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A STUDY OF PHYTOCONSTITUENTS INVOLVEMENT IN THE ENHANCEMENT OF INCREASED GUT FLORAE

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ABSTRACT

The human gut microbiota is one of the major natural habitats for a large bacterial community, however a lot of information is yet to be discovered. Gut microflorae consists of a variety of strains of bacteria along with some viruses that help keeping the gut healthy. Apart from all the benefits provided or health application, its further potential lies in prevention and treatment of various metabolic disorders. The studies mainly focused on the different phytochemicals that impact the gut florae and hence, indirectly improving the gut health. Phytochemicals are mainly natural chemicals that are introduced into the human gut through intake of various fruits and vegetables. It is clearly stated that different types of phytochemicals impact different strains of bacteria and thus, the phytochemicals included flavonoids, anthocyanin, hydrolysable tannins, carotenoids and fiber and butyrate. This review even deals with a variety of studies that were involved in the proliferation of different disease such as colon cancer, inflammatory bowel disease, obesity and diabetes mellitus along with the impact of gut microflorae on these particular diseases. The summarized data helps establishing a relationship between the pathogenesis of the disease and how improving the gut microflorae would act as a potent therapeutic cure.

KEYWORDS: Gut microflorae, Diet, Metabolic diseases, Bacteria, Phytoconstituents.

LIST OF ABBREVIATIONS

GM :Gut Microflorae

SPP :Species

HT :Hydrolysable Tannins

IBD :Inflammatory Bowel Disease
DM :Diabetes Mellitus
GIT :Gastrointestinal Tract
UC :Ulcerative Colitis
CD :Crohn's Disease
BCO2 KO :Beta carotene oxygenase 2 knockout
WT :Wild type

INTRODUCTION

In the intestinal lumen, bacteria (bacteriome), fungus (mycome)[1] and viruses (virome)[2] coexist in a harmonic and dynamic equilibrium which helps to keep the intestinal gut intact.[3] The normal gut flora consists of anaerobic bacteria by 100-1000 folds when compared with aerobic and facultative bacteria.[4] Approximately, the intestinal microbiota consists of 500-1000 species in total.[5,6]

Viruses play a pertinent role in the gut environment despite their lengthy neglect bacteriophages[7] make up about 90% of the gastrointestinal virome while other animals and plant viruses are introduced into the body via food and makeup 10% of the viral genome of the intestine.[3] Before birth, this microbial community begins to colonize the body and resides there until death in a mutualistic partnership. The microbial flora in the intestine promotes food metabolism, metabolic activities, immune system education and stimulation keeps the population together and protects the host from infections.[8,9] Many kinds of research have been carried out in the past to develop a relationship between the gut florae and various diseases and shocking studies have been found. Gut microflorae (GM) passes out signals that stimulate the release of cytokines which results to immune cell maturation and modulation of the host immune system's immunological functions.[10] The Nobel Laureate Eli Metchnikoff (1845-1916) claims that "the majority of diseases begin in the digestive tract when "good" bacteria are no longer able to control "bad" bacteria", calling this condition dysbiosis leading to countless pathologies inflammatory bowel disease (IBD), celiac disease, obesity, metabolic disorder, etc.[3,11] A diseased condition can alter the microbial ecosystem. Diet has the greatest impact on gut bacterial diversity which can also change its functional connections with the host dietary components are digested by intestinal bacteria during their passage through the gastrointestinal tract. *Firmicutes* and *Proteobacteria* grow in diets high in carbs and simple sugars whereas, *Bacteroidetes* and *Actinobacteria* thrive in diets high in

saturated fat and animal protein.[10,12] Diet plays an important role in influencing various physiological aspects of gut environment like micronutrient absorption, vitamin and nutraceuticals absorption and changes in gut pH which impact the GM balance.[10,13]

Several strategic remedies are being explored for this goal to restore and/or sustain the eubiotic state of the microbic intestinal ecosystem one of which is the use of phytoconstituents to increase the gut florae. Hence, along with the biological activity of the food GM also influences the target for the nutritional intervention to improve the health. Phytochemicals are naturally derived bioactive agents, widely dispersed in variety of fruits and vegetables.[14-16] A significant connection has been observed between the specific classes of the phytochemicals and the modification of the responding microbiota.[14,17-19]

In this review, we have covered the impacts of various phytochemicals on the human gut microbiota and the discussion about the connection between various diseases such as IBD, diabetes and obesity and the impact of the GM. The information regarding the potential triangular relationship between the GM, human diseases and phytochemicals are included with various factors that significantly affect the situation like life style choices and dietary factors. The goal of this study is to emphasize the relevance of interactions between phytochemicals and the gut microbiota as well as to show how the established information may be used to build many platforms for diagnosis and therapy, guiding future clinical trials.

