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Gut Dysbiosis- Precursor of Disease Pathogenesis - A Review

Janet Nivedha. D[1] | Anita R.J. Singh[2]

[1&2]P.G. and Research department of Biotechnology, Women's Christian college, College road, Chennai- 600 006, Affiliated to the University of Madras, Chennai, Tamilnadu

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ABSTRACT

The gut microbiota is a complex microbial community residing in the intestine and their collective genomes constitute the gut microbiome. The microbial community of the gut interact with the host through the secretion of metabolites making a profound impact on the human health and physiology. Coordination between the host, the microbiota and their metabolic products are necessary for the proper functioning of the host. Any disturbance in the gut microbiota due to a number of factors, paves the way in the pathogenesis of various intestinal and extra-intestinal disorders including COVID according to recent studies. This phenomenon known as 'Dysbiosis' is developed as a result of this gut microbial imbalance that disrupt the normal host function, which in association with oxidative stress contribute to various diseases, when the balance between oxidants and antioxidants is hampered. The commensal populations regulate the gut composition and balance by inducing gut immune responses. Gut immune homeostasis is dependent on balanced inflammatory mechanisms. If the communication between them is disrupted, disease is favoured. Physiological interaction of the gut with other organ systems in the host is necessary for the perfect co-ordination of various complex host machineries. Distorted interactions trigger host mechanisms, contributing to the pathogenesis of several conditions and diseases. Thus, a complex correlation and mutualistic host-microbiome relationship is vital for gut homeostasis. This article provides a note on the association between gut microbiome and its dysbiosis with disease pathogenesis in relation to oxidative stress, immunity and inflammation; followed by gut interactions with brain, liver, lung, joint and kidney and related diseases and finally the pathophysiology of various intestinal, extra-intestinal and respiratory disorder (COVID-19).

KEYWORDS:*Gut microbiota, endocrine organ, leaky gut, lipopolysaccharide, antioxidants, immune-mediated inflammatory disorders, hypothalamus–pituitary–adrenal (HPA) axis, antigenic mimicry, gut-lung axis*

I. INTRODUCTION

In humans, the gut microbiota consists of the highest number of bacteria and a vast diversity of species in comparison to other regions of the body. Establishment of the gut flora begins immediately after birth. The protective barriers that include the intestinal epithelium and mucosal barrier co-develops with the host, exhibiting support to beneficial flora, tolerance and defence to pathogenic organisms. The relationship between certain gut microbiota and human is mutual as both are benefitted with regard to metabolism of bile acids, xenobiotics; fermentation of dietary fibres into short-chain fatty acids (SCFAs) such as butyric acid which is taken by the host as energy;

vitamin B and K synthesis; etc. Variation in colonization of gut microbiota is observed over time displaying distinct composition at every stage. These variations can be contributed by various factors such as gestational age, mode of delivery, diet, medications, environmental stressors, etc. The gut flora functions as an endocrine organ and its dysregulation are correlated with host inflammatory and autoimmune conditions.

Oxidative stress occurs when there is an imbalance between the oxidants and antioxidants disrupting the normal cellular oxidative mechanism leading to onset of diseases.

A symbiotic relationship is established between humans and microbes over time, and any disturbances in this relationship have been associated with several immune-mediated inflammatory diseases (IMID) (**Table 2).** A balanced relationship between commensal microbes of the gut and host innate and adaptive immunity and between pro- and anti-inflammatory mechanisms **(Fig 4)** is essential for gut immune homeostasis. In a study, segmented filamentous bacteria (SFB) promoted the aggregation of pro-inflammatory T helper 1 (Th1) and Th17 cells in the small intestine in mice [1].

Studies have revealed that the healthy bacteria of gut may contribute to the physiological interactions with other systems such as the brain, cardiovascular organs, and metabolic activity related tissues and thus aid in fighting hypertension and progression of metabolic syndrome [2], (**Table 3).** Improper communication between the gut and the other systems can lead to related diseases such as nervous disorders when the gut-brain axis is disrupted, respiratory disorders when the gut-lung axis is disrupted and so on. The gut microbial composition influences the type of compounds produced that can negatively impact the host, culminating into diseases.

STRUCTURE OF THE PAPER:

Section I gives the introduction, structure of the paper and the objectives

Section II defines gut dysbiosis

Section III discusses the association of gut microbiota with diseased pathogenesis

Section IV provides the role of gut dysbiosis in disease pathogenesis

Section V gives an overview of disease pathophysiology and Dysbiotic condition and an emphasis on gut microbiota in relation with COVID-19

Section VI concludes the paper with references

OBJECTIVES:

Gut microbiota being an endocrine organ performing all the required functions, can be considered as a hotspot for disease study, diagnosis, treatment and prevention.

This article aims to provide an association between gut microbiota with disease pathogenesis, how the disrupted gut microbial composition can be a starting point for disease pathogenesis and the pathophysiology of various intestinal, extra-intestinal and respiratory disorder taking COVID-19 as an example.

II. GUT DYSBIOSIS

Balanced gut microbiota composition ensures perfect coordination in the host activities leading to the effective functioning of the host. Several factors can compromise the gut microflora, disrupting its balance leading to gut dysbiosis. Alterations in the native gut microbiota can damage the normal microbial community leading to its imbalance, contributing to dysbiosis. This can increase the pathogen infection risk, harmful pathobionts overgrowth, that may eventually lead to dysfunction of host machineries, hence paving way to the pathogenesis and/or progression toward a broad spectrum of diseases[3].

