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IMPACT OF GUT MICROBE IN HUMAN HEALTH AND DISEASES

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ABSTRACT

Gut bacteria are an important part of the human gut microbiome ecosystem, home to 10^{14} microorganisms, ten times more than human cells. Gut bacteria play important roles in human health, such as providing essential nutrients, synthesizing vitamin K, assisting in cellulose digestion, and promoting angiogenesis and enteric nerve function. However, when the intestinal ecosystem undergoes abnormal changes due to antibiotics, disease, stress, aging, improper diet and lifestyle, it can be potentially harmful due to changes in its composition. Dysbiosis of the gut bacterial community can lead to many chronic diseases such as: B. Inflammatory bowel disease, obesity, cancer, and autism. This review article summarizes and describes the role and potential mechanisms of gut bacteria in human health and disease.

Keywords: *gut bacteria, human health, cancer, obesity*

INTRODUCTION

The human intestinal mucosa is composed of epithelial cells, lamina propria, and muscularis mucosae colonized by 10^{14} microbes [1]. The number of these microbes is ten times the number of human cells. Gut bacteria are important components of the human gut microbiota ecosystem. Commensal bacteria colonize the gut shortly after birth and include about 1000 species, most of which are unknown species belonging to anaerobic strains [2,3]. The composition and temporal patterns of the gut microbiota of infants are very different and distinct from those of adults. Furthermore, the gut microbiota usually stabilizes to a more adult profile around 1 year of age after the introduction of solid food [4]. Furthermore, the composition of the gut bacterial community is primarily determined by intestinal motility, pH, redox status, nutrients, host secretions (gastric acid, bile, digestive enzymes, mucus), and the presence of an intact ileocecal valve [5]. Additionally, it can be affected by many factors, such as: B. Antibiotic use, illness, stress, aging, poor diet and lifestyle [5,6].

Intestinal bacteria and the host normally live in symbiosis. On the one hand, it can provide essential nutrients, synthesize vitamin K, support cellulose digestion, and promote angiogenesis and enteric nerve function [7,8,9]. Bacteroidetes and Firmicutes are the main bacteria involved in the metabolism of undigested food residues. They aid in the digestion of fiber and polyphenols through complex metabolic energy-generating mechanisms based on cross-feeding and co-metabolism.]. However, specialized intestinal bacteria carry out reduction reactions such as methanogenesis, acetogenesis, nitrate reduction, and sulfate reduction [11]. On the other hand, commensal bacteria and probiotics can promote barrier integrity and prevent antigens and pathogens from entering mucosal tissues [12].

GUT BACTERIA IN HEALTH

The main gut bacterial phyla, in the order of numerical importance, are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* and *Fusobacteria* [15]. *Firmic utes* are gram-positive bacteria with a low G + C content, including the large class of *Clostridia* and the lactic acid bacteria, while *Actinobacteria* are gram-positive bacteria with a high G + C content, including *Colinsella* and *Bifidobacterium* spp. Lactic acid bacteria and *Bifidobacteria* are two important types of gut bacteria, which are autochthonous ones from birth or acquired from digested food. *Lactobacillus* and *Leuconostoc* spp. are the main lactic acid bacteria found in the human intestine. *Bifidobacterium* spp. is the predominant bacteria found among the first colonizers of newborns, and persists at a low level in adults [16]. Gut bacteria play an important role in human health, including contributing to the host gut defense system and helping the gut to maintain normal function, while its composition can be influenced by the host .

GUT BACTERIA AND GUT IMMUNE SYSTEM

The gut resists pathogens through two barriers, the mechanical barrier and the immune barrier. The mechanical barrier consists of a monolayer of polarized intestinal epithelial cells, enterocytes and mucus. On the other hand, secretory immunoglobulin A (IgA), intraepithelial lymphocytes, macrophages, neutrophils, natural killer cells, Peyer's patches, and mesenteric lymph nodes form immune barriers. Probiotic bacteria and probiotics can promote the integrity of the gut barrier. Contribute to the defense system. Gut bacteria maintain resistance against the colonization of pathogenic bacteria by competing for nutrients and attachment sites on the mucosal surface in the colon, a phenomenon collectively known as “colonization resistance” [17]. The invasion of pathogenic bacteria is also prevented by commensal bacteria due to the reduction of the intestinal pH by the production of lactate and short-chain fatty acids (SCFAs) [9]. Another way is by producing toxic or carcinogenic metabolites to inhibit the growth or kill potentially pathogenic bacteria, together with volatile fatty acids that can inhibit the colonization of pathogenic bacteria. For example, proteolytic fermentation in the distal colon could produce toxic, carcinogenic metabolites such as bacteriocins, ammonia, indoles, and phenols by gut bacteria [18]. Lipopolysaccharides (LPSs) and peptidoglycan (PGN) components in the bacterial cell wall are two kinds of pathogen-associated molecular patterns, and they can individually or synergistically activate nuclear factor κB (NF-κB) effector and further induce the production of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and antimicrobial peptides in the defense against foreign pathogens. Chronic stimulation of pattern recognition receptors (PRRs) by PGNs can also minimize excessive tissue damage caused by intestinal antigen-presenting cells. This cell may produce inhibitory cytokines such as transforming growth factor-β (TGF-β) and IL-10 via the core oligomerization domain. - Two dependent paths [19]. Studies of animals housed under germ-free conditions have shown that germ-free animals have "vasculature, digestive enzyme activity, muscle wall thickness, decreased cytokine production and serum immunoglobulin levels, shrinkage of Peyer's patches, intraepithelial lymphocyte It was shown to have morphological, structural, and functional abnormalities such as “decreased” [21]. In another study, animals fed germ-free mouse cells developed early onset of colitis, and CD4+CD62L cells from germ-free mice compared with mice fed reconstituted conventional lymphocytes It failed to ameliorate colitis [22]. In this study, the high proportion of CD4+GITR+expressing lymphocytes and the production of IL-10 after dendritic cell priming suggested that germ-free mice had Treg cells. The absence was also assumed, indicating the presence of Treg cells in CD4+CD62L+ lymphocytes. showed a subgroup derived from mice reared conventionally. Butyric acid produced by commensal microorganisms during starch fermentation can promote extrathymic generation of Treg cells [23].

DIETARY INFLUENCE ON GUT BACTERIA

Gut bacterial colonization is affected by many factors, including: B. Living environment and nutrition (Figure 2). Infant diet has been reported to affect the composition of gut bacteria. Breast-fed infants had higher levels of bifidobacteria, whereas formula-fed infants had higher levels of Bacteroides species, Clostridium coccoides, and Lactobacillus species. Listed. [30,31,32]. In addition, host physiological

processes, anatomy, and gastrointestinal physiology are also important factors [24]. They can induce changes in the host's disease architecture. It has been proven that diet can affect the composition of gut bacteria.Studies have shown that mice fed a Western diet and a low-fat diet have different gut bacterial structures. I was. Relative abundance increased ~1.2-fold in Bacteroidetes, 18-fold in Proteobacteria, and decreased ~1.5-fold in Firmicutes when mice were fed a Western diet. Members of the Desulfovibrionaceae family were significantly enriched in the cecal contents of healthy mice fed a Western diet. Lactobacillus gasseri species were found, which accounted for an average of 4.3% of total bacteria, while Ruminococcus and other Lachnospiraceae members, Bacteroidetes, were also enriched in mice fed a low-fat diet. Lactobacillus gasseri species were also absent in mice fed a Western diet [33]. Some studies have also reported that long-term and short-term diet influences the composition and function of the human gut microbiota. Enterotypes were strongly associated with long-term diet, especially proteins and animal fats (Bacteroidetes) and carbohydrates (Prevotella). Although the composition of the microbiome clearly changed within he 24 hours from initiation of either a high-fat/low-fiber diet or a low-fat/high-fiber diet, this enterotypic identity was assessed in 10 subjects. In a controlled diet study he remained stable for 10 days [34]. . Another study found that short-term consumption of a diet consisting solely of animal meat, eggs, cheese, or plants rich in grains, legumes, fruits, and vegetables could alter microbial community structure and individual variability. was shown. Overwhelmed expression. Animal diet increased the abundance of bile-resistant microorganisms and decreased the concentration of Firmicutes, which metabolize food plant polysaccharides. Bile-resistant microorganisms included Aristipes, Virophila, and Bacteroidetes, and Firmicutes included Rosebria, Eubacterium rectal, and Ruminococcus bromi. Both diets altered the metabolic activity of the microbes. Animal diets had significantly lower content of carbohydrate fermentation products and higher concentrations of amino acid fermentation products compared to plant diets and baseline samples [35].

