Immunomodulation Activity of Hydroxyphenylpentanoic Acids and Hydroxyphenylpropanoic Acids

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An acknowledged therapeutic approach has been the immune functions modulation by the help of herbal vegetation as well as their products as a potential therapy. For the treatment of many illnesses and diseases, vegetation as well as minerals are being utilised since so long. Now it is recognised as the immunity modulation pertaining to the defence mechanism might offer a distinct option relating to various kind of illnesses to traditional chemotherapy, particularly, in case, when the host's mechanism of defence must get triggered within the circumstances of compromised defence response or else, in circumstances such as autoimmune disorders and organ transplantation, a selective immunosuppressant must be induced. Defence used to be a homeostatic system, a set of sophisticated, comprising of multiple cells as well as physiological processes which are delicately balanced, allowing a person to differentiate external particles by them as well as neutralise / remove external particles [1].

1. Immunomodulation

Developments in medical as well as untried field of study related to immunity intensely indicate that, due to stressful environmental factors associated with immune system suppression, many infectious diseases and disorders occur. This used to be evident as some forms pertaining to tension induce physical variations which impact the infection as well as malignancy susceptibility. In animals and humans, the ability to alter the immune response has emerged through the wish to provide better defence contrary to the infection causing agents by extensive and detailed comprehension pertaining to the working of the defence mechanism of the body as well as the methods by which non-specific as well as particular defence systems of the body have been evolved. Additional opportunities for modulating immune responses were provided by organically occurring or else manmade composites that are having the ability of changing certain systems [2].

1.1. Background

The branch of science which explores the immune system's structure and functions is known as immunology. It originates in medicine and early research at the reasons pertaining to illness tolerance. At the time of outbreak of plague in Athens in 430 BC, initially recorded mention of immunity was Thucydides observed it with no diminishing disease for the second time individuals that improved by previous bout pertaining to the pandemic, could nurture the people suffering from it [3]. In the 18th century, Pierre-Louis conducted scorpion venom trials plus found this venom was immune to some dogs and mice [4].

At the introduction of immunization in addition to the proposed germ theory, Louis Pasteur later used this and other findings of acquired immunity [5]. The theory of Pasteur was in direct contradiction to current disease theories, like the concept of miasma. This wasn't till evidence given by Robert K amidst 1891, intended for that, he got rewarded the Nobel Prize in the year 1905, as pathogens got deep-rooted as a reason pertaining to the transferable illness. During the year 1901, by the help of invention of yellow fever virus, viruses were reported as human pathogens.

2. Methods for testing immunological factors

The usual assays method consists of removing from herbal drugs a unitary component / a condensed portion, and evaluating the bioactivity of it by classical pharmacological methods. Most typical pharmacologic screening model is entire animal model, which used to be very important in the drug assessment aspect since this might obviously reply to effectiveness, ill effects and toxicity of drugs as a whole. Various in vivo, in vitro pharmacological screening procedures have been listed for medicinal plants having immunomodulatory activity [6].

2.1. *In-vitro* procedures

- Stopping the secretion of histamine by the mast cells
- The propagation of Mitogen which gets induced by lymphocytes
- Stopping the propagation of T-cells
- The chemiluminescence across the macrophages
- The PFC (plaque forming colony) assays *in-vitro*

- The stopping of dihydro-orotate dehydrogenase

2.2. *In-vivo* procedures:

- The natural autoimmune ailments in creatures.
- Critical general anaphylaxis in mice.
- The anti-anaphylactic activity (Schultz-Dale reaction)
- The passive dermal anaphylaxis.
- The delayed type sensitivity.
- Accessary arthritis in mice.
- Collagen type II induced arthritis in mice.
- Untried autoimmune thyroiditis

3. The immuno-stimulation process

The immunological protection used to be the complex interaction of non-specific then precise immune responses, the cellular then humoral resistant answers, immunocompetent cell activation also conquest, plus the effect on the immune system of endocrine and other pathways. T or B lymphocytes or the complement cell are the main targets of the immunostimulant, and an increase in macrophage and granulocyte phagocytosis plays a key role in immunostimulation [7]. In order to stay in contact with the reactive cell, the activation of macrophages is possibly necessary. Stimulus of T lymph cells, that may get accomplished, actively or else passively, through the macrophages, is the second most important task [8].

3.1. Immunosuppression

Across the auto immune disorders, hypersensitivity immune response, as well as the infectious agents of the diseases could be used to regulate pathological immune response. The full use of such agents for both the prevention of graft failure and prevention of autoimmune disorders has been removed from the list.

3.2. Allopathic drug immunomodulation

3.2.1. Immunosuppressant

Immunosuppression primarily means a reduction in infection tolerance, stress resistance and can arise due to environmental or chemotherapeutic influences [9].

The following are clinical immunosuppressant applications.

- It is used to suppress the refusal pertaining to tissues and the transplanted body parts.
- In bone marrow transplants, to prevent the graft versus host ailment (that is. the reaction of lymph cells across the graft to host the antigens).
- To treat a number of diseases that are thought to have a significant autoimmune aspect in their pathogenesis.
- The choosy immunosuppression in the treatment pertaining to the neonatal ailments, i.e., hemolytic Rh.

3.2.2. Immuno-stimulant agent

Idea of immune-stimulation involves a prophylactic or preventive concept directed at stimulating our non-specific immune system. This mainly implies the non-antigen-dependent stimulation of granulocyte, macrophage, complement and natural killer (NK) cell activity and performance.

3.2.3. Immuno-modulator drug side effects

Different ill effects are linked to usage pertaining to such medications, that is. The Myelosuppression, The Hepatic fibrosis, Pulmonary toxicity, Alopecia, elevated chances of cancer, hyperlipidemia, lymphoma, nephrotoxicity, toxicity of the neurons, Gastro Intestinal complaints, hyperglycemia as well as diabetes, kidney dysfunction, tremor, hypertension, hyperuricemia, hyperglycemia etc. [10].

3.3. Immunomodulation of medicinal plants

For their chemo-protective and immunomodulatory activities, the extracts of the plants which gets utilised in conventional treatment get assessed. Biological reaction inhibitors are immunomodulators; they achieve their antitumor impact by strengthening the pathways of host protection in case of cancer. It has a strong anti-proliferative result at the cancerous cells as well as therefore boost host's capacity of absorbing harmful substances that may be used to suppress cancer. For a number of diseased conditions, immunomodulatory treatment options may offer better other options to traditional chemotherapy, precisely when the defensive mechanisms of the host ought to get triggered within the circumstances of compromised defensive response or else

whence the selected suppression of the immune system needs to get persuaded in a circumstance like ailments, as well as the transplantation of the body organ or the bone marrow [11].