III. ASSOCIATION OF GUT MICROBIOTA WITH DISEASE PATHOGENESIS

a.GUT MICROBIOME AND OXIDATIVE STRESS

During oxidative cellular metabolism, there is lower intracellular production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as a by-product that has a basic role in different life processes [4]. Elevated levels of ROS/RNS can lead to cellular redox potential disturbances due to host defence mechanisms' inability to restore the balance which can damage cellular components (like proteins, DNA, and membranes), alter enzyme functions, and also act as signalling molecules leading to a number of diseases [4,6]. The gastrointestinal (GI) tract or gut is a major source of ROS [7] which are produced abundantly in their altered diseased state leading to disease development [4,6,7]**(Fig 1) (Table 1).**

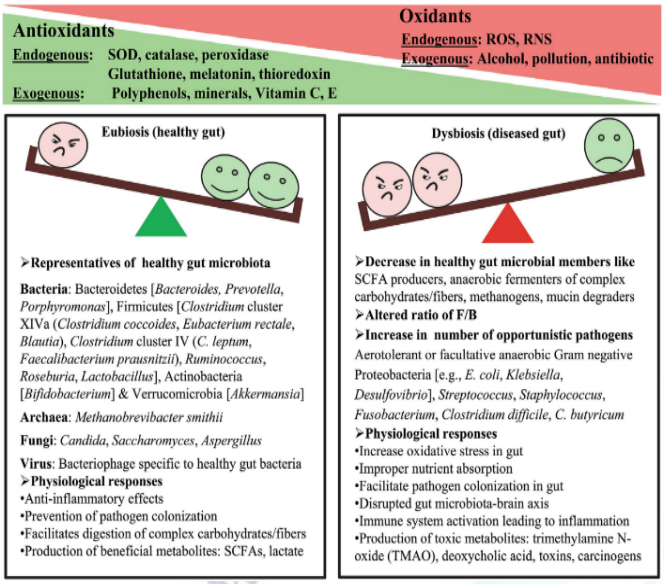


Fig 1: Gut microbiota role in combating oxidative stress [5]

OXIDATIVE STRESS-GUT DYSBIOSIS	DISEASES
A perfect balance is maintained between the endogenous (ROS/RNS) and exogenous (alcohol, pollution, antibiotic) oxidants produced in the gut and their detoxification by antioxidant systems in healthy individuals. Disruption in this homeostatic condition elevates the oxidative stress leading to dysbiosis condition alongside various diseases. There is altered *Firmicutes* and *Bacteroidetes* ratio, increase in opportunistic pathogens (*E. coli, Klebsiella, Fusobacterium, C. difficile etc.*), disrupted gut-brain axis, activation of immune system leading to inflammation [5].	Hepatic encephalopathy [8], Alzheimer's disease [9], Diabetes [10], Inflammatory bowel disease [11], Irritable bowel syndrome [12], Parkinson's disease [13]

TABLE 1: Disease pathogenesis in relation to gut dysbiosis and oxidative stress

b. GUT MICROBIOME AND HOST IMMUNITY AND INFLAMMATION

i. Gut-host relationship on the basis of immunity: The immune system comprises of an association of cells and molecules known for their defence mechanism against the foreign pathogens (non-self) by responding to it. This monitoring mechanism of perceiving the infectious microbes as threat by the immune system limits the pathogenesis of various diseases.

Co-evolution of the immune system with the diverse flora of the gut has helped in developing resilience for beneficial microbes [14]. As a result, there is a development of mutualistic relationship between the immune system and the gut microbiota, regulating and cooperating to support each other which is evident that 70–80% of the body's immune cells are prevalent in the gut [15]. The cross-talk between the immune system and the microbiota begins from the time of contact of our body with microbes i.e., during birth **(Fig 2).** As we age, the mutual relationship where the microbiota shapes the immune system development, and vice versa shaping the gut microbiota composition [16] sustains throughout life which is the basis for a healthy interaction between the gut microbiota and the immune system.

In normal conditions, the immune system maintains a balanced microbial community by encouraging the growth of beneficial microbes and in return, a healthy microbiota supports the development of immune cells by releasing molecular signals and adjusting immune responses [17, 18]. Hence, a healthy communication between the gut microbiota and the immune system aids in defence against pathogens, resilience to harmless microbes and their products and maintenance of the immune system to not produce any adverse effects to our own body.

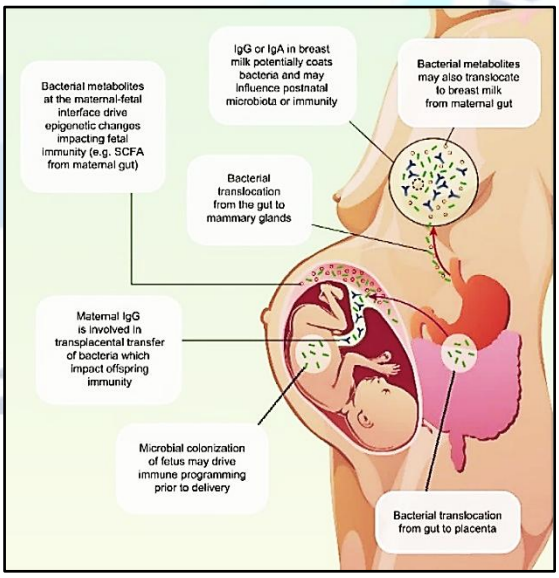


Fig 2: Potential crosstalk mechanisms between maternal microbiota and offspring immunity [19]

ii. Gut dysbiosis and Inflammation: The most predominant phyla of the healthy gut include *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* [20, 21].The host immune system has the role in blocking the invasion of pathogenic bacteria and facilitating the entry of beneficial gut microbiota [22]. Gut microbiota imbalance alters the host immune system, activating its response, leading to disease pathogenesis [22, 23]by the elevation of gut harmful bacteria [24], releasing enterotoxins that increase intestinal permeability and produce immunosuppressive proteins leading to immune disruption. This can damage the intestinal epithelial cells, affecting energy metabolism and finally, leading to intestinal inflammation [23]**(Fig 3).** Disease-relatedmicrobes (*Proteobacteria* species of the *Enterobacteriaceae* phylum) are seen in inflammatory bowel disease (IBD) and other diseases [20, 25].Intestinal inflamed environment (aerobic conditions, biological sources from intestinal epithelial cells (verge of death), and mucus lining optimal thickness) harbours organisms providing optimal environment for their growth. However, in most cases, the microbe itself is not responsible for the disease but can increase its susceptibility which is seen in the case of *Enterobacteriaceae* species increasing susceptibility to intestinal inflammation, leading to IBD development [24]. A change in the ratio of *Firmicutes* and *Bacteroides* species as a result of gut dysbiosis in IBD patients has been reported [26].

