A NARRATIVE OVERVIEW ON CRUCIAL ROLE OF GUT MICROBES IN CHRONIC INFECTIOUS AND INFLAMMATORY DISEASES

Abstract

Numerous microorganisms in the human gut microbiota fight pathogens in infectious diseases and suppress or induce inflammation in various immunological situations. A significant microbial community that is vital to human existence is the human gut microbiome. It promotes the proliferation, development, and differentiation of epithelial and immunological cells, which aids in maintaining intestinal homeostasis. Disorders that affect the microbiota induce an imbalance in the host’s & #39; immunological regulation. Research analysis suggests that the gut microbial ecology is linked to the onset and increment of several infectious and inflammatory disorders. Understanding the connection between gut microbiota and control of the immune system is therefore critical for understanding the mechanisms involved in various illnesses. The review focuses on the main gut bacteria capable of influencing the immune response in various pathologies, as well as a possible target for disease prevention and treatment due to the control and mechanism of GM on gastrointestinal, metabolic, and neurological diseases.

Keywords: Gut Microbiota, Neurodegenerative Disorders, Homeostasis, Gastrointestinal Diseases, Immune System.

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I. INTRODUCTION

Chronic infection is defined by the persistence of infectious viruses beyond the first infection and might involve chronic or recurring disease (Boldogh et al., 1996). Chronic infections are a significant public health problem. The challenge in influencing them would have been easy to comprehend if chronic foci bacteria had exhibited high antibiotic resistance or if immunological weaknesses were consistently observed in individuals with persistent infections. Nonetheless, there seem to be situations of severe disease during which the bacteria become antibiotic-resistant but the immunity of the body is functioning normally (Malyshkin, 2014). Inflammation is a medical condition. When an infecting agent comes into interaction with the host (including certain pathogens, or toxic chemicals) or suffers a trauma, the immune response is triggered. Immune mediators and inflammatory mediators are the immunological system's initial reactions. These cells generate an immune response in order to capture pathogenic microbes or to repair damaged tissue. Therefore, as a reaction, individuals might experience pain, inflammation, discoloration, or reddening. However, inflammation impacts biological systems that are not visible (Yang et al., 2022).

Infectious diseases continue to be the leading causes of human and animal morbidity and mortality rates, resulting in enormous healthcare spending in India. The introduction of new human infections and the revitalization of old diseases are severe issues in this decade (Mourya et al., 2019). India is the most populated country, with altering sociocultural and epidemiological patterns that have drawn international interest in recent times (Patil et al., 2002). In India, either contagious or non-modifiable diseases are said to affect various social and economic groups adversely (Banerjee & Dwivedi, 2016). Some common communicable diseases that have spread rapidly in India in recent years are COVID-19, Malaria, Typhoid, Tuberculosis, AIDS, Hepatitis, Influenza, and so on (Most Communicable Diseases in India, 2023). A disease's transmission does not end in a nation's territory. Germs spread more quickly as more people live in congested cities and travel to other nations. Communicable diseases that begin from one area of the globe can quickly spread to another. AIDS, Malaria, COVID-19, and Tuberculosis are among the primary diseases now afflicting countries around the world (Table 1). Several world health issues exist in addition to disease propagation. Medicine resistance, such as antibiotic resistance, seems to be increasing. This makes specific disorders more difficult to control. Natural and man-made calamities result in refugee populations experiencing both acute and long-term health issues. Extreme weather, as well as a scarcity of food and healthy drinking water, are international issues that can have an impact on people's health. Many regions and health authorities are cooperating and transmitting ideas on this or other health-related topics (Figure 1).

Table 1: Nowadays disease is not just trapped in one nation as more people live in congested cities and travel to other nations. Communicable diseases that begin in one area spread to another part of the globe. The table below represents the most prominent communicable diseases present both in India and globally and the pathogen that causes them (Did You Know?, 2021).

Prominent communicable diseases both in India and internationally in recent decades	Pathogens
1. Coronavirus-disease-2019	Severe acute respiratory syndrome coronavirus 2
2. AIDS	Human immunodeficiency virus (HIV)
3. Malaria	*P. falciparum, P. vivax, P. ovale and P. malariae*
4. Tuberculosis	*Mycobacterium tuberculosis*
5. Hepatitis	Hepatitis virus
6. Dengue	Dengue virus (Belongs to the Flavivirus family)

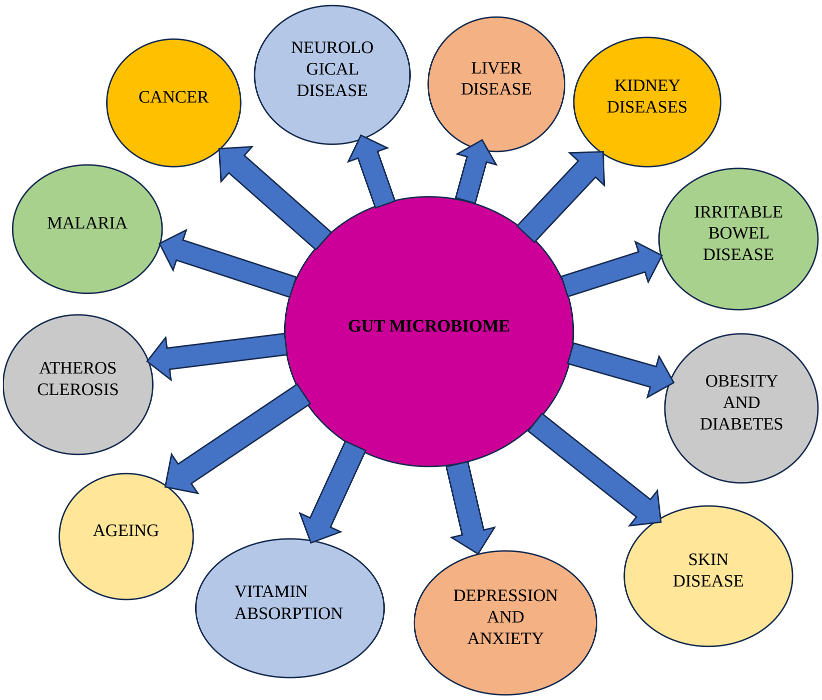

Figure 1: As we all know the microbiota present in the gut is a group of microscopic organisms that help to fight pathogens and can also prevent different diseases at the ground level. The above-shown arrow diagram represents how the microbiota present in the gastrointestinal tract is related to the majority of illnesses, as well as to different body functions in the human body (“Gut Microbiota,” 2023).

The contemporary era's enormous psychological and biological changes pose a severe threat to human wellness. An individual's microbiota contains a diverse agglomeration of microbiotas, which impacts the ratio of wellness and pathology in their environment. Such microbes provide significant biochemical advantages to their hosts, such as immunological modulation and disease resistance (Khor et al., 2021). The mutual link between gut bacteria and its symbiont organism has received a lot of attention. While the digestive tract's mechanics and anatomy are complicated in itself, the microbial residents of the gut all have their unique activities (Hill et al., 2014). Bacterial, archaebacteria, viral, and multicellular microorganisms inhabit the gastrointestinal tract and make up the gut microbiome (Ullah et al., 2023). Researchers have found that the microbiome in the gastrointestinal tract has quite a profound influence on the onset and progression of major human diseases for which there are presently no treatment options. Having fats in your liver is natural, but when it accounts for any further than 10% of its weight, it may end up suffering. Heavy drinking is a prevalent trigger for fatty liver disease. However, several individuals grow it without drinking heavily (Younossi et al., 2018). Non-alcoholic fatty liver disease (NAFLD) refers to a set of liver illnesses ranging from hepatic steatosis to non-alcoholic steatohepatitis (NASH), with or without fibrosis, and can lead to cirrhosis of the liver or hepatocellular cancer (Xia et al., 2022). NAFLD which is regarded as a major public health concern worldwide, has sparked rising interest in the field of liver disease research. Pathophysiological medication therapies for NAFLD are being studied, but the absence of licensed treatments is due to acknowledged rates. These pharmacological therapies tend to have limited effectiveness, mainly in treating fibrosis. Despite extensive drug development, there are currently no FDA-approved drugs addressing NASH, and no specialized treatment may be prescribed. The drugs that are now used to treat NASH are administered off-label all around the globe. Probiotics are used as microbial therapies in the treatment of NAFLD. Countless potential therapeutic investigations for the management and cure of NAFLD and NASH have been conducted as a consequence of the impacts of the gut microbiota. Nonetheless, probiotics such as *Lactobacillus*, *Bifidobacterium*, *and Pediococcus* are useful in the prevention of NAFLD in experimental studies. Probiotics eliminate NAFLD in rodents by reintroducing microbiological balance in the stomach, which decreases lipogenesis and, as a result, liver inflammation. Prebiotics, pre- and probiotic combinations (synbiotics), medications, and FMT (Fecal microbiota transplantation) are some of the other potential techniques (Figure 2) for modifying gut microbiome assemblages for NAFLD management (Gupta et al., 2022).

