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Review Article

Amelioration of Colitis from Nature and its Immunological Implications: Current and Future Perspectives

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Abstract

Inflammatory Bowel Disease (IBD) is a chronic immune-mediated inflammatory condition of the intestine. IBD is characterized by abdominal pains, diarrhea, fever, chills, cramps, and bloating and if not properly managed, it can be life-threatening. Interestingly, medicinal plants have been identified and validated to attenuate this condition due to the presence of natural products using different animal models via aryl hydrocarbon receptor and Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) signaling pathways. This review briefly discusses some of the natural products and medicinal plants, that can be used and developed as therapeutics for IBD treatment coupled with their immunological consequences. It recommends the need to use computational approaches to identify novel targets as well as the synthesis of structural analogs of endogenous ligands and natural products that are modulators of the identified and novel molecular targets coupled with the profiling of their biological activities and side effects.

Keywords: Colitis, Medicinal plants, Natural products, Aryl hydrocarbon receptor, Immunology

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC), are two major forms of Inflammatory Bowel Disease (IBD) a chronic immune-mediated inflammatory condition of the intestine. IBD, is characterized by abdominal pains, diarrhea, fever, chills, cramps, and bloating and if not properly managed, it can be life threatening (89). As a matter of fact, it has affected millions of people and its prevalence is on the increase everyday (1). IBD has been considered to be an autoimmune disease; a situation where the immune system dysregulates in certain part of the gastrointestinal tract and induce inflammation. (2,3). Ulcerative colitis may begin in the rectum and extend to the rest of the colon while Crohn disease can occur

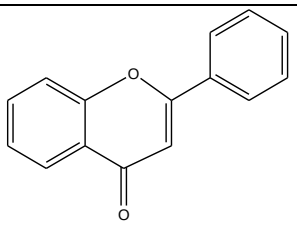
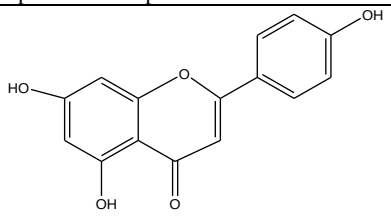
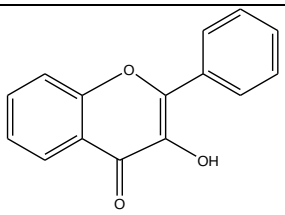
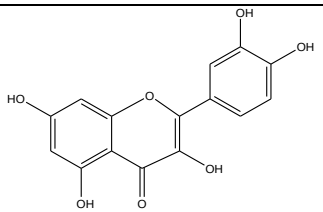
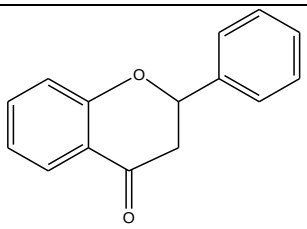
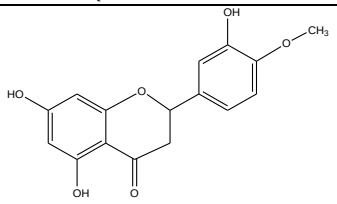
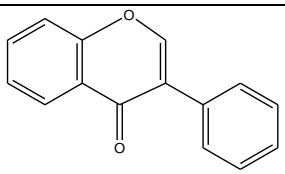
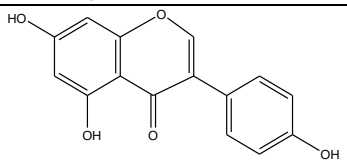
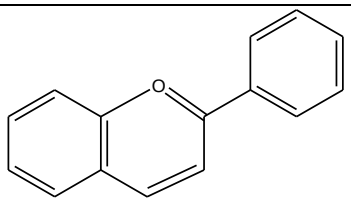
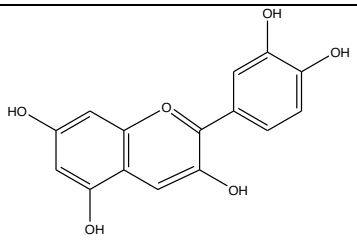
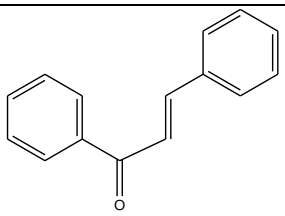
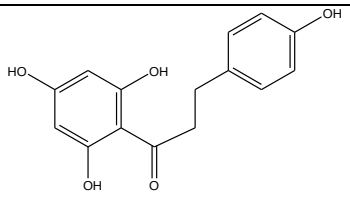
anywhere in the gastro intestinal tract. However, other organ systems may be involved. Although colitis is of inflammatory origin, there may be interplay of bacterial infections such as *E coli*, *Salmonella spp*, *Camphylobacter spp*, parasites and viruses which will invariably demand for an antibiotic therapy. Surprisingly, genetic and environmental influences are also involved in the pathogenesis of colitis but its etiology is not fully understood (3).