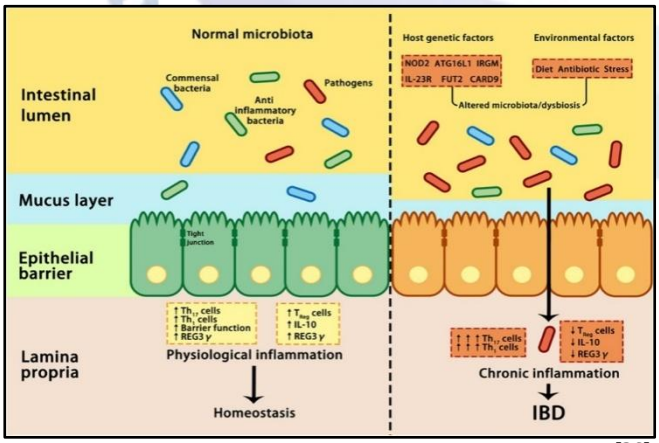


Fig 3: Gut dysbiosis leading to IBD [27]

The reverse can happen where inflammation can result in gut dysbiosis.

iii. Dysbiosis as a result of Inflammation-induced environmental changes:

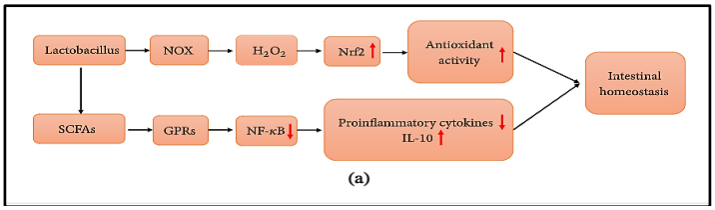
Many factors such as infection, injury etc., can lead to inflammatory host response in the gut. Studies have shown that an inflammatory tissue environment is an accessory to disturbances in the gut microbiota showing specific bacterial species blooms that have the ability to utilize nutrients more effectively in the inflamed gut. A study was reported in a mouse model invaded by a pathogen *Helicobacter hepaticus*, which caused considerable disturbances in the structure of the gut microbial community; reducing its diversity as a result of infection [28]. Pathogens within the family *Enterobacteriaceae,* such as *Citrobacter rodentium* and *Salmonella*, utilize virulence factors at first, to stimulate intestinal inflammation, which turns beneficial for their growth in the intestinal lumen [29, 30]. During oral infection with *Citrobacter rodentium,* the pathogen elicits inflammatory response, reducing the colonic microbial diversity facilitating the growth of facultative *Enterobacteriaceae*[31] .

PATHOPHYSIOLOGY	Diseases
IMMUNITY: Dysbiosis can result in the disruption of the epithelial barrier, elevating the susceptibility to infections. Also, dysbiosis can lead to faulty immune reactions to the gut microbiota, that can pave the way for chronic inflammation and tissue damage manifesting these consequences throughout the body making an impact on the tissue-specific immunity leading to organ dysfunctions. These abnormal communications may lead to allergies, compromising immunological self-tolerance, leading to autoimmune disorders [32]. **INFLAMMATION:** An imbalance in the gut microbiota result in shift towards a pro-inflammatory state affecting the host intestinal physiology where disruptions in the intestinal barrier are observed. When there is a disruption in the integrity of these tight junction protein complexes, the intestinal permeability increases, paving the way for the bacterial antigens like endotoxin lipopolysaccharide to move out of the	Inflammatory bowel disease [35] Type I diabetes [35] Obesity [35] Atherosclerosis [35] Non-alcoholic fatty liver disease [36]

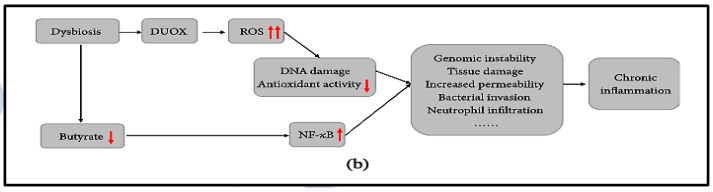
intestinal lumen and travel to other areas of the body; showing elevation in the blood stream which could result in systemic inflammatory effects [33]. These events can impact CNS immunity and affect the integrity of the blood–brain barrier [34]leading to neurological diseases.	Multiple sclerosis [37]

TABLE 2: Disease pathogenesis in relation to host immunity and inflammation

Therefore, microbes and metabolites produced in the gut are necessary in maintaining immunological equilibrium. Disturbances in the gut microbiota balance impacts the gut mucosa and systemic immune response. A 'leaky gut' is indicated by increased gut permeability, microbial imbalance, and impaired mucosal immunity which have been known to be responsible for the development of Immune-mediated Inflammatory Diseases (IMID) [38].



(a) Intestinal homeostasis is correlated with enteric bacteria residing in the intestinal lumen.

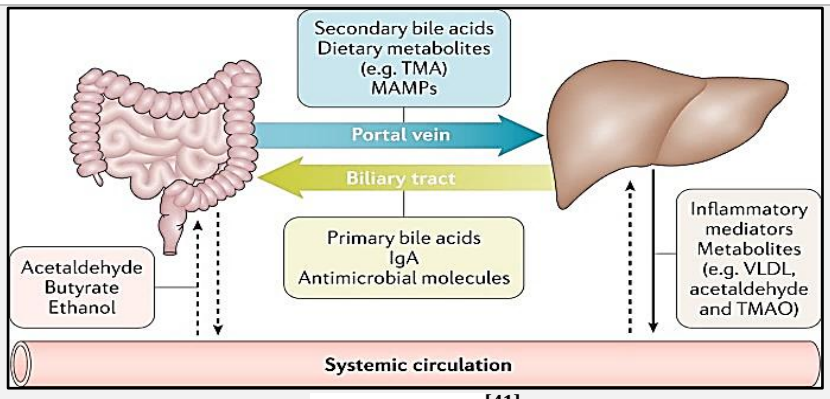
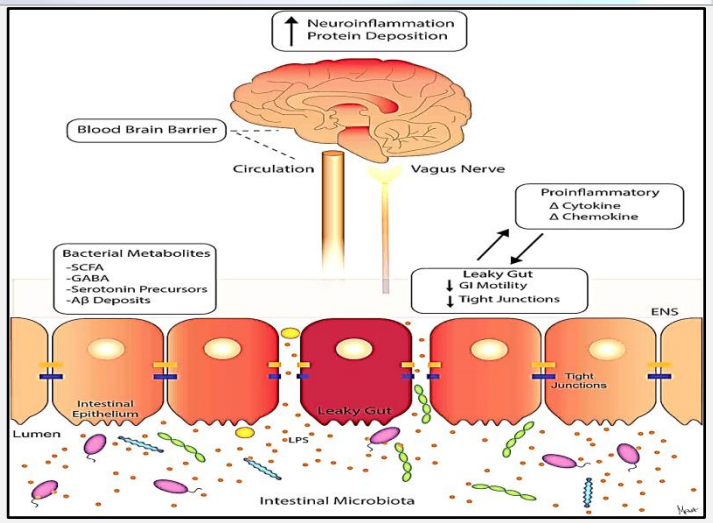


