Gut microbiota: - A key regulator of obesity

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ABSTRACT

The microbiome in the gut's possible role in the causes of obesity has received a lot of interest in the last few yrs. Several studies have found that the composition of gut microbiota is different in obese people and slim people since enteric bacteria are important players in lipid metabolism, so changes in gut microbiota composition are linked to changes in body weight and BMI(Body Mass Index). The review shows that microbiota regulates body weight by three main mechanism that is control of bile acid metabolism regulation, synthesis of short-chain fatty acid (SCFA) production, and induction/protection against metabolic endotoxemia. The role of probiotics on body weight is strain specific, according to research. The duration, dosage, and long-term benefits of microbial therapy in the reduction of overweight and obesity, however, are unclear. However, further investigation is necessary to completely understand the molecular modes of action of probiotics and prebiotics on people's wellbeing, as well as to show a link between the microbiome and overweight etiology using long-term, clinic-based therapy.

Keywords: Probiotics**,** Obesity**,** Microbiota**,** Weight loss**,** Fat mass, BMI(Body Mass Index)

1.0 INTRODUCTION

Obesity is becoming a worldwide epidemic, with rates rising significantly among adults, adolescence, and children. Obesity is believed to have a complex underlying cause that includes genomic, neurological, and neuroendocrine elements, in addition to food and active lifestyle behaviors embedded in a socio-cultural context. Obesity has lately been linked to structural changes in the microbiota of the gut in both Animalia and Homo sapiens, implying a causal relationship between this condition and certain microbial taxa or gene functions[1]. By influencing the breakdown of generally indigestible polysaccharides, which can make up to 10% of the body's daily energy supply, microbiota physiology can assist the host in gaining more energy from the meal[2], even though some oxidative products, such as propionate, have also been credited with beneficial roles[3].

The production of neuroendocrine factors in the gut and expression of genes involved in the metabolism of macronutrients, could all be affected by conventional microbiota, which could also affect energy balance[4,5]. The gut microbiota was proposed as one intestinal component that may contribute to the development of obesity in studies conducted by Jeffrey Gordon in St. Louis in 2004 and in subsequent years[6]. We predicted that widespread consumption of probiotics may increase obesity by changing the intestinal flora because numerous probiotic strains of Lactobacillus and Bifidobacterium are sold in goods for human consumption. Probiotics, on the other hand, have been utilized in farm animals for at least 30 years to manipulate the gut microbiota for growth promotion. *L. fermentum, L. plantarum, L. reuteri, L. casei,* and *L. acidophilus,* are the most prevalent Lactobacillus species utilized in farming. All of those findings point to Lactobacillus-containing probiotics (LCP) having an effect on weight control in both Animalia and Homo sapiens[7]. Normal intestine function and the preservation of the host's health depend heavily on the gut bacteria. It produces a huge amount of enzymes that may take energy from the host's diet and store it in fat stores. Whether or not this happens depends on the equilibrium between a variety of non-pathogenic microorganisms and potentially dangerous bacteria[8]. According to research on gut microbiota transplanting in which the recipient and donor followed different kinds of diets, changing one's diet is a simple way to modify one's gut microbiota[9]. Our gut microbes, or microbiota, have been shown to alter how fat is stored and how much energy is obtained, which suggests that they may affect whether or not weight loss and gain are successful. Changing the intestinal microbiota may be beneficial not only for weight loss but also for possibly preventing weight gain after loss, according to one study that found that overweight and obese teens' response to a strict diet and regular exercise programme depended on their microbiota prior to the treatment[10].

2.0 Overview Food intake is influenced by gastrointestinal hormones and their potential role in obesity development

2.1Ghrelin: Ghrelin is a neuropeptide hormone with 28amino acids that are produced when the bigger predictor pre-proghrelin is digested. The majority of this hormone is produced by the stomach mucosa of the gastro secretion gland, with minor amounts found in the small intestine and hypothalamus. The plasma level of ghrelin rises just before a meal and gradually decreases once it begins, depending on the food consumed. Ghrelin has also been linked to sleep problems, according to certain research. Blood ghrelin levels have been shown to increase during the first hour of sleep, and they are also connected with the production of slow-wave sleep stimulation and sleep-associated growth hormone. Sleep deprivation is also linked to higher ghrelin levels, lower leptin levels, and a higher BMI (Body Mass Index)[11]. The anterior nuclei of the hypothalamic are considered to control ghrelin's appetite-regulating actions. Ghrelin-induced food intake is also controlled by the brainstem and the vagus nerve. Not only does the brainstem send information to the arcuate, but it also has a specific hyperphagic effect[12]. Ghrelin is the only gastrointestinal hormone that has been identified as stimulating our appetite for food ingestion. Because obese people do not have a surge in ghrelin levels around mealtime, and their levels do not decline rapidly in response to meals, the hormone ghrelin is thought to have a long-time influence on body weight management. As a result, ghrelin blockade could help with obesity management in a variety of ways[13].