IMPORTANCE OF THE GUT FLORAE

All higher animals and vertebrates contain a wide variety of microorganisms which cover essentially all host mucosal surfaces but most of them reside within the gastrointestinal tract (GIT). Earlier researches concentrated on analyzing the microbiota's function during human disease. However, over the last ten years, the area of microbiota research has proliferated, leading to the release of a profusion of studies that outline different individuals in our intestinal microbiota as well as their extensive effects on host physiology. A recognition of the gut microbiota's mostly positive impact on human health has therefore replaced the conventional anthropocentric perception of it as harmful and only an immunological danger.[6] About 1014 bacterial cells or ten times as many as human cells in the body are found in the adult gut. Their collective genomes (collectively referred to as the microbiome) contain more than 5 million genes exceeding the genetic potential of the host by two orders of magnitude.[5,20] This extensive collection of gene products offers a wide variety of biochemical and metabolic functions to support host physiology. In fact, the intestinal

microbiota may be thought of as an extra organ because its metabolic capability is equal to that of the liver.

Numerous biological processes in the host are dependent on these microorganisms. For instance, they play a crucial role in the metabolism of otherwise indigestible polysaccharides, the production of essential vitamins, the development and differentiation of the intestinal epithelium and immune system of the host, the protection against invasion by the development and homeostasis of other host tissues such as the bone opportunistic pathogens and the maintenance of tissue homeostasis. Additionally, recent research has shown that the human microbiome has an effect on growth and homeostasis of other host tissues.[21] According to a new study, the brain-gut axis a bidirectional communication system is the main mechanism through which the gut microbiota influences brain activity and human behavior. These discoveries advance knowledge of mental diseases particularly depression.[22] The brain and intestine appear to have significant impacts on one another according to the two-way regulatory systems in the brain-gut axis. Thus, establishing a relationship between brain and the gut microflorae (intestine).[23]

DIFFERENT PHYTOCHEMICALS AND THEIR IMPACT

Diet regulates the composition of gut microbiota and affects the gut maturation process. Many medicinal plants and their phytochemicals act as prophylactic agents for multiple ailments. By sudden weaning corticosteroids stimulation with pancreatic or pancreatic-like proteases[24] and polyamines[25] among other things the normal process of gut maturation can be stimulated prematurely. A variety of medicinal herbs and phytochemicals may also have the ability to act as maturational agents for the growing gut according to a number of studies.[26]

For example

a) *Hibiscus sabdariffa* calyx extract was given orally to nursing rats for nine days. This caused the small intestine and cecum to mature earlier than expected as seen by considerably higher organ weights compared to the control group.[27,28]
b) Aloe vera extracts both aqueous and ethanolic given to rats for eight days while they were nursing accelerated the development of the cecum and its mucosal layers.[29]

Hence, these studies describe the impacts of various natural products on the gut maturation. Paneth cells found in tiny intestinal crypts have been implicated in critical GIT functions.[30]

Through the production of growth factors these cells support the integrity and cellular functions of the tiny intestinal crypts.[31] Additionally, they control the intestinal bacteria performing chemosensory functions[32] and affect the differentiation and maturation of gut cells.[33]

DIFFERENT PHYTOCHEMICALS MODIFYING THE GUT FLORAE

FLAVONOIDS

A significant subset of phenolics known as flavonoids which are found in a broad variety of fruits and vegetables including cranberries and blueberries that contains two phenyl rings and one heterocyclic ring.[14,34] The flavonoid content in food is severely influenced by pre-harvest and post-harvest factors such as plant genotype, food processing and storage.[35,36] Polyphenol consumption varies greatly but the average intake is probably 900 mg/day. Among various eating habits the average daily flavonoid intake ranges from 60 to 600 mg usually present in green tea, fruits, vegetables, legumes, nuts and all of them considerably increases the consumption of polyphenols.[37]