Interestingly, because of the diversity of nature, medicinal plants have been a platform for the treatment of various inflammatory diseases in different cultures of the world. As a matter of fact, medicinal plants have been scientifically proven to possess ranges of beneficial pharmacological and therapeutic

Table 1: Pharmacological and biological activities of selected medicinal plants and reported natural products.

Medicinal Plants	Morphological Parts	Compounds Isolated	Reported Biological Activities	References
Anacardium occidentales	leaves,cashew fruit, cashew apple juice	Agathisflavone, Quercetin-3-O-rhamnoside, Anacardic acids, 2-methylcardols	Antioxidant, antibacterial, cytotoxic	**(6-8)**
Ixora coccinea	Flowers, leaves, roots	Ixoroid Ursolic acid Ixoratannin A-2 Procyanidin A2 Cinnamtannin B1	Antioxidant Antimicrobial Anti-genotoxic Antinociceptive Catarrhal bronchitis Antileishmanial	**(9-11)**
Terminalia arjuna	Bark	Procyanidine, Arjunolic acid	Molluscicidal Anti acetylcholinesterase	**(12)**
Vernonia amygdalna	Flowers, leaves	Tricosane Vernolide Isorhamnetin Luteolin Vernolide Vernodalol	Antioxidant Neuroprotective Anti-alzheimer Anti-microbial Anti-lipid	**(13-15)**
Camella sinensis	leaves, flowers	Teadenol A Teadenol B Caffeine, myricetin-rhamnodiglucoside teasperol teasperin theaflavins thearubigins	Antioxidant, Antibacterial Cytotoxic Anticaries Antiparkinson Cardiovascular Anti-HIV	**(16-20)**
Chochorus olitorius	Leaves	Caffeic acid Chlorogenic acid Isorhamnetin	Antioxidant Hypoglycemic Hypolipidaemic Anti-hypertension Immunomodulatory	**(21-24)**
Mangifera indica	Stem bark,leaves, Seed	Tricuspid Mangiferin Tetragalloylglucose Ellargic acid Iriflophenone glucoside	Anti-fungi Analgesic Anti-inflammatory Antioxidant Immunomodulatory antiplatelet	**(25-28)**
Curcuma longa	Rhizome	Curcumin	Anti-inflammatory	**(29, 30)**
Azadirachta indica	Stem bark,leaves	Neemazal Azadirachtin A Azadirachtin B Nimbin Salannin	Antimicrobial Antimalaria	**(85, 86)**
Zingiber officinales	Rhizome	Terpens 4-gingerol 6-dehydrogingerdione	Antioxidant Antiinflamatory Anticoagulant Antimicrobial	**(87, 88)**

Figure 1. Classification of flavonoids with specific examples.

Flavonoid Classes	General Structures	Specific Examples
FLAVONE		 APIGENIN
FLAVONOL		 QUERCETIN
FLAVANONE		 HESPERETIN
ISOFLAVONE		 GENISTEIN
ANTHOCYANIDIN		 CYANIDIN
CHALCONE		 PHLORETIN

This figure is modified (31)

purposes ranging from antiviral, antioxidant, anti-inflammatory, antiinflammatory,antihypertensive, immunostimulating, cytotoxic and antibacterial properties (4, 5). Furthermore, the highlighted pharmacological and biological activities are mediated by the presence of one or more natural products and metabolites in the plant ranging from flavonoids, saponins, tannins, alkaloids, polyphenols, anthraquinones. This claims have repeated been validated by phytochemical screenings, bioassay