2.2 PYY (Peptide YY*)*: PYY is a neuropeptide Y (NPY) synthesized by cellular systems at various phases of the gastrointestinal system axis (PP) like pancreatic polypeptide. PYY is made by a specific endocrine cell in the distal stomach and is named after a

phenylalanine molecule. For both feeding and fasting situations, PYY3-36 is the most common type of plasma peptide[14]. PYY levels rise after eating, peak in 1–2 hours, and stayed high for a long time, indicating that it is primarily a contentment component instead of a dietary terminal. Exercise and stress can raise the level of circulating PYY, so keep that in mind when studying PYY in humans and animals.8 PYY3–36 was given intravenously for the first time in clinical research, and it lowered spontaneous meal intake by 30% at physiological plasma levels. In recent research of normal-weight adults, intravenous PYY3–36 administrations resulted in an amount of the drug reduction in intake of food consumption, while nausea occurred at larger dosages. The Y2-receptor is a kind of neurotransmitter present all through the central and peripheral nervous systems., is responsible for PYY's action. PYY3-36 controls feeding via the hypothalamus, as well as the brainstem and vagal afferents, which may directly influence hypothalamic control of food. Many areas of the brain except for the thermostatic region, according to a recent study, have an effect on hunger, which would be regulated by PYY 36[15].

2.3 Glucagon-like peptide-1: It is an incretin polypeptide generated in the gut that, among other things, enhances glucose-stimulated insulin release. GLP-1 is produced in two forms by gastrointestinal L cells: Glucagon-like peptide-11-36 and Glucagon-like peptide-11-37 amide. To obtain the various bioactive compounds GLP-17-37 and GLP-17-36 amide, subsequent disintegration is mandatory. GLP-17-36 is the predominant hormone in circulation[11]. The generation of this hormone is mostly dependent on nutrition. The timing and quantity of release are also affected by the meal's content. Quickly digested proteins, such as protein powder, promote the increased release, whereas delayed proteins, such as casein, cause a decrease in the release. Although the majority of investigations have found no differences in GLP-1 contents between obese and skinny patients, there is proof to support this conclusion that GLP-1 shows a role in obesity pathogenesis. In obese children and young adults, a reduction in fasting GLP-1 has been linked to weight loss. In comparison to lean controls, obese people show a lower postprandial GLP-1 response. Some research, on the other hand, found no link[16].

2.4 Cholecystokinin (CCK*)*: It was the first gut hormone to be discovered to lower food intake in both obese and lean people. In the small intestine's distal section, CCK is released by specialized cells known as I cells. The pro cholecystokinin gene is altered post-translationally, along with a cocktail of peptides, to make this hormone, which is then inactivated by enzymes such as tripeptide peptidase II. After eating, CCK levels rise in a biphasic fashion, peaking in roughly half an hour and staying high for roughly 3 hours. CCK is released in response to a variety of dietary variables, including chyme rich in fat and amino, coffee, and so on[11]. Common bile duct constriction, pancreatic enzyme release, psychological effects, and satisfaction are all important impacts of CCK. CCK-2 and CCK-1, which are both generated in the cerebellum and pituitary, are two of the most important CCK receptors. CCK-1 receptor is thought to be primarily responsible for CCK's appetite-suppressing actions, according to pharmacological and hereditary investigations. CCK-1 adhesion on the vagal is thought to cause satiation when CCK is administered. CCK can play a part in the growth of obesity, according to enough data[17].