3.3.1. Carboxylic Acids

The carboxylic acid is having a carboxyl group bound to R-group. A carboxylic acid's overall formula is R-COOH, where R corresponding the alkyl group. It exists extensively. The Amino acids and fatty acids are significant examples of this.

Table 1: Straight-chain, saturated carboxylic acids

Total no of Carbon atoms	Name	IUPAC Name	Common location or use
1	Formic acid	Methanoic acid	Insect stings
2	Acetic acid	Ethanoic acid	Vinegar
3	Propionic acid	Propanoic acid	Preservative for stored grains, body odour, milk, butter, cheese
4	Butyric acid	Butanoic acid	Butter
5	Valeric acid	Pentanoic acid	Valerian plant
6	Caproic acid	Hexanoic acid	Goat fat
7	Enanthic acid	Heptanoic acid	Fragrance
8	Caprylic acid	Octanoic acid	Coconuts
9	Pelargonic acid	Nonanoic acid	Pelargonium plant
10	Capric acid	Decanoic acid	Coconut and Palm kernel oil
11	Undecylic acid	Undecanoic acid	Anti-fungal agent

12	Lauric acid	Dodecanoic acid	Coconut oil and hand wash soaps
13	Tridecylic acid	Tridecanoic acid	Plant metabolite
14	Myristic acid	Tetradecanoic acid	Nutmeg
15	Pentadecylic acid	Pentadecanoic acid	Milk fat
16	Palmitic acid	Hexadecanoic acid	Palm oil
17	Margaric acid	Heptadecanoic acid	Pheromone in various animals
18	Stearic acid	Octadecanoic acid	Chocolate, waxes, soaps, and oils
19	Nonadecylic acid	Nonadecanoic acid	Fats, vegetable oils, pheromone
20	Arachidic acid	Icosanoic acid	Peanut oil

3.3.1.1. Uses of Carboxylic Acids

The carboxylic acids are substances that arise spontaneously at various life cycle stages or may get formed in research laboratory or on a wide scale production by the oxidation reactions of aldehydes, the primary alcohols as well as the hydrocarbons plus the oxidative cleavage of olefins in addition to the catalysed alcohol dehydrogenation or by oxidation of alcohols. In our contemporary society, organic acids play a major and varied function, as demonstrated by many uses across the fields related to pharmacy, livestock, medicines, poultry, plus different others also.

In the assembling of biopolymers, polymers plus cements, coatings, as well as remedy items, carboxylic acids with their byproducts gets utilized. These may likewise be utilized as solvents, antimicrobials, food added substances, and flavorings. In the food sector, organic acids play a significant role because they influence organoleptic characteristics (e.g., flavor, scent as well as color) plus consistency of eatable goods. Degree as well as type of these acids contained amidst the foods plus beverages offer appropriate data in consideration of tracking fermentation processes,

checking the stages of processing, storage and delivery, or detecting potential adulteration steps. For classifying with measuring concentrations pertaining to various acids found in the foods as well as drinks, analytical techniques must be continually established and implemented specifically for this reason. In terms of the composition and validity of goods, the liquor industry (juices and drinks) is one of the most managed and monitored industries.

These are regarded to be powerful stabilizers, as well as the antimicrobial activity get attributed toward their capacity for moving from the attached to a detached shape, rendering them effective antimicrobial agents based on the environmental pH. For starters, with stopping the further growth of fungus and bacterial load, certain natural salts like Na and Ca propionate, avoid decay and are utilised in the form of a preserving agent in milk as well as other eatables. They though keep positive impact at the microbes, aiding the development and serving like bacterial dietary vitamins. Over the years, numerous experiments have been performed at the inhibiting impact pertaining to different natural acids at the polyphenol oxidase (PPO), which is considered as an enzyme responsible for the browning of burned fruits as well as vegetables.

The good effects of such investigations used to have a good financial effect on eatable goods, simultaneously it is important to retain the good quality plus prolong the shelf life of products [12]. Across pharmaceutical fields, carboxylic acids also play a significant function. The organic acids are intermediate derivatives of entire major classes related to the natural cellular constituents; their excess existence in different fluids of the human body has been shown repeatedly to be related to the demonstration of some illnesses. Carbon-based acids are markers of biological aciduria correlated to distinct natural protein absorption failures. 65 + renowned circumstances now a days are attributed to enzyme dysfunction in the mechanisms of metabolism of amino acids, leading to a rise in circulating or excreted urinary organic acid concentration.

This poisonous aggregation of absorbents that are absent in the body due to physical circumstances induces a psychiatric disorder comparable to intoxication. For diagnosis, the pattern of urinary organic acid formed from these metabolic anomalies is important. Homo-Vanillic acid (HVA) as well as Vanillyl-Mandelic Acid (VMA) levels in the body fluids, for example, get utilised in evaluation pertaining to disabilities and nervous illness conditions. Metabolic fingerprint experiments integrate alternate, less effective fatty acid reduction mechanisms (leading to higher amounts of adipic and suberic acid in urinary excretion) with conditions such as autism.

In clinical samples, the levels of succinic acid suggest the presence of a microbial ailment with no likelihood pertaining to discriminating among the forms of air-requiring as well as not requiring bacteria. In essential areas related to metabolism, quantification of carbonic acid of body fluids may offer valuable data: the metabolism of neurotransmitter, GI activity, metabolism related to the cellular energy, for the goal of an early detection of multiple disorders, metabolism of the mitochondria, plus Amino Acid equilibrium. Pharmaceutical sector often profits from the presence of carboxylic acids and their roles. Chemical character of the operational group is used to clarify the significance of these acids as well as the byproducts at this huge industry of healthcare.

In pharmaceuticals, significant roles these acids perform used to be:

- The solubilizer that modulates the absorbability, as well as lipophilicity, plus cell permeability (e.g., classes of antibiotics / antihistamines);
- Prodrugs and/or bio-precursors that function as molecules that are not clinically active but transformed under particular circumstances into active compounds (e.g., antihypertensive, anti-thrombotic or antiviral drugs);
- Pharmacophore offers complex enzyme interactions that activate or inhibit its biological reaction.

