, an important carotenoid of saffron, has been widely studied in the prevention and as a therapy for cancer.[110]

With respect to saffron's effectiveness in UC, studies have shown that oral administration of crocetin to mice [Figure 1] (25-

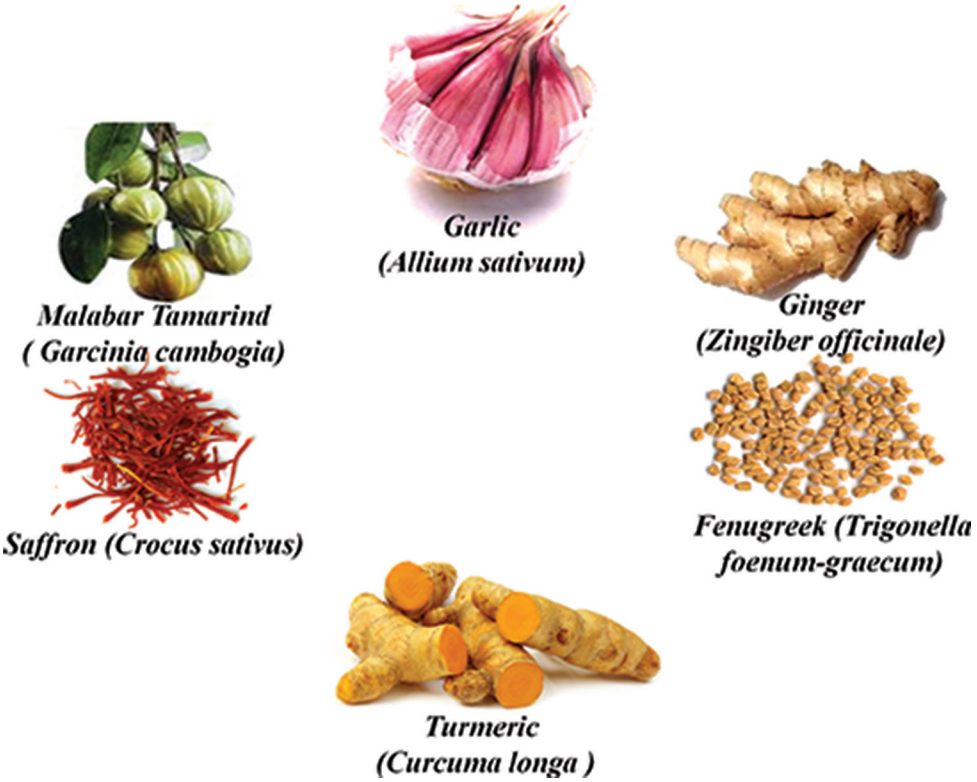

Figure 3. Indian medicinal plants reported to afford protection against inflammatory bowel disease in experimental studies

100 mg/kg b. wt. per day) for 8 days significantly ameliorated TNBS-induced UC.[111] The animals administered crocetin had reduced diarrhea and disruption of colonic architecture. Optimal effects were observed at 50 mg/kg/day dosage. Crocetin-treated mice had reduced levels of NO, neutrophil infiltration, and lipid peroxidation in the inflamed colon, favorable expression of TH1 and TH2 cytokines, and down-regulation of NF-κB. These observations indicate that crocetin exerts beneficial effects in experimental UC.[111]

Malabar tamarind

Garcinia cambogia, also known as Malabar tamarind, is a plant mostly utilized in India and parts of southeast Asia for its culinary uses and therapeutic effects.[112, 113] The fruits, which are the most important part, resemble a miniature pumpkin and are used as an acidulant in the curries and to prepare sherbat. Its main component is hydroxycitric acid (HCA), which is an inhibitor of adenosine triphosphate (ATP) citrate lyase that reduces the biosynthesis of fatty acid and thus aids in weight reduction.[114,115] The decoction of the fruit is an essential preparation to treat ulcers and inflammation. It has been shown that the fruit extract possesses hypolipidemic properties and anti-adipogenic and appetite-suppressor effects.[116,117] A recent finding suggests that the extract blocked TNBS-induced colitis in rats by preventing epithelial damage, decreasing the activity of MPO, decreasing the expression of COX-2 and iNOS, reducing colonic PGE2 and IL-1β levels, and reducing epithelial cell DNA damage.[117]