2.5 Pancreatic polypeptide (PP): The f cell of the pancreatic islets secretes pancreatic polypeptide (PP), which also has a minor expression in the distal intestine[11]. Circulating PP rises for around half an hour after some diet and stays high for a few moments afterward. The caloric intake of the meal is accompanied by a rise in plasma PP levels[18] The vagus nerve, including other accelerators such as activity, stomach dilatation, and gastrointestinal hormones such as Cholecystokinin, secretin, motilin, and gastrin is important in PP release activation. Somatostatin, on the other hand, prevents

PP from forming. Fasting people's PP levels follow a diurnal cycle, rising at about 9 p.m. and falling in the early morning hours. Moreover, research has suggested that after bariatric surgery, PP levels do not alter much, indicating that this hormone is not a critical facilitator of hunger weight control loss. It's unclear what role PP has in obesity pathophysiology. Some investigations have found that a suppressed second phase release, postprandially, results in a decreased fasting level. There have been no studies that have linked fasting and postprandial PP to changes in body weight.[11]

3.0 Treatment of obesity

The effects of this weight-gain tendency have grown increasingly evident during the last three decades. More than 300 million people worldwide are obese, according to the International Obesity Task Force, with another 800 million overweight. First time ever in history, the world's overweight population equals its underweight population. Although maintaining the lifestyle modifications required for optimal bodyweight is attainable in some people, it is uncommon, and current treatments for lifestyle adjustment (alone) as a cure for obesity are usually viewed as useless. Anti-obesity medication is advised for a restricted group of patients who have failed to change their lifestyle[19]. When combined with weight loss accomplished through lifestyle changes, most patients can attain weight loss thresholds of 5-10%. In high-risk individuals, the gastric lipase inhibitor orlistat decreases weight by around 3 kg on average and delays the course of diabetes; nevertheless, it is not without side effects[20]. Following bariatric surgery, there are numerous medical concerns. Patients with symptoms after bariatric surgery are increasingly being seen by gastroenterologists. Clinical gastroenterology, or clinical issues induced by malnutrition and malabsorption after bariatric surgery, is entering a new phase in medical practice. Although the short- and long-term effects of bariatric surgery on weight loss have been extensively studied, little is known about the long-term clinical and nutritional ramifications of altered intestinal structure and physiology as a result of various bariatric surgical procedures. Given the early age of patients who have bariatric procedures, the long-term repercussions of surgical modifications to gastrointestinal anatomy and function must be evaluated across several decades[21]. Patients with Type-2 diabetes and other weight-related comorbidities who have a BMI(Body Mass Index)between 27 and 30 kg/m2 may think about taking medication. Pharmacotherapy is the next logical line of treatment for individuals who have historically not benefitted from intensive lifestyle treatments and those who struggle to sustain weight loss over time. It is important to let patients know what to anticipate from their medicines, including both the advantages and disadvantages. All currently approved anti-obesity drugs, except for orlistat, assist patients to reduce their caloric consumption and adhere to their diet plan better. Reduced energy intake is primarily accomplished by increasing fullness and decreasing hunger and food cravings. Various methods for the treatment of obesity are listed in the table:1 below:[22]

“Table :1 Treatment of obesity”

Pharmacotherapy	**Medical devices**	**Surgery**

• Orlistat • Lorcaserin • Liraglutide • Phentermine/topiramate • Naltrexone/bupropion	• Intragastric balloon (orbera, reshape duo,obalon) • Electric stimulation system (Maestro) • Gastric emptying system (Aspire assist)	• Bariatric surgery Common surgical procedure: ➢ SG(Sleeve gastrectomy) ➢ RYGB(Roux-en-Y gastric bypass) ➢ LAGB(Laparoscopic adjustable gastric band)