As per evidence, flavonoids and their derivatives affect the gut microbiota's composition to boost host immune system and metabolism.[13,38,39] The metabolic process also indicates that flavonoids have both prebiotic and antibacterial effects.[40] When flavonoids were cocultured with bacteria it appeared that *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* species might grow more quickly while *Clostridium* and *Bacteroides* species might be inhibited. Fluorescence in-situ hybridization was used to measure the changes in the human gut microflora.[41]

An essential anticolitic mechanism is the capacity of flavonoids to alter microbiota. By altering the gut microbiota via the NOD-like receptor family pyrin domain containing 6 (NLRP6) protein, apigenin consumption prevented dextran sulphate sodium (DSS) induced colitis in mice.[42] Similar to this, flavonoids help obesity-related microbial dysbiosis. Consuming cranberries extract high in flavonoids reduces inflammation linked to diet induced obesity in mice through modifying Muciniphilia akkermansi.[35,43] Flavonoids even help to improve the health of the gut by decreasing the production of endotoxins, increasing the conversion of primary bile acids into secondary bile acids, maintaining gut immune homeostasis and encouraging nutrient absorption and increasing the beneficial genera like *Bifidobacterium* and *Lactobacillus*.[35,44]

Recent studies have concluded that quercetin sub-categorized as a Flavonoid inhibits the growth of various bacteria such as *Bacteroides galacturonicus*, *Lactobacillus*, *Escherichia coli*, *Enterococcus caccae* and *Ruminococcus gauvreauii* in a dose-dependent manner.[38] Other flavonoids, which were extensively used in the food sector have also displayed antibacterial effects against diet infections.[45] Using data from mixed cultures including the human microbiota it has been established that the breakdown of the flavanones naringin (a flavanone) and rutin (a flavonol) is microbiota-dependent.[14]

Hence flavonoids are observed to produce various functions such as.

a) flavonoids can modulate the microbiota thus confirming an important anti-colitic mechanism.
b) Consuming flavonoids affects how T cells differentiate which in turn affects how pro-inflammatory immune cells are activated and infiltrate the colon.
c) Flavonoids help to decrease the endotoxin exposure and even assists in repairing the disrupted intestinal barrier which has been caused due to chronic inflammation.

Hence according to all the evidences collected it can be summarized that there exists a vigorous connection between the gut florae and the flavonoid metabolism, suggesting that the gut microbiota has a strong impact on the flavonoid and the associated metabolites, thus leading to stronger health benefits.

ANTHOCYANINS

Anthocyanins are prominent subclass of flavonoids found in many vegetables and fruits consumed in the United State market such as blueberry, raspberry, purple cauliflower and lettuces.[14,46,47] They are water-soluble plant pigments that imparts deep rich hues of purple, red, and blue color to plant-based product. They have been shown to improve vision[48], cognition[49], blood pressure[50] and protect against risk factors for cardiovascular disease in epidemiological studies among other benefits to human health.[51,52] Only a tiny percentage of intact anthocyanins that are eaten by diet have been demonstrated to be able to pass through the intestinal wall using active transporters such the sodium-dependent glucose transporter 1 and facilitative glucose transporter.[53] In addition to being mostly present in methylated, sulphated or glucuronidated forms, anthocyanins are also metabolized as intact glycosides in very low amounts in biological fluids like blood (plasma) and urine (10-2000 nM).[54] Bioavailability of anthocyanin is limited however, a significant amount of food matrix bound can pass to large intestine and colon. They are further metabolized and degraded before being

absorbed into the bloodstream. Some of the resulting metabolites may have greater biological activity than the intact anthocyanins.[52,54,55]

The growth of the gut microbiota including that of *Bifidobacterium* spp., *Lactobacillus* spp., *Staphylococcus aureus* and *Salmonella typhimurium* was significantly influenced by anthocyanins derived from potato, black rice and malvidin 3-glucoside during in vitro fermentation.[41,56,57] Some studies have shown that black raspberry anthocyanins restored the growth of Lactobacillus spp., *Faecalibacterium prausnitzii* and *Eubacterium rectale* while limiting the formation of Desulfovibrio spp. and Enterococcus spp.[58] Raspberry anthocyanins greatly altered the luminal abundance and diversity of *Firmicutes* (Clostridium spp.) and *Bacteroidetes* (Barnesiella species).[59]