Drugs containing carboxylic acids play a significant part in the medicinal management of aching as well as ailments [13]. Carboxylic acids also get utilized in additives across cosmetics in large range of utilities. Organic Class alpha hydroxy acids are acids that play an important function in the cosmetic industry. Citric, malic, tartaric, & lactic as well as glycolic acids are relatively well known and thus are widely included in cosmetics for purposes like unclogging pores, boosting skin attractiveness, whitening, anti-wrinkle, or acne care. Aldobionic acid (ABAs), retinoic acid, vitamin C and azelaic acid are among the most powerful carboxylic acids in providing defense against antioxidants and anti-aging, as well as improving moisture conservation. The esters based on carboxylic acid are a very well compounds for their flavors and fragrances and are widely found in various products, including perfumes, plus deodorants. The fatty acids are a type of carboxylic acids popular by their use in the cosmetic industry and their water-soluble salts (soaps) have been used since ancient times as cleansers and are the most useful surfactants known.

3.3.2. Propionic acid

It is an organic acid having the $CH_3CH_2CO_2H$ formula. This substance is very close to body odour with a pungent and irritating scent. The $CH_3CH_2CO_2$ anion along with propionic acid salts & esters are famous in the form of propionates or propanoates. It is water-soluable, so by incorporating the salt, it can be separated from the water. As in acetic and formic acid, in both the liquid and the vapour, it comprises of hydrogen bound pairs of molecules. The general properties of carboxylic acids are expressed in propionic acid: amide, ester, anhydride, and chloride variants can form. The Hell-Volhard-Zelinsky reaction includes the alpha-halogenation of carboxyl group catalyzed by phosphorus tribromide to bromine, throughout this situation to form 2-bromopropanoic acid, $CH_3CHBrCOOH$. This compound was used to prepare a racemic alanine ammonolysis mixture [14].

3.3.2.1. Human occurrence

Several types of propionibacteria are present on human skin. The most prominent is Cutibacterium acnes that resides predominantly in the skin's glands and is key triggers of acne [15]. Propionate used to be most abundant SCFAs formed by gut microbiota in the large intestine [16]. A research in mice indicates that propionate is generated in the gut by Bacteroides, as well as some defence in protection from microbe Salmonella [17]. One more research suggests propionate fatty acids will relax the defensive cells which push up the BP, hence shielding the physique by harmful high BP results.

3.3.3. Pentanoic acid

The straight-chain alkyl acids having a chemical formula $CH_3(CH_2)_3COOH$ is pentanoic acid. It has an irritating odour, as most low-molecular-weight acids. It is present in *Valeriana officinalis*, a perennial evergreen tree that originally comes from that too. These salts are the key use in the production of its esters, and esters are referred to as pentanoates. Volatile esters of it tend to provide strong scents and are used in perfumes and cosmetics. Due to the fizzy tastes, some are used as dietary supplements.

3.3.3.1. Uses

It appears organically in certain eatables yet it is often utilised like a food preservative [18]. An FAO and WHO panel checked its protection in this application, finding of no safety issues regarding likely amounts of consumption [19]. Its esters that have good odour and fruity tastes, unlike the parent acid, and it is utilised for the formulation of byproducts. It is a slight produce of the abdominal microbes in humans [20] plus may be manufactured from the digestion of the esters contained across the food. Revival pertaining to this acid, levels in the abdominal cavity is suggested like a system which leads to the control the infection caused by clostridioides difficile after transplanting faecal microbes. These types of carboxylic acids are having some immunomodulation activity which can be illustrated as follows:

Due to its inhibitory impact on microorganisms, propionic acid (PPA) used to be a not so strong acid which is utilised as a preservative in the food items. A study was done on the PPA fungal killing mechanism, which demonstrated apoptotic characteristics. Second, by staining 2,7-dichlorodihydrofluorescein diacetate and CaspACE FITC-VAD-FMK, respectively, reactive oxygen species (ROS) aggregation plus metacaspase stimulation were observed. After exposure to PPA, increased fluorescence intensities were observed, suggesting that PPA created an oxidative environment via ROS generation and metacaspase activation, which can facilitate signaling of apoptosis. Based on the observations, it was established that by inducing apoptotic cell death, PPA exerts its antifungal impact. Furthermore, three additional mitochondrial studies demonstrated depolarization of the mitochondrial membrane; calcium aggregation and release of cytochrome c after cells were subjected to PPA, suggesting the mitochondria regulated the PPA-induced apoptosis cascade. To say, by mitochondria-mediated apoptosis, the PPA causes the cell death of fungus. The findings of this research lead to a better comprehension of the preventive effects of PPA.

The fungi coexist with humans and in many cases has infected man. The Infections of fungus in people with impaired immune function arising from AIDS, chemotherapy or organ transplantation may be life-threatening, inducing systemic illness and death. The pathologies involved with fungal infections and pharmaceutical methods of managing and treating these infections have been examined by several researchers over the years [21]. In everyday life, however, exposure to pathogenic fungi may occur [22]. Zygosaccharomyces, Saccharomyces with

Candida organisms pollute foods as well as generate kind of mycotoxins which from allergic reactions to immunosuppression may cause a range of adverse effects in humans. The spoilage of food due to fungal infection renders food items unsafe for human use [23]. Food poisoning and many foodborne fungal diseases may result from the ingestion of spoiled food containing mycotoxin. The need for spoilage management due to fungi in the food industry is therefore growing.

As food additives, certain mild or CAs such as Propionic Acid (PPA) which are the outcomes pertaining to the natural animal or bacterial metabolism are included. Many experiments have shown that microorganisms are hindered by causing a stress reaction and reducing the development and metabolic functions of energy reservoirs [24]. The metabolism of propionibacteria primarily generates propionic acid which used to be a poor CA which normally occurs in food items like cheese, yoghurt and milk. PPA used to the result of fermentation through anaerobic bacteria of polysaccharides, oligosaccharides and long-chain fatty acids in the human colon [25]. Several experiments have shown that PPA therapy prevents fungal food development and that PPA is an efficient food preservative [26]. PPA is therefore found in a broad variety of items, including baking products and cheese products, as a preservative [27].

