Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2022: 83.058
Volume 13, Issue 1 ; 2024, 01-16

ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Review Article

Inflammatory Bowel Disease and Gut Microbiota Dysbiosis: Current understanding and Future Direction

Ritu Verma[1], Km. Shiva[2], Ranveer Singh[3], Kajal Sherawat[4], Simran[5], Poonam Bhardwaj[6]

[1]Principal, Venkateshwara Institute of Pharmacy, Meerut Uttar Pradesh
[2]Assistant Professor, NGI College of Pharmacy, Near SVBP University, Modipuram, Meerut U.P.
[3]Associate Professor, NGI College of Pharmacy, Near SVBP University, Modipuram, Meerut U.P.
[4,5]Assistant Professor, Meerut Institute of Technology, Partapur Bypass Road, Meerut Uttar Pradesh
[6]Associate Professor, NKBR College of Pharmacy and Research Centre Phaphunda, Meerut Uttar Pradesh

Article Info: Received: 03-11-2023 / Revised: 08-12-2023 / Accepted: 29-12-2023
Address for correspondence: Poonam Bhardwaj
DOI: https://doi.org/10.32553/jbpr.v13i1.1043
Conflict of interest statement: No conflict of interest

Abstract:
Inflammatory Bowel Disease (IBD) represents a group of chronic, relapsing inflammatory disorders primarily affecting the gastrointestinal tract. The pathogenesis of IBD is multifaceted, involving genetic predisposition, environmental triggers, and dysregulation of the immune response. Recent research has illuminated the pivotal role of gut microbiota dysbiosis in the development and perpetuation of IBD. The human gut harbors a complex and dynamic ecosystem of microorganisms that profoundly influences host health and disease. Alterations in the composition, diversity, and function of the gut microbiota, termed dysbiosis, have been consistently linked to IBD. Shifts in microbial composition, reduction in microbial diversity, and imbalances in beneficial versus pathogenic microorganisms characterize the dysbiotic state associated with IBD.The intricate interplay between the host immune system and the gut microbiota is a key determinant in IBD pathogenesis. Dysbiosis triggers aberrant immune responses, leading to chronic mucosal inflammation and tissue damage. Furthermore, dysbiotic alterations disrupt essential microbial-derived metabolites and signaling molecules crucial for gut homeostasis, further exacerbating the disease. Advancements in high-throughput sequencing technologies and metagenomic analysis have enabled comprehensive characterization of microbial communities in IBD, uncovering microbial signatures and functional pathways associated with disease phenotypes and treatment responses. Therapeutic interventions targeting the gut microbiota, such as probiotics, prebiotics, fecal microbiota transplantation, and microbial-based therapies, have shown promise in preclinical and clinical studies for modulating dysbiosis and ameliorating IBD symptoms.
Keywords: Inflammatory Bowel Disease, Dysbiosis, Fecal microbiota, Probiotics

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two main chronic inflammatory gastrointestinal disorders that make up the category known as Inflammatory Bowel Disease (IBD). IBD is a complicated a etiology that combines immunological, environmental, and genetic components. The role that dysbiosis of the gut microbiota plays in the onset and course of inflammatory bowel disease (IBD) has garnered increasing attention in recent years. The term "inflammatory bowel disease" (IBD) refers to a broad category of gastrointestinal tract-related chronic immune-mediated inflammatory illnesses. There are two primary phenotypes of IBD, ulcerative colitis (UC) and Crohn's disease (CD) (Mandal, Jaiswal, et al. 2021)(Mandal, Jaiswal, and Shiva 2020). Chronic continuous and circumferential mucosal inflammation that is limited to the colon and extends proximally from the rectum is the hallmark of ulcerative colitis (UC). In contrast, the trans mural, patchy inflammation associated with CD can affect any area of the gastrointestinal system. The exact cause of inflammatory bowel disease (IBD) is unknown, but new research points to a complicated interaction between immunological dysregulation, genetics, and environmental stressors that may affect the gut flora. In the last ten years, one of the most researched human illnesses associated with the gut microbiota is inflammatory bowel disease (IBD). IBD includes ulcerative colitis (UC) and Crohn's disease (CD), which collectively impact over 3.6 million individuals. So far, extensive investigations on human genetics involving 75,000 cases and controls have identified 163 host susceptibility loci (Qiu et al. 2022). The pathways that interact with environmental variables to affect intestinal homeostasis are abundant in these loci (Mandal, Shiva, et al. 2021)(Reduction et al. 2021). The condition has become more common over the last several decades, which emphasizes the part that environmental variables play in the development of this illness. IBD was formerly a very rare disorder that only started to rise dramatically in incidence in North America and Europe in the second half of the 20th century, sometimes doubling every decade. In the last two decades, it has spread to developing nations, though there are more cases of UC than CD in these regions. Furthermore, concordance between monozygotic twin pairs for IBD is much less than 50%, with the lowest concordance in CD, according to many twin studies. Hence, IBD is a complex illness in which a number of environmental variables, in addition to immune system function and germ line genetics are significant contributors. The gut microbial community is one such component that is drawing more and more attention due to its impact on several facets of health in general and IBD in particular. The greatest reservoir of microorganisms in the body, the gut microbiota, coexists with its host in varying amounts throughout the gastrointestinal system (S. A. Ali, Ali, Rastogi, et al. 2023)(Kemenkes RI 2020)(Caron, Neuville, and Peyrin-Biroulet 2022). This community helps the host in several ways, such as by digesting substrates that the host's enzymes are unable to reach, boosting immunity, and inhibiting the proliferation of pathogenic microbes. Our understanding of the gut micro biota's role in health has improved due to the extensive use of low-resolution surveys of the microbial community structure in the past and the renewed efforts using next-generation sequencing for a high-resolution description of composition, function, and ecology. This is necessary because studying disease-related dysbiosis requires an understanding of the gut microbiota. Numerous factors, including genetics, nutrition, age, pharmacological treatment, smoking, and perhaps many more, can influence the makeup of the microbial gut population. While it is yet unknown how important each of these elements is in relation to the illness state, some of them are connected to it either directly or indirectly (Sweta et al. 2019)(Nishida et al. 2018)(Cai, Wang, and Li 2021).

IBD is thought to impact 1.4 million people in the United States at this time, and its prevalence has significantly increased over the previous several decades. This has given rise to the theory that environmental variables are essential to the pathophysiology of IBD. The disparity between the prevalence of IBD in industrialized and non-industrialized nations, as well as the increasing incidence of IBD in nations experiencing demographic and economic development, provide more evidence of the influence of the environment on the development of illness. Children who migrate from low-prevalence IBD nations to high-prevalence IBD countries face the same risk of getting IBD as their counterparts who have lived in high-prevalence IBD regions for many generations. Although more than 200 genes have been found to be predisposing to IBD, monozygotic twin studies—which show that incomplete penetrance of gene abnormalities predisposing to IBD in the general population exists—and concordance of IBD among monozygotic twin pairs—further emphasize the critical role of environment in the pathogenesis of IBD (Pal et al. 2022)(Mandal and Vishvakarma 2023a)(Godala et al. 2022).