Another study showed that rats fed with blackcurrant anthocyanins showed relative abundances of *Bacteroides*, *Prevotella*, *Porphyromonas* and *Lactobacillus* while a decline was observed in the *Bifidobacterium* and *Clostridium* species.[60] In a high-fat diet group berry anthocyanins enhanced the abundance of gamma proteobacteria while inhibiting the growth of the proinflammatory bacterium *Bilophila wadsworthia*.[61,62] In a study conducted where human subjects who took anthocyanin-rich red wine showed rapid amount of increase in different strains of bacteria such as *Eggerthella lenta*, *Bifidobacterium* and *Enterococcus* at the genus level in feces.[63] An 8-week study was performed on 51 participants who received anthocyanins and prebiotic fibers. They showed tremendous increase in different Bacteroidetes phylum levels and decreased *Firmicutes* and *Actinobacteria* phylum levels.[64] Anthocyanins are linked to the down-regulation of the transcription factor NF-B signalling pathway which is connected with a beneficial modulation of the microbiota and inflammatory indicators. The interaction between anthocyanins and the gut microbiota may be responsible for this impact which may lead to increased intestinal barrier function and less lipopolysaccharide (LPS) translocation into the bloodstream. Such elements could influence the diet treatment strategies that have been created for preventing chronic diseases and reducing inflammation altering the microbiota.[65] Despite having so many references and results further research explaining particular bacterial strains involved and their relation to anthocyanin interactions and different molecular mechanisms are to be studied in the near future.

HYDRALYZABLE TANNINS

Tannins referred to as polyphenols are water-soluble secondary plant chemicals found in a range of diets. Condensed or hydrolysable tannins are the most common kind of naturally occurring tannins. While hydrolysable tannins (HT) are made of phenyl carboxylic acids like gallic acid (Gallotannins) or ellagic acid (Ellagitannins) mostly found in the berries, walnuts, plant seeds and herbs[66] are esterified to its core component glucose which can further be hydrolyzed and decomposed by microbial enzymes and acidic conditions. Condensed tannins (CT) are polymers of flavonoids with high molecular weight that are not readily degraded in the digestive tract.[67] The ellagitannins are further gradually metabolized to produce urolithin A and urolithin B by the process of hydrolysis.[68] In addition, it has also been observed that urolithin C and urolithin D (antioxidants) were also present in large concentration in the intestine of animals.[69]

The human lower GI tract is wherein urolithin metabolites and tannins are largely produced and metabolized. According to human clinical studies, species from the genera Bacteroides, *Prevotella* and *Ruminococcus* are the predominant gut microbes found in subjects who ingested urolithin-enriched walnut and pomegranate extracts. These findings help to identify specific microbes that were involved in the metabolism of ellagitannin.[70] Other studies have reported that different bacterial genomes such as *Clostridium*, *Bifidobacterium*, *Lactobacillus* and Bacteroides are involved in the production of urolithins.[71,72] By analyzing the optical density of culture medium, it was discovered that *Bifidobacterium* and *Clostridium* species were also involved in the metabolism of pomegranate ellagitannin in a bacteria species-dependent manner.[69]

Gallotannin is one of the other types of hydrolysable tannin.[73,74] According, to the reports of a human clinical investigations it was revealed that free gallic acid was released in the GI tract when gallotannins underwent microbe-mediated metabolism.[75] According to recent researches carried out in this particular field it has been observed that they exist antibacterial, antiviral, antifungal activities related to hydrolyzable tannins and they even also exhibited considerable synergy with antibiotics.[76] Despite the fact that numerous studies have revealed that metabolism of hydrolyzable tannin is related to the microbiota. The complete processes underpinning the antioxidant and anti-inflammatory activities of tannin metabolites and urolithins in the improvement of human health are still unclear.[68]

CAROTENOIDS

All plants and algae and some bacteria, archaea and fungus produces carotenoids which are naturally occurring pigments made up of isoprene units. Carotenoids have anti-cancer and anti-oxidation actions according to recent studies.[77,78] Humans cannot produce carotenoids from endogenous precursors thus it should be taken through diet. Scavenger receptor class B type 1 (SRB1) which is controlled by beta-carotene oxygenase 1 (BCO1) activity via homeobox transcription factor intestinal-specific homeobox regulates the absorption of dietary carotenoids in the intestine at least in part ISX (Intestine specific homeobox).[17,79]