A research was performed to determine the possible antibacterial and immunomodulatory effects of hydroxyphenyl propionic acid (PA) on Nile tilapia when administered alone or in conjunction with Oxytetracycline (OTC) (Oreochromis niloticus). The seemingly perfect O. Niloticus (n = 240; 52 ± 3.75 g) is divided randomly into four comparable classes (n = 60/group): the control group supplied the basal diet alone and the other three groups supplied the basal diet alone or in combination (PA + OTC group) combined with either PA (200 mg/kg diet, PA group) or OTC (500 mg/kg diet, OTC group). Every population was subdivided into two subgroups (n = 30/subgroup, with a triplicate of 10 fish in each subgroup); subgroup (A) was used to assess the antibacterial effects of the 2-week feeding regimen referred to above and subgroup (B) was used to assess the immunomodulatory effects of the 2-week feeding regimen against infection with Aeromonas hydrophila.

The highest significant antibacterial activity ($p<0.0001$) of the four groups was shown by the PA + OTC group, as seen by the greatest inhibition zones against A. Hydrophila, and the lowest gastrointestinal gross bacterial count. In addition, since an essential significant impact was

observed, this group has the largest immunomodulatory power ($p<0.05$) improvement in total serum protein, globulin, IgM, phagocytic activity and index, lysosomal activity, and significant ($p<0.05$) upregulation (MHC I, MHC IIA, MHC IIB, Tlr7, IgM heavy chain, TNF alpha, and IL1β) of head-kidney immune-related gene expression levels. In particular, the combination of dietary PA and OTC improved haematological parameters and minimized OTC-induced hepatopancreatic and head-kidney oxidative injury. This data indicates that hydroxyphenyl propionic acid is the potential adjuvant to OTC in O. Niloticus diets to gain complete antibacterial and immunomodulatory advantages.

The following findings are demonstrated in the results of this report:

It strengthens the OTC antibacterial effect. Hydrophila had been a form of disc diffusion demonstrating substantial variations in the scale of the smallest region of inhibition (14.25 ± 0.95 mm, $p < 0.001$) for OTC, the medium zone (18.52 ± 0.8 mm, $p < 0.0001$) for PA as well as the biggest zone (21.85 ± 0.72 mm, $p < 0.0001$) besides PA + OTC contrasted to the traffic management zone (9.3 ± 0.82) for PA as well as the biggest zone (21.85 ± 0.72 mm, $p < 00001$) for PA + OTC. The antibacterial effects of PA and/or OTC nutritional supplementation have also been checked against the total bacterial count in the intestine of uncontested fish.The findings obtained indicated a substantial decline in bacterial load in the three treated classes, with the lowest number of bacteria (6.48 ± 0.18 mm, $p < 0.0001$) in the PA + OTC community, accompanied by (7.20 ± 0.12 mm, $p < 0.0001$) in the PA group and (8.10 ± 0.15 mm, $p < 0.01$) in the OTC category relative to the PA group and (8.10 ± 0.15 mm, $p < 0.01$) in the OTC group.

4. Improvements in hematological parameters

Improvements in hematological parameters as well as in variable leukocyte values after the feeding of hydroxyphenyl PA and/or OTC enriched non-challenged fish diets. In the PA + OTC community, accompanied with the PA group which is the strongest change in haematological parameters was noted. The OTC groups displayed a larger negligible improvement in all parameters relative to the control group, with the exception of thrombocyte numbers, that was slightly greater in OTC group than in the controller group.

Similarly, in the PA + OTC community, preceded by the PA group, White Blood Cells, lymph cells, and neutrophil counts were substantially higher than in the OTC and control groups.

There was also no substantial gap in the above two classes between their unequal leukocyte counts. Compared to the other two groups, monocyte numbers were slightly higher in the PA and PA + OTC groups. It also recovers the interrupted role and structure of the tissue caused by OTC. There were slightly ($p < 0.05$) greater amounts of the hepatic enzymes, urea plus creatinine in non-challenged (subtype A) fish fed diets augmented with OTC than in fish fed a basal diet alone.

In fish fed with a basal diet including PA alone or paired with OTC, serum biochemical parameters were significantly decreased, with the strongest impact on fish fed with PA only. Although no variation was found between the control and PA classes in the levels of certain parameters. The OTC group was having slightly lower GPx as well as SOD involvement plus greater hepatopancreatic and kidney MDA levels relative to the control group. However, in the hepatopancreas and kidney groups, hydroxyphenyl PA with PA + OTC groups had slightly greater GPx as well as SOD behaviors plus lower MDA levels than in the OTC community. The PA + OTC community progressed less than the PA category, though there were no major variations.

Histological tests showed normal hepato-pancreatic tissue in the control group of normal hepatocytes. A similar standard histological structure was also observed with mild hepatic vacuolation in the hepatopancreas of the PA community. However, remarkable tissue damage in the form of marked hepatocyte vacuolation, hemorrhage within the acini, and focal necrosis was observed in the OTC community. In the PA + OTC community, this disrupted tissue damage was partly repaired, showing only mild vacuolation. It efficiently improves antimicrobial plus immunomodulatory activity in a way greater than either alone. This impure PA besides OTC have enhanced haematological markers also reduced OTC-induced oxidative harms to the liver pancreas plus head and kidney. Hydroxyphenyl PA may thus, be used as an adjuvant to OTC in Niloticus food in order to achieve optimum antimicrobial plus immunomodulatory impact.

On the same lines, Pentanoic acid which is also known as Valeric acid also helps in immunomodulation. Valeric, the current acid in Valerian root, is successful in decreasing distress and enhancing the quality of sleep by influencing serotonin and noradrenaline levels; Valepotriates often induces improved sleep and pain relief, and drugs such as Baldrinal and Homobaldrinal from its study cause symptoms of anxiety to be decreased. The highest impact of valerian is to raise the amount of GABA, where distress therapy can be accomplished by reducing the activation of the vagus nerve by raising the level of GABA [28].

The Inflammatory Bowel Disease (IBD) used to be a multifactorial recurrent intestinal illness which may get categorized in 2 major health situations: i) Crohn's disease (CD) that predominantly involves the colon in addition to small intestine, as well as colitis ulcerative (CU). Subtypes of IBD get distinguished by persistent gastrointestinal tract inflammation with frequent remission and relapse periods. IBD is a prevalent disease, with over 1 million people reported to be impacted in the US and 2.5 million in Europe [29]. The full IBD aetiology and pathogenesis continue to be explained at present. Meanwhile the incidence has risen gradually worldwide [30]. While the UC as well as the CD seem distinct with the medical appearance, scholars agree as their pathogenesis might include similar risk factors [31].