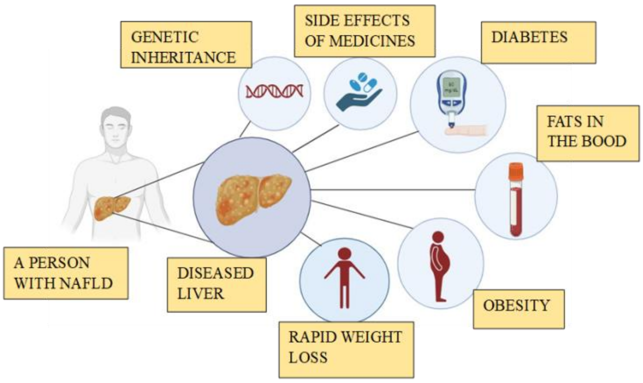

Figure 2: NAFLD, as the name implies is a fatty liver disease that is not caused by alcohol, and the causes of NAFLD in a non-drinker are represented in the picture above (NAFLD & NASH - Symptoms, Causes, Differences & Treatment Options, 2022).

II. GUT MICROBES AND INFLAMMATIONS

The microbiota is the aggregate of all microorganisms, including the bacterium, fungus, virus, and their related genes, that exist naturally occurring on and throughout biological systems. Despite bacteria being microscopic organisms that have to be viewed under a microscope, they have a significant impact on human health and welfare. They defend us from viruses, contribute to the formation of our immunity, and allow us to break down food to process energy (Cresci & Bawden, 2015).

The microbiome in the gut has an important role in immunological function and physiology, (Figure 3) involving microorganism invasion, prevention, and immunological reaction regulation (Xia et al., 2022). The links involving both gut microbiome formation and illness status have been heavily publicized, and current research has shown that the gut microbiome influences remote organs, mucosal response, and immunological activity. A significant amount of work is currently being put into investigating the biology of microbiota creation in individuals for medical consequences, as well as expanding our understanding of microbiome-host biomolecule interactions. These initiatives eventually aim to create effective methods for rehabilitating disrupted human microbial communities to restore safety and reduce disease. Configurational and physiological abnormalities in the gut microbiota have been observed in the case of various autoimmune disorders, and there is mounting consensus that agitated gut microbiome contributes to associated immunopathogenesis (Vijay & Valdes, 2021).

Even though the concentration of the human gut microbiota varies over time, in healthy communities, there is a diverse range of shared microbiological genes. Firmicutes and Bacteroidetes groups contribute to even more than 90% of the overall inhabitants of gut microbiota in most situations. The gut microbiota, on the other hand, varies widely between individuals and under illness situations. The change could be represented by decreased flora variation or varying microbiological density (Cheng et al., 2020). Gut flora diversity is widely assessed utilizing DNA-based approaches including analysis of the genes for 16S ribosomal RNA or all including genome sequencing permitting the interpretation of microbial functions. Bioconversion products can now be quantified in faeces and serum using metagenomic methods. The microbiota in the gut is essential for the digestion of substrates that are inadequately digested, such as dietary fibres and endogenous gastrointestinal mucus. Fermentation encourages the growth of bacteria that produce short-chain fatty acids (SCFAs) and fumes. The main SCFAs produced are acetate, propionate, and butyrate (Valdes et al., 2018).

Bile acids and short-chain fatty acids (SCFAs) from the gut microbiota can help maintain the host's health by providing nutrition and energy while also regulating the host's immune system. These molecules include both small compounds created directly by commensal bacteria and end products of dietary substrates digested by commensal bacteria, both of which play an important role in host health. Since they induce the production of host antimicrobial peptides, primary bile acids, such as chenodeoxycholic acids, have been found to have antimicrobial action against microbial pathogens. Secondary bile acids produced by biological agents and symbiotic products such as propionate also hinder bacterial pathobiont colonization such as C. difficile. Overweight, Vascular dementia, and disorders that disrupt intestinal epithelial integrity have all been linked to GM-derived SCFAs. SCFAs can also help to maintain intestinal homeostasis by modulating the immune system (Figure 4). Relative to healthy individuals, Crohn's disease (CD) patients have a lower concentration of butyrate-producing species of bacteria in the Ruminococcaceae family (Zhang et al., 2021).

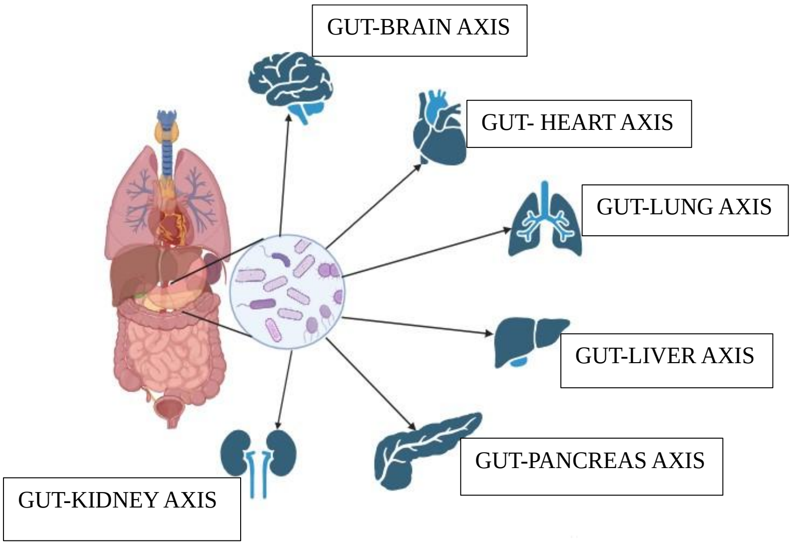

Figure 3: The above –shown picture is that of a whole digestive system, but the main focus is on the gut containing different microbes making up the gut microbiota or the gut microbiome, and as the picture depicts it correlates to every other organ and has an axis between them (Afzaal et al.,2022).

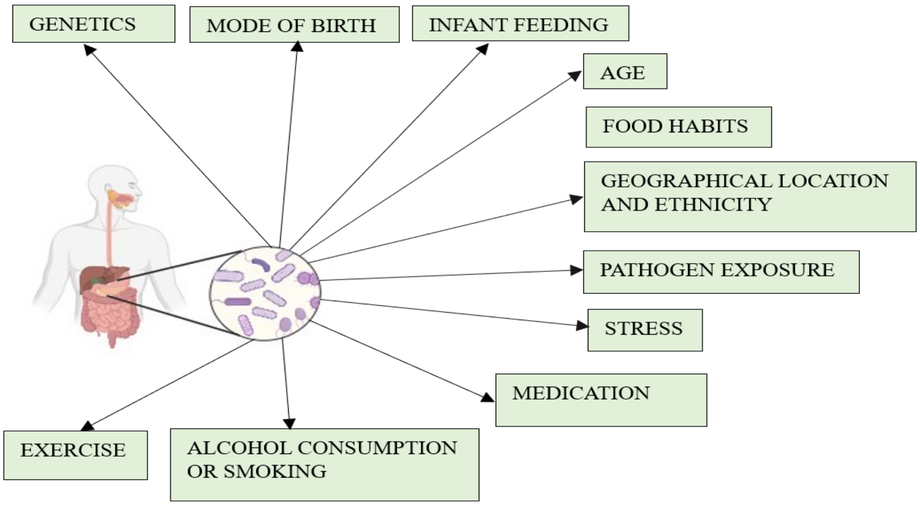

Figure 4: The microbiome of the gut is a combination of microorganisms comprised of many types of bacteria, fungi, viruses, and so on. Bacteroidetes and Firmicutes are both present in more amounts compared to the others in the gut of a healthy human. Many factors can disrupt the composition of these microorganisms present in the gut as shown in the picture above (Liang et al., 2022).