Carotenoids are subcategorized into Xanthophylls (lutein, zeaxanthin) and carotenes (alpha, beta, and astaxanthin) these substances have potent antioxidant activity that helps in maintaining the human health.[80-83] Astaxanthin is an oxycarotenoid found in certain microalgae and marine animals.[56,83-85] Recently a pilot study was conducted to determine the potential role of astaxanthin in the gut microflorae. The findings demonstrated that astaxanthin administration significantly changed the phylum-specific cecal microbiota which mainly varied by gender and BCO2 (Beta-carotene oxygenase 2) gene expression. Male and female BCO2 KO (Beta-carotene oxygenase 2 knockout) mice had considerably higher levels of OBP in particular *Proteobacteria* and *Bacteroides* that could be reduced in female WT (Wild type) and BCO2 KO only by astaxanthin treatment. Contrarily, only in male WT mice did astaxanthin significantly enhance the number of the commensal microbiome *Actinobacteria* and *Bifidobacterium*. Mice treated with astaxanthin have an increased abundance of more than a dozen commensal microbiota genera in the phylum *Firmicutes*. Hence, according to the data collected so far, astaxanthin treatment and the metabolic enzyme BCO2 are found to have a significant influence on the gut flora in mice.[17]

In *Helicobacter pylori*-infected BALB/cA (Albino mouse which is laboratory-bred strain of the house mouse from which many common strains were derived) mice, astaxanthin (200 mg per kg body weight per day) decreased the bacterial load of the gram-negative pathogen *Helicobacter pylori* 119/95p and decreased stomach inflammation and the production of *Helicobacter pylori*-specific T cell cytokines.[14]

FIBERS AND BUTYRATES

Dietary fibers composed of cellulose, non-cellulosic polysaccharides including hemicellulose, pectic materials, gums, mucilage and the non-carbohydrate lignin is that portion of plant material in the diet that is resistant to enzymatic digestion. Since, there intake has been linked

to a reduction in the occurrence of numerous illnesses, diets high in fiber such as those including cereals, nuts, fruits and vegetables, have a good impact on health.[86] The profile of the human gut microbiota is considerably altered by the principal bioactive components of whole food dietary treatments which include digestible fibers.[87,88] Recent studies have developed that dietary fiber is involved in decreasing the risk of type 2 diabetes mellitus (T2D)[89], colon cancer and cardiovascular diseases by reducing the digestion and absorption of macronutrients and decreasing the contact time of carcinogens within the intestinal lumen.[14]

Butyrate is a short-chain fatty acid that is commonly produced by microbial fermentation in the large intestine of humans and animals.[14,90] It's functions as a primary nutrient that gives colonocytes energy as well as a cellular mediator that controls a variety of functions in the gut and elsewhere, such as gene expression, cell differentiation, the development of gut tissue, immune modulation, oxidative stress reduction and diarrhoea control. Diverse forms of butyrate such as sodium butyrate and butyrate glycerides have been produced and tested for their impacts on gut health and development performance across different species due to the challenges of employing butyrate in practice i.e., disagreeable odour and absorption in the upper intestine. Generally speaking, butyrate and its derivatives have beneficial impacts on animal production such as improving gut development, reducing enteric infections, reducing inflammation, enhancing growth performance including carcass composition and altering gut microbiota. This fatty acid functions as an antioxidant, an anti-inflammatory agent, a promoter of brain health, a histone deacetylase inhibitor, an energy metabolite for ATP (Adenosine triphosphate) synthesis, an activator of G protein-coupled receptors and many more.[91]

Recent human clinical studies have found a high correlation between dietary fiber consumption and the abundances of particular gut microorganisms such as those belonging to the bacterial class *Clostridia*, phylum *Actinobacteria* and order *Bifidobacteriales.*[92] Furthermore, in a randomized human clinical investigation *Firmicutes* and *Bacteroidetes* and the families *Ruminococcaceae*, *Lachnospiraceae, Eubacteriaceae* and *Porphyromonadaceae* were identified as being altered by soluble maize fibers 21 g each day.[93] Consuming dietary fiber also stimulates various metabolic pathways such as metabolism of carbohydrates, nucleotides, vitamins and amino acids. Studies have even claimed that high-fiber diet

influences the composition of the intestinal microbiome indicating that the process of fiber fermentation is highly microbiota-dependent.[94]