3.1 Pharmacotherapy

- Orlistat:- Orlistat is the only one with a totally peripheral mechanism of action. It's a pancreatic and gastric lipase inhibitor that lowers calorie intake by reducing fat absorption in the stomach. For teenagers, Orlistat is the only weight-loss drug now on the market. Despite having a good safety profile, the use of orlistat is constrained by its gastrointestinal adverse effects, which include spotting/oil stools, fecal urgency, and flatus. Patients may be advised to take a daily multivitamin supplement to make up for the reduced absorption of fat-soluble vitamins. Contraindications and limitations are:-Chronic malabsorption syndrome; cholestasis[22].
- Lorcaserin:- Lorcaserin is a serotonergic medication that inhibits 5-HT2C receptors only. Nearly half of the weight loss was recovered when lorcaserin was continued for a second year[23]. Lorcaserin, when combined with behavioral modification, was linked to considerable weight loss and improved weight maintenance. Lorcaserin was also linked to lower levels of lipids, insulin resistance, inflammatory marker levels, and blood pressure, all of which are potential predictors of future cardiovascular events. Dizziness, tiredness, headaches, dry mouth, nausea, constipation, hypoglycemia, and cough are side symptoms that can occur in diabetic individuals. [22].
- Liraglutide:- It is a glucagon-like peptide-1 receptor agonist that has been licensed in doses of 1.8 mg or 3.0 mg for T2D or obesity. It's given as a subcutaneous injection once a day. Vomiting, constipation, nausea, dyspepsia, diarrhea, abdominal pain, headache, hypoglycemia, fatigue, and increased lipase are the adverse effects of liraglutide. Indications against use and restrictions include not using insulin or another GLP and having a personal or a history of medullary thyroid carcinoma in the family or other kinds of multiple endocrine neoplasia one agonists [22].
- Phentermine/topiramate[PHEN/TPM]:- It was the first combination therapy to be licensed in the United States for the treatment of obesity in 2012. Because topiramate, an antiepileptic medicine, has been linked to a teratogenic risk of mouth clefts, women of reproductive potential must have a negative pregnancy test before starting PHEN/TPM and every month thereafter. The most prevalent side effect of PHEN/TPM, especially at the onset of treatment, is paresthesia. The clinician must pay particular attention to any negative effects on mood or memory. The complicated dose titration of PHEN/TPM, as well as the risk of causing cognitive and mood-related side effects, necessitates the use of a qualified clinician[22].
- Naltrexone/bupropion (NB):- NB is the second combination therapy for obesity, approved in late 2014. Weight loss with NB does not lead to a reduction in blood

pressure or cholesterol. Nausea is a common with annoying side effect of NB therapy, resulting in high dropout rates in randomized controlled trials. NB is also linked to increased heart rate and blood pressure, prompting the FDA to order a CVOT, which was tragically halted due to the sponsor's improper sharing of data while the trial was continuing. Dose titration for NB is difficult[22].

3.2 Surgery

- Laproscopic adjustable gastric band (LAGB):- It is the least harmful of the four procedures, including the implantation of an adjustable silicone band around the stomach fundus via laparoscopic surgery. This technique offers the advantages of being able to be performed in an outpatient setting, having the fewest problems, and being reversible. The FDA has approved two band devices: Realize (Ethicon, Somerville, New Jersey) and Lap-Band (Apollo Endosurgery). In early 2017, the Realize Band was no longer active. After a year, LAGB resulted in a 14 percent to 30 percent weight loss. Even though weight return is more prevalent with LAGB than with other procedures, some patients have long-term benefits[22].
- Roux-en-Y gastric bypass (RYGB):- In many countries, the long-limb RYGB is now the preferred bariatric surgery. There is formed a little gastrointestinal pouch with a small exit with this treatment, which reduces food intake. Foods that have been swallowed pass through the pouch and into the jejunum's 'Roux limb.' Pancreatic enzymes and bile acids are released into the bypassed duodenum and transferred aborally by the jejunum's 'biliopancreatic limb.' A jejuno-jejunal anastomosis connects the two limbs, allowing food to interact with bile acids and digesting enzymes as it enters the 'common channel' of the small intestine. The Roux limb was originally 30 cm long, and the technique was thought to limit food intake. The Roux limb was then stretched to 150 cm to induce malabsorption, which would work in tandem with reduced intake to promote weight loss. The deficit in dietary intake, lack of gastric secretions, exclusion of the proximal duodenum and jejunum, or asynergia between food bolus and biliopancreatic secretions have all been proposed as plausible reasons for nutritional deficiencies following RYGB. In-depth studies to determine the extent to which the long-limb RYGB results in malabsorption have just recently been conducted[21]. Long-limb RYGB consistently generated fat malabsorption and occasionally triggered protein malabsorption, according to the researchers. Fat malabsorption showed a wide range and linked with the length of the proximal jejunum used to form the Roux-Y anastomosis biliopancreatic limb. In patients with 40 or 50 cm of jejunum in their biliopancreatic limbs, malabsorption decreased fat absorption by an average of 10 g/day, whereas malabsorption decreased fat absorption by an average of 40 g/day in patients with 70 and 75 cm of jejunum in their biliopancreatic limbs. There was also a varied effect of long limb RYGB on protein absorption in this investigation[24]. According to the authors, measuring total nitrogen or urea nitrogen excretion in the urine at regular intervals after long-limb RYGB enables adjustments in protein intake that provide the best protein absorption for each patient while preventing excessive energy absorption from protein supplements, which would defeat the purpose of RYGB. At 5 and 14 months after bypass, the severity of fat and protein malabsorption was identical on average, indicating that there was no evidence of intestinal adaptation throughout this period. When compared to food restriction, malabsorption performed a very minor impact in limiting energy absorption after long-limb RYGB. The procedure is more difficult than a sleeve gastrectomy and has a little higher risk of complications,

but it results in the most long-term weight loss and a very high incidence of T2D treatment[21].