According to current hypotheses of the pathophysiology of IBD, pathologic changes in the gut microbiota in genetically predisposed people cause an abnormal mucosal immune response, which in turn causes chronic intestinal inflammation. Intestinal "dysbiosis" refers to these pathologic changes in the makeup of gut microbes that are observed in IBD patients. Studies indicate that disruptions in the gut micro biome are not just a result of persistent inflammation, but also a critical component initiating inflammation in inflammatory bowel disease (IBD)(Shan, Lee, and Chang 2022)(Antonelli et al. 2021). The intestinal micro biome is crucial to the pathogenesis of IBD, as evidenced by the following: 1) a dysbiosis typical of CD, UC, and pouchitis is frequently seen in patients; 2) fecal stream diversion reduces disease activity in CD while reinfusion of fecal contents causes recurrent inflammation; and 3) most genetic polymorphisms associated with IBD susceptibility are related to host mucosal barrier function and host–micro biome interactions. Depletion of commensal microbes can lead to impaired mucosal healing, chronic mucosal inflammation, and colitis; 6) germ-free animals do not develop colitis without the introduction of fecal bacteria to induce inflammation; and 5) antibiotics and probiotics have been demonstrated to be effective for the induction or maintenance of remission in IBD (S. Ali, Ali, Kondrapu, et al. 2023)(S. Ali, Ekbbal, Salar, et al. 2023)(Lewin et al. 2020).

Many uncertainties remain, despite the fact that developments in bioinformatics, genomics, and experimental models of inflammatory bowel disease (IBD) have shown the ways in which environmental variables; including age, nutrition, and antibiotic exposure, contribute to the development of dysbiosis and abnormal gut microbial–host immunologic interactions. The objectives of the review that follows are to: 1) outline the elements that contribute to the formation of the intestinal micro biome; 2) delineate the characteristics of intestinal dysbiosis in IBD; and 3) investigate how existing understanding may facilitate the creation of therapeutic approaches through the use of the micro biome in the management of IBD (Ekbbal et al. 2023)(S. A. Ali, Ali, Jahan, et al. 2023)(Singh et al. 2022)(Dhaliwal et al. 2021).

Environmental Factors Impacting the Composition of the Micro biome

Nutrition

Dietary choice, which has been demonstrated to influence micro biome composition throughout mammalian history, is one of the most significant environmental influences determining microbial composition. When researching the function of the micro biome in disease, interactions between nutrition and bacteria must be taken into consideration, even if no particular diet has been demonstrated to directly cause, prevent, or treat IBD. Only a little amount of data has been collected on this subject in humans to date, most likely due to the

difficulties in establishing a large-scale controlled diet research. According to Wu et al., short-term fluctuations may not have a significant impact on the ratios of Bactericides, Prevotella, and Firmicutes over the long run. Furthermore, Zimmer et al. examined the effects of a strict vegan or vegetarian diet on the microbiota and discovered that while the overall bacterial load did not change, there was a notable decrease in the Bacteroides, Bifidobacterium, and Enterobacteriaceae species. Future research on the involvement of the micro biome in IBD should consider both short- and long-term dietary patterns, as the Enterobacteriaceae are among the taxa that are regularly observed to be elevated in individuals with IBD (see the paragraph that follows). Including such information will probably only be possible in a large cohort study due to the intricacy of food impacts ("Alopecia Areata" 1995)(Jain et al. 2022)(Booth et al. 2022)(Cavalcante et al. 2020).

Age

The distribution of IBD phenotypes shows age-related heterogeneity, with three discrete phases of onset. The normal peak age of onset is between 15 and 30 years old; late-onset instances tend to occur around 60 years of age, while early-onset cases occur at or below 10 years of age. Notably, throughout the last ten years, the incidence of the latter category has increased significantly. These phases line up with the times when the diversity and stability of the gut microbiota change. A low-complexity, low-stability micro biome characterizes early life (Keyashian et al. 2019). It is more erratic, contingent on the mode of birth, and subject to variations in response to illnesses, puberty, and dietary changes (such as moving from breast milk to solid meals). The microbial assemblage doesn't attain its maximum stability and complexity until maturity, at which point its resistance to disturbances improves. However, older participants (60 years of age or more) have shown decreasing stability. A separate function for the micro biome in disease beginning and progression should be taken into consideration in light of these differing features of the micro biome at the three different phases of illness development (Maimoona et al. 2011)(Markowitz, Gurley, and Gurley 2020)(Segura-Sampedro et al. 2022).

Effects of diet and microbiota interactions on human health through metabolism

Food particles that are not fully broken down in the small intestine, together with endogenous substances like digestive enzymes and lost epithelial cells and mucus, find their way into the colon where they are fermented by the colonic microbiota. These substances are converted by bacteria into a wide range of metabolites that are in close proximity to the cells of their host. These metabolites have the ability to impact the host's metabolic phenotype and hence the risk of illness. Proteins and undigested carbs make up the majority of the substrates available to the microbiota (Bischoff et al. 2023)(Li et al. 2019). A variety of metabolites, such as branched chain fatty acids (SCFA), ammonia, amines, phenolic compounds, and gases including hydrogen, methane, and hydrogen sulphide, are produced during the fermentation of these substrates. Furthermore, the gut microbiota has a role in vitamin synthesis, the conversion of prodrugs to their bioactive forms, the alteration of bile acids and xenobiotics, and the activation or inactivation of bioactive dietary components including isoflavanoids and plant lignans (Incognito et al. 2022)(Mandal and Vishvakarma 2023b).

Table 1: The autoimmune and the intestinal microbiota

Disease	Microbiota status	Disease impact
Inflammatory bowel disease	Germ free, antibiotics or probiotics	No disease or reduced severity
Spontaneous arthritis	Germ free	No disease
Autoimmune arthritis	Germ free	No disease
Autoimmune encephalomyelitis	Germ free	Weak severity
Systemic lupus erythematosus	Germ free	No disease
Type 1 diabetes	Germ free	No disease
Spontaneous ankylosing enteropathy	Germ free or probiotics	No disease

Inflammatory bowel disease and dysbiosis

The two most common types of inflammatory bowel disease (IBD), which are marked by persistent, recurrent inflammation of the intestinal mucosa, are Crohn's disease (CD) and ulcerative colitis (UC). There is growing evidence that gut microbial dysbiosis plays a role in the pathogenesis of IBD, despite the fact the etiology of both disorders is unclear. Overall, patients show a decline in the functional diversity, stability, and microbial population of their gut microbiota, with a concurrent rise in facultative anaerobes such Enterobacteriaceae and a drop in some Firmicutes (Baldelli et al. 2021)(Tamboli et al. 2004). There are also noticeable variations in the micro biome between CD and UC patients. Five bacterial species have been linked to the predominant dysbiosis in CD; changes in Faecalibacterium prausnitzii abundance have been linked to the extension of disease remission, and this bacterium has been shown to have therapeutic effects in colitis models in animals. On the other hand, Mycobacterium paratuberculosis and adherent-invasive E. coli have been linked to CD pathogenesis, albeit a causal connection has not yet been shown. In fact, it is still unknown whether intestinal microbial dysbiosis causes the inflammation associated with inflammatory bowel disease (IBD) or if it is just the outcome of an unbalanced GI tract environment (Gleeson, Fein, and Whitehead 2021)(Noolu, Heera Lal, and Pillai 2018).