Further research has found that dietary factors such as polyphenols, fiber and carbohydrates can alter the balance of gut bacteria.Phenolic acids and flavonoids are the most important polyphenols in our dietary intake. Tea phenols and their derivatives have been shown to inhibit the growth of certain pathogens such as Clostridium perfringens, Clostridium difficile and Bacteroides. It inhibits and inhibits commensal anaerobic bacteria such as Clostridium and Bifidobacterium. and the genus Lactobacillus. less impact. [36]. Parker et al. [37] found that dietary polyphenols can indirectly alter the balance of gut bacteria through biotransformation products rather than the original plant compounds. and decreased the ratio of Firmicutes to Bacteroidetes compared to controls. Furthermore, among the polyphenols studied, caffeic acid stimulated the greatest absolute increase in gut bacteria at 100 mg/ml. Polyphenols also stimulated the production of short-chain organic acids by intestinal bacteria. Dietary fiber was another dietary factor that influenced gut bacterial composition. One study found that subjects receiving a fiber-rich enteral formula had fewer negative symptoms related to urgency, and the reduction in total bacterial counts and bifidobacteria counts was less severe compared to fiber-free formulas. [38]. Polyphenols and dietary fiber were considered beneficial dietary factors. Functional foods based on these beneficial nutritional factors may offer opportunities to modulate the microbial balance in the gut. It has been shown that it can affect diversity [39].

However, some dietary factors can be harmful, such as: B. Dietary iron. Iron, primarily from red meat and fortified grains, can also alter the composition of gut bacteria. Other luminal iron comes from smoking. Increased iron availability enhances the growth and virulence of intestinal bacteria and increases the permeability of the intestinal barrier. One study showed that increased exposure to iron contributes to the colonization of certain bacterial pathogens, including Salmonella [40].May be a risk factor for colon cancer. Gut bacterial composition may also be regulated by traditional Chinese herbs. Five hydroxyanthraquinone derivatives from *Rheum palmatum* had inhibitory effects on juvenile growth of *Bifidobacterium* [41]. Rhein was the most effective component of *R. palmatum* to inhibit the growth of B. adolescentis.

It was proved that prebiotics could influence the composition of gut bacteria to benefit the host. Prebiotics are defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating

the growth and/or activity of one or a limited number of bacteria in the colon, and thus improving the hosts' health [42]. Prebiotics are carbohydrate-like compounds, such as lactulose and resistant starch, and have been used in the food industry to modify the composition of the microbiota species to benefit human health in recent years [43]. Inulin is one type of prebiotics. These prebiotics mostly target bifidobacteria and lactobacilli, which are two kinds of probiotics [44]. Probiotics are living non-pathogenic organisms used as food ingredients to benefit the hosts' health. They may be lactic acid bacteria, *Bifidobacteria*, or yeasts, such as *Saccharomyces cerevisiae* [45,46]. Furthermore, probiotics can be used in the treatment of hepatic encephalopathy, inflammatory bowel diseases, infections, hypertension, cancer, and atopic dermatitis in children [46,47,48,49,50].

GUT BACTERIA AND DISEASES

Intestinal bacteria and the host normally live in symbiosis. But when ecosystems undergo extraordinary changes, gut bacteria can potentially become harmful. Abnormalities in the gut bacterial community in patients or animal models can lead to many diseases. For example, antibiotic therapy and surgery cause pseudomembranous colitis due to toxin production by Clostridium difficile and sepsis from Escherichia coli, Enterococcus faecalis, and Enterococcus faecium, and intraabdominal abscess due to Bacteroides fragilis [51]. An imbalance in gut bacterial composition is associated with intestinal symptoms such as bloating, abdominal pain and diarrhea. Uncultured phylotypes from Clostridium clusters IV and XIVa were statistically significantly positively correlated with flatulence. Anaerotruncus colihominis, Ruminococcus callidus, and Lachnospira pectinoschiza were higher when flatulence was recorded. Bifidobacterium frequency may be negatively correlated with abdominal pain. In addition to Bifidobacterium, Clostridium cluster IV, a phylotype within Ruminococcus lactaris, was significantly reduced in pain-related samples. Among the positive correlations, uncultured potentially pathogenic phylotypes within uncultured Clostridium II, Anaerotrunks colihominis, and Ruminococcus callidus increased more than 10-fold when pain was recorded [twenty five]. Diarrhea is associated with reduced numbers of streptococci, particularly S. alactolyticus [15]. In addition, many other diseases are associated with gut bacteria, including inflammatory bowel disease, obesity, diabetes, liver disease, chronic heart disease, cancer, HIV, and autism.

INFLAMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is most common in the developed countries [24]. Reciprocal interaction between commensal gut bacteria and the host may induce allergies and IBD. Overly aggressive Th-1 mediated cytokine response to commensal bacteria may be the pathogen of chronic intestinal inflammation [52]. In addition, disorders in bacterial recognition by macrophages are strongly related to pathogenesis of IBD. Furthermore, IBD could results from an abnormal immune response against the commensal microbiota in a genetically susceptible host. Jostins *et al.* [53] have identified 163 risk loci associated with IBD, and found that many loci were involved in the sensing and elimination of bacteria. A hypothesis is that the innate immune system in IBD patients could be deficient, which in turn leads to an uncontrolled adaptive response.

Ulcerative colitis (UC) is one of the two major idiopathic IBDs [54]. In UC patients, the disease is limited to the colon. Numbers of lactobacilli were significantly lower during the active phase of the disease, and denaturing gradient gel electrophoresis analysis suggested that *Lactobacillus salivarus*, *Lactobacillus manihotivorans* and *Pediococcus acidilactici* were present in remission, but not during active inflammation [55]. Besides, the colonic bacterial communities from diseased mice were less complex, indicating less diversity of bacterial composition during acute inflammation. Bacteria of the *Clostridiales* group were more prominent in samples from the inflamed colon, indicating these bacteria might accumulate during colitis [56].

Crohn's disease (CD) is another type of IBDs. It has been thought to be an autoimmune disease, in which the body's immune system attacks the gastrointestinal tract and causes inflammation [60]. Seksik *et al.* [61] found that the fecal microflora in patients with both inactive and active colonic CD contained significantly more enterobacteria than in healthy subjects. In addition, about 30% of the dominant bacteria did not belong to the usual dominant phylogenetic groups. Another study found that five bacterial species characterised dysbiosis in CD patients, which were a decrease in *Dialister invisus*, an uncharacterised species of *Clostridium* cluster XIVa, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis*, and an increase in *Ruminococcus gnavus*. There was a different composition of gut microbiota in unaffected relatives of patients with CD compared with healthy controls. This dysbiosis was not characterized by lack of butyrate producing-bacteria as observed in CD but suggested mucin-degradation capacity of microorganisms [62].

DIABETES

High-fat diet induced obesity is associated with inflammation that contributes to the development of insulin resistance, which may cause type-2 diabetes (T2D). Diabetes (a metabolic disease) has been a big problem all over the world, and it has been shown to be strongly associated with gut bacteria. There are two types of diabetes, type-1 diabetes (T1D) and T2D. Changes in the gut bacteria contribute to diabetes. The occurrence of diabetes is impacted by early intestinal microbial colonization at birth, which is affected by the feeding ways, birth weight, and the delivery method at birth [82]. In addition, LPS was thought to be a novel factor triggering the onset of high-fat diet-induced T2D [83].T1D is a destructive islet β-cell specific autoimmune disease with loss of ability of insulin production, which results from interaction between genetic and environmental factors. Gut bacteria manipulation modulated mucosal oxidative stress and pro/anti-inflammatory balance to protect against T1D, and eventually restored the intestinal mucosal barrier function [84]. Impaired intestinal mucosal barrier and altered mucosal immunity were involved in the pathogenesis T1D. Aberrant gut bacteria may contribute to the pathogenesis of T1D, since cross-talk between gut bacteria and the innate immune system may be involved in islet destruction [85].

LIVER DISEASES

The gut and liver have a close interplay based on the evidence that the gut absorbs beneficial substances produced by the liver. The liver receives approximately 70% of its blood supply from the intestinal venous outflow, which represents the first line of defense against gut-derived antigens and is equipped with a broad array of immune cells, including macrophages, lymphocytes, natural killer cells, and dendritic cells, to accomplish this function [91]. Gut bacteria play a key role in the maintenance of gut-liver axis health. Ethanol, ammonia, and acetaldehyde produced by the intestinal microflora are generally metabolized by the liver and control Kupffer cell activity and cytokine production.