Current studies got conducted at the relationship pertaining to host chromosomal vulnerability, immunological irregularities, main function of gut microbiota (GM) plus the metabolites generated, as well as distinct ecological aspects. Maximum researched bacterial metabolites in IBD remain Short Chain Fatty Acids. These are secondary metabolites produced by fermentation by the GM of dietary substrates such as proteins, peptides, resistant starches, and undigested fibres. To date compromised SCFAs-fermentative mechanisms got correlated by dysbiotic disease in IBD patients, suggesting a reduced volume of SCFAs-producing bacteria as well as lower volume pertaining to faecal SCFAs [32]. In addition, this development of SCFAs has been correlated with a decreased risk of IBD [33]. Short Chain Fatty Acids used to be a category of fatty acids comprising fewer than 6 carbon atoms, including propionic as well as Pentanoic acid whose development, on the lines of the availability or non-availability as well as concentration of particular commensal bacteria, is affected by several factors, like host diet as well as Gut Microbiota variety [34].

The Propionate is mostly formulated with the help of associates of Bacteroidetes. Short Chain Fatty Acids may get used like energy supply with the colonocytes inside the eukaryotic host or else they may get transmitted to the circulation of the blood as well as different tissues. Amusingly, there are different output ratios and physiological processes of the major SCFAs (i.e., propionate) as well as the concluding configuration provided by the acids will vary in entire gut's numerous locations. In both the large and small intestines, propionate is observed in depth, although a higher butyrate content has been found in the cecum and colon [35]. As for the synthesis

of Short Chain Fatty Acids, propionate may be provided by Firmicutes via the lactate pathway and/or succinate pathway by Bacteroidetes phylumumetes [36].

The recent discovery of the ability of Short Chain Fatty Acids to fix receptors like GPR41, GPR43 plus GPR109a (generally articulated in a wide variety of kinds of cells) has made it possible to understand the regulatory role of IBD SCFAs. Besides this, the usage of SCFAs by intestinal epithelial cells (IECs) as an energy supply, Short Chain Fatty Acids show modulating impact at the cells of defence mechanism. SCFAs can be, in particular, influence development as well as migration pertaining to the cytokines, cytolytic function, and epigenetic regulation. In addition to the altered Short Chain Fatty Acid concentrations in IBD patients, metabolomic testing showed a decreased serum amount of the Trp and Trp metabolites. Multiple pathways that are all substrates of the gut mucosa and GM enzymes may involve Trp's bacterial metabolism. Trp is derived from dietary substrates and is absorbed by a neutral amino acid transporter based on sodium (SLC6A19/B0AT1).

Trp is a precursor to several MMPBs that can execute various host roles, such as immune homeostasis, but also functions of inflammatory response. The availability of Trp is significant for protein synthesis, the production of indol and nicotinamide derivatives through kynurenine, and for serotonin synthesis [37]. The disrupted interaction among the GM and immune cells, often concerning unusual signaling by immunomodulatory metabolites, may cause the dysbiotic condition in IBD. In reality, whether a dysbiotic microbiota has a main pathogenetic function in IBD patients or is ancillary to the inflammatory also antibacterial responses caused through the sequence of the ailment is still under consideration [38]. In each step of the inflammatory process, Short Chain Fatty Acids may play a crucial role in MMPBs, controlling the function of almost every form of immune cell.

In particular, SCFAs stops stimulus-induced manifestation of adhesion molecules, development of chemokines, and consequently suppress the recruitment of monocytes/macrophages and neutrophils, indicating a possible in vivo anti-inflammatory function. Furthermore, multiple analyses of IBD mouse models demonstrated a defensive function for SCFAs. There is still, however some research supporting the pro-inflammatory activity of Short Chain Fatty Acids. This disparity can be partly explained by the existence of microbes that trigger infections in anaerobic places where there is a high concentration of SCFAs in loco because of the

resulting loss of intestinal epithelial integrity, which can contribute to neutrophil aggregation and increase of inflammatory processes [39]. Various particular mechanisms could control Short Chain Fatty Acid-mediated immunomodulation: (I) GPCR activation, (II) stimulus of histone acetyl transferase, (III) histone deacetylase (HDAC) stop, and (IV) stabilization of hypoxia-inducible influences [40].