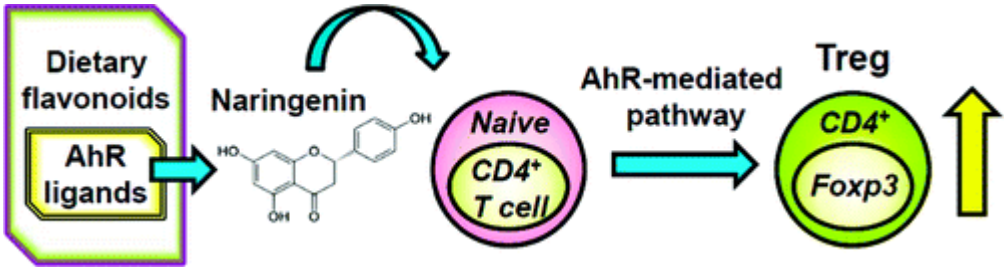


Figure 2. Immunological response mediated by the activation of Aryl hydrocarbon receptor by a dietary flavonoid.

guided fractionations and the use of animal models (6). In this review we will briefly discuss on some of the natural products and medicinal plant that can be use and develop as therapeutics for IBD treatment coupled with their immunological consequences.

Flavonoids and its diversity

One of the most common alternative medicine compound groups comes from Flavonoids. Flavonoids are a group of polyphenolic compounds, diverse in chemical structure and characteristics, found ubiquitously in many plants. Therefore, flavonoids are part of the human diet in many countries around the world. The structural requirements for the antioxidant and free radical scavenging functions of flavonoids include a hydroxyl group in carbon position three, a double bond between carbon positions two and three, a carbonyl group in carbon position four, and polyhydroxylation of the A and B aromatic rings (32). Flavonoids also widely occur in Fabaceae, Polygonaceae and Rosaceae families.

Flavonoids have been identified to ameliorate colitis. Specifically, Extracts containing eupatilin and quercetin-3-β-D-glucuronopyranoside ameliorated the inflammatory response and colonic injury in acute colitis by decreasing oxidative stress and neutrophil activation (90).

There are different classes of flavonoids ranging from flavones, flavanones, flavonols, isoflavones, biflavonols and each of the chemical compounds have a characteristic modulatory effect of the aryl hydrocarbon receptor; a target that is indicated in the inflammatory pathway of the IBD as well as in many autoimmune diseases. Some of the compounds are proven to be inhibitory and some are stimulatory (32). Hence, there is a need to identify medicinal plants that are more richer in the flavonoids with stimulatory effect which can invariably be of help in the formulation of herbal medicines.

Aryl Hydrocarbon Receptor

Aryl hydrocarbon receptor is a transcriptor factor embedded in the cytosol with functioning domains and binding sites (33, 34). Reports have shown that there is high expression of it in the liver, kidney, placenta, lungs, thymus (35). The AhR and its nuclear translocator (ARNT) belong to the bHLH-PAS superfamily of transcription factors, the acronym for basic Helix-Loop-Helix and Periodic (PER)-ARNT Single minded (SIM) (36). AhR is capable of exhibiting a conformational changes and its ability of translocation to the nucleus to bind to its dimerization partner; nuclear translocator forms a complexes once activated by an agonist (37-39). The formation of complexes initiates the transcription of genes and other molecular events.

Aryl hydrocarbon receptor has been an evolving pharmacological target in the management in cancer, inflammation, autoimmune diseases and ageing (40, 41). It has plays a role in the induction of cytochrome P450 enzymes and other metabolizing enzymes such as cytosolic phospholipase and cyclooxygenase enzymes. Immunological, carcinogenic effects, inflammatory responses, endocrine disruptions has been linked to Aryl hydrocarbon receptor mediated activity (42). It has also been implicated in key physiological functions such as cell cycle regulations, resilience against stress, homeostasis, immunity and regulation of neural functions in vertebrate and invertebrates (43, 44). The functional diversities of this receptor has made it to be tagged a *"promiscuous receptor"* of chemical entities (45). However, the activity mediated by this receptor is ligand dependent and calls for a profiling of natural products in this regard. For example, when comparing the activity of apigenin, a flavone with its analogue genistein; an isoflavone there is a loss of agonistic effect. A

modification from position 2 to position appears to be the reason for the loss of the agonist effect (32). These non-general perspective was further strengthened when the interaction of 2,3,7,8-tetrachlorodibenzo-p-dioxin with aryl hydrocarbon receptor resulted into reduced experimental autoimmune encephalomyelitis (EAE) by promoting the development of Foxp3+ Treg cells, whereas 6-formylindolo(3,2-b) carbazole enhances EAE by inducing the differentiation of IL-17-producing T cells (46-48).