- Sleeve gastrectomy (SG):- A staple line is put along the larger curvature of the stomach, and then roughly 80 percent of the lateral side of the stomach is removed vertically in the SG surgery. Because of the procedural ease and lower frequency of major problems, SG has grown in popularity over the last decade[22].

3.3 Medical devices

Medical devices aimed at the gastrointestinal system fill this void, targeting a variety of hypothesized gut-brain interactions to provide significant weight loss with a lower risk than surgery.

- Intragastric balloons:- Three intragastric balloons (Orbera, Reshape, and obalon) have been approved for usage in individuals with BMIs between 30 and 40 kg/m^2 for up to 6 months to help them lose weight. Orbera is a single balloon that is inserted during an endoscopic procedure into the stomach. The balloon is then expanded by adding 400–700 ml of saline when it is in place. ReShape is similar, but it employs two balloons instead of one. An inflation catheter is used to inflate the swallowable capsule known as Obalon with air once it has opened within the stomach. The maximum recommended lifespan for each of the three gastric balloons is six months. Some weight is acquired in the months after the gadgets are taken out of use[22].
- Electric stimulation system:- The Maestro Rechargeable System is a type of vagal nerve obstruction that works by blocking neuronal transmission between the stomach and the brain, resulting in improved satiety and lower calorie intake. The gastro-esophageal junction's vagus nerve trunks are connected to a neuroregulator, a chargeable pulse generator that is fixed subcutaneously. Obviously, it is more intrusive than gastric balloons, and it necessitates the use of laparoscopic surgeons[22,25].
- Gastric emptying system:- A gastrostomy tube called AspireAssist is attached to a cutaneous port outside the abdomen. After each meal, the patient opens the skin port's valve and connects an external connection and tubes. Twenty to thirty minutes later, the patient flushes the food out. Food must be completely chewed to avoid obstruction in the tube. Electrolytes in the blood should be checked. Potassium supplements may be required in some people[22].

4.0 GUT MICROBIOTA

Microorganisms have a close association with all higher organisms. A microbiota is a term used to describe a group of microorganisms that coexist in a habitat, such as the gut. Bacteria, viruses, fungi, archaea, and protozoa make up a microbiome. Every surface that comes into contact with the outer world has them, but they are especially prevalent on the mucosal membranes of the digestive system [26]. The ratio of bacterial to human cells, according to a recently updated estimate, is closer to 1:1. The host and the microorganisms that live inside it are sometimes referred to as a "superorganism" because of the enormous number of bacterial cells in the body. The microbiota serves the host in a variety of physiological ways, including enhancing gut integrity, forming the intestinal epithelium, generating energy, warding off infections, and controlling host immunity[27]. Regardless of how it was previously considered that the microbiome consisted of 500-1000 microbe species, a new large-scale study estimates that the human intestinal bacteria have approximately 35000 species of bacteria. The phyla Bacteroidetes and Firmicutes make up the majority of the healthy gut microbiota. Over 70% of all bacteria discovered in the body are found in the large intestine, and gut flora,

which is commonly mentioned in the disease's context condition, generally refers to the colonic flora. Bacteroidetes and Firmicutes are the most common phyla found in the large intestine. The Firmicutes: Bacteroidetes ratio has traditionally been linked to illness susceptibility [28].