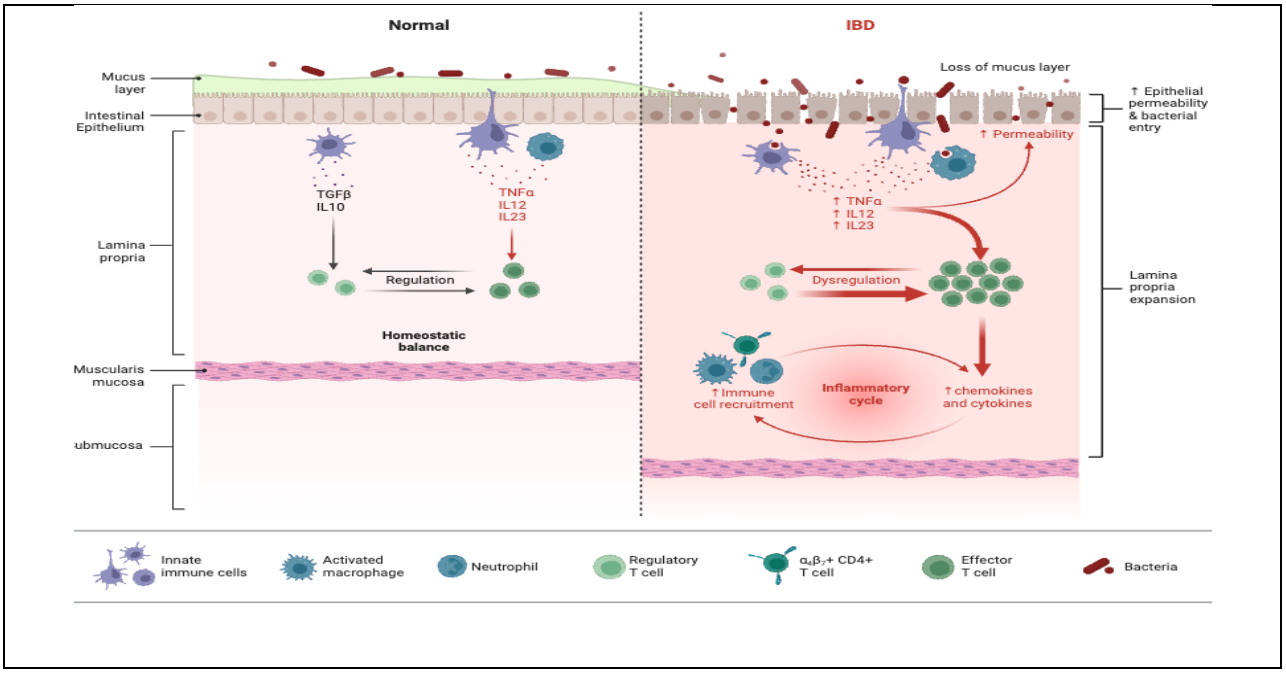

Figure 1: Immune Response in Inflammatory Bowel Disease (IBD)

Dysbiosis and other GI tract conditions

The intestinal microbiota has been linked to a number of additional (chronic) GI-related illnesses and disorders, including irritable bowel syndrome (IBS), celiac disease, and colorectal cancer (CRC), in addition to IBD, metabolic disorders, obesity, and type 2 diabetes. Though the alterations are not consistent, variations in the microbiota makeup of the various IBS subtypes have been reported when compared to healthy persons. Changes in the makeup of the microbiota have also been linked to celiac disease and colorectal cancer (CRC), with more variety and richness shown in comparison to control people. However, no clear pattern of alterations in the microbiota has been discovered in any of these disorders thus far. However, a new study on celiac disease has illuminated the relationship between host genetics and micro biome makeup and the development of the illness. The development of celiac disease is strongly associated with the expression of the leukocyte antigen DQ2. Before a disease manifests itself clinically, children with this haplotype have a different microbiota composition than non-HLA DQ2 people (Halpern et al. 2015)(Puvvada et al. 2012). Because some bacterial species are able to digest gliadin and may lessen its immunopathogenicity when consumed, celiac disease is caused by CD4 T-cell responsiveness to dietary gliadin.

The microbiome in health: elements affecting the growth, modification, and preservation of structure and function

The human body's largest and most varied microbial ecosystem is found in the gut. A small portion of the complexity of the intestinal micro biome, which consists of a wide variety of microbial genes and microbiota gene products, is made up of the intestinal microbiota, or population of microorganisms in the gut. In periods of optimal health, the gut microbiota collaborates with the host immune system to generate vitamins, inhibit the growth of pathogenic microorganisms, and aid in the breakdown of food components. Furthermore, the development of the enteric immune system and the regeneration of gut epithelial cells are facilitated by the micro biome. Throughout the gastrointestinal system, this varied community of bacteria, fungi, bacteriophages, and archaea live in colonies at different densities, with the colon having the maximum microbial density at 10^{12} cells/g of luminal contents. There have been many and rather inconsistent attempts to define the microbial makeup of a "healthy" gut micro biome. With over 1000 possible bacterial species that may colonize the human intestines, the diversity and variety of the faecal microbiome make it challenging to define a "healthy" micro biome. Even though a person's micro biome might vary greatly, the Bacteroidetes and Firmicutes phyla account for the bulk of species (>90%). Over time, the gut microbiota's makeup shifts. The gut micro biome of an individual is more flexible throughout infancy and early childhood, becomes more stable and comparable to the general population during maturity, and then becomes less diverse as an individual ages. The gut microbiota is usually not very complex during infancy and is impacted by nutrition and delivery method. The makeup of the newborn intestinal microbiota is affected differently depending on the mode of delivery (vaginal vs caesarean), with the newborn gut being colonized by the vaginal and fecal flora in the case of vaginal birth and the newborn skin flora in the case of caesarean section birth. Caesarean sections were linked to a somewhat elevated risk of inflammatory bowel disease (IBD), according to a Danish cohort study of infants born between 1973 and 2008. However, Bernstein et al. recently refuted this finding, noting that patients with IBD had no higher likelihood of having had a caesarean section than controls or their siblings without IBD (Mandal, Jaiswal, and Shiva 2020)(Panthee et al. 2022)(Shreiner, Kao, and Young 2015)(Harding and Bishop 2022).

Changes in the gut microbiota linked to the onset of IBD

Although intestinal dysbiosis and IBD are unmistakably linked, no one bacterium or microbial milieu has been shown to be the cause.

By reducing or maybe gaining "pathobionts," intestinal dysbiosis may have a role in the pathophysiology of inflammatory bowel disease. The way that pathobionts differ from bacterial pathogens is that the former only turn pathogenic when exposed to a certain environmental stimuli in genetically predisposed people. Numerous studies have been able to detect intestinal dysbioses that are present in individuals with IBD thanks to recent advancements in genetic sequencing and functional microbial investigation. The findings of a generalized drop in biodiversity (alpha diversity) and a lower representation of many particular taxa, such as Firmicutes and Bacteroidetes, among persons with IBD are supported by similar themes across research, despite some relatively divergent results.10–16 Furthermore, certain taxonomic changes, such as a relative rise in the number of Enterobacteriaceae, which includes Fusobacterium and Escherichia coli, have been linked to IBD. Patients who are newly diagnosed and have not started therapy offer a perfect human research group to evaluate the potentially pathogenic intestinal dysbioses associated with IBD. Remarkably, ileal and rectal biopsy samples showed lower number of Bacteroidales and Clostridium and increased abundance of Enterobacteriaceae, Pasteurellaceae, Veillonellaceae, and Fusobacteriaceae in a large cohort of newly diagnosed, treatment-naïve children with CD. Showed that individuals with active colonic inflammation (UC) and those with normal mucosa not only had different mucosa-associated microorganisms, but also that there seemed to be a longitudinal fluctuation in mucosal bacterial populations in UC that was related to the severity of the disease (Ray and Longworth 2019)(Abdelkawi et al. 2023)(Haller 2017).