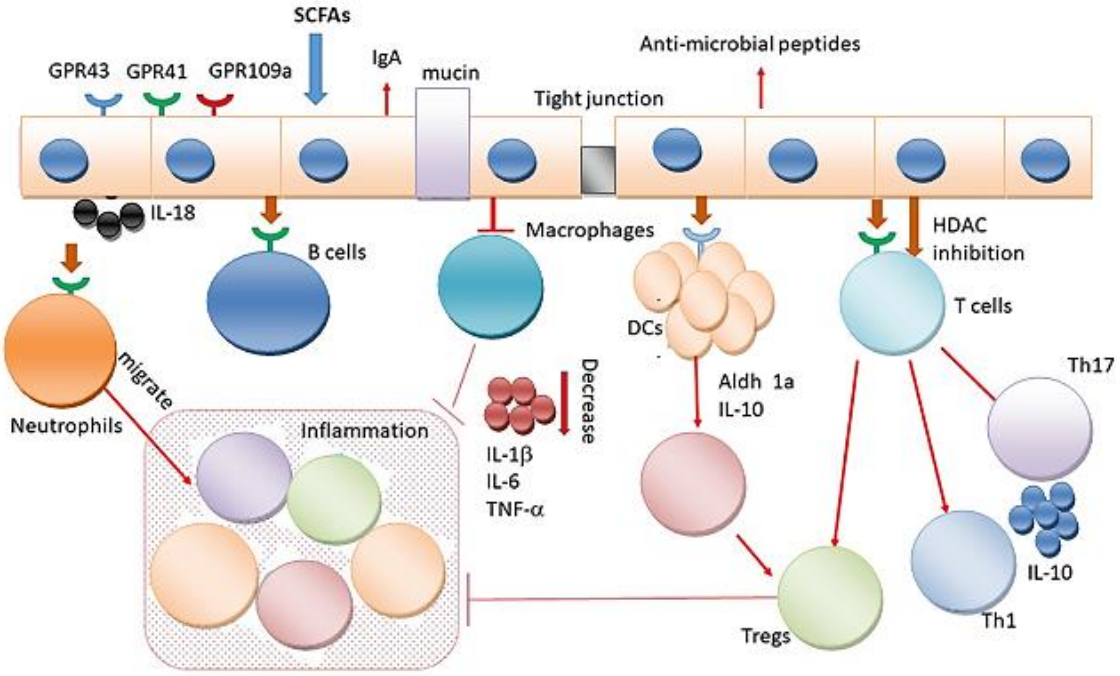

Figure 1: Immunomodulation effects of short chain fatty acids

In maintaining mucosal immunity, SCFAs used to be important because they increase barrier action of IECs that function on close junction permeability [41]. In vitro human cell model showed that in reaction to Short Chain Fatty Acid stimuli, abdominal epithelial cells are capable for promoting mucin gene transcription [42]. It has been shown that IL-18 is indulged with the development of antibacterial proteins, mucin output plus GM composition regulation to avoid colitogenic phenotype in the rat [43]. The TLRs of different cells can recognize MMPBs at the time of innate immune responses at the mucosal sites. A mouse research has shown that propionate and butyrate can inhibit DC maturation that connects the innate plus adaptive defence system [44]. TLRs used to be the strategic distinctive insusceptible receptors capable of detecting microbe-linked molecular designs that are a special microbial "molecular autograph." These TLRs may start inflammatory reactions after activation of PAMPs and delete these microbial intruders. A research

found the SCFAs have an influence at the development of pro-inflammatory proteins in IECs with enhancing the activation of NF-μB in TLR ligand reactions [45].

The effect of SCFAs at the growth of TNF-alpha plus IL8 offers another process by which it is predicted that MMPBs will affect gut health. In specific, by affecting the epithelial to mesenchymal transformation as well as the reverse mechanism, TNF-alpha plus IL8 are both indulged in preserving epithelial homeostasis [46]. These two approaches are cell trans-distinction systems from where the mesenchymal characteristics are obtained by epithelial cells and vice versa [47]. Growing evidence has supported the function of EMT in the pathogenesis of IBD-associated intestinal fibrosis, especially in the sense of intestinal illness [48]. In addition, the actions of mouse DCs that may create the proteins and communicate with the T-cells can be modulated by SCFAs. Introduction of DCs to butyrate is being shown to enhance distinctiveness of the naive T-cells in Tregs, inhibiting their transformation in IFN-γ-creating T cells [49]. The butyrate may control the function of colon lamina propria in mouse macrophages with inhibiting the transformation of proinflammatory molecules, supplying a GM tolerance status [50].

Short Chain Fatty Acids might too apply immunomodulating function in the T as well as B cells with respect to adaptive defensive responses. SCFAs control this differentiation of T cells which may be arbitrated by 2 kinds of methods: by indirectly controlling DCs plus by specifically influencing the T cells. To conclude, activation of Th17, Th1, plus Tregs is often moderated in multiple protein conditions by the SCFAs [51]. The microbiota is the microbial synthesis of tryptophan that may control tissue-level immune maturation. Trp metabolites have been known to have immunomodulatory function in experimental colitis or IBD patients [52]. The aryl hydrocarbon (AhR) receptor used to be a cytoplasmic transcript aspect present in many immune cell groups. The Kynurenine is a tryptophan-derived metabolic artifact which may be endogenous AhR ligand. This seems active to regulate the growth of endogenous lymph cells, thus, leads towards preservation of proper intestinal mucosal working [53].

IL-22 secretion is caused by diet-derived AhR ligand, which in response stimulates the development of mucin plus antibacterial proteins in intestine, hence supplying microbes tolerance as well as mucosal defence. Trp is used as an energy supply by a commensal bacteria division and generates indole-3-aldeyde that again stimulates AhR in ILCs, causing IL-22 secretion (Figure 2). The procedure in mice influences these both mucosal curing as well as the arsenal of anti-bacterial

proteins [54]. Indole decreases inflammatory gene expression and up-regulates close junction protein expression that interacts with the AhRR. In mice, AhR activation decreases dextran sulphate sodium-induced colitis through the use of tryptophan metabolites [55].