(b) Dysbiosis and oxidative stress in the gut as contributors of intestinal diseases pathogenesis.

Fig 4: Associations between gut microbiota, intestinal inflammation, and oxidative stress [39]

IV. ROLE OF GUT DYSBIOSIS IN DISEASE PATHOGENESIS

INTERACTION OF GUT WITH LIVER, BRAIN, LUNG, JOINT, KIDNEY	
GUT-LIVER AXIS	
DESCRIPTION	The gut-liver axis is the bidirectional relationship between the gut, its microbiota, and the liver, as a result of the integration of signals produced factors (diet, genetic, environment), through the portal vein which aids in the transport of gut-derived products directly to the liver, and the liver products (bile and antibody secretion) to the intestine. The intestinal mucosal and lining of the vascular system form the functional and anatomical structure for the gut-liver interactions, restricting the systemic microbial and toxin circulation and facilitating the nutrients to access the circulation and reach the liver. Maintenance of the microbial communities influences the gut-liver axis balance, and in turn the liver shapes intestinal microbial communities. Alcohol damages the gut-liver axis at various interconnected levels, that also consists of gut microbiome, mucus barrier, epithelial barrier and at the stage of antimicrobial peptide production. This can increase the chances of exposure to microbes and the pro-inflammatory environment of the liver. The pathogenetic role of microbe-derived metabolites (trimethylamine, secondary bile acids, short-chain fatty acids and ethanol) in the pathogenesis of non-alcoholic fatty liver disease have also been reported [40].

ILLUSTRATION	 Gut liver axis[41]
DISEASES	Irritable Bowel syndrome, Inflammatory Bowel disease, Non-alcoholic fatty liver disease, Hepatic encephalopathy, etc.
GUT-BRAIN AXIS	
DESCRIPTION	The gut-brain axis (GBA) is the link between the central nervous system (CNS) and the enteric nervous system (ENS) of the body and the gastrointestinal tract, that includes direct and indirect pathways between cognitive and emotional centres in the brain with peripheral intestinal functions. Biochemical signals are passed between the gut–brain axis through the vagus nerve. The nervous system is stimulated by neurotransmitters and SCFAs produced by the gut bacteria. Memory and stress regulation are found to be enhanced by certain bacteria types [42]. Imbalance in the intestinal microbiota result in extra-intestinal diseases and disrupt the 'gut–brain–axis', hence affecting the CNS and behaviour and cognitive function by direct reprogramming of the hypothalamus–pituitary–adrenal (HPA) axis, which is a stress (infection and psychological)-activated pathway. Enteric infections can cause anxiety, depression, and cognitive dysfunction. Commensal bacteria may alter brain mechanisms through gamma-Aminobutyric acid (GABA), which can directly influence immune and neural receptors within the ENS and CNS [33, 34], as GABA is a CNS inhibitory neurotransmitter, involved in regulating physiological and psychological processes. Anxiety and depression pathogenesis is favoured by disturbances in the central GABA receptor expression [43].
ILLUSTRATION	 Gut-brain axis[44]