III. MACROPHAGE AND INFLAMMATION

Macrophages are a special (myeloid) type of immune cell that is spread throughout the body. They participate in phagocytosis, the elimination of bacteria and other harmful organisms (Varol et al.,2015). Macrophages are also known as antigen-presenting cells. Having MHC class II on their surface, they serve the purpose of presenting antigens to T lymphocytes to initiate the process of inflammation by releasing cytokines that help to activate other immune cells (Harding et al.,1992). Macrophages developed from CD14+CD16+ monocyte cells that departed from the circulation and differentiated in different tissues such as infection or tumor sites, to encourage continued inflammation or tissue healing. (Yang et al.,2014)

There are different names for tissue macrophages according to the site where they are present; for example, macrophages that are present in adipose tissue are known as adipose tissue macrophages; Kupffer cells are found in hepatic; The central nervous system (CNS) contains microglial cells.; There are osteoclast cells in bone tissues etc. (Italiani et al., 2015).
Inflammation plays a crucial role in your body’s ability to repair. During injury Immune cells or inflammatory cells travel to the injured region and cause the inflammatory process to begin to heal that site. Chronic inflammation may result from inflammatory cells remaining too long (Inflammation: What Is It, Causes, Symptoms & Treatment, n.d.). There are two types of inflammatory macrophages found in humans and higher animals. M1 macrophages and M2 macrophages, both of which are responsible for the inflammatory response. M1 macrophages are recognized for their pro-inflammatory reaction, whereas M2 macrophages are recognized for their anti-inflammatory reaction. (Yunna et al., 2020) The human body is very complex; whenever it faces injury from inside or outside, it goes through a complete series of cellular responses to heal that injury, starting from inflammation to tissue damage and then to healing. They also promote fibrosis and clear cell debris (Oishi et al.,2018). The inflammatory process needs some signal for initiation and also needs signals to stop. Both signals work in a controlled manner, but whenever the two signals are out of balance, the inflammation process spreads unchecked and leads to tissue damage. In the inflammatory activity, macrophages play 3 important tasks. 1. Presenting antigen to T lymphocyte 2. Cellular ingestion, and 3. Very important, immunomodulation by releasing various cytokines and growth factors (Fujiwara et al., 2004)

Pattern recognition receptors or inflammatory lymphokine such as interferon Gama (IFN-γ) stimulate the activation of M1 macrophage after the activation of the M1 macrophage it starts releasing Pro-inflammatory cytokines like tumor necrosis factor alpha (TNF- α), interleukin 1(IL-1), and IL-6. However, M2 macrophages also activate alternatively by some interleukin (like-4, 13, and 10) and express some receptors such as Arginase 1 (Arg-1), and CD206. Anti-inflammatory macrophages’ main responsibilities include tissue repair and homeostasis, whereas proinflammatory macrophages’ key responsibilities include the destruction of tumors and infections through the generation of inflammatory cytokines and phagocytosis. M1 Macrophage Pro inflammatory macrophage presents the antigen to CD8+ T lymphocytes similar to a dendritic cell. Comparable to how immature DCs cross-present, anti-inflammatory macrophages may also serve in immunological tolerance to “self” proteins, commensal microorganisms, and dietary components. Anti-inflammatory macrophages help in tissue regeneration or tissue repair, proliferation, angiogenesis, and immunomodulation (Muntjewerf et al., 2020).

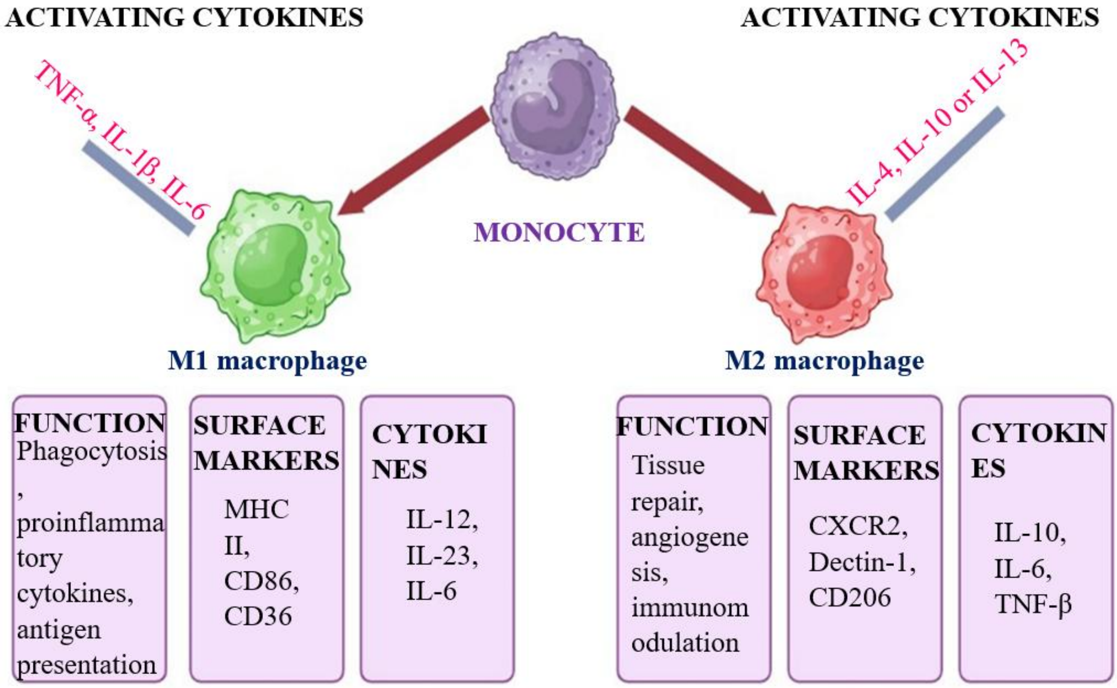

Figure 5: Macrophage is a special type of immune cell that has a diverse role. It is essential in causing inflammation. The above figure represents the origin of different tissue resistant macrophage from monocytes their function, surface marker, and cytokine (Kadomoto et al., 2021)

IV. MACROPHAGE IN WOUND HEALING

There are different stages of wound healing, which is the process by which damaged tissue is repaired and returned to homeostasis after being subjected to mechanical or infectious trauma. (Kim et al. 2019)

The key actor in the process of tissue repair is the M2 macrophage. it is activated by cytokines (like IL-4, IL-13) of Th2 cells. TNF-α, IL-6, IL-1, ROS, and nitric oxide (NO) are all produced by pro-inflammatory macrophages. Additionally, MMP-2 and MMP-9 are secreted by these cells to degrade the extracellular matrix and create space for inflammatory cells to invade. To promote cellular proliferation (Figure 6) the creation of granulation tissue, and angiogenesis, Growth factors like Platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), Vascular endothelial growth factor (VEGF), and Transforming growth factor 1 (TGF-1) are secreted in greater amounts by macrophages that promote wound healing (Krzyszczyk et al. 2018).

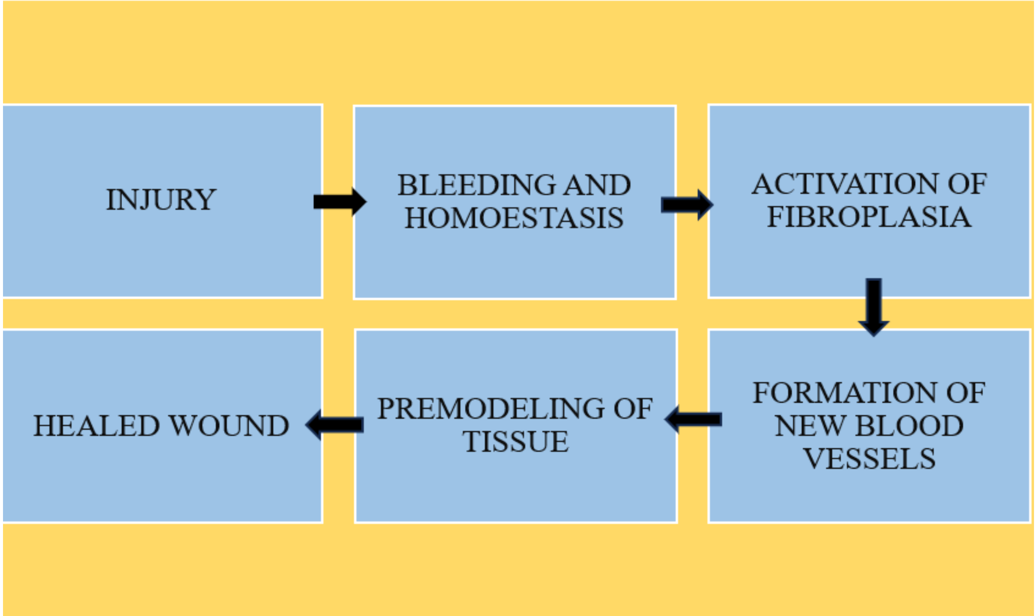

Figure 6: wound healing is an important physiological mechanism of all living organisms. It starts from homeostasis and ends with tissue healing. The above figure represents the common steps in wound healing (Themes, 2017).