Furthermore, IBD-associated microbiota in individuals with UC appears to be stable during remission, and the composition of the fecal microbiota in active UC is constant across age, gender, and geographic location. While the particular function of fungus in the spread of inflammation in IBD has received less research, they are a common element of the gut micro biome. When compared to healthy controls, intestinal fungal communities in colonic and ileal biopsy samples exhibit more variety in CD. Five fungal taxa—Saccharomyces cerevisiae, Calvispora lusitaniae, Cyberlindnera jadinii, Candida albicans, and Kluyveromyces marxianus—have been linked to CD in pediatric patients. Furthermore, fungal microbiological elements are employed in the diagnosis and prognosis of CD; in particular, anti-saccharomyces cerevisiae antibodies (ASCA) function as a serological marker for ileal CD by reacting with a polysaccharide found in the yeast cell wall. Serratia marcescens and E. coli abundance in biofilms, as well as ASCA titers, were shown to be connected with the higher abundance of Candida tropicalis in CD patients when compared to their unaffected relatives, according to a recent research.

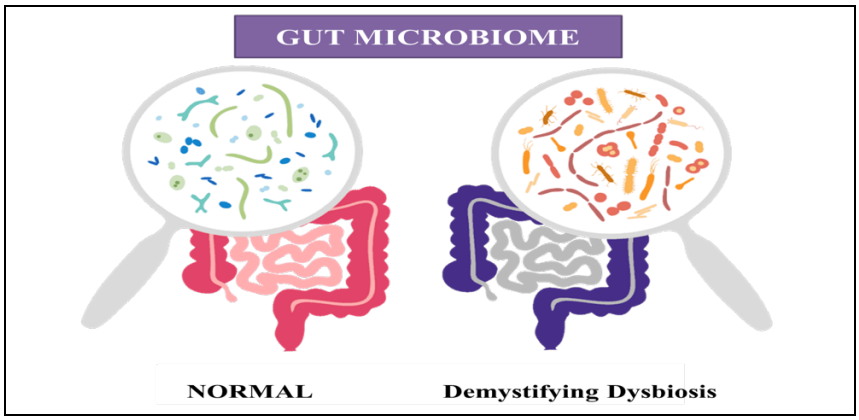

Figure 2: Gut microbiota dysbiosis

Similar to fungi, bacteriophages are a poorly understood group within the gut micro biome. Compared to healthy controls, colonic mucosal biopsy samples from CD patients contained significantly more bacteriophage. However, further research is needed to have a better understanding of how alterations in these populations may lead to IBD because there is a relative lack of information regarding the functional involvement of fungi, viruses, and archaea in the gut micro biome (Ciocîrlan, Ciocîrlan, and Diculescu 2019)(Ng 2018)(M. et al. 2017).

Environmental variables influencing the development of IBD and the gut micro biome

Antibiotic exposure before the onset of IBD is linked to incident IBD, despite the fact that antibiotics may be helpful in cases with existing IBD, according to many researches. Children who were exposed to antibiotics had a higher relative risk of having IBD in a retrospective cohort of Danish children. Similarly, a Finnish study showed that the number of courses of antibiotics purchased starting at birth was associated with an increased risk of CD with a pediatric onset. An extensive retrospective cohort research conducted in the UK showed that an 84% relative increase in the incidence of inflammatory bowel disease (IBD) was linked to childhood antibiotic exposure, especially anaerobic antibiotics. A recent meta-analysis revealed that childhood antibiotic exposure was linked to an elevated risk of CD but not UC. Collectively, these data imply that early life and frequent antibiotic exposures may have long-lasting, perhaps harmful impacts on the gut microbiota, which may aid in the etiology of inflammatory bowel disease (IBD). The fecal microbiota is significantly impacted by food, as was previously established. In light of this, several extensive longitudinal studies have shown a link between a diet high in fruits and vegetables and a lower risk of inflammatory bowel disease (IBD) and a diet heavy in animal fats and refined sugars that increases the risk of IBD. Furthermore, it has been shown that Western diets heavy in fat raise the risk of IBD; in particular, a high ratio of pro-inflammatory omega-6 fatty acids to anti-inflammatory omega-3 fatty acids has been linked to an increased prevalence of ulcerative colitis. A diet high in n-6 polyunsaturated fatty acids made colitis worse in rats and led to pro-inflammatory Enterobacteriaceae and Clostridia spp. being more abundant in the gut micro biome (2022 2018)(M. et al. 2017)(Lu et al. 2023)(Suematsu, Shimomura, and Vaziri 2017).

Utilizing the gut microbiota as a tool for diagnosis and treatment

Prior research on the intestinal micro biome in health vs. illness concentrated on species characterization; however, developments in metagenomics and metabolomics have highlighted the significance of comprehending the functional characteristics of the intestinal micro biome in IBD. Such functional investigations have specifically shown variations between the state of IBD and health in the following areas: microbial adhesion and invasion, cell wall disintegration, transport/metabolism of carbohydrates and lipids, and generation of exotoxins. It is recommended to use the understanding of the functional role of the intestinal microbial community in health and illness to treat a sick micro biome by using food, probiotics, prebiotics, antibiotics, and/or fecal microbiota transplantation (FMT). Because diet has a major impact on the diversity and expansion of the gut micro biome, it has been thoroughly studied as a potential therapy for IBD. Research on the efficacy and microbiological changes associated with exclusive enteral nutrition (EEN) is likely the largest body of work on the application of food as a targeted therapy for IBD. Patients following the EEN diet are not allowed to eat at tables and must consume formula for all of their daily calorie needs. An EEN can be completed with entire, semi-elemental, or elemental protein formulations. Research based on metagenomics has demonstrated alterations in the gut microbiota before to and during EEN treatment. It has been shown that the micro biome can change as quickly as one week after EEN

introduction. Interestingly, the gut micro biomes of these individuals were not like those of healthy individuals. Gerasimidis et al. observed comparable outcomes in a prospective, case-control study evaluating alterations in the intestinal microbial diversity and metabolic activity of 15 CD children treated with EEN. Early in the EEN treatment period, there was a loss in the variety of the fecal microbiota, which coincided with a decrease in the amounts of previously documented commensal bacteria. These results were linked to an improvement in clinical disease activity and a decrease in inflammatory markers (Brandon Brown et al. 2021)(Pop et al. 2020)(Collij et al. 2021).