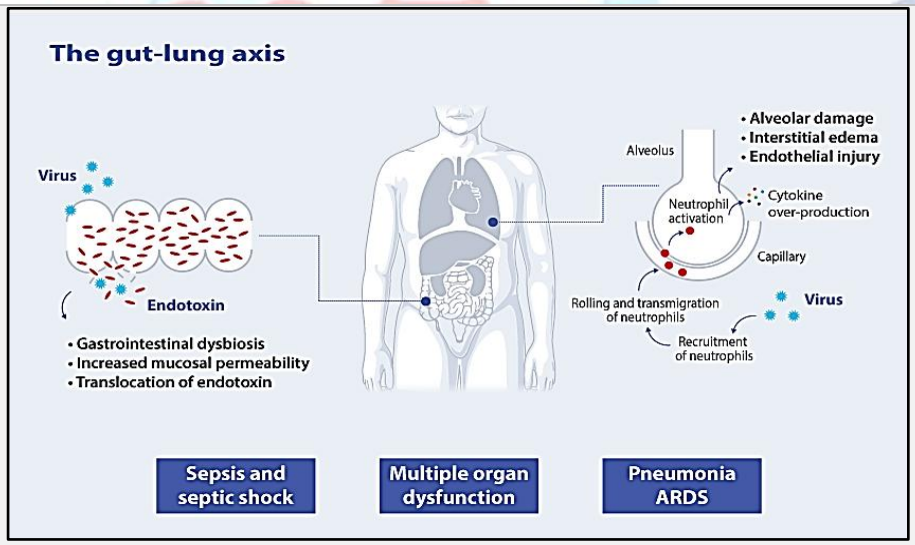
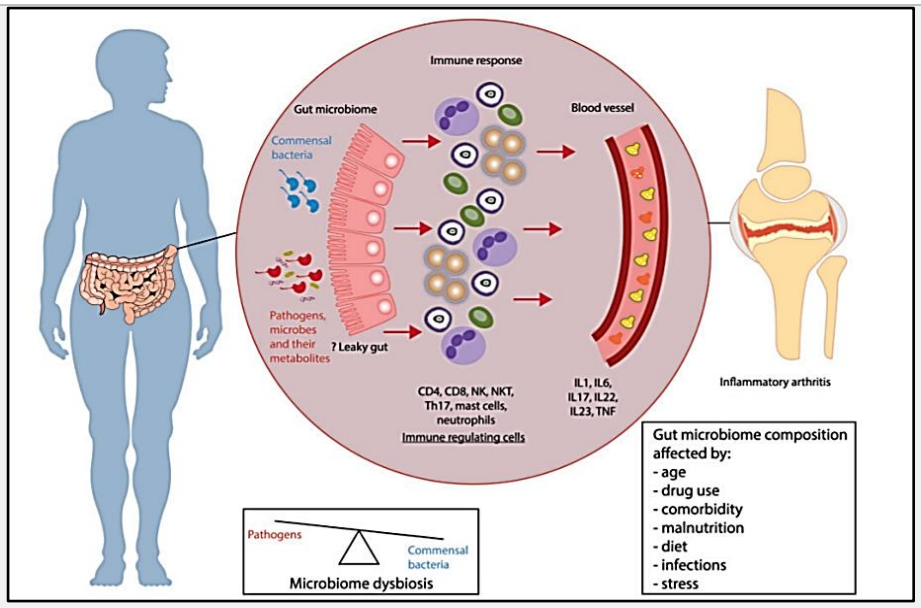
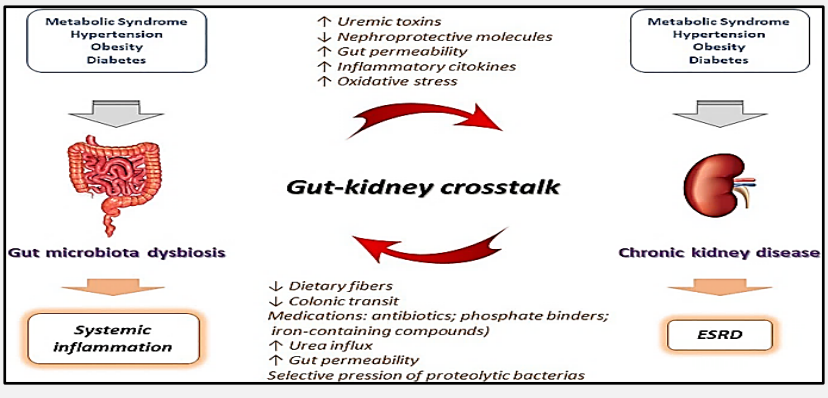
DISEASES	Inflammatory arthritis, Irritable Bowel syndrome, Alzheimer's disease, Parkinson's disease, Autism spectrum disorder, etc.
GUT-LUNG AXIS	
DESCRIPTION	Gut-lung axis is the bidirectional cross-talk between gut microbiota and lungs [45]. Metabolites produced by the gut microbiota travel via blood and reach the lung, damaging it. When an inflammation occurs in the lung, it can affect the gut microbiota as well [46, 47]. Dysbiosis occurs during infections, inflammation and metabolic disorders, that can change disease outcomes in the nearby region and also in distant organs, such as the respiratory tract. Gut dysbiosis and metabolites produced by the microbes affect immune responses, recruit pro-inflammatory cytokines and neutrophils resulting in inflammation, and damage to the lungs (Alveolar damage, intestinal swelling, endothelial injury), leading to disease development. The respiratory microbiome includes *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* phyla inhabiting each niche and playing a protective role in immunity. Influenza facilitates the attachment of pathogenic bacteria to respiratory cells, increasing risk of infection and disease *in vivo*[48], implying an interaction between viral pathogens and bacteria not only in gut, but also in the respiratory tract.
ILLUSTRATION	 Gut-lung axis[49]
DISEASES	Inflammatory arthritis, COVID-19, etc.
GUT-JOINT AXIS	
DESCRIPTION	Gut-joint axis is the relationship between the gut and the joints. Gut dysbiosis can result in leaky gut which increases the permeability of the gut wall lumen. Hence, the pathogens, microbes and their metabolites are exposed to the immune system, that activates the immune regulating cells such as CD4, CD8, NK, Th 17, mast cells, neutrophils, etc. These cells pass through the blood and reach the joints producing an inflammation by the accumulation of interleukins (IL) and tumor necrosis factor (TNF) [50].

ILLUSTRATION	 Gut-joint axis [50]
DISEASE	Rheumatoid arthritis, Inflammatory bowel disease
GUT-KIDNEY AXIS	
DESCRIPTION	The bidirectional inter-organ communication of kidney with the gastrointestinal tract is the gut-kidney axis. Antibiotics, reduced dietary fibres impact intestinal tight junctions, lead to increased intestinal permeability, and translocation of bacterial metabolic products across the intestinal barrier. This evokes an immune response, resulting in systemic inflammation, contributing to deteriorating kidney disease. Increased gastrointestinal urea secretion leads to gut microbiota dysbiosis and increased toxic ammonia formation [51]. Uraemia affects gut microbiota composition and metabolism. Uremic toxins originate from microbial metabolism. Gut dysbiosis lead to epithelial barrier disruption, ultimately resulting in elevated exposure of the host to endotoxins. The uremic and endotoxins migrate to kidney and damage it leading to chronic kidney disease [52].
ILLUSTRATION	 Gut-kidney axis [53]

DISEASES	Chronic kidney disease, cardiovascular disease, IgA nephropathy, nephrolithiasis, hypertension, acute kidney injury, haemodialysis and peritoneal dialysis

TABLE 3: Physiological interaction of gut with other systems

V. DISEASE PATHOPHYSIOLOGY AND DYSBIOTIC CONDITION

A vast number of metabolic products and other compounds are produced by microbes that can directly interact with various physiological host processes. To maintain these processes, the immune system checks the metabolic state of the gut microbiota and communicates that information to other body tissues. Composition of the gut flora influences the type of compounds produced by the gut microbiota. Hence, any imbalances in the gut microbiota (dysbiosis) can influence the production of the molecular signals needed for effective communication between the gut microbiota and our physiological pathways [54] disrupting the normal functioning of the host, leading to production of microbial-derived products or metabolites which might pose harm to the host causing diverse range of diseases [55] **(Fig 5) (Table 4)**