Small intestinal bacteria overgrowth (SIBO) may be an important pathogenesis of nonalcoholic steatohepatitis (NASH). Small intestinal movement was decreased by small intestinal bacteria overgrowth in NASH rats. Antibacterial treatment can alleviate the severity of NASH [92]. In the study, *E. coli* was excessively increased in NASH rats, as was the serum level of aminopherase. TNF-α may be an important mediator in the promotion of NASH by SIBO, which was supported by the fact that the level of aminopherase went up and down with the serum level of TNF-α. Nevertheless, another study suggested the severity of Concanavalin-A (ConA) induced hepatitis was increased when intestinal bacterial flora were suppressed by antibiotics. Reconstitution of intestinal flora with H_2-producing *E. coli* alleviated the ConA-induced liver inflammation. But H_2-deficientmutant *E. coli* did not have this effect. These results suggested that H_2 released from intestinal bacteria can suppress ConA induced inflammation in liver [93]. Recent

evidence [94] also indicated that the gut microbiota is associated with alcoholic associated liver damage. Gut-derived endotoxin and other luminal bacterial products may be cofactors for the development of alcoholic liver disease. Daily alcohol consumption could affect the composition of colonic microbiome, which suggests that dysbiosis in the gut bacteria communities may be an important mechanism of alcohol-induced endotoxemia [94].

CANCERS

The presence of microbial pathogens or a disorder in the native intestinal bacterial community contributes to the development of cancers, such as gastrointestinal cancer and prostate cancer. Commensal bacteria were recognized as important cofactors in the carcinogenesis of colon. It was reported that gut bacteria can trigger macrophages to produce diffusible clastogens, or chromosome-breaking factors. This action was through a bystander effect which mediated DNA damage and induced chromosomal instability in neighboring cells. In addition, peroxidative stress may play an important role in ileal and colonic pathology and inflammation in bacteria-associated intestinal cancers [103].

The composition of the gut bacteria community is different between healthy individuals and colon cancer patients. Several butyrate-producing bacterial genera were under-represented in the stool of colorectal cancer patients compared to healthy individuals. Two of the *Prevotella* species identified were completely absent from the colon cancer samples analyzed. *Prevotella* was hypothesized to help maximize energy harvest from a plant-based diet. The higher levels of *Prevotella* in the healthy cohort may reflect differences in the intake of fiber and other plant compounds compared to the individuals with colon cancer. On the other hand, *Acidaminobacter*, *Phascolarctobacterium*, *Citrobacter farmer*, and *Akkermansia muciniphila* significantly over-represented in colorectal cancer (CRC) stool samples [104]. *Akkermansia muciniphila* are mucin-degrading species. These may influence the quantities of metabolites in the intestinal tract. Butyric acid was significantly lower in the faeces of colon cancer patients, since species of butyrate producing bacteria (such as *Ruminococcus* spp. and *Pseudobutyrivibrio ruminis*) were lower in stool samples from CRC patients compared to healthy controls. Butyrate is quite an important nutrient for normal colon cells, which was shown to reduce proliferation and induce apoptosis of human colon carcinomas cells alone or in combination with propionate. In another study, over 26 novel species assigned to the *Helicobacter genus* (more than 90% similarity) have been identified, only some of which have been directly associated with gastrointestinal cancers [105].

Dietary administration of *Bifidobacterium longum* had significant suppression of colon tumor incidence, tumor multiplicity and tumor volume. It was suggested that oral supplement of *B. longum* exerted strong antitumor activity, as modulation of the intermediate biomarkers of colon cancer indicated antimutagenic effects [106]. In addition, ingestion of *B. longum* has been showed to inhibit azoxymethane-induced cell proliferation, ornithine decarboxylase activity and expression of ras-p21 oncoprotein activity significantly.

HIV

The recent hypothesis is that microbial alterations at gastrointestinal tract level play a key role in the pathogenesis of chronic HIV infection [110]. It was found that gut bacteria of HIV/AIDS patients shared more than 90% sequences of HIV-1. These bacteria were mostly specified as *E. coli* (negative in serotypization), *Proteus mirabilis*, *Citrobacter freundii*, *Staphylococcus* sp. and *Enterobacter aerogenes* [111]. These results provided hypothesis that gut bacteria are involved in the pathogenesis of HIV. HIV infection results in deterioration of gut homeostasis, which leads to increased bacterial compounds in the circulation. These bacterial components including LPS, peptidoglycan, and bacterial

DNA may further stimulate the vicious circle of immune activation, which in turn contributes to viral replication and the progression of disease [110]. Imbalance of the intestinal immune barrier, translocation of immunostimulatory microbial products, and chronic systemic inflammation was thought to drive HIV infection to AIDS.

Vujkovic-Cvijin *et al.* [112] found that 579 taxa were enriched and 45 taxa were depleted in viremic untreated (VU) HIV-infected subjects compared to HIV^- subject samples. The most enriched taxon was *Erysipelotrichaceae* in the class *Mollicutes*, which has been associated with obesity and heightened cardiovascular morbidity. Members of the phylum *Proteobacteria* were included in the most enriched taxa in VU subjects. Enriched genera from the *Enterobacteriaceae* family included *Salmonella*, *Escherichia*, *Serratia*, *Shigella*, and *Klebsiella* species, which were known as pro-inflammatory pathobionts. Additionally, *Staphylococcus*, *Pseudomonas*, and *Campylobacter* spp. were highly enriched in the mucosae of VU subjects, and they are known as opportunistic pathogens and sources of bacteremia in HIV-infected subjects. The relative abundance of specific members of *Clostridia* and *Bacteroidia* were significantly reduced in VU subjects, with the greatest degree of depletion among members of the *Bacteroides* and *Alistipes genera*. More importantly, the study also found that HIV-infected subjects seemed to harbor the enteropathogenic bacteria community that can catabolize tryptophan into immunomodulatory kynurenine derivatives, which is known to correlate with the progression of disease and contribute to mucosal immune disruption.

Patients living with HIV showed a dramatic decline of lactobacilli and bifidobacteria and a higher concentration of pathogenic species including *Candida albicans* and *Pseudomonas aeruginosa* [113,114]. Probiotics such as *Lactobacillus rhamnosus* GR-1 have significant promise in supporting the immune function of people living with HIV [115]. Gori *et al.* [110] found that *bifidobacteria* increased significantly, with decreasing *Clostridium coccoides*, *Eubacterium rectale*, *Clostridium lituseburense*, and *Clostridium histolyticum* when prebiotics were supplied. The study also found dietary supplementation with a prebiotic oligosaccharide mixture reduced sCD14, $CD4^+$ T-cell activation (CD25), and improved NK cell activity in highly active antiretroviral therapy-naive HIV-1 infected adults.

AUTISM

Autism spectrum disorders (ASDs) are neurodevelopmental disorders, which are characterized as cognitive impairments, stereotyped behaviors, and impairments in social skills. ASDs include autism, Asperger's syndrome, and pervasive developmental disorder not otherwise specified (commonly abbreviated as PDD-NOS). The number of people diagnosed with autism has been increasing dramatically since the 1980s. Autism has been thought to be linked to gastrointestinal symptoms, such as diarrhea, combined with genetic predisposition and environmental factors [116]. There might be a gut-brain axis in the pathogenesis of autism. Gut bacteria possibly communicate with the central nervous system through neural, endocrine and immune pathways to influence brain function and behavior [117]. Several intestinal bacteria are involved in the pathogenesis of autism. Individuals with ASDs responded well to the antibiotics vancomycin and metronidazole, although vancomycin is not absorbed from the gastrointestinal tract. Overgrowth of *Clostridia* and a decrease in *Bifidobacteria* could be involved in ASD pathogenesis [118], as clostridium produces exotoxins and propionate, the latter worsened ASD-like behavior.

Autistic (AD) children have a distinct and less diverse gut microbial community structure, and showed significantly lower levels of genera *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* [119]. Two organisms (*Bacteroides vulgatus* and *Desulfovibrio* species, including *D. desulfuricans*, *D. fairfieldensis*, and *D. piger*) were more commonly found in stools of AD children than in the control

children's stools. *Firmicutes* and *Actinobacteria* accounted for less of the total flora of AD children's stools than the control children's stools [120]. The most striking finding was that significant numbers of non-spore-forming anaerobes and microaerophilic bacteria were found in gastric and duodenal specimens from children with autism, while such bacteria are totally absent in the gut and duodenum from control children [121]. Another study also suggested that *Desulfovibrio* was more common in AD children than in controls. In addition, siblings of AD children had intermediate counts of *Desulfovibrio*, suggesting possible spread of the organism in the family environment [122].Based on 16S-rRNA and culture-dependent data, De Angelis *et al.* [123] . *Sarcina* and *Clostridium genera* were higher in AD children compared with healthy children. The composition of *Lachnospiraceae* family also differed in AD children. The level of *Eubacteriaceae* in fecal samples of AD children was lower, except for *Eubacterium siraeum*. The levels of some *Alistipes* and *Akkermansia* species as well as almost all the identified *Sutterellaceae* and *Enterobacteriaceae* were also higher in AD children. If the differences of gut bacteria between AD and healthy children are one of the causes or the consequence of autism, they may be clues for a specific diagnostic test, and/or for prevention and treatment.