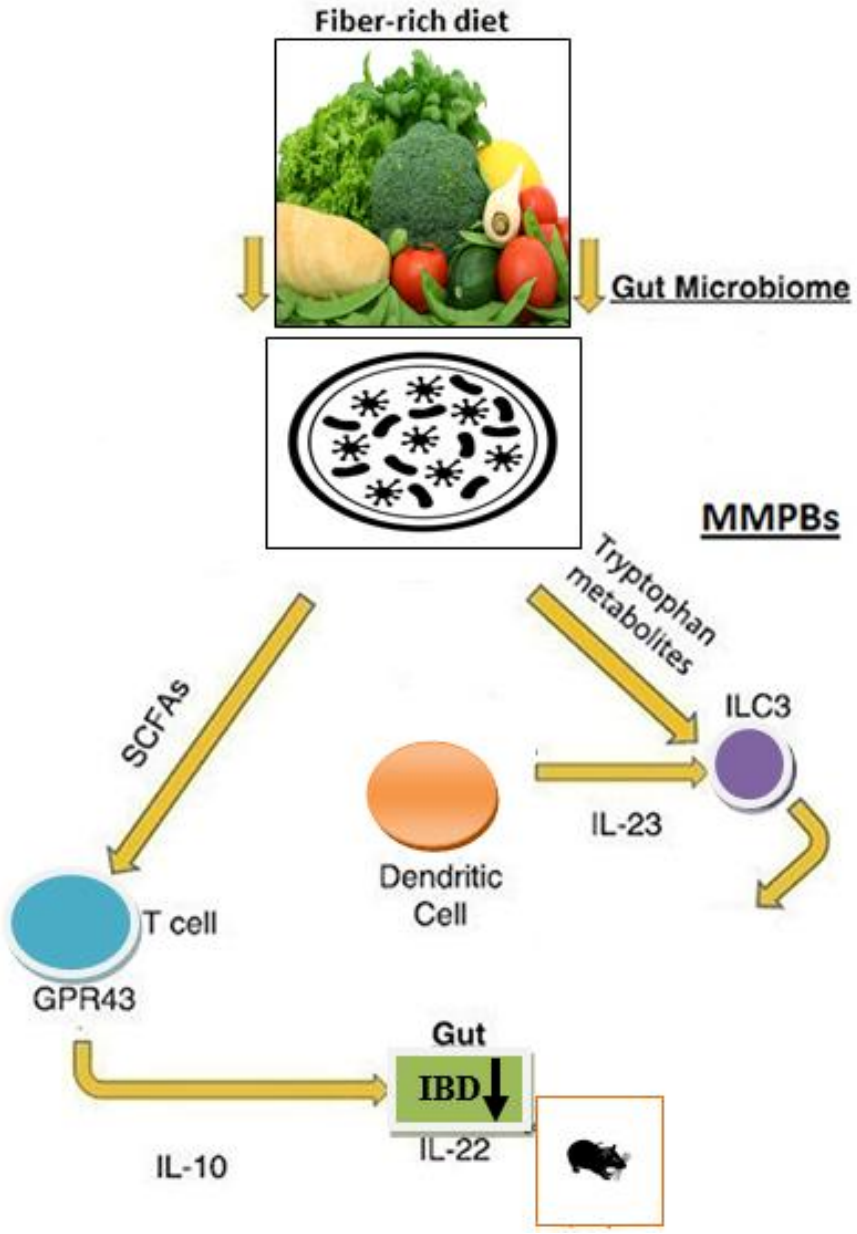

Figure 2: Microbiome-modulated post-biotics in IBD

Researches have been considered to study the different beneficial results of SCFAs on IBD models in rats in multiple ways, with the taking the drug through oral cavity and the usage of enemas. In humans, while SCFAs which improve Short Chain Fatty Acid supply have useful in

vitro effects on the inflammation in the intestine, positive medical impact in real life is not consensual [56]. Specifically, SCFAs got documented to increase colonocyte mucosal generation, crypt duration, and DNA material, improving the symptoms of UC in sick people plus mice administered with trinitrobenzene sulfonic acid injection [57]. Although, butyrate enemas had only mild effects on colonic inflammation and oxidative stress in UC patients in clinical remission who obtained 60 ml rectal enemas comprising 100 mm sodium butyrate (n=17) or saline (n=18) every day for a duration of 20 days [58].

In addition, recent study has shown that the microbial metabolite Urolithin A (UroA) (a major microbial metabolite isolated from polyphenolic berries and pomegranate fruits) and its analogue UAS03 substantially enhance the functionality of the intestinal barrier and avoid unjustified inflammation. Oral UroA/UAS03 treatment greatly lowered systemic inflammation and colitis, suggesting potential therapeutic applications for the safety of colonic disease and IBD therapy [59]. In order to further refine particular IBD pathogenesis plus to reduce occurrence of complications in CD and UC, an alternate strategy focused on dietary regulation targeting the immune system against post-biotic GM could be tested more broadly. For distinguishing against microbes as well as commensals, it is known that intestinal colonization through microbial population is necessary in order to the proper exercise of the defence mechanism. Growing research records the immunomodulatory impact of MMPSs on a broad variety of defence mechanism and encourages daunting frontier in the deterrence plus management of IBD. Actually, these applications of post-biotics have initiated a fresh chance towards multiple inflammatory disorders to discover and study the possible applications of microbiota-derived materials as fresh treatments. IBD therapies today concentrate on suppressing inflammation that characterizes IBD and repairing abdominal blockades. Immunonutrition used to be an under-exploited as well as under-studied research subject which may include a controllable method used to minimize unhealthy intestinal inflammation in IBD in the future.

References

1. Thangadurai, K., et al., *Immunomodulatory action of traditional herbs for the management of acquired immunodeficiency syndrome: A review.* 2018. **6**(6): p. 10-14.
2. Quinn, P., *Mechanisms of action of some immunomodulators used in veterinary medicine*, in *Advances in veterinary science and comparative medicine*. 1990, Elsevier. p. 43-99.
3. Retief, F.P. and L.J.S.A.M.J. Cilliers, *The epidemic of Athens, 430-426 BC.* 1998. **88**(1): p. 50-53.
4. Lemire, L., *Ces savants qui ont eu raison trop tôt: De Vinci à nos jours. Une histoire surprenante des découvertes*. 2013: Tallandier.
5. Plotkin, S.A.J.N.m., *Vaccines: past, present and future.* 2005. **11**(4): p. S5-S11.
6. Vogel, H.G., *Drug discovery and evaluation: pharmacological assays*. 2002: Springer Science & Business Media.
7. Owen, J.A., J. Punt, and S.A. Stranford, *Kuby immunology*. 2013: WH Freeman New York.
8. Wagner, H., et al., *In vitro phagocytosis stimulation by isolated plant materials in a chemoluminescence-phagocytosis model.* 1985(2): p. 139.
9. Makare, N., S. Bodhankar, and V.J.J.o.e. Rangari, *Immunomodulatory activity of alcoholic extract of Mangifera indica L. in mice.* 2001. **78**(2-3): p. 133-137.
10. Kremer, J.M., et al., *Methotrexate for rheumatoid arthritis.* 1994. **37**(3): p. 316-328.
11. Upadhyay, S.N. *Plant products as immune response modulators*. in *Proceedings of the International Ayurveda Conference, Sanjay Gandhi, Lucknow*. 1997.
12. Zhou, L., et al., *Different modes of inhibition for organic acids on polyphenoloxidase.* 2016. **199**: p. 439-446.
13. Kalgutkar, A.S., J.S.J.M. Daniels, Pharmacokinetics, and T.o.F.G.I.o.C.B.B.o. ADMET, *Carboxylic acids and their bioisosteres.* 2010: p. 99-167.
14. Zelinsky, N. and R. type Substitution, *Hell–Volhard–Zelinsky halogenation.*
15. Bojar, R.A. and K.T.J.C.i.d. Holland, *Acne and Propionibacterium acnes.* 2004. **22**(5): p. 375-379.
16. Rogers, G., et al., *From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways.* 2016. **21**(6): p. 738-748.
17. Jacobson, A., et al., *A gut commensal-produced metabolite mediates colonization resistance to Salmonella infection.* 2018. **24**(2): p. 296-307. e7.