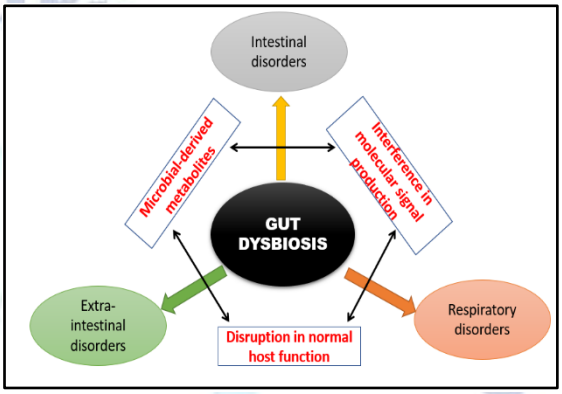


Fig 5: Gut dysbiosis influencing pathway communication

S. NO	Disease category	Pathophysiology	Dysbiosis condition	Disease
1) INTESTINAL DISORDERS				
	i.	A disorder of the gut–brain axis. Factors such as diet, genetic and infections, disturb the intestinal microbiota; alter the gastrointestinal motility, alter the permeability of intestinal wall, resulting in immune activation and low-grade mucosal inflammation. The altered permeability condition disrupts the bile salt and serotonin metabolism. These conditions ultimately alter the brain function [56].	↑*Enterobacteriaceae, Lactobacillaceae, Bacteroides* ↓*Faecalibacterium, Bifidobacterium* [57]	Irritable Bowel syndrome (IBS)
	ii.	Gut dysbiosis leads to a series of conditions: Alterations in the intestinal mucosal permeability, activation of antigen-presenting cells by Toll-like receptors (TLRs) and Nod-like receptors (NLRs) (innate immune sensors), citrullination of peptides by enzymatic action, antigenic mimicry, T cell differentiation, and migration of Th 17 into the peripheral lymphoid tissue resulting in secretion of IL-17 that induce systemic B cell differentiation and antibody	↑*Prevotella* ↓ *Bifidobacterium, Bacteroides* [58]	Inflammatory arthritis

		production [25] leading to inflammation. This can lead to autoimmune disease development via molecular pattern recognition (PRR) from gut microbiota [58]		
	iii.	Environmental factors cause dysbiosis of the intestine, resulting to abnormal immune response (to pathogens, commensal microbes), leading to chronic inflammation[59]of the digestive tract. Crohn' disease displays inflamed regions scattered in the gut. Ulcerative colitis is the continuous inflammation of the colon [60]	CD: ↑*Enterobacteriaceae*, *Pasteurellaceae*, *Veillonellaceae*, *Fusobacteriaceae*, ↓ *Erysipelotrichales*, *Bacteroidales*, *Clostridiales* UC: ↑ proteobacteriae ↓ Firmicutes *Bacteroidales*, *Clostridiales* [43]	Inflammatory Bowel Disease (IBD): Crohn's disease and (CD), Ulcerative colitis (UC)
	iv.	Antibiotics such as clindamycin, ciprofloxacin, cephalosporin, and fluoroquinolones used for *C. difficile*-associated disease (CDAD) treatment, suppress *C difficile* and the endogenous protective microflora. Following *C difficile* ingestion, its spores germinate and the toxin-producing cells start growing. This can alter the gut epithelium and invoke an immune response. Recurrence of infection occurs when *C difficile* spores survive in the gut despite antibiotic treatment, which eventually germinate, resulting in toxin production from vegetative cells beginning the cycle of CDAD symptoms. Until the normal gut flora recovers, the *C difficile* recovers faster than normal gut microbiota, causing recurrence [61].	Antibiotics: ↓*Bifidobacterium, Clostridium, Bacteroides, Lactobacilli* Proton pump inhibitors: ↑ *Firmicutes Streptococcus* ↓*Bacteroidetes* Age: ↑*Bacteroidetes Proteobacteria* ↓ *Bifidobacterium Lactobacillus* [62]	*Clostridium difficile* infection (CDI)
	v.	Genetic predisposition (HLA-DQ2 and HLA-DQ8 haplotypes) and exposure to prolamines [proteins (proline + glutamine) of wheat gluten] contribute to the Celiac Disease pathogenesis [63]. Following gluten digestion, an immune response is triggered, that causes inflammation and damage to the small intestine and gut dysbiosis, leading to the malabsorption of iron, folate, calcium, and vitamin D in genetically susceptible individuals [64].	↑*Bacteroides–Prevotella, Clostriudiumhystolitic um, Eubacterium rectale– C.coccoides, Atopobium, Staphylococcus* ↓*Bifidobacterium* [65]	Celiac Disease (CD)
	vi.	20% of all tumours are preceded by chronic inflammation [66]. During carcinogenesis stimulated by growth and angiogenic factors, production of inflammatory	↑ *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Enterococcaceae* or	Colorectal cancer (CRC)

		cytokines and chemokines by cancer cells attract immature myeloid cells or pro-inflammatory Th cells and suppress antitumor T-cell responses [67]favouringtumour progression. Gut microbiota dysbiosis and increased intestinal permeability are highly associated to colon inflammation. This could be a critical factor in the initiation and/or progression of colorectal cancer [68].	*Campylobacter, Peptostreptococus, Enterococus faecalis, Escherichia coli, Shigella Streptococcus gallolyticus*, ↓*Faecalibacterium*, *Bl autia, Clostridium, Bifidobacterium*, *Roseburia*[69]	
2) EXTRA-INTESTINAL DISORDERS				
A	**METABOLIC DISORDERS**			
	i.	High-fat diet and over food consumption can lead to dysbiosis of the gut microbiota. This is accompanied by increased energy harvest, enhanced gut permeability and inflammation, leading to metabolic diseases. Certain bacteria are known for their efficient energy harvest role. Gut dysbiosis leads to elevated levels of these species. The gut of obese women with metabolic disorder had a higher proportion of bacteria, *Clostridium coccoides,* which can efficiently harvest energy from nutrients in the gut [70].	↑ *Firmicutes* ↓ *Bacteroidetes* [71]	Obesity
	ii.	High-fat diet increases lipopolysaccharide (LPS) levels modifies the gut microbiota, increasing harmful bacteria that release endotoxins and increase intestinal permeability (alteration of microvilli, leakiness of tight junctions) that results in the uptake of LPSs. These conditions can impact the immune system, leading to inflammation and Type I diabetes predisposition [72].	↓*Firmicutes* ↑*Bacteroidetes* *Proteobacteria*[73]	Type-I Diabetes
	iii.	Gut dysbiosis can contribute to the development and progression of atherosclerosis through two major pathways—metabolism-independent pathway [outer bacterial membrane components such as lipopolysaccharides (LPS) promote foam cells (macrophages, phagocytic immune cells, having low density lipoprotein (LDL) cholesterol) formation, which are a major component of atherosclerotic plaque] and the metabolism-dependent pathway [dysbiosis exert pro-atherosclerotic effects by altering the metabolism of bile acids (BAs), and the	↑*Lactobacillus (Firmicutes)* ↓*Bacteroidetes* [73]	Cardiovascular diseases