OTHER DISEASES

Gut bacteria are also related with several other diseases and malaise, such as bad sleep, rheumatic diseases, and kidney diseases. Sleep in functional constipation subjects may be worse than that in control subjects, that is to say wake after sleep onset (WASO) and WASO (%) (WASO/total sleep time multiplied by 100) in functional constipation patients were longer and greater. The study also found *Bifidobacterium* counts per gram of wet stools and proportion in total bacterial cell counts were significantly lower in functional constipation patients [124]. Bad sleep, functional constipation, and low *Bifidobacterium* proportion may have some connection.

The relationship between rheumatic diseases (RA) and microbial components has been elucidated. It was found that joint inflammation did not develop in germ-free conditions in animal models of human spondylarthropathy in HLA-B27 transgenic rats or in B10.BR mice [125,126]. Rheumatic arthritis patients had significantly reduced fecal carriage of *Bifidobacteria* and *Bacteroides fragilis*. Obesity may be a factor in the aetiology of RA. Increased LPS uptake through the gut lumen to other tissues occurs in obese murine models, and enhanced systemic exposure to LPS could increase the risk of RA [127].

In addition, intestinal bacteria may be involved in chronic kidney disease. It was assumed that intestinal bacteria promote the uraemic syndrome by the production of uraemic toxins [128]. Tyrosine or phenylalanine fermentation by intestinal bacteria generates p-cresol, which is circulated mainly as *p*-cresyl sulfate (*p*-CS). The *p*-CS, known as uremic retention solute, accumulates in the blood of chronic kidney disease patients. Composition of microbiota was suggested to influence the production of p-cresol. *Bacteroides fragilis* and *Clostridium difficile* were reported to produce p-cresol *in vitro* [129]. Th1-type cellular immune response, which plays an important role in protection against infectious diseases, was suppressed by intestinal bacteria-derived *p*-CS [130].

CONCLUSION

This review provides current understanding of the role of gut bacteria in human health and diseases. Gut bacteria have been found to be involved in many diseases, such as IBD, obesity, diabetes, carcinoma, HIV, and autism. When the gut bacteria undergo some imbalance, several diseases may occur. Immunoregulatory activity is the main function of gut bacteria in the pathogenesis of these diseases. Diet-induced dysbiosis affects disease susceptibility, including IBD, diabetes, and obesity. In recent years, prebiotics and probiotics

have been widely used in the treatment of some diseases, and have shown great effects. Fecal microbiota transplant is also a way to modulate gut bacteria. However, there are many questions open, for example, if the changes of gut microbiota are the causes or the consequences of the diseases? Furthermore, some studies have even obtained different results. In order to explore the exact pathogenesis of the gut bacteria related diseases and the role of gut bacteria in these diseases, further studies should be carried out. Butyrate has been shown to be quite an important nutrient for normal colon cells, and could reduce proliferation and induce apoptosis of human colon carcinomas. More studies, therefore, should be carried out to identify butyrate-producing bacteria. In addition, mixed use of prebiotics and probiotics should be further investigated, considering their benefits on human health. Since gut bacteria have important impacts on human health and diseases, they can be used as a novel target to prevent and treat many chronic diseases, and further studies are guaranteed to target them in different ways to fight against gut bacteria-related diseases. Furthermore, special attention should be paid to gut microbiomics to better understand the relationship between gut microbiota and human health, which will provide perspectives for personalized gut microbiota management and bacteriotherapy.

REFERENCES

1. Clark J.A., Coopersmith C.M. Intestinal crosstalk: A new paradigm for understanding the gut as the "motor" of critical illness. *Shock.* 2007;28:384–393. doi: 10.1097/shk.0b013e31805569df. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

2. Honda K., Takeda K. Regulatory mechanisms of immune responses to intestinal bacteria. *Mucosal Immunol.* 2009;2:187–196. doi: 10.1038/mi.2009.8. [PubMed] [CrossRef] [Google Scholar]

3. Bischoff S.C., Kramer S. Human mast cells, bacteria, and intestinal immunity. *Immunol. Rev.* 2007;217:329–337. doi: 10.1111/j.1600-065X.2007.00523.x. [PubMed] [CrossRef] [Google Scholar]

4. Palmer C., Bik E.M., DiGiulio D.B., Relman D.A., Brown P.O. Development of the human infant intestinal microbiota. *PLoS. Biol.* 2007;5:1556–1573. doi: 10.1371/journal.pbio.0050177. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Gerritsen J., Smidt H., Rijkers G.T., de Vos W.M. Intestinal microbiota in human health and disease: The impact of probiotics. *Genes Nutr.* 2011;6:209–240. doi: 10.1007/s12263-011-0229-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

6. Woodmansey E.J. Intestinal bacteria and ageing. *J. Appl. Microbiol.* 2007;102:1178–1186. doi: 10.1111/j.1365-2672.2007.03400.x. [PubMed] [CrossRef] [Google Scholar]

7. Hill D.A., Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. *Annu. Rev. Immunol.* 2010;28:623–667. doi: 10.1146/annurev-immunol-030409-101330. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

8. Mueller C., Macpherson A.J. Layers of mutualism with commensal bacteria protect us from intestinal inflammation. *Gut.* 2006;55:276–284. doi: 10.1136/gut.2004.054098. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

9. Guarner F., Malagelada J.R. Gut flora in health and disease. *Lancet.* 2003;361:512–519. doi: 10.1016/S0140-6736(03)12489-0. [PubMed] [CrossRef] [Google Scholar]

10. Tsuji M., Suzuki K., Kinoshita K., Fagarasan S. Dynamic interactions between bacteria and immune cells leading to intestinal IgA synthesis. *Semin. Immunol.* 2008;20:59–66. doi: 10.1016/j.smim.2007.12.003. [PubMed] [CrossRef] [Google Scholar]

11. Tuohy K.M., Hinton D.J., Davies S.J., Crabbe M.J., Gibson G.R., Ames J.M. Metabolism of Maillard reaction products by the human gut microbiota—implications for health. *Mol. Nutr. Food Res.* 2006;50:847–857. doi: 10.1002/mnfr.200500126. [PubMed] [CrossRef] [Google Scholar]

12. Ulluwishewa D., Anderson R.C., McNabb W.C., Moughan P.J., Wells J.M., Roy N.C. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J. Nutr.* 2011;141:769–776. doi: 10.3945/jn.110.135657. [PubMed] [CrossRef] [Google Scholar]

13. Macfarlane G.T., Cummings J.H. Probiotics and prebiotics: Can regulating the activities of intestinal bacteria benefit health? *BMJ.* 1999;318:999–1003. doi: 10.1136/bmj.318.7189.999. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

14. Akaza H. Prostate cancer chemoprevention by soy isoflavones: Role of intestinal bacteria as the "second human genome" *Cancer Sci.* 2012;103:969–975. doi: 10.1111/j.1349-7006.2012.02257.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Hermann-Bank M.L., Skovgaard K., Stockmarr A., Larsen N., Molbak L. The gut microbiotassay: A high-throughput qPCR approach combinable with next generation sequencing to study gut microbial diversity. *BMC Genomics.* 2013;14 doi: 10.1186/1471-2164-14-788. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

16. Vaughan E.E., Heilig H., Ben-Amor K., de Vos W.M. Diversity, vitality and activities of intestinal lactic acid bacteria and bifidobacteria assessed by molecular approaches. *FEMS Microbiol. Rev.* 2005;29:477–490. doi: 10.1016/j.fmrre.2005.04.009. [PubMed] [CrossRef] [Google Scholar]

17. Stecher B., Hardt W. The role of microbiota in infectious disease. *Trends Microbiol.* 2008;16:107–114. doi: 10.1016/j.tim.2007.12.008. [PubMed] [CrossRef] [Google Scholar]

18. Beaud D., Tailliez P., Anba-Mondoloni J. Genetic characterization of the β-glucuronidase enzyme from a human intestinal bacterium, *Ruminococcus gnavus*. *Microbiology.* 2005;151:2323–2330. doi: 10.1099/mic.0.27712-0. [PubMed] [CrossRef] [Google Scholar]