CNS-related diseases and dysbiosis

Additional intestinal illnesses, particularly those that might influence the "gutbrainaxis" and effect the central nervous system, behavior, and cognitive function, have also been linked to intestinal microbial dysbiosis. Numerous investigations have concentrated on the idea that gut microbiota might directly rewire the hypothalamic pituitaryadrenal (HPA) axis, a common route that is triggered by infections and disturbed by psychological stresses, to affect cognition and behavior. Enteric infections are known to induce anxiety, depression, and cognitive dysfunction; in contrast to conventionalized mice, germ-free mice, lacking an intestinal microbiota, exhibit changes in stress-responsively, central neurochemistry, and behavior suggestive of decreased anxiety. For instance, alterations in the expression of their receptors and the synthesis of neurotrophic factors and hormones have been linked to elevated anxiety-like behavior in germ-free mice. Campylobacter jejuni, a frequent cause of gastroenteritis, can produce brainstem activity (the nucleus tractus solitarius and lateral parabrachial nucleus) and anxiety-like behavior in pathogen-infected rats. Commensal bacteria may alter the structure of the brain via influencing GABA, which directly affects immunological and neurological receptors in the central nervous system (ENS and CNS). The primary inhibitory neurotransmitter in the central nervous system, GABA has a role in controlling both physiological and psychological functions. Anxiety and depression are associated with changes in the expression of the central GABA receptor. It is well recognized that the postnatal development of the enteric nervous system depends on the early microbial colonization of the digestive tract. Therefore, gut microbiota may affect how the central nervous system develops and functions. A model of maternal immune activation (MIA) mice, in which pregnant animals are given the viral mimetic ploy, show increased intestinal permeability and develop stereotypical abnormalities in behavior, social ability, and communication that resemble ASD. This model provides evidence of a potential causal role of the intestinal microbiota in the development of autism spectrum disorder (ASD) (Varesi et al. 2022)(Collij et al. 2021)(Papaiakovou et al. 2022)(Jiang et al. 2022).

Future strategies include bacteriotherapy to restore the gut micro biome

Determining the pathophysiology of IBD requires more than just defining the features of "disease" and "health" in the gut microbiota. Intestinal microbiota profiles have not proven helpful as a diagnostic test or biomarker for IBD to yet. More research is needed to determine whether features of the micro biome might be helpful in phenotyping the disease or forecasting treatment response. Determining the causal relationship between microbial alterations linked to IBD has shown to be difficult in several previous investigations. Furthermore, given the diversity of microbiological samples and significant clinical features of disease, such as disease phenotype, disease geography, and previous pharmaceutical exposures, meaningful meta-analysis to draw conclusions has been difficult(Axelrad et al. 2021)(Kho and Lal 2018). Fortunately, there is potential to go beyond defining the phenotypic footprint of the micro biome in IBD and determine how the micro biome contributes to: 1) the onset and propagation of disease; and possibly more significantly, 2) how we may manipulate the

micro biome as a future treatment of IBD. This is made possible by evolving experimental technologies that aid in the functional characterization of the micro biome. The microbiota in sick or at-risk people can be greatly enhanced, maintained, or restored by manipulation (Stott et al. 2021)(Philips et al. 2021)(Burgos et al. 2022)(Rosso et al. 2022). Determining what a "healthy" micro biome is during life is a crucial prerequisite for bacteria-based therapy, also known as bacteriotherapy. This definition might vary depending on the population and the person. Further investigation is required to explore the variety of species and strains found in the GI tract, the diversity of microbial genes (micro biome), and the role these genes play in the GI tract during human development from conception to death! Probiotic-based therapeutic techniques and the more extreme and rudimentary strategy of wholesale microbiota replacement tactics based upon fecal transplantation have been utilized for ages, with varying degrees of effectiveness. Manipulating the gut microbiota to preserve health and treat disease is a supplement that goes into further depth on the application of these techniques(Petersen and Round 2014)(Abbas-Egbariya et al. 2022). In order for bacterial/probiotic therapies to reach their full potential in the treatment and management of human health, it will be necessary to understand the molecular mechanisms of action of these and other more sophisticated approaches utilizing chemically defined bacterial products in the clinic, as well as the unique features of each host that require personalization of approach (Yu et al. 2023)(Zhao et al. 2022)(Clemente et al. 2016)(Mayo-Martínez et al. 2021).

Conclusion:

In conclusion, while the connection between IBD and gut microbiota dysbiosis has been established, significant gaps in knowledge persist. Future research should focus on elucidating causal relationships, identifying microbial biomarkers, understanding functional interactions, and translating these findings into effective, personalized therapeutic strategies. A multidisciplinary approach integrating clinical, microbiological, and computational expertise is crucial to advance our understanding and improve outcomes for individuals affected by IBD. The intricate relationship between Inflammatory Bowel Disease and Gut Microbiota Dysbiosis has been extensively explored, shedding light on the pivotal role of the gut microbiome in maintaining intestinal homeostasis. The existing body of research strongly suggests that dysbiosis, characterized by an imbalance in the composition and function of the gut microbiota, plays a crucial role in the initiation and perpetuation of inflammatory responses in IBD. Current understanding emphasizes the multifactorial nature of IBD, with genetic, environmental, and microbial factors interplaying to influence disease susceptibility. The gut microbiota, acting as a dynamic ecosystem, modulates immune responses, maintains barrier integrity, and participates in metabolic processes crucial for overall gut health. Dysbiosis in IBD is associated with a reduced diversity of microbial species, alterations in microbial metabolites, and a shift towards pro-inflammatory microbial profiles. Therapeutic strategies targeting the gut microbiota, such as fecal microbiota transplantation, prebiotics, probiotics, and antibiotics, have shown promise in preclinical and clinical studies. However, the heterogeneity of IBD and the complex interactions within the gut microbiome highlight the need for personalized and precision medicine approaches.

Future directions in this field involve deeper investigations into the specific microbial signatures associated with different subtypes of IBD, the development of innovative microbiome-targeted therapies, and the exploration of the gut-brain axis and its role in IBD pathogenesis. Integrating multi-omics approaches, including metagenomics, metatranscriptomics, and metabolomics, will enhance our understanding of the functional aspects of dysbiosis and guide the development of more targeted interventions. While significant strides have been made in unraveling the

intricate link between IBD and Gut Microbiota Dysbiosis, much remains to be explored. Continued research and collaboration between clinicians, microbiologists, and geneticists will pave the way for a deeper understanding of the causative factors and novel therapeutic avenues for IBD, ultimately improving the quality of life for those affected by this challenging condition.