		production of trimethylamine-n-oxide (TMAO), and butyrate][73].		
	iv.	Disruption of gut microbiota leads to NAFLD through different mechanisms: a) energy homeostasis regulation via carbohydrate fermentation into SCFAs which results in de novo lipogenesis (DNL) in the liver; b) modulation of the endocannabinoid system; c) modulation of choline metabolism for very-low-density lipoprotein (VLDL) synthesis and liver lipid export; (d) modulation of bile acid homeostasis; (e) endogenous ethanol formation; and (f) increase of lipopolysaccharide (LPS), which results in the production of pro-inflammatory cytokines in liver macrophages, causing inflammation of hepatocytes [74, 75], liver cirrhosis, liver failure.	↑*Proteobacteria, Enterobacteriaceae, Lachnospiraceae, Escherichia,* ↓*Prevotella Firmicutes, Bacteroidetes* (reduction or no change) [76]	Non-alcoholic fatty liver disease (NAFLD)
	v.	Altered gut flora leading to high levels of pathogenic colonic mucosal bacteria and by-products such as ammonia, amino acid metabolites (indoles, oxindoles), endotoxins, etc. that increase the intestinal permeability, impaired intestinal motility, Small Intestinal Bacterial Overgrowth (SIBO), immune dysfunction and systemic inflammation. Decreased bile acids synthesis and defective enterohepatic circulation can contribute to altered gut microbiota [77].	↓*Bacteroidetes* ↑*Proteobacteria Fusobacteria*[77]	Hepatic encephalopathy
B		**NERVOUS SYSTEM-RELATED DISORDERS** Reduction in the host's resident microbiota compromised microglia cell shape and maturation, leading to blunted early responses, which was followed by an exposure to microbial-related molecule (lipopolysaccharide (LPS)) or pathogen (lymphocytic choriomeningitis virus). Defects of microglia (altered cell number, immature development), can happen when there is a depletion of the complex host microbiota, which can in turn, affect the immune responses, leading to pathogenesis of various Central Nervous System (CNS) diseases [78]. Permeability of the BBB is also affected by gut microbiota and microbial metabolites, which in their absence can become more permeable to macromolecules and reduces the expression of tight-junction proteins in the brain endothelium. Hence, gut microbiota maintains microglia and the blood brain barrier (BBB) [79]. Any disruption in these can lead to CNS disorders [80].		
	i.	Gut dysbiosis promote amyloid-beta aggregation, neuroinflammation, oxidative stress, and insulin resistance in the pathogenesis of Alzheimer's disease (AD) [81].	↓ *Firmicutes Bifidobacterium,* ↑ *Bacteroidetes* [81]	Alzheimer's disease
	ii.	Gut dysbiosis leads to an altered ratio of short-chain fatty acids (SCFA) and microglial signalling in the brain that leads	↑*Lactobacillus,* ↓*Clostridium coccoides, Bacteroides*	Parkinson's disease (PD)

		to disease development and display of PD-associated motor symptoms. Autonomous nervous system (ANS) dysfunction is observed as PD advances which leads to delayed GI motility and small intestinal bacterial overgrowth (SIBO) leading to motor fluctuations (due to abnormalities of levodopa bioavailability from GI tract, and malabsorption associated SIBO due to alteration in chyme composition). SIBO impairs levodopa absorption by intestinal mucosa inflammation or altered metabolism of drug by intraluminal bacteria [82].	*fragilis, Prevotella* (hydrogen sulphide producer) [83]	
	iii.	Gut dysbiosis leads to intestinal barrier disruptions (leaky gut) where the tight junction protein complexes integrity declines, increasing the intestinal permeability. Hence, the bacterial antigens (Lipopolysaccharide) move out of the intestinal lumen and migrate to other body locations and starts to increase in the blood circulation which could have systemic inflammatory effects. This could impact CNS immunity and integrity of the blood–brain barrier, hence allowing passage of autoreactive lymphocytes into the CNS and directly access the myelin sheath (autoimmune disorder) [37].	↑*Methanobrevibacter, Akkermansia,* ↓*Butyricimonas* (butyrate producer)[80]	Multiple sclerosis
	iv.	Gut microbiota and their metabolites can directly affect the immune system, that induce immune cell differentiation. Immune system impairments such as higher circulating pro-inflammatory cytokines, dysfunctional immune cells or antibodies targeting brain proteins are observed. Treg/Th17 balance is influenced by an altered microbiota. Neuroglial alterations favour ASD pathophysiology, as microglia and astrocytes play a role in neurodevelopment [84].	↑*Lactobacillaceae, Veillonellaceae Lactobacillus, Desulfovibrio, Bacteroides vulgatus, Bacteroidetes* ↓ *Bifiobacterium*[80]	Autism spectrum disorder (ASD)
	v.	Cortisol released due to stress leads to leaky gut facilitating systemic inflammatory responses. A pro-inflammatory state is observed with increased levels of TNF-a, interferon-gamma, IL-6 (activates HPA axis, downregulates glucocorticoid receptors that supresses HPA axis). These eventually lead to over-sensitive HPA axis. Reduced hippocampal serotonin and Brain-derived neurotrophic factor (BDNF) expression is observed. All these lead to	↓*Bifidobacterium, Lactobacillus, Faecalibacterium* ↑*Enterobacteriaceae, Alistipes*[80]	Major depressive disorder