19. Fung Q.M., Szilagyi A. Carbohydrate elimination or adaptation diet for symptoms of intestinal discomfort in IBD: Rationales for "Gibsons' Conundrum" *Int. J. Inflamm.* 2012;2012 doi: 10.1155/2012/493717. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

20. Lanning D.K., Rhee K.J., Knight K.L. Intestinal bacteria and development of the β-lymphocyte repertoire. *Trends Immunol.* 2005;26:419–425. doi: 10.1016/j.it.2005.06.001. [PubMed] [CrossRef] [Google Scholar]

21. Compare D., Coccoli P., Rocco A., Nardone O.M., De Maria S., Carteni M., Nardone G. Gut–liver axis: The impact of gut microbiota on non alcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis.* 2012;22:471–476. doi: 10.1016/j.numecd.2012.02.007. [PubMed] [CrossRef] [Google Scholar]

22. Strauch U.G., Obermeier F., Grunwald N., Gurster S., Dunger N., Schultz M., Griese D.P., Mahler M., Scholmerich J., Rath H.C. Influence of intestinal bacteria on induction of regulatory T cells: Lessons from a transfer model of colitis. *Gut.* 2005;54:1546–1552. doi: 10.1136/gut.2004.059451. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

23. Arpaia N., Campbell C., Fan X.Y., Dikiy S., van der Veeken J., DeRoos P., Liu H., Cross J.R., Pfeffer K., Coffer P.J., Rudensky A.Y. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature.* 2013;504:451–455. doi: 10.1038/nature12726. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

24. Macfarlane S., Steed H., Macfarlane G.T. Intestinal bacteria and inflammatory bowel disease. *Crit. Rev. Clin. Lab. Sci.* 2009;46:25–54. doi: 10.1080/10408360802485792. [PubMed] [CrossRef] [Google Scholar]

25. Jalanka-Tuovinen J., Salonen A., Nikkila J., Immonen O., Kekkonen R., Lahti L., Palva A., de Vos W.M. Intestinal microbiota in healthy adults: Temporal analysis reveals individual and common core and relation to intestinal symptoms. *PLoS ONE.* 2011;6:e23035. doi: 10.1371/journal.pone.0023035. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

26. Landete J.M. Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health. *Food Res. Int.* 2012;46:410–424. doi: 10.1016/j.foodres.2011.12.023. [CrossRef] [Google Scholar]

27. Fuentealba C., Figuerola F., Estevez A.M., Bastias J.M., Munoz O. Bioaccessibility of lignans from flaxseed (*Linum usitatissimum* L.) determined by Single Batch *in vitro* simulation of the digestive Pprocess. *J. Sci. Food. Agric.* 2014;94:1729–1738. [PubMed] [Google Scholar]

28. Clavel T., Henderson G., Alpert C.A., Philippe C., Rigottier-Gois L., Dore J., Blaut M. Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. *Appl. Environ. Microbiol.* 2005;71:6077–6085. doi: 10.1128/AEM.71.10.6077-6085.2005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

29. Atkinson C., Frankenfeld C.L., Lampe J.W. Gut bacterial metabolism of the soy isoflavone daidzein: Exploring the relevance to human health. *Exp. Biol. Med.* 2005;230:155–170. [PubMed] [Google Scholar]

30. Brown K., DeCoffe D., Molcan E., Gibson D.L. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients.* 2012;4:1095–1119. doi: 10.3390/nu4081095. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

31. Harmsen H., Wildeboer-Veloo A., Raangs G.C., Wagendorp A.A., Klijn N., Bindels J.G., Welling G.W. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *J. Pediatr. Gastroenterol. Nutr.* 2000;30:61–67. doi: 10.1097/00005176-200001000-00019. [PubMed] [CrossRef] [Google Scholar]

32. Fallani M., Young D., Scott J., Norin E., Amarri S., Adam R., Aguilera M., Khanna S., Gil A., Edwards C.A., Dore J. Intestinal microbiota of 6-week-old infants across Europe: Geographic influence beyond delivery mode, breast-feeding, and antibiotics. *J. Pediatr. Gastroenterol. Nutr.* 2010;51:77–84. doi: 10.1097/MPG.0b013e3181d1b11e. [PubMed] [CrossRef] [Google Scholar]

33. Tachon S., Lee B., Marco M.L. Diet alters probiotic *Lactobacillus* persistence and function in the intestine. *Environ. Microbiol.* 2014;16:2915–2926. doi: 10.1111/1462-2920.12297. [PubMed] [CrossRef] [Google Scholar]

34. Wu G.D., Chen J., Hoffmann C., Bittinger K., Chen Y.Y., Keilbaugh S.A., Bewtra M., Knights D., Walters W.A., Knight R., et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334:105–108. doi: 10.1126/science.1208344. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

35. David L.A., Maurice C.F., Carmody R.N., Gootenberg D.B., Button J.E., Wolfe B.E., Ling A.V., Devlin A.S., Varma Y., Fischbach M.A., et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505:559–560. doi: 10.1038/nature12820. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

36. Lee H.C., Jenner A.M., Low C.S., Lee Y.K. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Res. Microbiol.* 2006;157:876–884. doi: 10.1016/j.resmic.2006.07.004. [PubMed] [CrossRef] [Google Scholar]

37. Parkar S.G., Trower T.M., Stevenson D.E. Fecal microbial metabolism of polyphenols and its effects on human gut microbiota. *Anaerobe.* 2013;23:12–19. doi: 10.1016/j.anaerobe.2013.07.009. [PubMed] [CrossRef] [Google Scholar]

38. Koecher K.J., Thomas W., Slavin J.L. Healthy subjects experience bowel changes on enteral diets; addition of a fiber blend attenuates stool weight and gut bacteria decreases without changes in gas. *J. Parenter. Enter. Nutr.* 2013;25:132–138. [PubMed] [Google Scholar]

39. Sofi M.H., Gudi R., Karumuthil-Melethil S., Perez N., Johnson B.M., Vasu C. pH of drinking water influences the composition of gut microbiome and type 1 diabetes incidence. *Diabetes.* 2014;63:632–644. doi: 10.2337/db13-0981. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

40. Kato I., Boleij A., Kortman G., Roelofs R., Djuric Z., Severson R.K., Tjalsma H. Partial associations of dietary iron, smoking and intestinal bacteria with colorectal cancer risk. *Nutr. Cancer.* 2013;65:169–177. doi: 10.1080/01635581.2013.748922. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

41. Wang J., Zhao H., Kong W., Jin C., Zhao Y., Qu Y., Xiao X. Microcalorimetric assay on the antimicrobial property of five hydroxyanthraquinone derivatives in rhubarb (*Rheum palmatum* L.) to *Bifidobacterium adolescentis*. *Phytomedicine.* 2010;17:684–689. doi: 10.1016/j.phymed.2009.10.009. [PubMed] [CrossRef] [Google Scholar]

42. Gibson G.R., Roberfroid M.B. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J. Nutr.* 1995;125:1401–1412. [PubMed] [Google Scholar]

43. Gibson G.R., Probert H.M., Loo J.V., Rastall R.A., Roberfroid M.B. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. *Nutr. Res. Rev.* 2004;17:259–275. doi: 10.1079/NRR200479. [PubMed] [CrossRef] [Google Scholar]

44. Macfarlane G.T., Steed H., Macfarlane S. Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. *J. Appl. Microbiol.* 2008;104:305–344. [PubMed] [Google Scholar]

45. Ljungh A., Wadstrom T. Lactic acid bacteria as probiotics. *Curr. Issues Intest. Microbiol.* 2006;7:73–89. [PubMed] [Google Scholar]

46. Bongaerts G., Severijnen R., Timmerman H. Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy. *Med. Hypotheses.* 2005;64:64–68. doi: 10.1016/j.mehy.2004.07.029. [PubMed] [CrossRef] [Google Scholar]

47. Kruis W. Review article: Antibiotics and probiotics in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 2004;20:75–78. doi: 10.1111/j.1365-2036.2004.02051.x. [PubMed] [CrossRef] [Google Scholar]

48. Lye H.S., Kuan C.Y., Ewe J.A., Fung W.Y., Liong M.T. The improvement of hypertension by probiotics: Effects on cholesterol, diabetes, renin, and phytoestrogens. *Int. J. Mol. Sci.* 2009;10:3755–3775. doi: 10.3390/ijms10093755. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