Immunological Dysregulations

In a bid to have an understanding of the immunological consequences associated with inflammation in IBD, it involves the use of different animal models. The approach has been to specifically delete the Aryl hydrocarbon receptor in T cells or Macrophages in mice and also the use of dextran sulphate sodium(DSS) or trinitrobenzenesulfonic acid (TNBS), to induce colitis in mice (49,50,51). Aryl hydrocarbon receptor is expressed in normal T cells, dendritic cells, macrophages and cells in the gut.

T Cells and Functions

T cells are vital player in the regulation of adaptive immunity, immune responses and tissue inflammation. Experimental and clinical evidence have also shown that chemokines and cytokines plays a crucial role in the regulation of colitis by promoting the migration of leucocytes to the site of inflammation leading to tissue disruption and damage (52). Data have also shown that there is a significant increase in the circulating level of specific chemokines and cytokines of colitis patients when compared to normal healthy subjects (52). The specific inflammatory cytokines are IL-16, IFN-γ, IL-1β and TNF-α (52). The inhibition of the activities of the inflammatory mediators can be explored to either ameliorate or reverse colitis symptoms.

Most major T cell types are expressed in the thymus, although extrathymic generation of some T cell subsets has been described (53, 54). T cells are classified into the major TCR-α β and minor γ δ T cell groups. αβ T cells are highly heterogeneous and grouped into CD4＋ conventional T cells, CD8＋ conventional T cells, NKT cells, and other innate TCRα - expressing T cells such as mucosal-associated invariant T (MAIT) cells (55,56,57,58). CD4＋ conventional T cells are further divided into FoxP3＋ regulatory and FoxP3− T cells (59,60). FoxP3− CD4 ＋ T cells include various effector and regulatory T cells based on their cytokine phenotype (IFNγ, IL-17, IL-22, IL-4, IL-9, IL-10, IL-35, and/or LAP-TGFβ1) (60,61). These T helper cells include IFNγ ＋ Th1 cells, IL-17/IL-22＋ Th17 cells, IL-4＋ Th2 cells, IL-9＋ Th9 cells, IL-21＋ T-FH cells, and IL-10/IL-35/ TGFβ 1＋ Tregs (61,62). All of these T helper cell subsets are generated mainly in the periphery from naïve T cells made in the thymus.

Driven by the conviction to dig into nature, *Pycnoporus sanguineus* (L) Murril is a saprotrophic fungus. Recently, polysaccharides from the plant have been reported to ameliorate colitis which manifested by the lowered disease activity index (81). The mechanism of action was also documented to be due to inhibition of helper T cells mediated immune response by decreasing the proportions of Th cells (including Th2 cells, Th 17 cells and regulatory T cells) with an accompanied reduction in myeloperoxidase (MPO) activities and release of several interleukins and chemokines within the colon.

Activation of aryl hydrocarbon receptor, a transcriptor factor by flavonoids plays a considerable role in the regulatory T cell (Treg) induction (63). The induction of this T cells regulate and suppress allergies and autoimmune disease; Crohn disease as a typical example

The activation of Aryl hydrocarbon receptor by flavonoids and its ability to ameliorate inflammatory conditions is also believed to be due to its free radicals scavenging effects, inhibition of oxidative stress and attenuation of Reactive Oxygen Species(ROS) (64, 65).

Table 2: Biological and Immunological Implications of Selected Natural Products.