A long-term inflammatory condition that affects the digestive tract is inflammatory bowel disease. The two subtypes are ulcerative colitis and Crohn's disease (Fabián et al., 2022). In Crohn's illness, different people face inflammation in different parts of the small intestine. On the other hand, people with ulcerative colitis, face inflammation in the large intestine and ultimately develop ulcers due to unusual immune system reactions. IBD is very common among the group of people aged 15–30; it is not specific to any age or gender It can develop in people at any time (Inflammatory Bowel Disease: Symptoms, Treatment & amp; Diagnosis, n.d.).

There is no specific reason for the cause of this disease, but somehow there is some hypothetical reason for this disease, such as when environmental triggers for example the unbalanced microorganism in the gut make an improper immune reaction, Due to which inflammation occurs in the digestive tract. Additionally, genetics appear to be important. It is more likely for someone to experience this incorrect immune response if their family has a history of IBD (Ko et al., 2014).

There are specific microbes in the human gut that are crucial to maintaining good health. In newborns, the gut microbiome differs significantly from that of adults in terms of composition and temporal pattern. In addition to strengthening the host's natural defenses, gut bacteria also support the gut's regular functioning. Imbalance of microorganisms in the gut. Due to which the good microorganisms in the gut decrease and the bad microorganisms increase and damage the intestinal microbial barriers is a common symptom of inflammatory bowel disease. Different metabolites can be manufactured by different microorganisms present in the gut. To stop the spread of harmful bacteria Along with encouraging intestinal homeostasis. The mucus released by path cells and the bacteria in the gut are essential components of the digestive tract's chemical barrier. The imbalanced microbiota in humans leads to inflammatory bowel disease (Thursby & Juge, 2017).

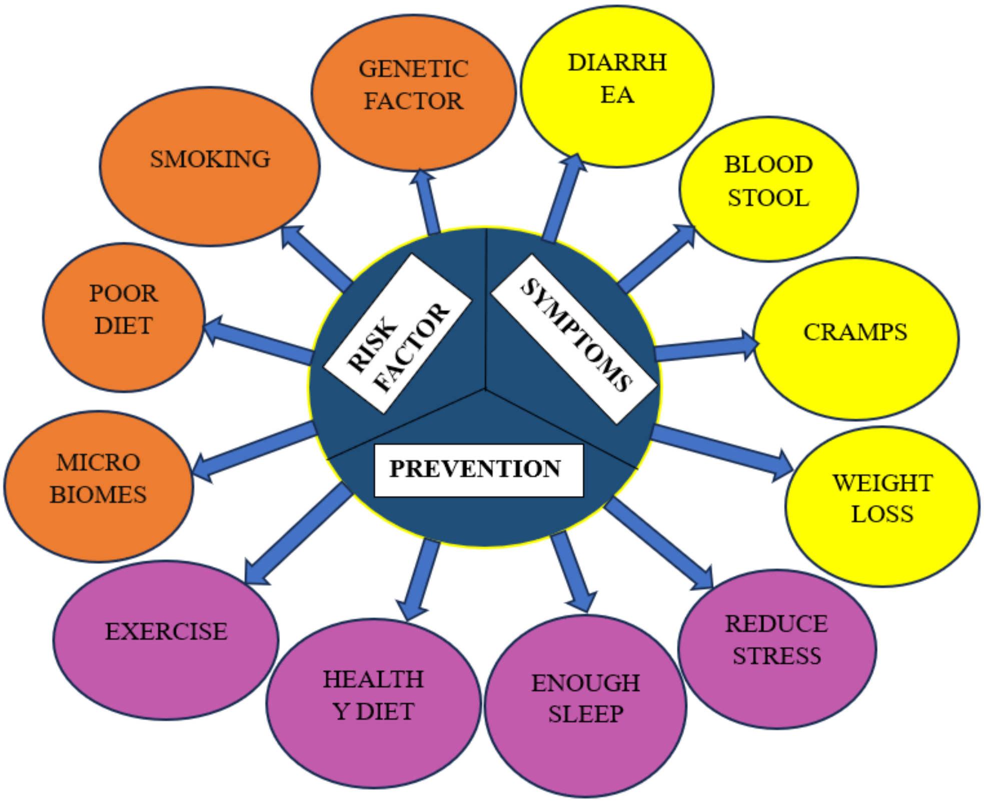

Figure 7: IBD is a long-term inflammatory condition that occurs in the intestine. The above figures represent symptoms, prevention, and risk factors of inflammatory bowel disease (Kumar et al., 2019).

V. MICROBIOTA IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

From the studies, it is supposed that certain types of probiotic supplements and Fecal microbiota transplantation (FMT) may be used in the treatment of intestinal inflammation in some animal models for example in E. coli and salmonella growth can be inhibited by a probiotic known as Nissle 1917. Due to the critical role gut microbiota plays in the etiology of BD, fecal microbiota transplantation can help IBD patients reestablish intestinal mucosal immunological homeostasis. A good diet plays a very important role in keeping the balance of good microorganisms in the gut to control inflammatory bowel disease. The effects of diet mainly occur through three mechanisms. First, certain diets have the potential to alter the intestine microbiology's composition while also indirectly influencing the intestinal immune system. Some dietary components can control IBD to some extent. Healthy people have good microorganisms in their gut (As shown in Table 2) as compared to IBD patients (Qiu et al., 2022).

Table 2: The gut microbiota has diverse functions in living organisms. There are various types of Microorganisms present in the person's gut and play different functions there. The above table represents some good microorganisms and some bad microorganisms and their amounts in healthy humans and IBD patients (Aldars-García et al., 2021).

Good Microorganism	**Amount in a Healthy Person**	**Amount in IBD Patient**	**Bad Microorganism**	**Amount in a Healthy Person**	**Amount in IBD Patient**
Clostridium groups lV	More	Less	*Ruminococcus gnavus*	Less	More
Bifidobacterium	More	Less	*Proteobacteria*	Less	More
Lactobacillus	More	Less	*Fusobacterium sp.*	Less	More
Faecalibacterium prausnitzii.	More	Less	*Candida albicans*	Less	More
Saccharomyces cerevisiae	More	Less	*Caudovirales*	Less	More

VI. GUT MICROBIOTA AND OBESITY

Gut-intestinal flora refers to the class of bacteria, fungi, protozoas that reside in the human body. These microorganisms are important in human metabolic activities. These gastro-intestinal flora are referred to as the human microbiota (Jandhyala SM et al., 2023) The bacteria that live in the gut of humans are referred to as gastro-intestinal flora or gut microbiota or gut flora. Gut is generally the internal part-stomach(Gastrointestinal tract)which secrete HCL,hence highly acidic in nature(Sasso JM et al., 2023).The digestive tract constitute the part of human body from mouth to anus. Firmicutes (which includes lactobacilli), Proteobacteria (which includes Escherichia), Bacteroidetes, Actinobacteria (which includes Bifidobacteria), and are the four classes of microbiota that reside in the human body. The Fusobacteria and Verrucobacteria are two more phyla that are less prevalent.The class of these bacteria are represented in the figure below. *Bacteroides sp.,Ruminococcus sp.*, *Peptococcus sp.*, *Peptostreptococcus sp.*, *Clostridium sp.*, *Fusobacterium sp.*, *Eubacterium sp.*, and *Bifidobacterium sp.* are the most common bacterial genera.To begin, the phylum Actinobacteria includes the class Actinobacteria (gram-positive organisms)- Corynebacterium, Bifidobacterium, Streptomyces and Nocardia. Firmicutes (gram positive) constitute two classes- Clostridium and Bacillius eg.Staphylococcus, Enterococcus,Faecalibacterium, Lactobacillus, Ruminococcus, Clostridium,etc. The phylum Bacteroidetes includes the class Bacteroidetes(gram-negative)-Bacteroides and Prevotella. The phylum Proteobacteria(gram-negative) is divided into two sub- classes (1) β-proteobacteria and (2) γ-proteobacteria, which contain species such as Escherichia, Helicobacteria, Vibrio, etc (Figure 8).