49. Kumar M., Kumar A., Nagpal R., Mohania D., Behare P., Verma V., Kumar P., Poddar D., Aggarwal P.K., Henry C.J., et al. Cancer-preventing attributes of probiotics: An update. *Int. J. Food Sci. Nutr.* 2010;61:473–496. doi: 10.3109/09637480903455971. [PubMed] [CrossRef] [Google Scholar]

50. Meneghin F., Fabiano V., Mameli C., Zuccotti G.V. Probiotics and atopic dermatitis in children. *Pharmaceuticals.* 2012;5:727–744. doi: 10.3390/ph5070727. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

51. Wilcox M.H. *Clostridium difficile* infection and pseudomembranous colitis. *Best Pract. Res. Clin. Gastroenterol.* 2003;17:475–492. doi: 10.1016/S1521-6918(03)00017-9. [PubMed] [CrossRef] [Google Scholar]

52. Hoentjen F., Welling G.W., Harmsen H.J., Zhang X., Snart J., Tannock G.W., Lien K., Churchill T.A., Lupicki M., Dieleman L.A. Reduction of colitis by prebiotics in HLA-B27 transgenic rats is associated with microflora changes and immunomodulation. *Inflamm. Bowel Dis.* 2005;11:977–985. doi: 10.1097/01.MIB.0000183421.02316.d5. [PubMed] [CrossRef] [Google Scholar]

53. Jostins L., Ripke S., Weersma R.K., Duerr R.H., McGovern D.P., Hui K.Y., Lee J.C., Schumm L.P., Sharma Y., Anderson C.A., et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491:119–124. doi: 10.1038/nature11582. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

54. Cummings J.H., Macfarlane G.T., Macfarlane S. Intestinal bacteria and ulcerative colitis. *Curr. Issues Intest. Microbiol.* 2003;4:9–20. [PubMed] [Google Scholar]

55. Bullock N.R., Booth J.C.L., Gibson G.R. Comparative composition of bacteria in the human intestinal microflora during remission and active ulcerative colitis. *Curr. Issues Intest. Microbiol.* 2004;5:59–64. [PubMed] [Google Scholar]

56. Heimesaat M.M., Fischer A., Siegmund B., Batra A., Loddenkemper C., Liesenfeld O., Blaut M., Gobel U.B., Schumann R.R., Bereswill S. Shifts towards pro-inflammatory intestinal bacteria aggravate acute murine colitis and ileitis via toll-like-receptor signaling. *Int. J. Med. Microbiol.* 2007;29743:81–82. [Google Scholar]

57. Kamada N., Hisamatsu T., Okamoto S., Sato T., Matsuoka K., Arai K., Nakai T., Hasegawa A., Inoue N., Watanabe N., Akagawa K.S., Hibi T. Abnormally differentiated subsets of intestinal macrophage play a key role in Th1-dominant chronic colitis through excess production of IL-12 and IL-23 in response to bacteria. *J. Immunol.* 2005;175:6900–6908. doi: 10.4049/jimmunol.175.10.6900. [PubMed] [CrossRef] [Google Scholar]

58. Machiels K., Joossens M., Sabino J., de Preter V., Arijs I., Eeckhaut V., Ballet V., Claes K., van Immerseel F., Verbeke K., et al. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut.* 2014;63:1275–1283. doi: 10.1136/gutjnl-2013-304833. [PubMed] [CrossRef] [Google Scholar]

59. Lepage P., Haesler R., Spehlmann M.E., Rehman A., Zvirbliene A., Begun A., Ott S., Kupcinskas L., Dore J., Raedler A., Schreiber S. Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. *Gastroenterology.* 2011;141:227–236. doi: 10.1053/j.gastro.2011.04.011. [PubMed] [CrossRef] [Google Scholar]

60. Bhattacharjee A. Oral micro-particulate colon targeted drug delivery system for the treatment of Crohn's disease: A review. *Int. J. Life Sci. Pharm. Res.* 2012;1:31–39. [Google Scholar]

61. Seksik P., Rigottier-Gois L., Gramet G., Sutren M., Pochart P., Marteau P., Jian R., Dore J. Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. *Gut.* 2003;52:237–242. doi: 10.1136/gut.52.2.237. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

62. Joossens M., Huys G., Cnockaert M., de Preter V., Verbeke K., Rutgeerts P., Vandamme P., Vermeire S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. *Gut.* 2011;60:631–637. doi: 10.1136/gut.2010.223263. [PubMed] [CrossRef] [Google Scholar]

63. Gevers D., Kugathasan S., Denson L.A., Vazquez-Baeza Y., van Treuren W., Ren B., Schwager E., Knights D., Song S.J., Yassour M., et al. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe.* 2014;15:382–392. doi: 10.1016/j.chom.2014.02.005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

64. Leach S.T., Mitchell H.M., Eng W.R., Zhang L., Day A.S. Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease. *Aliment. Pharm. Ther.* 2008;28:724–733. doi: 10.1111/j.1365-2036.2008.03796.x. [PubMed] [CrossRef] [Google Scholar]

65. Tighe M.P., Cummings J., Afzal N.A. Nutrition and inflammatory bowel disease: Primary or adjuvant therapy. *Curr. Opin. Clin. Nutr. Metab. Care.* 2011;14:491–496. doi: 10.1097/MCO.0b013e328349eb4d. [PubMed] [CrossRef] [Google Scholar]

66. Ding S.L., Chi M.M., Scull B.P., Rigby R., Schwerbrock N., Magness S., Jobin C., Lund P.K. High-fat diet: Bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS ONE.* 2010;5:e12191. doi: 10.1371/journal.pone.0012191. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

67. Hildebrandt M.A., Hoffmann C., Sherrill-Mix S.A., Keilbaugh S.A., Hamady M., Chen Y., Knight R., Ahima R.S., Bushman F., Wu G.D. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology.* 2009;137:1716–1724. doi: 10.1053/j.gastro.2009.08.042. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

68. Armougom F., Henry M., Vialettes B., Raccah D., Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in *Lactobacillus* in obese patients and Methanogens in anorexic patients. *PLoS ONE.* 2009;4:e7125. doi: 10.1371/journal.pone.0007125. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

69. Cluny N.L., Reimer R.A., Sharkey K.A. Cannabinoid signalling regulates inflammation and energy balance: The importance of the brain-gut axis. *Brain Behav. Immun.* 2012;26:691–698. doi: 10.1016/j.bbi.2012.01.004. [PubMed] [CrossRef] [Google Scholar]

70. Leung J., Burke B., Ford D., Garvin G., Korn C., Sulis C., Bhadelia N. Possible association between obesity and *Clostridium difficile* infection. *Emerg. Infect. Dis.* 2013;19:1791–1798. [PMC free article] [PubMed] [Google Scholar]

71. Lin H.V., Frassetto A., Kowalik E.J., Jr., Nawrocki A.R., Lu M.M., Kosinski J.R., Hubert J.A., Szeto D., Yao X., Forrest G., Marsh D.J. Butyrate and propionate protect against diet-Induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLoS ONE.* 2012;7:e352404. [PMC free article] [PubMed] [Google Scholar]

72. Moran C.P., Shanahan F. Gut microbiota and obesity: Role in aetiology and potential therapeutic target. *Best Pract. Res. Clin. Gastroenterol.* 2014;28:585–597. doi: 10.1016/j.bpg.2014.07.005. [PubMed] [CrossRef] [Google Scholar]

73. Gorissen L., Raes K., Weckx S., Dannenberger D., Leroy F., de Vuyst L., de Smet S. Production of conjugated linoleic acid and conjugated linolenic acid isomers by *Bifidobacterium* species. *Appl.*

Microbiol. Biotechnol. 2010;87:2257–2266. doi: 10.1007/s00253-010-2713-1. [PubMed] [CrossRef] [Google Scholar]

74. Lee H.Y., Park J.H., Seok S.H., Baek M.W., Kim D.J., Lee K.E., Paek K.S., Lee Y., Park J H. Human originated bacteria, *Lactobacillus rhamnosus* PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochem. Biophys. Acta.* 2006;1761:736–744. [PubMed] [Google Scholar]

75. Poutahidis T., Kleinewietfeld M., Smillie C., Levkovich T., Perrotta A., Bhela S., Varian B.J., Ibrahim Y.M., Lakritz J.R., Kearney S.M., et al. Microbial reprogramming inhibits western diet-associated obesity. *PLoS ONE.* 2013;8:e685967. [PMC free article] [PubMed] [Google Scholar]

76. Mozaffarian D., Hao T., Rimm E.B., Willett W.C., Hu F.B. Changes in diet and lifestyle and long-term weight gain in women and men. *N. Engl. J. Med.* 2011;364:2392–2404. doi: 10.1056/NEJMoa1014296. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