References

1. 2022, Cochrane. 2018. "Cochrane 2022." *Journal of the American Academy of Dermatology*.
2. Abbas-Egbariya, Haya, Yael Haberman, Tzipi Braun, Rotem Hadar, Lee Denson, Ohad Gal-Mor, and Amnon Amir. 2022. "Meta-Analysis Defines Predominant Shared Microbial Responses in Various Diseases and a Specific Inflammatory Bowel Disease Signal." *Genome Biology*. https://doi.org/10.1186/s13059-022-02637-7.
3. Abdelkawi, Abdullah, Diban Sabbagh, Muhamed Hobi, and Yashwant V. Pathak. 2023. "Effects of Psychological, Environmental, and Physical Stressors on the Gut Microbiota." In *Anxiety, Gut Microbiome, and Nutraceuticals: Recent Trends and Clinical Evidence*. https://doi.org/10.1201/9781003333821-9.
4. Ali, Sayad Ahad, Shadab Ali, Iram Jahan, and Shadab Ali. 2023. "Allergies to Infections : Understanding the Spectrum of Conjunctivitis," no. 1: 46–56.
5. Ali, Sayad Ahad, Shadab Ali, Sameer Rastogi, Jhakeshwar Prasad, Pydiraju Kondrapu, Bijander Kumar, Aniketa Sharma, and Kartikey Pandey. 2023. "Endometriosis : A Brief Review of Pharmacological and Non-Pharmacological Treatment" 12 (12): 1359–79. https://doi.org/10.48047/ecb/2023.12.si12.123.
6. Ali, Shadab, Sayad Ahad Ali, Pydiraju Kondrapu, Nidhi Tripathi, Pramod Bhaskar Kumar, P Dharani Prasad, and Manisha Madhukar Tonape. 2023. "A Brief Review Of Pathophysiology And Management Of Different Types Of Arthritis" 12 (12): 199–230. https://doi.org/10.48047/ecb/2023.12.si12.016.
7. Ali, Shadab, Rustam Ekbbal, Sapna Salar, Sayad Ahad Ali, Aakash Kumar Jaiswal, Mhaveer Singh, Dinesh Kumar Yadav, and Santosh Kumar. 2023. "Quality Standards and Pharmacological Interventions of Natural Oils: Current Scenario and Future Perspectives." *ACS Omega* 8 (43): 39945–63. https://doi.org/10.1021/acsomega.3c05241.
8. "Alopecia Areata." 1995. *Geneesmiddelenbulletin*.
9. Antonelli, Elisabetta, Gabrio Bassotti, Marta Tramontana, Katharina Hansel, Luca Stingeni, Sandro Ardizzone, Giovanni Genovese, Angelo Valerio Marzano, and Giovanni Maconi. 2021. "Dermatological Manifestations in Inflammatory Bowel Diseases." *Journal of Clinical Medicine*. https://doi.org/10.3390/jcm10020364.
10. Axelrad, Jordan E., Ken H. Cadwell, Jean Frederic Colombel, and Shailja C. Shah. 2021. "The Role of Gastrointestinal Pathogens in Inflammatory Bowel Disease: A Systematic Review." *Therapeutic Advances in Gastroenterology*. https://doi.org/10.1177/17562848211004493.
11. Baldelli, Valerio, Franco Scaldaferri, Lorenza Putignani, and Federica Del Chierico. 2021. "The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases." *Microorganisms*. https://doi.org/10.3390/microorganisms9040697.
12. Bischoff, Stephan C., Palle Bager, Johanna Escher, Alastair Forbes, Xavier Hébuterne, Christian Lodberg Hvas, Francisca Joly, et al. 2023. "ESPEN Guideline on Clinical Nutrition in Inflammatory Bowel Disease." *Clinical Nutrition*. https://doi.org/10.1016/j.clnu.2022.12.004.
13. Booth, Alexander, Wilson Ford, Emily Brennan, Gayenell Magwood, Erin Forster,

and Thomas Curran. 2022. "Towards Equitable Surgical Management of Inflammatory Bowel Disease: A Systematic Review of Disparities in Surgery for Inflammatory Bowel Disease." *Inflammatory Bowel Diseases*. https://doi.org/10.1093/ibd/izab237.

14. Brandon Brown, Bandar E Almansouri, Diane E Heck, and Hong Duck Kim. 2021. "Surveillance Utilizes Multi-Omics in Cardiovascular Disease: Diet and Its Potentiality in Preventive Index." *GSC Biological and Pharmaceutical Sciences*. https://doi.org/10.30574/gscbps.2021.17.3.0323.
15. Burgos, Fernando, Tomás Herrero, Jorge Martínez, Omar Tabacco, and Gabriel Vinderola. 2022. "Immunomodulation Properties of Biotics and Food Allergy in Pediatrics." *Archivos Argentinos de Pediatria*. https://doi.org/10.5546/aap.2022.eng.274.
16. Cai, Zhaobei, Shu Wang, and Jiannan Li. 2021. "Treatment of Inflammatory Bowel Disease: A Comprehensive Review." *Frontiers in Medicine*. https://doi.org/10.3389/fmed.2021.765474.
17. Caron, Bénédicte, Elise Neuville, and Laurent Peyrin-Biroulet. 2022. "Inflammatory Bowel Disease and COVID-19 Vaccination: A Patients' Survey." *Digestive Diseases and Sciences*. https://doi.org/10.1007/s10620-021-07040-z.
18. Cavalcante, Regina Márcia Soares, Murilo Moura Lima, José Miguel Luz Parente, Mayara Storel Beserra de Moura, and Nadir do Nascimento Nogueira. 2020. "Inflammatory Bowel Diseases and Diet: An Integrative Review." *Revista Da Associacao Medica Brasileira*. https://doi.org/10.1590/1806-9282.66.10.1449.
19. Ciocîrlan, M, M Ciocîrlan, and M Diculescu. 2019. "IBD and Intestinal Microbiome-Use and Misuse of PPI and Antibiotics." *Journal of Gastrointestinal and Liver Diseases*.
20. Clemente, Maria Grazia, Claudia Mandato, Marco Poeta, and Pietro Vajro. 2016. "Pediatric Non-Alcoholic Fatty Liver Disease: Recent Solutions, Unresolved Issues, and Future Research Directions." *World Journal of Gastroenterology*. https://doi.org/10.3748/wjg.v22.i36.8078.
21. Collij, Valerie, Marjolein A.Y. Klaassen, Rinse K. Weersma, and Arnau Vich Vila. 2021. "Gut Microbiota in Inflammatory Bowel Diseases: Moving from Basic Science to Clinical Applications." *Human Genetics*. https://doi.org/10.1007/s00439-020-02218-3.
22. Dhaliwal, Amritpal, Jonathan I. Quinlan, Kellie Overthrow, Carolyn Greig, Janet M. Lord, Matthew J. Armstrong, and Sheldon C. Cooper. 2021. "Sarcopenia in Inflammatory Bowel Disease: A Narrative Overview." *Nutrients*. https://doi.org/10.3390/nu13020656.
23. Ekbbal, Rustam, Aakash Kumar Jaiswal, Mansi Aggarwal, Mhaveer Singh, Shadab Ali, Sayad Ahad Ali, and Gaurav Gautam. 2023. "Indian Medicinal Plants for the Management of Endometriosis : A Comprehensive Review on Their Phytopharmacology."
24. Gleeson, John P., Katherine C. Fein, and Kathryn A. Whitehead. 2021. "Oral Delivery of Peptide Therapeutics in Infants: Challenges and Opportunities." *Advanced Drug Delivery Reviews*. https://doi.org/10.1016/j.addr.2021.03.011.
25. Godala, Małgorzata, Ewelina Gaszyńska, Hubert Zatorski, and Ewa Małecka-Wojciesko. 2022. "Dietary Interventions in Inflammatory Bowel Disease." *Nutrients*. https://doi.org/10.3390/nu14204261.
26. Haller, Dirk. 2017. "Dysbiosis in Chronic Intestinal Inflammation and Tumorigenesis: Can We Apply Koch's Postulates?" *Toxicology Letters*. https://doi.org/10.1016/j.toxlet.2017.07.015.
27. Halpern, Vera, Randy M. Stalter, Derek H. Owen, Laneta J. Dorflinger, Anja Lendvay, and Kate H. Rademacher. 2015. "Towards the Development of a Longer-Acting

Injectable Contraceptive: Past Research and Current Trends." *Contraception*. https://doi.org/10.1016/j.contraception.2015.02.014.