"Table:2 Composition of the normal human gut microbiota"[28]

Organ	**Microbes distribution**
Esophagus	*Bacteroides, ,Prevotella,Rothia sps.,Streptococcus,Veillonella, Gemella, Megasphaera,Pseudomonas*
Colon	*Porphyromonas,Prevotella,Eubacterium,Enterobacterium, , Streptococcus Peptostreptococcus ,Enterococcus,Clostridium, Lactobacillus, , Fusobacteria ,Bacteroides Ruminococcus*
Stomach	*Prevotella , Helicobacter pylori, Streptococcus, Enterococcus, Lactobacillus*
Caecum	*Fusobacteria, Roseburia, Lachnospira, Fecalibacterium, Ruminococcus, Butyrivibrio*
Small intestine	*Lactobacillus, Clostridium, Enterococcus, Streptococcus, Bacteroides, g-Proteobacteria*

The human body becomes more colonized with microorganisms before and after birth as a result of the newborn coming into touch with the mother's feces, vagina, and skin microbiota. The composition of the gut microbiota is then affected by factors like age, sex, immune system development, and environmental influences, becoming more stable between the ages of 6 and 36 months. One of the most well-known variables that may alter the composition of the gut microbiota is diet, and this has been demonstrated in studies of elderly adults[29]. Aging causes the diet to drastically change, which may be related to taste and smell loss as well as trouble chewing. These ailments frequently cause people to favor meals high in carbohydrates and fats while consuming less foods of a plant origin[30]. Although Firmicutes bacteria predominate in adulthood and Bacteroidetes in the elderly, most members of the genera Firmicutes and Bacteroidetes continue to be prominent[31].According to Biagi et al.[32], the gut microbiota of the elderly has an odd makeup. This investigation compared four groups in a confined area in Italy. 21 participants between the ages of 99 and 104, 22 between the ages of 63 and 76, 20 between the ages of 25 and 40, and then 21 descendants of centenarians between the ages of 59 and 78. The results showed that bacterial diversity is not very great. The gut microbiota of very elderly persons is still dominated by Firmicutes and Bacteroidetes in particular, but there have been changes in the relative number of Firmicutes subgroups, including a decline in Bacilli and an increase in Bacilli and a rearrangement of the Clostridium cluster IV. This likely means that particular gut microbial elements are indicative of long life. When comparing older individuals to young adults, a decline in bifidobacteria and an increase in the mucin-degrading Akkermansia muciniphila were also found. Sex hormones and the gut's development both undergo significant changes at the same time. These systems exhibit sex differences at comparable ages, suggesting that the gut microbiome and gender are in communication[33].In research including 1135 people, females displayed higher gut microbial diversity. Particularly among females, Akkermansia muciniphila was widespread. Pre-menopausal women had larger ratios of the intestinal incretins glucagon-like peptide-1, Lachnospira and Roseburia, and the Firmicutes: Bacteroidetes, which are released by enteroendocrine cells in the gut to improve glucose clearance in response to meal ingestion. In comparison to post-

menopausal women, pre-menopausal women showed a reduced relative abundance of the Prevotella, Parabacteroides, and Bilophila genera[34].

4.1 Functions of microbiota:-

The gut mucosa and the microbiota work together synergistically in a healthy individual to offer important physiological, immunologic, and gastrointestinal protective functions. A self-contained organ with a broad metabolic range and considerable functional flexibility, the gut bacteria obtain nutrition from the host's food and sheds epithelial cells[35]. Due to these features of the gut microbiome, the emphasis of study has switched from the amount and variety of microbial members to functional issues. The primary functions of the gut microbiota are briefly summarised in this section.

- The main source of nutrition for the gut flora is dietary carbohydrates. Colonic organisms like Fecalibacterium, Roseburia, Bifidobacterium, Enterobacteria, and Bacteroides ferment carbohydrates that escaped proximal digestion and indigestible oligosaccharides to generate short-chain fatty acids (SCFA) like acetate, propionate, and butyrate which are abundance forms of energy for such hosts [36,37].
- Organisms like Bifidobacterium, Lactobacillus species, and Oxalobacter formigenes species counteract the oxalate produced in the intestine owing to carbohydrate breakdown and bacterial fermentation, lowering the possibility of oxalate stone formation in the kidney[38,39].
- The intestine microbiome has also been demonstrated to improve lipogenesis by reducing adipocyte lipoprotein lipase inhibition. Moreover, Bacteroides thetaiotaomicron has been shown to improve the effectiveness of lipid hydrolysis by upregulating the production of a colipase that is necessary for lipid digestion by pancreatic lipase[40].
- The gut microbiota's importance in retaining the form and composition of the gastrointestinal tract is supported by a large body of research.
- The desmosome is maintained at the epithelial villus by the small proline-rich protein 2A, and Bacteroides thetaiotaomicron has been found to stimulate its production[41].