77. De los Reyes-Gavilan C.G., Delzenne N.M., Gonzalez S., Gueimonde M., Salazar N. Development of functional foods to fight against obesity Opportunities for probiotics and prebiotics. *Agro Food Ind. Hi Tech.* 2014;25:35–39. [Google Scholar]

78. Kelishadi R., Farajian S., Safavi M., Mirlohi M., Hashemipour M. A randomized triple-masked controlled trial on the effects of synbiotics on inflammation markers in overweight children. *J. Pediatr.* 2014;90:161–168. doi: 10.1016/j.jped.2013.07.003. [PubMed] [CrossRef] [Google Scholar]

79. Ridaura V.K., Faith J.J., Rey F.E., Cheng J., Duncan A.E., Kau A.L., Griffin N.W., Lombard V., Henrissat B., Bain J.R., et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science.* 2013;341 doi: 10.1126/science.1241214. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

80. Walker A.W., Parkhill J. Fighting obesity with bacteria. *Science.* 2013;341:1069–1070. doi: 10.1126/science.1243787. [PubMed] [CrossRef] [Google Scholar]

81. Davies S.S., Chen Z.Y., Guo L.L., Zhang Y.Q., Stien X., Coulon D. Incorporation of therapeutically modified bacteria into gut microbiota prevents obesity. *Free Radic. Biol. Med.* 2012;532 doi: 10.1016/j.freeradbiomed.2012.10.250. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

82. Burcelin R., Serino M., Chabo C., Blasco-Baque V., Amar J. Gut microbiota and diabetes: From pathogenesis to therapeutic perspective. *Acta Diabetol.* 2011;48:257–273. doi: 10.1007/s00592-011-0333-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

83. Cani P.D., Neyrinck A.M., Fava F., Knauf C., Burcelin R.G., Tuohy K.M. Selective increases of bifidobacteria in gut microflora improve high-fat diet induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia.* 2007;50:2374–2383. doi: 10.1007/s00125-007-0791-0. [PubMed] [CrossRef] [Google Scholar]

84. Musso G., Gambino R., Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annu. Rev. Med.* 2011;62:361–380. doi: 10.1146/annurev-med-012510-175505. [PubMed] [CrossRef] [Google Scholar]

85. Nara N., Alkanani A.K., Ir D., Robertson C.E., Wagner B.D., Frank D.N., Zipris D. The role of the intestinal microbiota in type 1 diabetes. *Clin. Immunol.* 2013;146:112–119. doi: 10.1016/j.clim.2012.12.001. [PubMed] [CrossRef] [Google Scholar]

86. Brown C.T., Davis-Richardson A.G., Giongo A., Gano K.A., Crabb D.B., Mukherjee N., Casella G., Drew J.C., Ilonen J., Knip M., et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS ONE.* 2011;6:e25792. doi: 10.1371/journal.pone.0025792. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

87. Murri M., Leiva I., Gomez-Zumaquero J.M., Tinahones F.J., Cardona F., Soriguer F., Queipo-Ortuno M.I. Gut microbiota in children with type 1 diabetes differs from that in healthy children: A case-control study. *BMC Med.* 2013;11 doi: 10.1186/1741-7015-11-46. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

88. Larsen N., Vogensen F.K., van den Berg F., Nielsen D.S., Andreasen A.S., Pedersen B.K., Abu Al-Soud W., Sorensen S.J., Hansen L.H., Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE.* 2010;5:e90852. [PMC free article] [PubMed] [Google Scholar]

89. Amar J., Chabo C., Waget A., Klopp P., Vachoux C., Bermudez-Humaran L.G., Smirnova N., Berge M., Sulpice T., Lahtinen S., et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: Molecular mechanisms and probiotic treatment. *EMBO Mol. Med.* 2011;3:559–572. doi: 10.1002/emmm.201100159. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

90. Brugman S., Klatter F.A., Visser J., Wildeboer-Veloo A., Harmsen H., Rozing J., Bos N.A. Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding diabetes-prone rat. Is the gut flora involved in the development of type 1 diabetes? *Diabetologia.* 2006;49:2105–2108. doi: 10.1007/s00125-006-0334-0. [PubMed] [CrossRef] [Google Scholar]

91. Morowitz M.J., Carlisle E.M., Alverdy J.C. Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. *Surg. Clin. N. Am.* 2011;91:771–785. doi: 10.1016/j.suc.2011.05.001. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

92. Wu W.C., Zhao W., Li S. Small intestinal bacteria overgrowth decreases small intestinal motility in the NASH rats. *World J. Gastroenterol.* 2008;14:313–317. doi: 10.3748/wjg.14.313. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

93. Kajiya M., Sato K., Silva M., Ouhara K., Do P.M., Shanmugam K.T., Kawai T. Hydrogen from intestinal bacteria is protective for Concanavalin A-induced hepatitis. *Biochem. Biophys. Res. Commun.* 2009;386:316–321. doi: 10.1016/j.bbrc.2009.06.024. [PubMed] [CrossRef] [Google Scholar]

94. Mutlu E., Keshavarzian A., Engen P., Forsyth C.B., Sikaroodi M., Gillevet P. Intestinal dysbiosis: A possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol. Clin. Exp. Res.* 2009;33:1836–1846. doi: 10.1111/j.1530-0277.2009.01022.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

95. Llovet J.M., Bartoli R., March F., Planas R., Vinado B., Cabre E., Arnal J.C., Pere A., Vicenc G., Miquel A. Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: Molecular epidemiologic evidence. *J. Hepatol.* 1998;28:307–313. doi: 10.1016/0168-8278(88)80018-7. [PubMed] [CrossRef] [Google Scholar]

96. De Gottardi A., McCoy K.D. Evaluation of the gut barrier to intestinal bacteria in non-alcoholic fatty liver disease. *J. Hepatol.* 2011;55:1181–1183. doi: 10.1016/j.jhep.2011.05.003. [PubMed] [CrossRef] [Google Scholar]

97. Sandek A., Bauditz J., Swidsinski A., Buhner S., Weber-Eibel J., von Haehling S., Schroedl W., Karhausen T., Doehner W., Rauchhaus M., et al. Altered intestinal function in patients with chronic

heart failure. *J. Am. Coll. Cardiol.* 2007;50:1561–1569. doi: 10.1016/j.jacc.2007.07.016. [PubMed] [CrossRef] [Google Scholar]

98. Sandek A., Anker S.D., von Haehling S. The gut and intestinal bacteria in chronic heart failure. *Curr. Drug. Metab.* 2009;10:22–28. doi: 10.2174/138920009787048374. [PubMed] [CrossRef] [Google Scholar]

99. Krack A., Sharma R., Figulla H.R., Anker S.D. The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur. Heart J.* 2005;26:2368–2374. doi: 10.1093/eurheartj/ehi389. [PubMed] [CrossRef] [Google Scholar]

100. Bosch M., Fuentes M.C., Audivert S., Bonachera M.A., Peiro S., Cune J. *Lactobacillus plantarum* CECT 7527, 7528 and 7529: Probiotic candidates to reduce cholesterol levels. *J. Sci. Food Agric.* 2014;94:803–809. doi: 10.1002/jsfa.6467. [PubMed] [CrossRef] [Google Scholar]

101. Lam V., Su J.D., Koprowski S., Hsu A.N., Tweddell J.S., Rafiee P., Gross G.J., Salzman N.H., Baker J.E. Intestinal microbiota determine severity of myocardial infarction in rats. *FASEB J.* 2012;26:1727–1735. doi: 10.1096/fj.11-197921. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

102. Kang M.J., Ko G.S., Oh D.G., Kim J.S., Noh K., Kang W., Yoon W.K., Kim H.C., Jeong H.G., Jeong T.C. Role of metabolism by intestinal microbiota in pharmacokinetics of oral baicalin. *Arch. Pharm. Res.* 2014;37:371–378. doi: 10.1007/s12272-013-0179-2. [PubMed] [CrossRef] [Google Scholar]

103. Chu F.F., Esworthy S., Chu P.G., Huycke M., Doroshow J. Bacteria-induced intestinal cancer in mice with disrupted *Gpx1* and *Gpx2* genes. *Free Radic. Biol. Med.* 2003;351:165–166. [Google Scholar]

104. Weir T.L., Manter D.K., Sheflin A.M., Barnett B.A., Heuberger A.L., Ryan E.P. Stool microbiome and metabolome differences between colorectal cancer patients and healthy adults. *PLoS ONE.* 2013;8:e70803. doi: 10.1371/journal.pone.0070803. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