GUT FLORAE AND RELATED DISEASES

The gut microflorae and the chronic diseases related to them have been studied in the recent years. According to an increasing number of research microbial profiles accurately depict the interactions between the gut microbiota and metabolites formed from the microbiome. Hence, the profile of different disease depends on the chronic diseases that are exhibited by the subject.

Microflorae are considered to perform 3 basic functions that includes:[95]

1) Metabolic functions

Energy is recovered as short-chain fatty acids, vitamin K is produced and ions are absorbed during the fermentation of non-digestible food waste and endogenous mucus.

2) Trophic functions

Control of immune system development and homoeostasis, regulation of epithelial cell differentiation and proliferation.

3) Protective functions

Protects against the pathogens, called the barrier effect.

COLON CANCER

Having slightly more cases in men colorectal cancer is the second most frequent cancer in women and the third in men worldwide. Around half of all cancer cases resulted in death in 2012, according to reports of 1,361,000 new cases worldwide (10 % of the overall cancer cases).[96] It is one of the so-called westernized diseases with the highest incidence rates in North America, Australia, New Zealand and Europe (all >40 cases per 100,000) and lowest in rural Africa (<5 cases per 100,000) and Asia (variable).[97] Most of the colon cancer are sporadic greatly affected by eating habits of the person. The rate of carcinogenesis is determined by the penetrance of the genetic defect and by the aggressiveness of the environmental insult. Although the genetic factors behind colon cancer are known but the impact of environmental factors such as diet might also have a major role in the development of sporadic cancer.[98] It has been stated that greater consumption of red meat, particularly processed meat and meals containing more amount of dietary fat are directly linked to a high

risk of colon cancer.[99] Contrarily, a high consumption of fruits, vegetables, whole grain cereals, seafood and calcium has been linked to a lower risk of developing certain diseases.[99,100] Events that take place in the large intestinal lumen play a role in the interaction between dietary and hereditary factors.[95]

The main question that arises is that what defines the role of the colon microbiota in colon cancer pathogenesis? The chances are that the causative microbe (the microbe that causes the disease) is no longer present when the sickness is diagnosed. This creates one of the main difficulties in determining the bacterium which has led the disease to spread. The instigating bacteria may have been eradicated as a result of this alteration in the microenvironment or the microbe may have used a "hit and run" technique to induce the disease.[101]

A growing body of research shows that intestinal microflora performs protective, metabolic, trophic and immunological tasks and can establish communication with the immune system that makes up the mucosal immunity which consists of cellular and soluble components. Microbiota interact with the immune system via toll-like receptor signaling[102] and the development of colonic cancer has been linked to inflammasome sensing nucleotide-binding oligomerization domain (NOD)-like receptors.[103] Because NOD1 identifies bacterial antigens and initiates an immune response, ApcMin/+ mice and an inflammation-related tumor model both developed more tumors when NOD1 was lacking.[104,105]

According to a work published recently by Sears et. al., there are mainly three models that are involved in the pathogenesis of colon cancer. A particular subset of bacteria with sufficient virulence mechanisms to cause disease are represented by the first model. Whereas the second model focuses on the need for a host genetic component that allows a single microbe's pathogenicity to cause the disease. In order to understand the third model one or two microbial community should be functioning together or successively such that it promotes dysbiosis and colon cancer development.[101,106] Therefore, it is widely accepted that dysbiosis and improper immune response to microbial flora play a pivotal role in the pathogenesis and development of IBD associated colon cancer.