28. Harding, Shari L., and Jordan Bishop. 2022. "The Gut Microbiome, Mental Health, and Cognitive and Neurodevelopmental Disorders: A Scoping Review." *Journal for Nurse Practitioners*. https://doi.org/10.1016/j.nurpra.2022.04.019.
29. Incognito, Giosuè Giordano, Gisella D'Urso, Dalila Incognito, Chiara Lello, Alessia Miceli, and Marco Palumbo. 2022. "Management of a Giant Uterine Smooth Muscle Tumor of Uncertain Malignant Potential in a 32-Year-Old Woman: Case Report and Review of the Literature." *Minerva Obstetrics and Gynecology*. https://doi.org/10.23736/S2724-606X.22.05126-0.
30. Jain, Sameeksha, Arpana Purohit, Prakhar Nema, Harshna Vishwakarma, and Prateek Kumar Jain. 2022. "A Brief Review on Nutraceuticals and Its Application." *Asian Journal of Dental and Health Sciences*. https://doi.org/10.22270/ajdhs.v2i1.10.
31. Jiang, Haixiao, Wei Zeng, Xiaoli Zhang, Yunlong Pei, Hengzhu Zhang, and Yuping Li. 2022. "The Role of Gut Microbiota in Patients with Benign and Malignant Brain Tumors: A Pilot Study." *Bioengineered*. https://doi.org/10.1080/21655979.2022.2049959.
32. Kemenkes RI. 2020. "PERATURAN MENTERI KESEHATAN REPUBLIK INDONESIA NOMOR 12 TAHUN 2020 TENTANG AKREDITASI RUMAH SAKIT." *Molecules*.
33. Keyashian, Kian, Melody Dehghan, Lindsay Sceats, Cindy Kin, Berkeley N. Limketkai, and K. T. Park. 2019. "Comparative Incidence of Inflammatory Bowel Disease in Different Age Groups in the United States." *Inflammatory Bowel Diseases*. https://doi.org/10.1093/ibd/izz092.
34. Kho, Zhi Y., and Sunil K. Lal. 2018. "The Human Gut Microbiome - A Potential Controller of Wellness and Disease." *Frontiers in Microbiology*. https://doi.org/10.3389/fmicb.2018.01835.
35. Lewin, Sara, Charles Lees, Miguel Regueiro, Ailsa Hart, and Uma Mahadevan. 2020. "International Organization for the Study of Inflammatory Bowel Disease: Global Strategies for Telemedicine and Inflammatory Bowel Diseases." *Journal of Crohn's and Colitis*. https://doi.org/10.1093/ecco-jcc/jjaa140.
36. Li, Suqing, Michael Ney, Tannaz Eslamparast, Ben Vandermeer, Kathleen P. Ismond, Karen Kroeker, Brendan Halloran, Maitreyi Raman, and Puneeta Tandon. 2019. "Systematic Review of Nutrition Screening and Assessment in Inflammatory Bowel Disease." *World Journal of Gastroenterology*. https://doi.org/10.3748/wjg.v25.i28.3823.
37. Lu, Xingbing, Li Xiong, Xi Zheng, Qiuju Yu, Yuling Xiao, and Yi Xie. 2023. "Structure of Gut Microbiota and Characteristics of Fecal Metabolites in Patients with Lung Cancer." *Frontiers in Cellular and Infection Microbiology*. https://doi.org/10.3389/fcimb.2023.1170326.
38. M., Schirmer, Vlamakis H., Denson L.A., Davis S., Rufo P.A., Baker S.S., Strople J.A., et al. 2017. "Microbial Dysbiosis Associated with Disease Severity in Treatment Naive Pediatric Patients with New-Onset Ulcerative Colitis." *Gastroenterology*.
39. Maimoona, Alya, Ismat Naeem, Zeb Saddiqe, and Khalid Jameel. 2011. "A Review on Biological, Nutraceutical and Clinical Aspects of French Maritime Pine Bark Extract." *Journal of Ethnopharmacology*. https://doi.org/10.1016/j.jep.2010.10.041.
40. Mandal, Suraj, Vishakha Jaiswal, Manoj Kumar Sagar, and Sachin Kumar. 2021. "FORMULATION AND EVALUATION OF CARICA PAPAYA NANOEMULSION FOR TREATMENT OF DENGUE AND THROMBOCYTOPENIA." *PLANT ARCHIVES*.

https://doi.org/10.51470/plantarchives.2021.v21.no1.179.

41. Mandal, Suraj, Vishakha Jaiswal, and Km Shiva. 2020. "A Review on Marketed Carica Papaya Leaf Extract (CPLE) Supplements for the Treatment of Dengue Fever with Thrombocytopenia and Its Drawback." *International Journal of Pharmaceutical Research*. https://doi.org/10.31838/ijpr/2020.12.03.205.
42. Mandal, Suraj, Km. Shiva, K Pavan Kumar, Sweta Goel, Ramesh Kumar Patel, Shital Sharma, Renu Chaudhary, Arti Bhati, Netra Pal, and Ashwani Kumar Dixit. 2021. "Ocular Drug Delivery System (ODDS): Exploration the Challenges and Approaches to Improve ODDS." *Journal of Pharmaceutical and Biological Sciences*. https://doi.org/10.18231/j.jpbs.2021.012.
43. Mandal, Suraj, and Prabhakar Vishvakarma. 2023a. "Future Aspects and Applications of Nanoemulgel Formulation for Topical Lipophilic Drug Delivery." *European Journal of Molecular*.
44. ———. 2023b. "Nanoemulgel: A Smarter Topical Lipidic Emulsion-Based Nanocarrier." *Indian Journal of Pharmaceutical Education and Research*. https://doi.org/10.5530/ijper.57.3s.56.
45. Markowitz, John S., Patrick C. Gurley, and Bill J. Gurley. 2020. "Medical Foods—A Closer Look at the Menu: A Brief Review and Commentary." *Clinical Therapeutics*. https://doi.org/10.1016/j.clinthera.2020.05.011.
46. Mayo-Martínez, Laura, Francisco J. Rupérez, Gabriel Martos-Moreno, Montserrat Graell, Coral Barbas, Jesús Argente, and Antonia García. 2021. "Unveiling Metabolic Phenotype Alterations in Anorexia Nervosa through Metabolomics." *Nutrients*. https://doi.org/10.3390/nu13124249.
47. Ng, S C. 2018. "Understanding Epidemiology and Microbiome in IBD." *Digestive Endoscopy*.
48. Nishida, Atsushi, Ryo Inoue, Osamu Inatomi, Shigeki Bamba, Yuji Naito, and Akira Andoh. 2018. "Gut Microbiota in the Pathogenesis of Inflammatory Bowel Disease." *Clinical Journal of Gastroenterology*. https://doi.org/10.1007/s12328-017-0813-5.
49. Noolu, Venkatesh, M. Heera Lal, and Rakesh J. Pillai. 2018. "Multi-Scale Laboratory Investigation on Black Cotton Soils Stabilized with Calcium Carbide Residue and Fly Ash." *Journal of Engineering Research*.
50. Pal, Netra, Suraj Mandal, Km Shiva, and Bijender Kumar. 2022. "Pharmacognostical, Phytochemical and Pharmacological Evaluation of Mallotus Philippensis." *Journal of Drug Delivery and Therapeutics*. https://doi.org/10.22270/jddt.v12i5.5675.
51. Panthee, Bimala, Saroj Gyawali, Pratiksha Panthee, and Kuaanan Techato. 2022. "Environmental and Human Microbiome for Health." *Life*. https://doi.org/10.3390/life12030456.
52. Papaiakovou, Marina, D. Timothy J. Littlewood, Stephen R. Doyle, Robin B. Gasser, and Cinzia Cantacessi. 2022. "Worms and Bugs of the Gut: The Search for Diagnostic Signatures Using Barcoding, and Metagenomics–Metabolomics." *Parasites and Vectors*. https://doi.org/10.1186/s13071-022-05225-7.
53. Petersen, Charisse, and June L. Round. 2014. "Defining Dysbiosis and Its Influence on Host Immunity and Disease." *Cellular Microbiology*. https://doi.org/10.1111/cmi.12308.
54. Philips, Cyriac A, Sasidharan Rajesh, Dinu C Nair, Rizwan Ahamed, Jinsha K Abduljaleel, and Philip Augustine. 2021. "Hepatocellular Carcinoma in 2021: An Exhaustive Update." *Cureus*. https://doi.org/10.7759/cureus.19274.
55. Pop, Oana Lelia, Dan Cristian Vodnar, Zorita Diaconeasa, Magdalena Istrati, Adriana Bințințan, Vasile Virgil Bințințan, Ramona Suharoschi, and Rosita Gabbianelli.