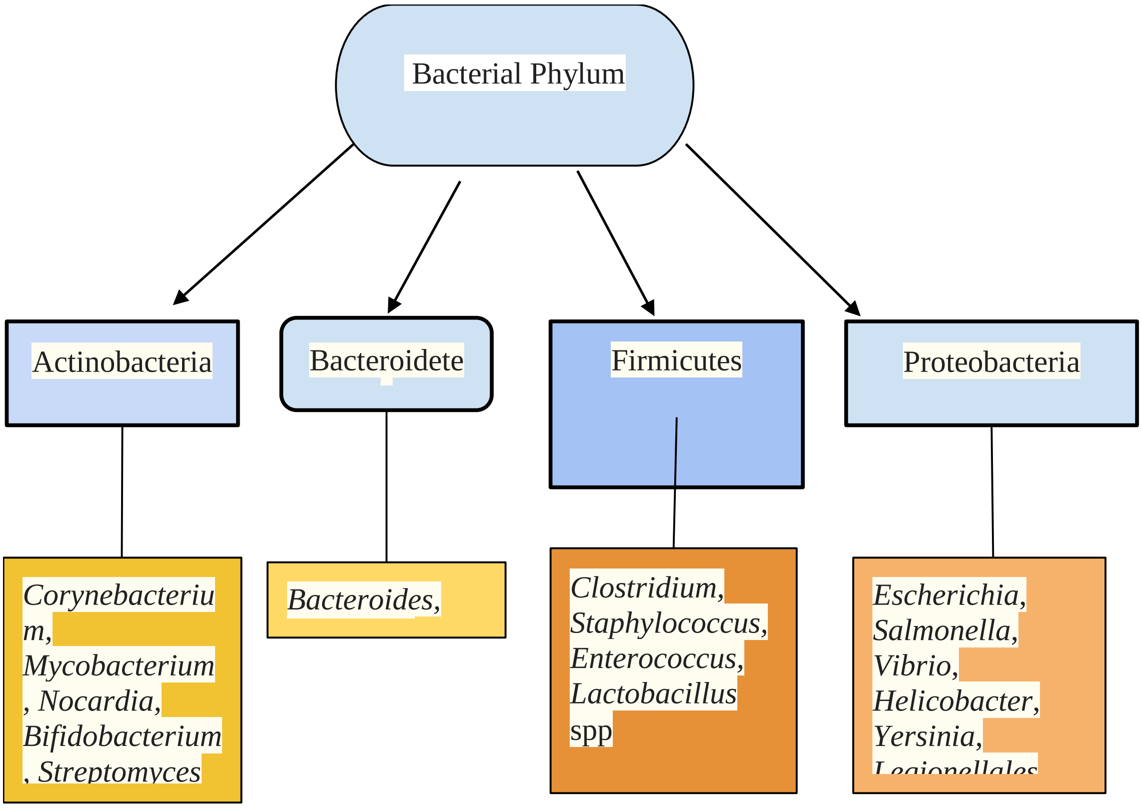

Figure 8: Different classes of bacterial phylum which includes- Actinobacteria, Bacteriodetes, Firmicutes, Proteobacteria with their examples (Sasso JM et al., 2023).

There are substantially fewer members of other genera, such as Escherichia and Lactobacillus (Thomas et al., 2012). The human gut consists of 20-25 species of bacteria from the genus Bacteroides(30%) (Jandhyala et al., 2015). Dysbiosis due to IBD (Inflammatory bowel disease) is particularly linked to both- decline in Firmicute diversity and an increase in Proteobacteria. Firmicutes generate necessary short-chain fatty acids (SCFAs) like acetic and butyric acids, having Antiphlogistic properties, they are low in numbers. When there in low count of Firmicutes in the human body then it is an indicator of dysbacteriosis in inflammatory bowel diseases in patients. Therefore, it is seen that the observed abnormalities, such as a decreased ability of the irritable bowel syndrome microbiota to produce butyrate, are due to the reduction of these bacterial groups in inflammatory bowel disease. Firmicutes serve as the primary source of energy for intestinal cells (colonocytes), improves the attachment of the epithelial barrier, and reduces inflammation. Butyrate is used in treatment for IBD. Gut homeostasis may be restored by a probiotics treatment which is human uptake of bacteria (which synthesises butyrate)to promote in- situ(inside body) butyrate production. According to a recent study, taking a combination of bacteriodetes that target a strain of Klebsiella pneumoniae related to IBD orally lowered intestinal inflammation. Human body is made up of billions of cells (30 trillion), but it is interesting to know that he human body contains more bacterial cells(40 trillion) than human cells. The role of gut microbiota in human body is in food absorption, regulators of barrier function and immune homeostasis, defence against infection etc (Dekaboruah et al,2020). Gastro-intestinal microbiota helps in nutrients production (Vitamin), chemical transformation in human body (xenobiotic), and fermentation of carbohydrates, immunological function and protection from pathogens. The gut microbiota are responsible for the development of diseases such as obesity, asthma, Parkinson's disease, digestive and skin disorders etc (Figure 9).

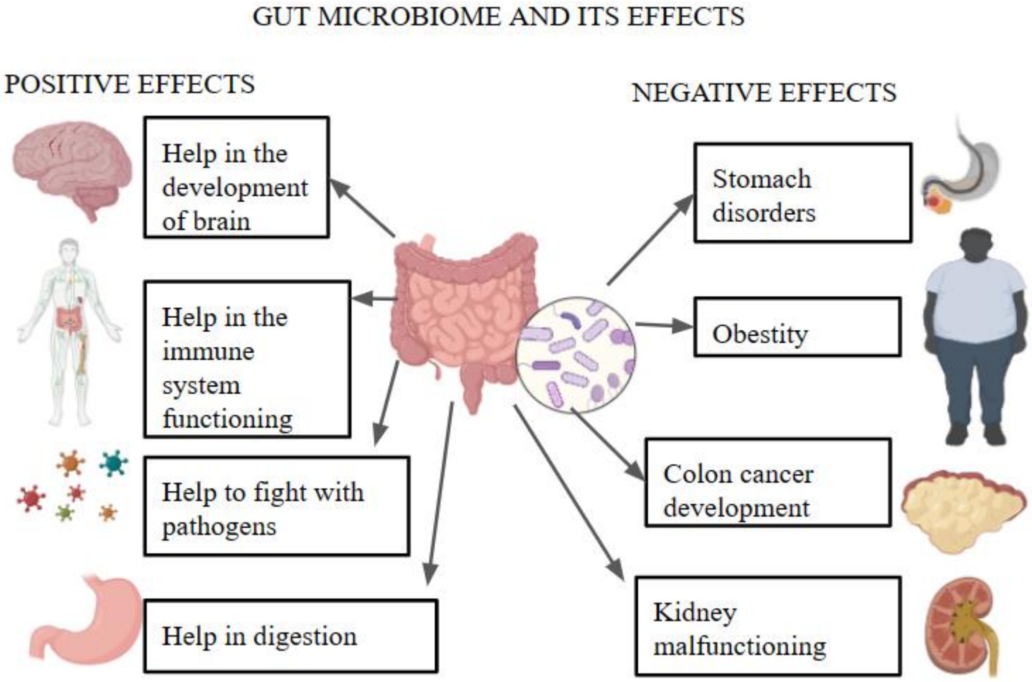

Figure 9: Gut microbiome and its effects-positive and negative effects in human body (Dekaboruah et al., 2020).

Our stomach and brain are correlated and microbiota play a important role in the coordination of the brain and the stomach and it is called as microbiota- gut- brain axis. Signaling pathway also regulates the gut and the stomach (Macfarlane et al., 2003). Mainly vagus nerve in the immune system are responsible for the connection between the gut and the stomach. Bacterial metabolites and the product it produces also play a role in gut and brain axis. The hormone secreted by the gut are also responsible for the regulation of gut brain axis. If the hormones and bacterial metabolites are not properly functioning in the human body then it causes disruption in microbio homeostasis which can lead to neuro generative disorders. The gut- microbes can be affected due to many reasons that include the lifestyle of a person, the drug it uptakes and the infection the person is having and most importantly the diet which a human body intakes. These are the factors that may lead to decrease or increase in the gut microbiota numbers in human body. the gut microbiota in the human body can be detected by the following methods which include 16s ribosomal RNA amplicon sequencing using benchtop sequences, meta transcriptomics ,microbial micro-array, fluorescence-based polymerase chain reaction- where the microbial cells attached with fluorescence protein and the amplification of the DNA or RNA content for their easy detection etc.

VII. FATTINESS

Fattiness also referred to as Obesity which is a condition in which human body gains it weight. It can be due to several factors including the consumption of fast food, packed food items etc. it is the deposition of fat in the human body which is due to improper lipid metabolism in the human body. The lipids are responsible for different activities in human body but if it does not convert to glucose as required by the body then it gets deposited gradually in the human body leading to obesity. Obesity can be measured by body mass index of a person which is the weight of a person in kilogram to the height of a person in metres square.