Fenugreek

Trigonella foenum-graecum, colloquially known as fenugreek and belonging to the Fabaceae family, is an important dietary and medicinal agent.[118,119] The plants are native to India and northern Africa and have been used in the various traditional and folk systems of medicine to treat numerous indications, including labor induction, aiding digestion, and as a general tonic to improve metabolism and health.[119] Scientific studies have shown that fenugreek possesses pleiotropic actions and is useful in the amelioration of hypertension, cataract, inflammation, thyroid dysfunction, malaria, endothelial dysfunction, hyperlipidemia, and diabetes.[119]

With regard to its protective effects, animal studies in colitis have shown that saponin diosgenin [Figure 1], a compound in fenugreek, suppresses inflammation.[120] Diosgenin was also found to suppress ovalbumin-induced intestinal allergic reaction; gut inflammation, which reduced the frequency of diarrhea; infiltration and degranulation of mast cells; and increased the presence of mucin-containing goblet cells in mice's duodenum.[121] Furthermore, diosgenin reduced the crypt depth in the intestinal epithelium and inhibited systemic ovalbumin-specific IgE and total IgE.[121] Another anti-inflammatory property of diosgenin is that it suppresses TNF-induced NF-κB activation as determined by DNA binding, activation of IκBa kinase, IκBa phosphorylation, IκBa degradation, p65 phosphorylation, and p65 nuclear translocation through Akt inhibition.[120] It also down-regulated TNF-induced expression of NF-κB–regulated gene products involved in cell proliferation (cyclin D1, COX-2, c-myc) and anti-apoptosis (IAP1, Bcl-2, Bcl-XL, Bfl-1/A1, TRAF1, and cFLIP).[120]

Turmeric (薑黃Jiāng Huáng)

Curcuma longa Linn., a perennial shrub belonging to the family Zingiberaceae, is an indigenous plant of India, but is also cultivated in China, Sri Lanka, and other tropical countries nowadays.[122] The roots are the most important part of the plant and are used as a religious, culinary, and medicinal agent in India.[122] Turmeric is one of the highly investigated plants and studies have shown it to contain curcuminoids like curcumin [Figure 1], Desmethoxycurcumin, bisdemethoxy curcumin, monodememthoxy curcumin, dihydro curcumin, and cyclocurcumin.[122] Curcumin has been shown to possess potent antioxidant,[123] anti-inflammatory,[124] and cytoprotective effects.[125]

With respect to its protective effects in UC, numerous preclinical studies have shown that when administered orally or systemically, either as a prophylactic or curative agent, curcumin improved the survival rate, and decreased the wasting and discomfort induced by various ulcerogens, such as DSS,[126-130] dinitrobenzene sulfonic acid (DNB),[131] dinitrochlorobenzene (DNCB),[132] TNBS,[133,134] acetic acid, and also in genetically predisposed IL-10–knockout[135,136] and mdr1a-/- mice.[137,138] The results from these observations have all been summarized in Table 1.

At the tissue level, curcumin decreased the macroscopic scores of mucosal erosions significantly.[139] It has the property of scavenging the free radicals, influencing multiple signaling pathways, especially involving the kinases, extracellular signaling kinase (AKT, MAPK,ERK), inhibiting COX-1, COX-2, lipoxygenase,[140] TNF-α, IFN-γ, iNOS, inhibiting transcription factors such as NF-κβ and AP-1, and modulating Nrf2-dependent cytoprotective pathways.[137] Cumulatively, these studies strongly indicate that curcumin is a promising medication for improving remission in IBD patients and that randomized controlled clinical investigations in large cohorts of patients are needed to fully evaluate its clinical potential in the treatment of IBD.[137]

The most encouraging observations were accrued from a clinical study where curcumin (360 mg) reduced the relapse episodes in patients with quiescent IBD, when administered three or four times a day for 3 months.[141] Additionally, recent studies by Suskind and coworkers have also shown that curcumin was well tolerated at a high dose by children with IBD. In the study, the investigators prescribed 500 mg of curcumin twice per day for 3 weeks along with the standard therapy, and then by using the forced-dose titration design enhanced the curcumin doses to 1 g twice per day at week 3 for a total of 3 weeks and then to 2 g twice per day at week 6 for 3 weeks. At the end of the study period, it was observed that all patients tolerated curcumin well and that the only untoward symptom observed was increase in flatulence. The authors also observed that combining curcumin with the standard therapy resulted in the improvement of Pediatric Crohn's Disease Activity Index (PCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI) score and suggested that curcumin may be useful as an adjunctive therapy in IBD.[142]

Table 1. List of articles published on the protective effects afforded by curcumin in IBD in experimental animals with emphasis on the mechanism/s of action