2020. "An Overview of Gut Microbiota and Colon Diseases with a Focus on Adenomatous Colon Polyps." *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms21197359.

56. Puvvada, Nagaprasad, B. N.Prashanth Kumar, Suraj Konar, Himani Kalita, Mahitosh Mandal, and Amita Pathak. 2012. "Synthesis of Biocompatible Multicolor Luminescent Carbon Dots for Bioimaging Applications." *Science and Technology of Advanced Materials*. https://doi.org/10.1088/1468-6996/13/4/045008.
57. Qiu, Peng, Takatsugu Ishimoto, Lingfeng Fu, Jun Zhang, Zhenyong Zhang, and Yang Liu. 2022. "The Gut Microbiota in Inflammatory Bowel Disease." *Frontiers in Cellular and Infection Microbiology*. https://doi.org/10.3389/fcimb.2022.733992.
58. Ray, Greeshma, and Michelle S. Longworth. 2019. "Epigenetics, DNA Organization, and Inflammatory Bowel Disease." *Inflammatory Bowel Diseases*. https://doi.org/10.1093/ibd/izy330.
59. Reduction, Drudgery, Acceptability Of, Drudgery Reducing, Tool In, and O F Dairy Animals. 2021. "Plant Archives" 21 (table 1): 2184–85.
60. Rosso, Ayelén D., Pablo Aguilera, Sofía Quesada, Florencia Mascardi, Sebastian N. Mascuka, María C. Cimolai, Jimena Cerezo, et al. 2022. "Comprehensive Phenotyping in Inflammatory Bowel Disease: Search for Biomarker Algorithms in the Transkingdom Interactions Context." *Microorganisms*. https://doi.org/10.3390/microorganisms10112190.
61. Segura-Sampedro, Juan J., Carla Jiménez-Giménez, Enric Jane-Salas, Daniel Cabanillas-Balsera, Jenifer Martín-González, Juan J. Segura-Egea, and José López-López. 2022. "Periapical and Endodontic Status of Patients with Inflammatory Bowel Disease: Age- and Sex-Matched Case–Control Study." *International Endodontic Journal*. https://doi.org/10.1111/iej.13747.
62. Shan, Yue, Mirae Lee, and Eugene B. Chang. 2022. "The Gut Microbiome and Inflammatory Bowel Diseases." *Annual Review of Medicine*. https://doi.org/10.1146/annurev-med-042320-021020.
63. Shreiner, Andrew B., John Y. Kao, and Vincent B. Young. 2015. "The Gut Microbiome in Health and in Disease." *Current Opinion in Gastroenterology*. https://doi.org/10.1097/MOG.0000000000000139.
64. Singh, Arshdeep, Ramit Mahajan, Saurabh Kedia, Amit Kumar Dutta, Abhinav Anand, Charles N. Bernstein, Devendra Desai, et al. 2022. "Use of Thiopurines in Inflammatory Bowel Disease: An Update." *Intestinal Research*. https://doi.org/10.5217/ir.2020.00155.
65. Stott, Katie J., Bethan Phillips, Lee Parry, and Stephanie May. 2021. "Recent Advancements in the Exploitation of the Gut Microbiome in the Diagnosis and Treatment of Colorectal Cancer." *Bioscience Reports*. https://doi.org/10.1042/BSR20204113.
66. Suematsu, Yasunori, Akihiro Shimomura, and Nosratola D. Vaziri. 2017. "Uremic Toxins and Gut Micro Biome." *Japanese Journal of Nephrology*.
67. Sweta, Koka, Pancholi Mamta, Sharma Vijay, and Gayakwad Devshree. 2019. "Formulation and Evaluation of Topical Antifungal Herbal Gels Containing Hydroalcoholic Extract of Catharanthus Roseus and Aloe Vera." *Available Online on Www.Ijppr.Com International Journal of Pharmacognosy and Phytochemical Research*.
68. Tamboli, C. P., C. Neut, P. Desreumaux, and J. F. Colombel. 2004. "Dysbiosis in Inflammatory Bowel Disease." *Gut*. https://doi.org/10.1136/gut.53.1.1.
69. Varesi, Angelica, Elisa Pierella, Marcello Romeo, Gaia Bavestrello Piccini, Claudia Alfano, Geir Bjørklund, Abigail Oppong, et al. 2022. "The Potential Role of Gut Microbiota in Alzheimer's Disease: From Diagnosis to Treatment." *Nutrients*.

https://doi.org/10.3390/nu14030668.

70. Yu, Suyun, Huiping Zhang, Liping Wan, Min Xue, Yunfeng Zhang, and Xiwen Gao. 2023. "The Association between the Respiratory Tract Microbiome and Clinical Outcomes in Patients with COPD." *Microbiological Research*. https://doi.org/10.1016/j.micres.2022.127244.
71. Zhao, Zelong, Jingwei Jiang, Yongjia Pan, Ying Dong, Bai Wang, Shan Gao, Zhong Chen, Xiaoyan Guan, Xuda Wang, and Zunchun Zhou. 2022. "Sea Cucumber Body Vesicular Syndrome Is Driven by the Pond Water Microbiome via an Altered Gut Microbiota." *MSystems*. https://doi.org/10.1128/msystems.01357-21.