18. Shahidi, F., et al., *Meat flavor volatiles: A review of the composition, techniques of analysis, and sensory evaluation.* 1986. **24**(2): p. 141-243.
19. Meeting, J.F.W.E.C.o.F.A. and W.H. Organization, *Evaluation of certain food additives and contaminants: sixty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives*. Vol. 68. 2007: World Health Organization.
20. Markowiak-Kopeć, P. and K.J.N. Śliżewska, *The Effect of Probiotics on the Production of Short-Chain Fatty Acids by Human Intestinal Microbiome.* 2020. **12**(4): p. 1107.
21. Raman, V., H.T. Horner, and I.A.J.J.o.p.r. Khan, *New and unusual forms of calcium oxalate raphide crystals in the plant kingdom.* 2014. **127**(6): p. 721-730.
22. Roemer, T. and D.J.J.C.S.H.P.i.M. Krysan, *Antifungal drug development: challenges, unmet clinical needs, and new approaches.* 2014. **4**(5): p. a019703.
23. Pitt, J.J.B.m.b., *Toxigenic fungi and mycotoxins.* 2000. **56**(1): p. 184-192.
24. Brul, S. and P.J.I.j.o.f.m. Coote, *Preservative agents in foods: mode of action and microbial resistance mechanisms.* 1999. **50**(1-2): p. 1-17.
25. Al-Lahham, S.a.H., et al., *Regulation of adipokine production in human adipose tissue by propionic acid.* 2010. **40**(5): p. 401-407.
26. Suhr, K.I. and P.V.J.I.j.o.f.m. Nielsen, *Effect of weak acid preservatives on growth of bakery product spoilage fungi at different water activities and pH values.* 2004. **95**(1): p. 67-78.
27. Razavi-Rohani, S. and M.J.J.o.f.s. Griffiths, *Antifungal effects of sorbic acid and propionic acid at different pH and NaCl conditions.* 1999. **19**(2): p. 109-120.
28. Gharib, M., et al., *The effect of valeric on anxiety severity in women undergoing hysterosalpingography*. 2015. **7**(3): p. 358.
29. Kaplan, G.G.J.N.r.G. and hepatology, *The global burden of IBD: from 2015 to 2025*. 2015. **12**(12): p. 720-727.
30. Ananthakrishnan, A.N.J.N.r.G. and hepatology, *Epidemiology and risk factors for IBD.* 2015. **12**(4): p. 205-217.
31. Nishida, A., et al., *Gut microbiota in the pathogenesis of inflammatory bowel disease.* 2018. **11**(1): p. 1-10.
32. Huda-Faujan, N., et al., *The impact of the level of the intestinal short chain fatty acids in inflammatory bowel disease patients versus healthy subjects.* 2010. **4**: p. 53.

33. Machiels, K., et al., *A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis.* 2014. **63**(8): p. 1275-1283.
34. Canfora, E.E., J.W. Jocken, and E.E.J.N.R.E. Blaak, *Short-chain fatty acids in control of body weight and insulin sensitivity.* 2015. **11**(10): p. 577.
35. Vogt, S.L., J. Peña-Díaz, and B.B.J.A. Finlay, *Chemical communication in the gut: Effects of microbiota-generated metabolites on gastrointestinal bacterial pathogens.* 2015. **34**: p. 106-115.
36. Louis, P., G.L. Hold, and H.J.J.N.r.m. Flint, *The gut microbiota, bacterial metabolites and colorectal cancer.* 2014. **12**(10): p. 661-672.
37. Richard, D.M., et al., *L-tryptophan: basic metabolic functions, behavioral research and therapeutic indications.* 2009. **2**: p. IJTR. S2129.
38. Celiberto, L.S., et al., *Inflammatory bowel disease and immunonutrition: novel therapeutic approaches through modulation of diet and the gut microbiome.* 2018. **155**(1): p. 36-52.
39. Vinolo, M.A., et al., *Regulation of inflammation by short chain fatty acids.* 2011. **3**(10): p. 858-876.
40. Kelly, C.J., et al., *Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function.* 2015. **17**(5): p. 662-671.
41. Fukuda, S., et al., *Bifidobacteria can protect from enteropathogenic infection through production of acetate.* 2011. **469**(7331): p. 543-547.
42. Willemsen, L., et al., *Short chain fatty acids stimulate epithelial mucin 2 expression through differential effects on prostaglandin E1 and E2 production by intestinal myofibroblasts.* 2003. **52**(10): p. 1442-1447.
43. Elinav, E., et al., *NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis.* 2011. **145**(5): p. 745-757.
44. Singh, N., et al., *Blockade of dendritic cell development by bacterial fermentation products butyrate and propionate through a transporter (Slc5a8)-dependent inhibition of histone deacetylases.* 2010. **285**(36): p. 27601-27608.
45. Lin, M.Y., et al., *Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone deacetylases.* 2015. **6**: p. 554.

46. Zhao, Z., et al., *Epithelial-mesenchymal transition in cancer: role of the IL-8/IL-8R axis.* 2017. **13**(6): p. 4577-4584.
47. Kalluri, R. and R.A.J.J.o.C.I. Weinberg, *Erratum: The basics of epithelial-mesenchymal transition (The Journal of Clinical Investigation (2009) 119, 6,(1420-1428.* 2010. **120**(5).
48. Tanjore, H., et al., *W1846 Identification of Epithelial to Mesenchymal Transition as a Novel Source of Fibroblasts in Intestinal Fibrosis.* 2010. **138**(5): p. S-752.
49. Gurav, A., et al., *Slc5a8, a Na+-coupled high-affinity transporter for short-chain fatty acids, is a conditional tumour suppressor in colon that protects against colitis and colon cancer under low-fibre dietary conditions.* 2015. **469**(2): p. 267-278.
50. Chang, P.V., et al., *The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition.* 2014. **111**(6): p. 2247-2252.
51. Park, J., et al., *Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR–S6K pathway.* 2015. **8**(1): p. 80-93.
52. Wikoff, W.R., et al., *Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites.* 2009. **106**(10): p. 3698-3703.
53. Quintana, F.J. and D.H.J.P.r. Sherr, *Aryl hydrocarbon receptor control of adaptive immunity.* 2013. **65**(4): p. 1148-1161.
54. Qiu, J., et al., *Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora.* 2013. **39**(2): p. 386-399.
55. Ji, T., et al., *Aryl hydrocarbon receptor activation down-regulates IL-7 and reduces inflammation in a mouse model of DSS-induced colitis.* 2015. **60**(7): p. 1958-1966.
56. Galvez, J., et al., *Effects of dietary fiber on inflammatory bowel disease.* 2005. **49**(6): p. 601-608.
57. Jacobasch, G., et al., *Dietary resistant starch and chronic inflammatory bowel diseases.* 1999. **14**(4-5): p. 201-211.
58. Hamer, H.M., et al., *Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission.* 2010. **29**(6): p. 738-744.
59. Singh, R., et al., *Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway.* 2019. **10**(1): p. 1-18.