Inducing agent	Animal model reference	Results and observations
Dextran sulfate sodium (DSS)	Swiss albino rats[126]	Treatment with curcumin before DSS administration decreased the colonic bloody diarrhea and increased the colonic length as well as decreased hyperemia produced by DSS alone A 37% reduction in the relative colonic weight/length ratio and reduction in severe submucosal edema, erosion, ulceration, inflammatory cell infiltration and crypt abscesses 46% decrease in the concentration of serum TNF-α, 57% in MPO activity, 56% in lipid peroxidation and 65% in NO levels. 117% increase in GSH and 79% in GST
	BALB/c mice[127]	Curcumin reduced levels of MPO activity, number of infiltrating neutrophils, as well as CD4 and CD8 T cells and blocked NF-κB activation in infiltrated inflammatory cells and epithelial cells
Dinitrobenzene sulfonic acid (DNB)	C3H mice[131]	Curcumin attenuates activation of p38 MAPK and immunohistochemical studies confirmed that the effect was especially at the level of the mucosa
Dinitrochlorobenzene (DNCB)	Wistar rats[132]	Treatment with NCB-02 showed a dose dependent protection against DNCB-induced colonic damage as indicated by normalization of colon length, reduction in colon weight both total and distal colons) NCB-02 at a dose 100 mg/kg b. wt. inhibited the DNCB-induced expression of NFκ-B and iNOS
Acetic acid	Rats[163]	Co-administering curcumin decreased the activity of colonic MPO, levels of MDA and prevented programmed cell death Curcumin restored immunreactivity of MAPKs in the colons of colitic rats
Trinitrobenzene Sulfonic Acid	BALB/c mice[164]	Curcumin significantly reduced the loss in body weight, decreased the extent and severity of the injury of the large intestine Curcumin pretreatment caused decrease in the elevated levels of both NO and superoxide production, decreased lipid peroxidation, MPO and serine protease activity Curcumin pretreatment suppressed IFN-γ and IL-12 p40 The iNOS mRNA expression and the NF-κB DNA binding activity was decreased by curcumin pretreatment
	Rats[165]	Curcumin therapy decreased the expression of proinflammatory and inflammatory cytokines and improved expression of PPARγ Curcumin therapy decreased the expression of COX-2 and increased the expression of PGE2 and J2 (15d-PGJ2)
	C57BL/6 mice[166]	Reversed the effects of TNBS on Phex gene expression by attenuating the transcription of TNF-α which then contributed towards counteracting of the detrimental effect of TNBS on Phex gene expression[166]
	TNBS-induced colitis and carbachol-induced colon contraction in Sprague Dawley rats[167]	Curcumin had no effect on sensitivity of the colon to carbachol but reversed the decrease in carbachol-induced contraction associated with trinitrobenzene sulphonic acid treatment
Tumor necrosis factor alpha TNF-α	Male NMRI mice [168]	Curcumin reduced the TNF-α-induced colitis in mice by decreasing the levels of myeloperoxidase, nitrites and malondialdehyde, and apoptosis
Transgenic animals	IL-10 knockout mice[135]	Proximal and distal colon morphology showed a mild protective effect of curcumin only at 0.1%. IL-10 and curcumin act synergistically to downregulate NF-κB activity in IEC and IL-12/23p40 production by splenocytes and dendritic cells
	mdr1a-/-) mice[138]	Curcumin alleviated colonic inflammation and reduced the histological injury

DNCB: Dinitrochlorobenzene, NMRI: National medical research institute; TNBS: Trinitrobenzene sulfonic; TNF: Tumor necrosis factor; GSH: Glutathione S-transferase; IEC: Intestinal epithelial cells; GST: Glutathione S-transferase; iNOS: Inducible Nitric oxide synthase; MPO: Myeloperoxidase

PHYTOCHEMICALS WITH BENEFICIAL EFFECTS

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a phytoalexin produced by several plants including grapes, peanuts, mulberries, raspberries, and blueberries.[143,144] Its polyphenolic compound possesses multiple pharmacological benefits.[145,146] Preclinical studies provided evidence that resveratrol is effective in preventing DSS- and TNBS-induced colitis in mice and rats, respectively.[145-148] It was also shown that resveratrol (300 ppm) reduced the tumor burden of AOM + DSS-induced colorectal inflammation and cancer in mice.[147]

In 2010, Sánchez-Fidalgo and coworkers observed that mice fed with a diet enriched with 20 mg/kg of resveratrol for 30 days and administered 3% DSS for 5 days showed lower clinical scores, lower inflammation, and an increase in survival rate, as compared to the DSS-treated mice which were fed control diet. Therefore, resveratrol can be linked to a better disease prognosis in case of acute UC. Subsequent studies have also shown the ability of resveratrol to halt the weight loss and reduce the colonic inflammation in mice treated with DSS[145,147] and rats treated with TNBS.[146] It also causes a concentration-dependent reduction in inflammation.