INFLAMMATORY BOWEL DISEASE

IBD is a gut related disease that occurs due to over aggressiveness and imbalance of immune response towards commensal microorganisms particularly expressed by pathogens.[107,108] Ulcerative colitis (UC) and Crohn's disease (CD) are the two main subtypes included in the

IBD. Recently due to the advancement of gene sequencing technology, metagenomic sequencing and robust bioinformatics tools have increased the dependability and precision of the 16S ribosomal RNA (ribonucleic acid) along with the gut microbial composition and even the bacterial functions during intestinal inflammation in IBD.[109,110] Ulcerative colitis is described as continuous inflammation in the colon. Sudden reduction and microbial instability (over- or under-expression of specific species) and negative side effects from treatments and medications as compared to the "normal" gut microbiota are the main hallmarks of the disease.[108] As per the information gathered from the human clinical trials, UC patients showed alterations of the gut microbiota including complete loss of the phyla *Firmicutes* and *Bacteroidetes.*[111] However, other clinical studies have revealed that individuals with UC have higher concentrations of the phyla *Actinobacteria* and *Proteobacteria* and lower bacterial diversity.[112-114] In contrast to UC, CD affects the whole GI tract including both healthy and inflammatory parts.[108] The prevalence of *Mycobacterium avium* subspecies paratuberculosis was found to be positively linked with CD after a thorough study and meta-analysis.[115] Patients with CD also had higher concentrations of *Escherichia coli* and *Ruminococcus gnavus* and decreased abundances of the genera *Faecalibacterium* and *Roseburia*[116] as per the recent data collection we can conclude that the main causes of IBD are found to be intestinal chronic inflammation and mucosal immune response dysfunctions which results in decreased gut bacterial diversity and microbial dysregulation. Dietary intervention has emerged as a crucial and effective strategy for re-establishing the gut microbiota's equilibrium and preventing IBD.[117]

Strong anti-inflammatory action demonstrated by phytochemicals for both in vivo and in vitro studies suggests that they may be used as potent treatment of IBD.[118-121] 40 IBD patients were examined in 40 human clinical studies on an IBD-AID (Inflammatory bowel disease anti-inflammatory diet regimen).[122-124] Various constituents like fish, egg and various fruits and vegetables were included in IBD-AID diet to improve the carbohydrate modification, ingestion of pre and probiotics, balance of the fatty acids intake and overall dietary in different IBD patients. The clinical trials revealed that more than 60% of IBD patients responded well or extremely well to nutritional therapy. Other phytochemicals like flavonoids and polyphenols reduced the relative number of *Escherichia coli* and *Fusobacteria* while increasing the quantity of *Bacteroidetes* thus ultimately boosting gut bacterial diversity and acting as anti-inflammatory agents against IBD. However, the complete mechanism related to symptoms reduction was not found.[14,125,126]

GUT MICROBIOTA, OBESITY AND DIABETES

Obesity is frequently defined as body mass index (BMI) values greater than 30 kg/m^2.[14,127,128] Obesity is also frequently characterized by the pathophysiology of fat buildup in body compartments and increased pro-inflammatory adipokine release by adipocytes and macrophages. Different Metabolic syndromes which increased the risk of heart disease, diabetes mellitus and stroke can be brought on by obesity and insulin resistance. These syndromes include high glucose levels, high blood pressure, high serum triglyceride levels, low high-density lipoprotein levels and large waist circumferences.[129] It has been observed that environmental factors like high-caloric diet and sedentary lifestyle have more weightage than genetic factors during the proliferation of the disease.[130-132]

The causative role of the gut microflorae in obesity was observed by a revolutionary study which demonstrated that germ-free mice transplanted with the gut microbiota from obese (ob/ob) mice exhibited noticeably increased adiposity compared to mice transplanted with the gut microbiota from lean (ob/+) mice.[133] The elevated amounts of acetate and butyrate provided evidence for the mechanism's greater capacity for energy harvesting. Similar findings were also observed in C57BL/6J mice that had developed obesity as a result of a western diet, and the microbiota profile had changed to include more Firmicutes and fewer Bacteroidetes.[134]