		depression [85].		
	vi.	Gut microbiota alterations influence neural development, cognition, and behaviour through the bidirectional interaction with the brain–gut–microbiota axis gut. inflammation was shown to increase the risk of MSA [86].	↑*Bacteroides* ↓*Paraprevotella*[80]	Multiple system atrophy (MSA)
3) RESPIRATORY DISORDERS				
	i.	SARS-CoV-2 infection damages the lung cells and evokes a local immune response that recruit macrophages and monocytes, release cytokines, and adaptive T and B cell intervention. Twenty blood proteomic biomarkers predicting severe COVID-19 progression were identified and this proteomic risk score is correlated with proinflammatory cytokines mainly among older individuals. Gut +microbiota features are found to be greatly -associated with proinflammatory cytokines in 366 individuals as per the study [87].	↑SARS-CoV-2 *Klebsiella oxytoca*, Lactic Acid Bacteria, *Faecalibacterium prausnitzii*, *Tobacco mosaic virus* (TMV) [87]	COVID-19

TABLE 4: Pathogenesis of various diseases as a result of gut dysbiosis.

GUT MICROBIOTA IN RELATION WITH COVID-19

Respiratory infections are correlated with gut microbiota composition alterations [88], hence stating the role of the novel SARS-Cov2 on the impact of the gut microbiota. Pneumonia and Acute respiratory distress syndrome (ARDS) progression are the major clinical manifestations of Covid-19 where the gut microbiota play an important role [89], particularly in immune-compromised elderly patients [90]. Inflammation is possible due to the role of the gut-microbial–host-immune axis. Faecal metabolomics analysis showed amino acid-related pathways connecting gut microbiota to inflammation and COVID-19 severity. Decreased bacterial diversity is linked to increased low-grade inflammation. Modification of gut microbiota during ageing can cause inflammation. It is shown that the transfer of gut microbiota from old mice to young germ-free mice triggers "inflammaging" mimicking responses displaying elevated pro-inflammatory cytokine genes expression such as TNF-α, increased intestinal epithelium permeability due to inflammation, which results in increased pro-inflammatory bacterial compounds circulation. Chronic inflammation can produce dysbiosis that can lead to altered epithelial functioning and consequent disease and infection [87].

Angiotensin converting enzyme 2 (ACE2), located on the outer surface, facilitates the entry of SARS-CoV-2 into cells, followed by viral replication [91]. ACE2 is present in the arterial and the venous endothelial lining of most organs, the arterial smooth muscle cells and the cholangiocytes (epithelial cells of the bile duct). ACE2 expression is especially high in renal, cardiovascular, and gastrointestinal tissues, showing infection of COVID-19 to other organs, causing also extra-pulmonary symptoms [92]. Being largely expressed in small intestinal enterocytes [93], it regulates intestinal inflammation, and is involved in diarrhoea. Usually COVID-19 transmission occurs through respiratory droplets and secretions, but the gastrointestinal tract could also be a possible route of infection, since in 10%–20% of COVID-19 (SARS-CoV-2) cases, gastrointestinal disorders are correlated with respiratory symptoms (cough, dyspnea). SARS-CoV-2 has also been detected in COVID-19 patients' stool [94], coming to a hypothesis of gut involvement in infection. It was found in 50% of COVID patients, the virus is also found in the faeces,

but showing a negative oral swab, showing a higher viral stability [95]. Faecal microbiomes of COVID-19 patients had reduced symbionts and increased opportunistic pathogens, which remained even after SARSCoV-2 clearance (**Fig 6).**

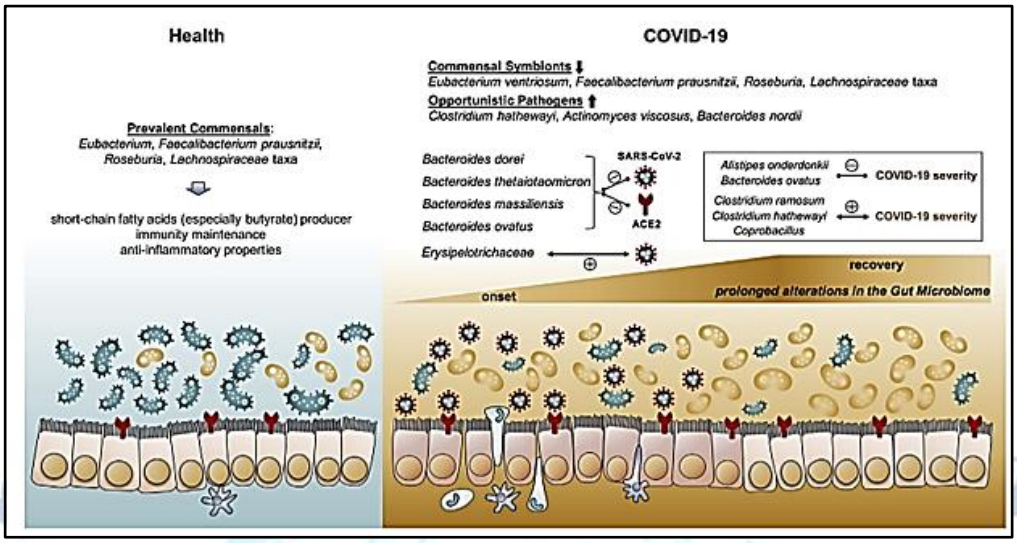


Fig 6: Gut microbiome dysbiosis in COVID-19 and its correlation with faecal SARS-CoV-2 virus shedding and severity of disease [93]

VI. CONCLUSION

Co-ordination and maintenance of body activities is done by the gut flora. On the contrary, altered gut microbiota due to various factors and products obtained by disrupted cellular mechanisms state can negatively impact the human body and drive disease pathogenesis. As discussed, oxidative stress, impact in host immunity and inflammation are the main drivers of diseases. Also, any interruption in the interaction between the gut and other systems can cause abnormal conditions and finally diseases. The pathophysiology of various diseases due to these interruptions have also been discussed which can act as a potential disease biomarker, aiding in effective disease treatment. Gut microbiota making a positive impact in the human body by regulating its activities, enhances the need for a balanced microbial composition. Hence, increasing the requirement of research in microbiome engineering for gut microbial manipulation, ensuring its balance.

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