VIII. RELATIONSHIP BETWEEN GUT MICROBIOTA AND OBESITY

Studies show that gut microbiotia also play a role in increasing the body weight of a person. A decrease number of microbiotia in the humans can lead to increase in obesity. Studies showed that people having higher levels of Firmicutes: Bacteriodetes ratio,Proteobacteria are present in obese people. If compared between a mother and a daughter who are obese(adult female monozygotic and dizygotic twins) concluded that patient with obesity has low levels of Bacteriodetes and largely levels of Actinobacteria. Fatty people have rich gut microbiota in their human body as compared to lean people. Our body must have a good amount of microbiotia for maintaining all the metabolic functions of a human body. Excess of microbiome can lead to obesity and brain-gut-axis problem. There should be maintenance of inter-organ communication for living a healthy life.

IX. MECHANISM OF OBESITY BY GUT MICROBIOTA

Energy absorption-the gut microbiota residing the human body play an important role in the absorption of energy from the stomach and intestine. This absorption of energy occurs through the epithelial cells present in the stomach and intestine. The food we uptake can be broken down into smaller sub-units for the absorption in the human body. Carbohydrate, lipid,protein metabolism occurs in the human body after we uptake food. The carbohydrate, protein, lipid metabolism does results in the formation of simpler unit's glucose, amino acids, triglycerol etc. which are utilised by the gut microbiome residing the human body for their metabolic activities and as an energy source. It has been reported that an obese people have huge amount of gut microbiota and large energy is uptake by the microorganisms in the human body for their metabolic activities. This may results in more energy absorption in the human body, leading to energy build up in the human body. The gut microbiota converts shots chain fatty acids into glucose which are absorbed by the stomach or eliminated in the faces. Lipid metabolism can be enhanced by butyrate producing bacteria in the gut microbiota.

Chronic inflammatory condition- chronic inflammation is referred to as a long term inflammation, that last for years or several months. Chronic inflammation can be caused by the gut microbiota residing in the human body. when there is obesity or other neurological disorders than it lead to an increased number of microbiota in the human gut which serves in chronic inflammation.chronic inflammation is caused in the metabolic organs like liver and adipose tissue that are broken by the gut microbiota and its metabolites. If a person has low count of gut microbiota in the human body then by the help of fecal transplantation, we can introduce gut microbiota into the normal healthy individuals. By the introduction of fecal microbiota into the normal individuals or healthy individuals we can able to improve condition in humans with chronic intestinal inflammation. Endo-toxin is a chemical released by the micro-organisms. as in obese people the amount of microbiota are huge in numbers thus secrete a large amount of endotoxin lipopolissaccharide (LPS) that are deposited in obese people and causes inflammation of adipose tissue. Lipolysaccharide are responsible for cascade of reaction in the human body as it interacts with toll like receptor on immune cells. The binding of lipopolissaccharide to toll like receptor reduces the butyrate production. So due to this the butyrate production reduces chronic inflammation. Shorts in fatty acid also play an important role in chronic inflammation. Short chain fatty acids are responsible for a cascade of reaction that occurs in the human body. The role of butyrate is that it blocks the production of cytokines in the cell,adipolysis, mitochondrial oxidative phosphorylation which leads to increase energy expenditure in the body and hence can lead to prevention of obesity. Acetate also plays a major role in the control of obesity and the gut-flora. Acetate production that occurs in human body through different metabolic activities of the cells can lead to increase in blood cholesterol level and also elevate the risk of fattism.

X. PREVENTION OF OBESITY

1. **Probiotics:** Probiotics consist of beneficial bacteria including Lactobacillus, Bifidobacterium, and Streptococcus (Swanson et al., 2020).

2. **Prebiotics:** Prebiotics are intentionally fermented foods that improve the human health by changing the composition and alter the function of gastrointestinal tract.

3. **Synbiotics:** Probiotics and prebiotics are combined to form "synbiotics" .When compared to prebiotic or probiotic consumption alone, synbiotics are responsible for more gut microbiota population. They encourage the growth and survival of live microbial dietary supplements in the gasto-intestinal tract in humans.

XI. NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are disorders that are mainly seen in people who are aged that means in aged peoples (Sorbon et al., 2022). Neurodegenerative disorders are caused due to degeneration in the nerve or neurons which are caused due to aging. As when a person moves from adolescent to adulthood (above 60 to 70 years) then there immune system starts degenerating and the immune cells also starts depleting resulting in a neurodegenerative diseases in the people. As the WBC is unable to fight the infections, people are found to have Alzheimer disease, Parkinsonism, multiple sclerosis, Lou Gehrig's disease etc. These diseases are fatal. The development of these neurogenerative disorders can also be caused due to environmental factors and the diet. The levels of microbiotia affect the brain and lead to these neurodegenerative diseases (Figure 10).

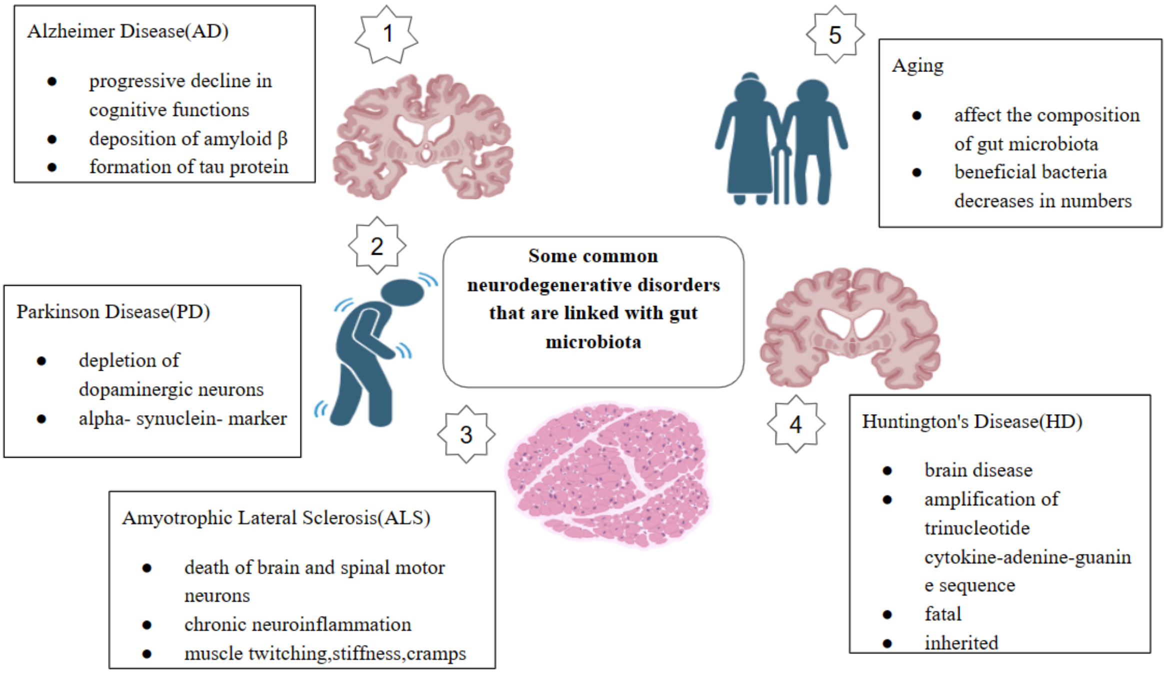

Figure 10: Some common Neurodegenerative disorders that are linked with gut microbiota- 1.Alzheimer’s Disease 2. Parkinson’s disease 3. Amyotrophic Lateral Sclerosis 4.Huntington’s Disease 5. Aging and their characteristics (Sorboni et al., 2022).

XII. NEURODEGENERATIVE DISORDERS AND THE ROLE OF GUT MICROBIOTA

The gut microbiotic play an important role and connect or makes link between the gut and brain axis. if there is any infection or the increase in number of gut microbiota in the stomach then it will also cause some effects on the human brain(Ojeda,2021). Gut microbiota can interact with gut and brain and causes the regulation of signaling pathway between the two. The gut and brain are connected by Vagus nerve and the autonomous nervous system in the spinal cord provide direct communication between the brain and the gut. if there is any mis-functioning of gut microbiota then it will lead to abnormalities in the brain coordination which can lead to disfunction in cognition, regulation of the body activities, thinking power, normal activities of humans like walking, eating, drinking,sleeping behaviours etc. Vagus stimulation is very beneficial to the gut microbiota and results in anti-inflammatory properties. Due to the increase or decrease level of gut microbiota their can be unbalanced in homeostasis.