105. Boleij A., Tjalsma H. Gut bacteria in health and disease: A survey on the interface between intestinal microbiology and colorectal cancer. *Biol. Rev.* 2012;87:701–730. doi: 10.1111/j.1469-185X.2012.00218.x. [PubMed] [CrossRef] [Google Scholar]

106. Singh J., Rivenson A., Tomita M., Shimamura S., Ishibashi N., Reddy B.S. *Bifidobacterium longum*, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. *Carcinogenesis.* 1997;18:833–841. doi: 10.1093/carcin/18.4.833. [PubMed] [CrossRef] [Google Scholar]

107. Viaud S., Saccheri F., Mignot G., Yamazaki T., Daillere R., Hannani D., Enot D.P., Pfirschke C., Engblom C., Pittet M.J., et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science.* 2013;342:971–976. doi: 10.1126/science.1240537. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

108. Poutahidis T., Cappelle K., Levkovich T., Lee C.W., Doulberis M., Ge Z.M., Fox J.G., Horwitz B.H., Erdman S.E. Pathogenic intestinal bacteria enhance prostate cancer development via systemic activation of immune cells in mice. *PLoS ONE.* 2013;8:e739338. [PMC free article] [PubMed] [Google Scholar]

109. Sugiyama Y., Masumori N., Fukuta F., Yoneta A., Hida T., Yamashita T., Minatoya M., Nagata Y., Mori M., Tsuji H., et al. Influence of isoflavone intake and equol-producing intestinal flora on prostate cancer risk. *Asian Pacific. J. Cancer Prev.* 2013;14:1–4. doi: 10.7314/APJCP.2013.14.1.1. [PubMed] [CrossRef] [Google Scholar]

110. Gori A., Rizzardini G., Van'T Land B., Amor K.B., van Schaik J., Torti C., Bandera A., Knol J., Benlhassan-Chahour K., Trabattoni D., et al. Specific prebiotics modulate gut microbiota and immune activation in HAART-naive HIV-infected adults: Results of the "COPA" pilot randomized trial. *Mucosal Immunol.* 2011;4:554–563. doi: 10.1038/mi.2011.15. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

111. Zajac V., Stevurkova V., Matelova L., Ujhazy E. Detection of HIV-1 sequences in intestinal bacteria of HIV/AIDS patients. *Neuroendocrinol. Lett.* 2007;28:591–595. [PubMed] [Google Scholar]

112. Vujkovic-Cvijin I., Dunham R.M., Iwai S., Maher M.C., Albright R.G., Broadhurst M.J., Hernandez R.D., Lederman M.M., Huang Y., Somsouk M., et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan aatabolism. *Sci. Transl. Med.* 2013;5 doi: 10.1126/scitranslmed.3006438. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

113. Gori A., Tincati C., Rizzardini G., Torti C., Quirino T., Haarman M., Ben Amor K., van Schaik J., Vriesema A., Knol J., et al. Early impairment of gut function and gut flora supporting a role for alteration of gastrointestinal mucosa in human immunodeficiency virus pathogenesis. *J. Clin. Microbiol.* 2008;46:757–758. doi: 10.1128/JCM.01729-07. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

114. Wolf B.W., Wheeler K.B., Ataya D.G., Garleb K.A. Safety and tolerance of *Lactobacillus reuteri* supplementation to a population infected with the human immunodeficiency virus. *Food Chem. Toxicol.* 1998;36:1085–1094. doi: 10.1016/S0278-6915(98)00090-8. [PubMed] [CrossRef] [Google Scholar]

115. Hemsworth J., Hekmat S., Reid G. The development of micronutrient supplemented probiotic yogurt for people living with HIV: Laboratory testing and sensory evaluation. *Innov. Food Sci. Emerg. Technol.* 2011;12:79–84. doi: 10.1016/j.ifset.2010.11.004. [CrossRef] [Google Scholar]

116. Adams J.B., Johansen L.J., Powell L.D., Quig D., Rubin R.A. Gastrointestinal flora and gastrointestinal status in children with autism-comparisons to typical children and correlation with autism severity. *BMC Gastroenterol.* 2011;11 doi: 10.1186/1471-230X-11-22. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

117. Cryan J.F., Dinan T.G. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* 2012;13:701–712. doi: 10.1038/nrn3346. [PubMed] [CrossRef] [Google Scholar]

118. Heberling C.A., Dhurjati P.S., Sasser M. Hypothesis for a systems connectivity model of autism spectrum disorder pathogenesis: Links to gut bacteria, oxidative stress, and intestinal permeability. *Med. Hypotheses.* 2013;80:264–270. doi: 10.1016/j.mehy.2012.11.044. [PubMed] [CrossRef] [Google Scholar]

119. Song Y.L., Liu C.X., Finegold S.A. Real-time PCR quantitation of clostridia in feces of autistic children. *Appl. Environ. Microb.* 2004;70:6459–6465. doi: 10.1128/AEM.70.11.6459-6465.2004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

120. Finegold S.M. State of the art; microbiology in health and disease. Intestinal bacterial flora in autism. *Anaerobe.* 2011;17:367–368. doi: 10.1016/j.anaerobe.2011.03.007. [PubMed] [CrossRef] [Google Scholar]

121. Finegold S.M., Molitoris D., Song Y.L., Liu C.X., Vaisanen M.L., Bolte E., McTeague M., Sandler R., Wexler H., Marlowe E.M., et al. Gastrointestinal microflora studies in late-onset autism. *Clin. Infect. Dis.* 2002;351:6–16. doi: 10.1086/341914. [PubMed] [CrossRef] [Google Scholar]

122. Finegold S.M. *Desulfovibrio* species are potentially important in regressive autism. *Med. Hypotheses.* 2011;77:270–274. doi: 10.1016/j.mehy.2011.04.032. [PubMed] [CrossRef] [Google Scholar]

123. De Angelis M., Piccolo M., Vannini L., Siragusa S., de Giacomo A., Serrazzanetti D.I., Cristofori F., Guerzoni M.E., Gobbetti M., Francavilla R. Fecal microbiota and metabolome of children with autism and Pervasive Developmental Disorder Not Otherwise Specified. *PLoS ONE.* 2013;8:e76993. doi: 10.1371/journal.pone.0076993. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

124. Ono S., Komada Y., Kamiya T., Shirakawa S. A pilot study of the relationship between bowel habits and sleep health by actigraphy measurement and fecal flora analysis. *J. Physiol. Anthropol.* 2008;27:145–151. doi: 10.2114/jpa2.27.145. [PubMed] [CrossRef] [Google Scholar]

125. Taurog J.D., Richardson J.A., Croft J.T., Simmons W.A., Zhou M., Fernandez-Sueiro J.L., Balish E., Hammer R.E. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J. Exp. Med.* 1994;180:2359–2364. doi: 10.1084/jem.180.6.2359. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

126. Rehakova Z., Capkova J., Stepankova R., Sinkora J., Louzecka A., Ivanyi P., Weinreich S. Germ-free mice do not develop ankylosing enthesopathy, a spontaneous joint disease. *Hum. Immunol.* 2000;61:555–558. doi: 10.1016/S0198-8859(00)00122-1. [PubMed] [CrossRef] [Google Scholar]

127. Yeoh N., Burton J.P., Suppiah P., Reid G., Stebbings S. The role of the microbiome in rheumatic diseases. *Curr. Rheumatol. Rep.* 2013;15 doi: 10.1007/s11926-012-0314-y. [PubMed] [CrossRef] [Google Scholar]

128. Kotanko P., Carter M., Levin N.W. Intestinal bacterial microflora—a potential source of chronic inflammation in patients with chronic kidney disease. *Nephrol. Dial. Transpl.* 2006;21:2057–2060. doi: 10.1093/ndt/gfl281. [PubMed] [CrossRef] [Google Scholar]

129. Smith E.A., Macfarlane G.T. Enumeration of human colonic bacteria producing phenolic and indolic compounds: Effects of pH, carbohydrate availability and retention time on dissimilatory aromatic amino acid metabolism. *J. Appl. Bacteriol.* 1996;81:288–302. doi: 10.1111/j.1365-2672.1996.tb04331.x. [PubMed] [CrossRef] [Google Scholar]

130. Shiba T., Kawakami K., Sasaki T., Makino I., Kato I., Kobayashi T., Uchida K., Kaneko K. Effects of intestinal bacteria-derived *p*-cresyl sulfate on Th1-type immune response *in vivo* and *in vitro*. *Toxicol. Appl. Pharm.* 2014;274:191–199. doi: 10.1016/j.taap.2013.10.016. [PubMed] [CrossRef] [Google Scholar]