Various phytochemicals were seen involved during the pathogenesis of obesity. Recent studies stated that obese mice fed with high-fat/high-sugar diet including cranberry extracts made up of phenolic acid, flavanols, anthocyanins and proanthocyanidins decreased weight gain, visceral adiposity and insulin resistance. Thus, cranberries extracts improved metabolic homeostasis and increased the amount of Akkermansia in a favorable condition.[135] Other studies revealed that when mice were given 1% concord grape polyphenols that were rich in anthocyanins, flavan-3-ols and flavanols they showed very consistent results. Akkermansia muciniphila was significantly more prevalent as a result of grape polyphenols which changed the expression of intestinal genes. This resulted in enhanced lipid deposition that reduces adiposity and weight gain and glucose tolerance along with decreased glucose absorption and increased insulin secretion, which in turn controlled intestinal epithelial integrity and inflammatory marker levels.[136] However, a negative link between weight increase and enrichment of microbial pathways involved in flavonoid biosynthesis was found in obese rats fed with cafeteria meal. Hence, these findings suggest that obesogenic diet-induced dysbiosis

might interfere with the manufacture of flavonoids which may result in a reduction in host utilization of flavonoids and an obesity phenotype. In a nutshell it can be said that modulation of the gut microflorae is the most prominent method for the treatment of obesity.[137]

Diabetes mellitus is one of the major complications affecting the public health and quality of life of people. It is basically categorized into one of the metabolic illnesses and further defined as hyperglycemia brought on by abnormalities in insulin production and/or activity.[89] There are various types of diabetes depending upon the pathogenesis. First of all, the Type 1 diabetes (T1D) which results in absolute insulin deficiency due to B-cell destruction and on the other hand type 2 diabetes (T2D) that is characterized by a progressive loss of insulin secretion on the backdrop of insulin resistance, gestational diabetes mellitus (GDM) and other subtypes of diabetes such as monogenic diabetes syndromes, drug or chemical induced diabetes, etc.[138] As it is already known that there exist trillions of bacteria in the gut which were found to have relation with good health therefore, a correlation between diabetes mellitus and GM was estimated through various studies. Observations revealed that the beginning and progression of T2D were associated with abnormal gut microbiota composition however, the findings differed between studies due to the limited repeatability of the data from genomic sequencing due to factors including ethnicity, dietary habits, geography, disease state and sequencing methods. Other studies even revealed that patients having T2D showed symptoms of dysbiosis which was charecterized by deficiency in butyrate-producing bacteria like Clostridiales sp. SS3/4, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Roseburia intestinalis*, etc. as well as an increase in the concentrations of some *Lactobacillus* species and opportunistic pathogens like Desulfovi. However, other studies have found variations in the proportion of the main phyla Firmicutes/Bacteroidetes in T2D patients.[139,140]

Involvement of Different phytochemicals in the pathogenesis of diabetes was also observed in recent studies. Firstly, polysaccharide administration was discovered to enhance metabolic indicators and insulin sensitivity in diabetic patients.[141] It was shown that the consumption of the amounts of the polysaccharide from *Plantago asiatica* L., *Bacteroides ovatus*, *Bacteroides vulgates* and other colon bacteria. In addition to *Prevotella loescheii* and *Lactobacillus fermentum* the amount of Alistipes obesity (a species isolated from in diabetic rats) in a grossly obese person's excrement. Serum insulin sensitivity levels and fecal SCFA (Short chain fatty acid) concentrations both significantly rose at the same timely.[142]

Secondly, by slowing sugar absorption and creating a bulking effect in the stomach fiber intake consequently directly improves postprandial glucose and insulin response and the increased safety leads to a decrease in energy intake. Hence, according to findings related to dietary fibers it can be concluded that they might have anti-diabetic benefits.[143]

Therefore, many studies have helped to establish a connection between the GM and metabolic diseases like obesity and diabetes though further investigation and many more clinical trials may fetch more clear understanding in the near future.

CONCLUSION

Gut flora plays an essential role in human health contributing to gut defense system and maintenance of body. Imbalance in the gut flora leads to metabolic disorders namely as chronic inflammation, colon cancer, etc. due to dysbiosis. Multiple evidences prove that various phytochemicals play important role in enhancing gut flora thereby preventing various disorders. Polyphenols (flavonoids, anthocyanins and hydrolysable tannins) polysaccharide like fibers, carotenoid and butyrate are the major phytochemicals that are involved in promoting the gut florae. According, to current studies it is prominent that these phytochemicals are either directly or indirectly involved in retarding the pathogenesis of disorders such as colon cancer, IBD, obesity, diabetes mellitus and many others related to metabolic dysfunction. Future investigations might further involve clinical studies and interactions of phytochemicals and gut florae thus, providing a strong foundation for understanding more about the impacts of phytochemicals on the human gut.

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