XIII. COMMUNICATION OF GUT AND BRAIN THROUGH CHEMICAL SIGNALLING

The gut and brain communication has fascinated us for centuries .The gut access transform information via the Vagus nerve from food. Neurotransmitters like dopamine, GABA also play a role in gut and stomach connections (Thomas et al., 2012).Once human ingest food, digested food particles enter the small intestine which is covered with a velvatory layer of villi. Each villus is lined with a single layer of epithelial cells .the layer is made up of different cell types one of them the enteroendocrine cell is unlike the other which serves as our gut sensor. In addition to communicating through hormones, we discovered that enteroendocrine cells also synapse with nerves including the vagus nerve. These enteroendocrine cells synapsing with nerves neuropoid cells. This sense and react to the environment .They sense mechanical, thermal and chemical such as nutrients or bacterial by-products in the gut lumen. Inside neuropoid cells, signals from stimuli are converted into tiny electrical pulses. These pulses propagate via synapses on to the efferent neuron of the vagus nerve. Vagul neuron carry the sensory information to the brain stem linking the signals generator inside the small intestine to the brain. The neuropoid cell connection with the Vagus nerve serves as a conduict for food in the gut to influence brain function within seconds. This connection is also a potential portal for gut pathogens to access the brain this new knowledge is a foundation for designing therapist to treat disorders related to altered gut -brain signaling.

XIV. MENTAL DETERIORATION

The mental deterioration also called the Alzheimer's disease is one of the irreversible brain condition that causes memory loss in the people and results in degradation of brain cells. In the population majority of the elder group people suffer from this kind of disease. People suffering from mental distortion have low memory power, behavior and difficulty in learning the problems and doing daily tasks. In this type of disease condition there is loss of amyloid-beta clumping around the neuron. Due to the deposition of protein and aggregation of the tau-protein result in the decrease microtubules stability and disruption of calcium homeostasis in neuron which ultimately results in the death of neurons. Due to this the neurotransmitters are affected and they are blocked to do signaling activity. There could not have been a proper cure for the mental deterioration for several decades. There have been some signs with the findings that the gut microbiota may play a role in pathogenesis of mental deterioration (Mucke et al., 2012). The levels of fermicutes and actinobacteria are found lower in these patients. But the ratio of proteobacteria and bacteriodetes where higher and are found large in number in the Alzheimer disease patients (Wimo et al., 2017). In a study where people samples are collected from 25 disease participants. 20 Alzheimer disease participants agents acts match control participants and were performed with bacterial 16s ribosomal RNA gene sequencing on these people samples and the bottom line of the technique is it allows to determine what bacteria is there and how much of it is there and was found that the gut microbiome of Alzheimer disease is decreased in terms of microbial richness and microbial diversity and it's just the difference between Alzheimer disease control to investigate this relationship in animal models of mental detoriation. It was observed that there are any bacterial species or bacterial facts that are differently abundant in Alzheimer disease genetic control and that there are differences in both in terms of species level all the way up through the phylum level that are different.

XV. PARKINSONISM

Parkinson disease is a neuro generative disorder caused by the accumulation of alpha synuclein in nerves of the brain (Braak et al., 2006). A cascade of reactions takes place in the body which affect the activity of human body and results in neurodegeneration. Studied have been showed that Parkinsonism is related to the risk factor for the development and progression of Parkinson disease which is caused due to aging of an individual (Poewe et al., 2017). if we talk about the signs of Parkinson's disease there is no exact symptoms present but it includes the instability in the posture of an individual ,stiffness in muscle etc. in children and adults parkinsonism is not seen generally but as a person starts aging there is a high chance of getting Parkinson's disease in a human. Due to the degeneration of neurons a person's non-mortar symptoms are affected including gastrointestinal tissues, human behavior is affected like sadness in an individual some other problems like constipation dysfunction in the stomach etc. are also observed the exact symptom of parkinsonism is unknown but the symptoms differ from person to person (Twelves, Perkins, K. S & Counsell, 2003). Due to the deposition of the Alpha-nuclein in the enteric nervous system it can be predicted that gastro intestinal problems can occur in the Parkinsonism patients (Dickson et al., 2009). 80% of the people population experience with Parkinsonism having abnormal gastro intestinal function including constipation and disregulation in the motor neurons. It has been seen that parkinsonism patients have high number of bifidobacterium, corynebacterium, lactobacillus etc. (Varesi et al., 2022) in there stomach while less number of fecal bacterium. Some common bacteria's are also responsible for modulation of immune activities like robustria, prevotella, coprococcus species etc. so it can be concluded that gut microbiota is somewhere responsible in causing the Parkinsonism by regulating the motor neurons activities in a human body.

XVI. GUT MICROBIOTA TO COMBAT STRESS

Stress is a response, that causes physical, emotional, and other intellectual reactions. Stress alters the shape and activity of the gut microbial community, which is now widely acknowledged as one of the causes of dysbiosis (Carding et al., 2015). Both the brain and hormone levels change as a result of stress. This can, in extreme circumstances, have detrimental consequences on the heart and possibly cause heart failure or a heart attack. More frequently, it might cause mood swings, irregular or difficult menstrual cycles, and gastrointestinal (GI) symptoms brought on by stress. Other facets of your health may suffer as a result of stress. Risky behaviors like smoking (Yoon et al., 2021), binge drinking, abusing drugs, and addiction may become more prevalent. Stress indirectly raises your chance of having a stroke (Table 3).

Table 3: Common health problems related to stress .(stress can cause the release of cholesterol in blood stream causing heart diseases and increase level of cortisol on abdomen causing obesity. Takotsubo syndrome is due to high level of epinephrine, norepinephrine. Irregular periods, occur when stress affects hormones regulating the reproductive system.

Health Problems Related to Stress	
1) Heart diseases	6) Alzheimer’s disease
2) Takotsubo Syndrome	7) Inflammation
3) Obesity	8) Irregular Periods
4) Headache	9) Infections
5) Gastrointstinal issues	10) Hyperglycemia

XVII. MECHANISM OF STRESS

Several brain regions, including the hypothalamus, amygdala, and prefrontal cortex (Buijs & Van Eden, 2000) are involved in the stress response and anxiety. The hypothalamus is hypothesized to play a role in the physiological stress response, which involves receiving information about the stressful circumstance and then controlling the endocrine, autonomic, and behavioral systems. The process of categorizing situations according to their emotional valence determines how the individual will react to them. For instance, if a situation is judged to be positive, the individual will approach it; however, if the situation is judged to be negative, the individual will try to avoid it or become defensive against it. Positive and negative emotional valence has diverse effects on the activity of hypothalamic corticotropin neurons; negative emotional valence results in increased activity, whereas positive emotional valence results in decreased activity. Acute stress activates the noradrenergic projections in the locus coeruleus, which consequently causes an increase in behaviors associated with anxiety (Alpár et al., 2018). The strengthening of memories is another process involving the locus coeruleus noradrenergic projections; in this case, noradrenaline release brought on by stress enables the person to be extremely vigilant, which facilitates memory consolidation.

XVIII. ROS (REACTIVE OXYGEN SPECIES) AND IT'S ROLE IN MITOCHONDRIA

ROS are highly oxidizing agents formed from diatomic oxygen (O_2) (Chakraborti, et al., 2019). In other words ROS is a broad term used collectively for free radicals and non-free radicals of the biological system. Electron Transport Chain (ETC): The primary source of ROS production in mitochondria is the electron transport chain, which is responsible for generating cellular energy in the form of ATP. During the ETC, electrons move through a series of protein complexes, ultimately transferring energy to generate ATP. However, a small fraction of electrons can prematurely leak from the ETC, particularly at complex I and complex III. These leaked electrons can interact with molecular oxygen (O_2) to generate superoxide anion radicals (O_2^-), which is an example of ROS.

1. **Complex I (NADH-Ubiquinone Oxidoreductase):** Complex I is a significant site of electron leakage in the ETC. Electrons from NADH (a molecule that carries high-energy electrons) are transferred through complex I to ubiquinone. Some electrons Superoxide is created when some electrons break free from the chain and interact with oxygen.

2. **Complex III (Ubiquinol-Cytochrome C Oxidoreductase):** Complex III is a significant additional source of ROS. Here, ubiquinol transfers its electrons to cytochrome c. Similar to complex I, electron leakage can happen and result in the creation of ROS.