Natural Products	Targets	Modulatory Effects	biological and immunological implications	References
Beberine	AMPK	Activation	1.Inhibition of oxidative phosphorylation 2. BBR suppressed inflammatory cytokines of LP CD4+ T cells from colitis SciD mice in vitro. 3 BBR increased the AMPK activity and regulated the IFN-γ and IL-17A secretion from colitis LP CD4+ T cells.	(68, 75)
Narigenin	Aryl hydrocarbon Receptor	Activation	Induction of regulatory T Cells	(63)
Resveratrol	Aryl hydrocarbon receptor,AMPK	Activation	Reduction of COX-2 expression,neutrophil mobilization Decrease mitochondrion fatty acid oxidation Decrease IL 6 expression and TNF-alpha release Activation of myeloid derived suppressor cells	(49, 75)
Quercetin	AMPK	Activation	Amelioration of IgE-mediated allergic intestinal inflammation	(75, 76)
Sinapic Acid	Antioxidant enzymes	Activation	Enhancing the activites of superoxide dismutase,glutathione peroxidase. Inhibition of Myeloperoxidase activites	(77)
Myricetin & Myricetin-3-O-B-d-lactose sodium salt	Intestinal microbiota	Normalization	Normalization of proportion of firmicutes and actinobacteria. Inhibition of pathogenic microorganisms such as Ruminococcus and Parabacteroides. Increase in probiotics such as akkermansia	(78)
Curcumin	Proinflammatory cytokines	Inhibition	Inhibition of IFN and TNF alpha Inhibition of COX-2 Obstruction of p38 MAPK signaling Reduction in the Infilteration of leucocytes	(29, 30, 75)
Epigallocatechin-3-gallate	Proinflammatory cytokines	Inhibition	Increase in antioxidant enzymes (SOD and GPO) activities. Inhibition of the production of proinflammatory cytokines	(75-80)

It is interesting that another new target in the pathogenesis of chronic colitis has been identified and reported (66-68). AMPK is an enzyme that plays a role different fundamental cellular processes, including the cell proliferation, survival and metabolism and in cellular energy homeostasis (69-71). Energy metabolism changes in immune cells have been identified to be crucicial for immune cells regulation. Recently, it was reported that Berberine, a traditional Chinese herbal medicine extracted from Phellodendron bark and *Coptis japonica* ameliorate chronic colitis through the activation of AMPK, inhibition of oxidative phosphorylation and suppression of the exaggeration of IFN-γ- and Il-17A-producing LP CD4+ T cells (68). Novel animal model (T cell transfer colitis model) which involves the transfer of naïve ($CD4+CD45RB^{high)}$ T cells into congenic immunodeficiency mice to induce CD4+ T cell-specific colitis were used to validate the claim (68, 72). Infact, it reflects the chronic inflammatory process. Although, several reports have used chemical agents like DSS to induce colitis (73, 74), it can only be used for acute colitis models.

Biological and Immunological Implications of Selected Natural Products

Carbon Monoxide (CO); an endogenously produced signaling molecules has been identified to be a promising therapeutic agent against inflammation and some form of cellular stress related diseases (83, 84). Although it is a pollutant produced by the incomplete combustion of carbon, it is a *"glorified"* pollutant.

Reports have shown its ability to ameliorate colitis and effort are ongoing to obtain its pharmacokinetic and clinical data and its delivery form optimization. CO was shown to downregulate pro-inflammatory cytokines TNF-α, IL-1β (82, 84).

Conclusion

Although, Aryl hydrocarbon receptor, AMPK are vital molecular targets in the pathogenesis of colitis, Computational approaches can be leveraged on to identify additional novel promising targets, multiple activators of receptor sites which can be characterized and exploited in drug design and discovery. A synergistic effect of chemical compounds that are of therapeutic value will be of help in this regard.

Furthermore, synthesis of structural analogues of endogenous ligands and natural products that are modulators of the identified molecular targets can be launched coupled with the profiling of their biological activities and side effects.

This report has shown the beauty of nature, target diversity and the abundant of natural products. Medicinal plants can be repurpose for this indication; colitis and some other known and evolving autoimmune diseases.

The medicinal value of dietary supplements, fruits, herbal medicines will complement the orthodox drugs in the management of colitis and other inflammatory disease to improve the quality of life of the patients and if need be, there can be a switch to nature if the side effects of orthodox drugs are pronounced.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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