Mechanistically, resveratrol decreases the percentage of neutrophils in the mesenteric lymph nodes and lamina propria[147] and modulates the number of CD3 (+) T cells[147] and down-regulates inflammatory and stress markers, namely p53

and p53-phospho-Ser (15) proteins.[147] Resveratrol prevented the depletion of glutathione[146] and reduced the levels of MPO[145,146] and lipid peroxides in the colon,[145,146] concomitantly increasing the activities of SOD and GSH-Px in the colonic tissue.[145]

- Furthermore, studies have been successful in showing a decrease in the expression levels of TNF-α,[145,147,148] IL-1β,[148] IFN-γ,[145,147] IL-8,[145] p22(phox),[145] and gp91(phox),[145] and an increase in the levels of the anti-inflammatory cytokine IL-10[148] with resveratrol administration. Additionally, resveratrol also caused a reduction in the levels of PGE synthase-1 (PGES-1), COX-2, and iNOS protein expressions by down-regulation of p38-mediated MAPK signaling pathway[148] and suppressing intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) levels in the colon and serum.[146]

Quercetin

Quercetin [2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one] [Figure 1] is a flavonoid ubiquitously found in fruits, vegetables, leaves, and grains, and is one of the highly investigated phytochemicals.[149] It is a glycone form of a number of other flavonoid glycosides, such as rutin and quercitin, found in citrus fruit, buckwheat, and onions. Quercetin possesses many pharmacological benefits, including scavenging the free radicals, and has antioxidant and anti-inflammatory properties.[150] Animal studies have shown that quercitin (1 and 5 mg/kg) is effective when administered in the early stages (24 h) of TNBS-induced colitis.[151] Biochemical end points showed that treatment with the flavonoids prevented an increase in colonic MDA, inhibited iNOS and alkaline phosphatase activities, but had no significant effects on observable damage. However, histopathologic observations showed no changes in the neutrophil infiltration.[151]

Kaempferol

The flavanoid kaempferol [3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] [Figure 1] is ubiquitously present in many edible plants such as broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes, and in plants or botanical products commonly used in traditional medicine (e.g. *Ginkgo biloba*, *Tilia* spp, *Equisetum* spp, *Moringa oleifera, Sophora japonica*, and propolis).[152] Myriad preclinical studies have shown that kaempferol and some of its glycosides have a wide range of pharmacological activities, including anticancer, antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anti-osteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic activities, and cardioprotective, and neuroprotective activities.[153]

With regard to its role in UC treatment, recent studies by Park *et al*.[165] have shown that feeding kaempferol (0.1% or 0.3%) was effective in decreasing the DSS-induced colitis in mice. They found lower levels of plasma leukotriene B4 (LTB4) in all the groups fed kaempferol, while the levels of NO and PGE2 and the activity of MPO in colonic mucosa were significantly decreased in 0.3% kaempferol pre- and post-fed groups. Additionally, the level of Trefoil factor 3 (TFF3) mRNA, a marker for goblet cell function, was up-regulated in kaempferol pre-fed animals indicating its usefulness.[154]

Rutoside or rutin

Rutoside, also known as rutin, quercetin-3-*O*-rutinoside, or sophorin, is a flavonol glycoside between quercetin and the disaccharide rutinose [α-l-rhamnopyranosyl-(1 → 6))-β-d-glucopyranose] [Figure 1]. It is found in many plants such as buckwheat, tobacco, forsythia, hydrangea, and viola, and has important pharmacological effects.[155] Studies revealed that oral pre- and