3. **Flavin-Containing Enzymes:** Several flavin-containing enzymes, such as those involved in fatty acid oxidation and the Krebs cycle (TCA cycle), can also contribute to the formation of ROS inside the mitochondrial matrix. As they engage in redox interactions with oxygen, flavin molecules can produce ROS (Figure 11).

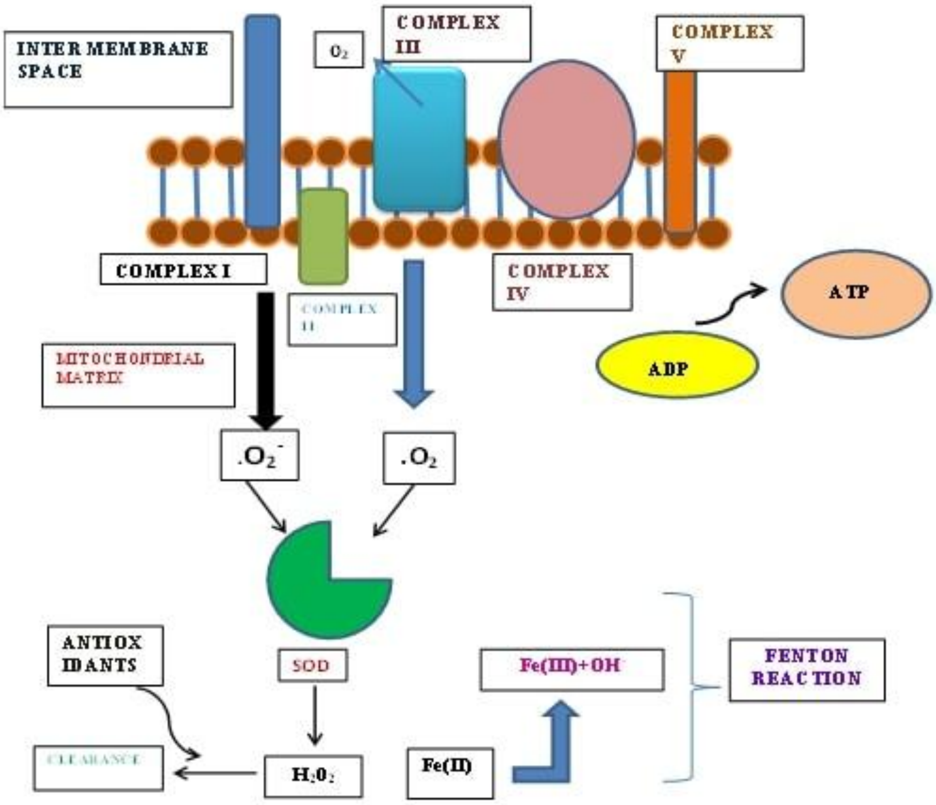

Figure 11: Diagram depicting formation of ROS in mitochondria. Comprises of 5 complexes. Superoxide anion radicals (O_2) are a natural by-product of the electron transport chain (ETC) activity that causes (OXPHOS) Oxidative phosphorylation is the formation of O_2^- , complex I ,III,OH^- via iron mediated reaction known as Fenton reaction.

Mitochondrial Membrane Potential (m): During electron transport, the inner mitochondrial membrane develops a potential that might affect the generation of ROS. The chance of electron leakage and ROS can rise with a greater membrane potential. Although ROS are thought to be detrimental chemicals because of their ability to produce oxidative stress, it is crucial to remember that cells have developed antioxidant defense systems to combat their negative effects. Superoxide dismutase (SOD) (Lui et al., 2019) catalase and glutathione peroxidase are a few examples of the enzymes that operate to combat ROS and stop cellular damage.

XIX. HEALTHY GUT AND DISEASED GUT

Gut is said to be healthy if the gastrointestinal tract is having a good balance of gut bacteria and can properly digest and absorb nutrients. Both health and sickness are greatly influenced by the relationship between the host and the microorganisms. The diversity of the gut microbiota is strongly influenced by a variety of host characteristics, such as diet, human lifestyle, age, and environmental influences. The gut microbiota is now thought to be modulated by a number of important factors, including nutrition. The human microbiota has the potential to change appetite, increase nutritional uptake, and exert energy from different food constituents. Additionally, microbes play a crucial part in the metabolism of xenobiotics (Sutherland et al., 2020) In the process of xenobiotic metabolism; different gut microorganisms change the chemical composition of numerous foods, medications, pollutants, and many pesticides (Adhikary et al., 2023; Banerjee et al., 2022) (Figure 12).

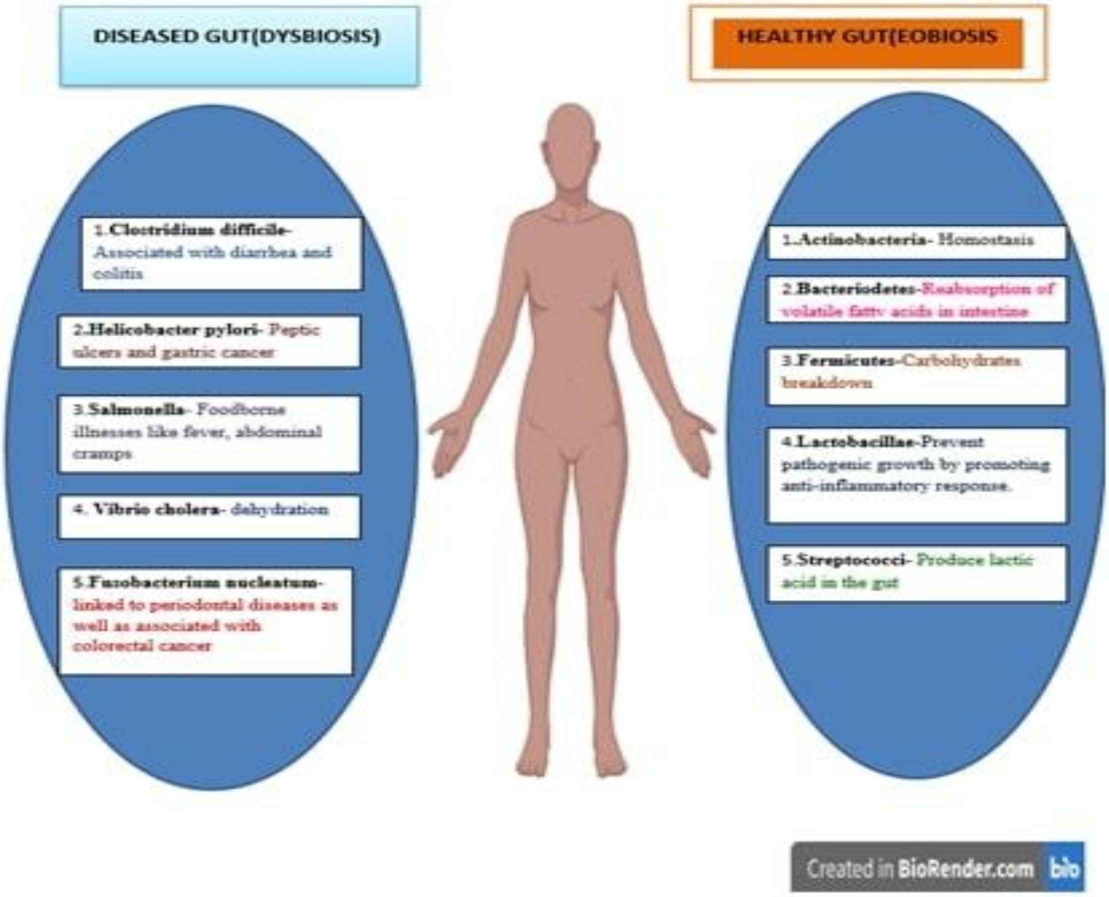

Figure 12: Diagram showing list of healthy and diseased gut microbes.

XX. CONCLUSION

India spends a staggering amount of money on healthcare since infectious illnesses continue to be the main causes of human and animal morbidity and death rates. Bile acids and short-chain fatty acids (SCFAs), two types of gut microbiome metabolites that influence host immunity as well as provide nutrition and energy, can maintain the host healthy. These metabolites include minute compounds made directly by commensal bacteria as well as the byproducts of commensal bacteria digesting dietary substrates, both of which are essential for the health of the host. Much emphasis has been paid to the relationship between gut bacteria and the creature that serves as their symbiont. While the mechanics and structure of the digestive system are already complex, each of the microbial inhabitants of the gut has its own special functions. The gut microbiome is made up of bacteria, archaea, viruses, and eukaryotic creatures that live inside the digestive tract. The onset and progression of serious human diseases for which there are now no effective treatments have been revealed to be significantly influenced by the gut flora.

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