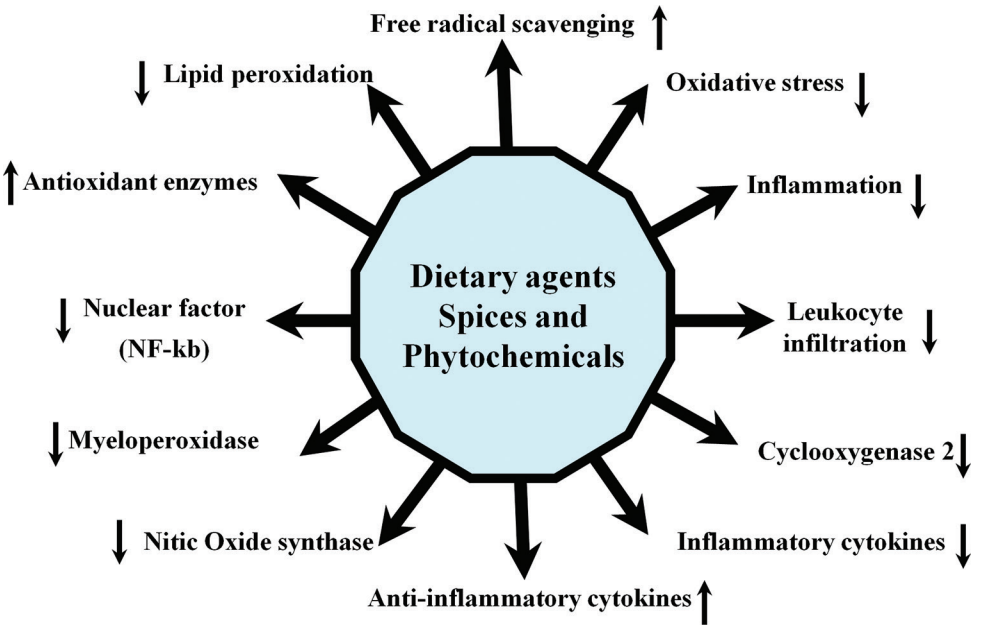

Figure 4. Molecular targets affected by various dietary agents and their phytochemicals in the prevention/amelioration of ulcerative colitis. ↑, increase; ↓, decrease

post-treatment of rutoside (10 or 25 mg/kg) was effective in ameliorating TNBS-induced colitis. It promoted colonic healing in rats[156] by increasing the levels of colonic glutathione and reducing the levels of colonic oxidative stress.[156] In another study, a diet containing 0.1% rutin, but not quercetin, ameliorated 5% DSS-induced body weight loss and shortening of the colorectum, and dramatically improved colitis histological scores in ICR mice.[157] Importantly, pretreatment with rutin for 2 weeks or therapeutic post-treatment for 4 days starting 3 days after DSS administration was shown to produce significant beneficial effects by attenuating proinflammatory gene expression levels, namely IL-1β and IL-6, in colonic mucosa, in a dose-dependent manner.[157]

Naringenin

One of the major polyphenols isolated from the citrus fruit is naringenin. It has been shown to possess nephro- and hepatoprotective,[158] antioxidative,[159] anti-inflammatory, and anticancer[160] properties, as suggested by several cell- and animal model–based studies. Naringenin was found to be effective in reducing the lead-induced oxidative stress in rat models by increasing the activities of SOD, CAT, and GPx.[69,159] It reduces inflammation by inhibition of pro-inflammatory cytokines NF-κB and COX-2 and phosphorylation of transcription factor proto-oncogene–encoded AP-1 in macrophages in lipopolysa ccharide (LPS)-induced model.[161] Naringenin ameliorates the DSS-induced colitis by reducing colonic damage, shortening the colon length, protecting the tight junction barrier, and decreasing pro-inflammatory cytokines' expression, especially those of IFN-γ, Il-6, MIP-2, and IL-17A.[162] These *in vivo* and *in vitro* studies make naringenin a strong contender for clinical studies for colitis and other related disease models.

CONCLUSIONS

A number of dietary supplements and phytochemicals are widely used in preventing or alleviating the symptoms of UC in experimental animal models [Graphical summary]. Studies on the efficacy and mechanism of various dietary plant extracts and pure phytochemicals in this field are reviewed and highlighted here [Figure 4]. Such evidence-based updated information is very important for IBD patients and healthcare providers to make informed decisions about the benefits and limitations of the use of dietary bioactive compounds. We also emphasize the need for further clinical studies assessing the long-term efficacy and safety of most commonly used dietary bioactives in UC. Studies providing deeper mechanistic insights using *in vitro* systems and *in vivo* animal models will also be equally important to help develop better compounds or combination therapies ultimately aimed at the development of more optimized, robust, and safer treatment strategies in future based on natural dietary supplements and phytochemicals. There is a need for more clinical studies to declare these bioactive compounds as completely safe and effective.

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All authors have read and approved the final manuscript.

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