4.2 Role of the microbiota in digestion:-

The microbiota, as a suggested endocrine organ, is also capable of producing and regulating hormones, playing an important role in food processing, synthesis of vitamins, pathogen displacement, and influencing functions of distant systems and organs. The efficient connection between the brain and intestines and microbiota ensures the maintenance of the digestive tract homeostasis, with the bidirectional brain and gut axis playing an important role in the regulation of digestion[42]. What sorts of bacteria reside in the colon depends heavily on factors including nutrition, environment, and drug usage. More complex carbs like starches and fibers are not as easily digested and may go lower to the large intestine. Sugars like table sugar and lactose (milk sugar) are swiftly absorbed in the top region of the small intestine. There, the digestive enzymes produced by the microbiota aid in the breakdown of these substances. Short-chain fatty acids (SCFAs), which may be utilized by the body as a source of nutrition and also play a significant role in muscular function and perhaps the prevention of chronic illnesses like certain cancers and bowel problems, are created when indigestible fibers are fermented[43]. Short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate are produced during the breakdown of dietary fiber by bacteria in the large intestine. Butyrate encourages programmed cell death (apoptosis) in malignant epithelial cells lining the large

intestine, hence lowering the risk of bowel cancer, whereas propionate is expected to play a significant role as a satiety molecule, with the potential to contribute to the turning off of hunger. The gut microbiota breaks down and ferments food fibre, producing huge volumes of gases like odorless methane, carbon dioxide, and hydrogen as well as fewer of strong odoriferous gases like hydrogen sulfide[44]. For the metabolism of nondigestible carbohydrates, such as large
polysaccharides like cellulose, hemicellulose, pectins, and gums; some indigestible oligosaccharides; unabsorbed sugars and alcohols from the diet[45]; and host-derived mucins, some microbiomes provide the essential biochemical pathways[46]. As a result of this capability, the host is provided with energy and absorbable substrates as well as a source of nutrients for bacterial growth and proliferation. In the colon, a significant source of energy is the breakdown of carbohydrates. Numerous intestinal bacteria generate antimicrobial substances, compete with one another for nutrition, and utilize the gut lining as a site of attachment, deterring disease colonization. The barrier or competitive-exclusion effect refers to this behavior. Compared to carbs and lipids, the host's ability to digest proteins varies considerably[47]. Protein catabolism in the gut is typically viewed negatively because it can produce substances that are poisonous to the host, such as amines, phenols/indoles, and sulfurous chemicals. It's crucial to remember that not all amino acids are digested into harmful byproducts as a result of gut microbial activity; in fact, SCFAs are the most prevalent byproducts. Therefore, the host may not necessarily suffer an adverse effect from protein catabolism. For the first stage of amino acid catabolism, a microbe can use one of two strategies: deamination, which results in a carboxylic acid plus ammonia, or decarboxylation, which results in an amine plus carbon dioxide. It has been assumed that excessive ammonia production might harm the host because ammonia can impede mitochondrial oxygen consumption and reduce SCFA degradation by (intestinal epithelial cells) IECs. Ammonia is also quickly assimilated by the gut microbiota into microbial amino acid biosynthetic activities [48,49,50], and host IECs can further regulate ammonia levels by converting it to citrulline and glutamine or by slowly releasing it into circulation[51].

4.3 REGULATORY ROLE OF GUT MICROBIOTA IN BODY WEIGHT

It's necessary to know how gut microorganisms affect body weight and glucose metabolism to identify which intestinal bacteria are involved. The induction/protection against metabolic endotoxemia, control of bile acid metabolism, and short-chain fatty acid (SCFA) synthesis are the three key mechanisms.

4.3.1 Short chain fatty acid production:-

Undigestible polysaccharides are broken down by gut bacteria to produce a lot of SCFAs, principally acetate, butyrate and propionate [52]. Short-chain fatty acids bind to the Gpr41 and Gpr43 G-protein-coupled receptors, which are found on gut vascular endothelium[53], promoting glucagon-like peptide one(GLP-1) and peptide YY (PYY) production. Gut motility is reduced by these two gut hormones[54], which increase satiety and reduce energy expenditure[55]. Furthermore, interactions between SCFA and Gpr41 and Gpr43 promote the synthesis of leptin[56] and have a significant impact on inflammatory responses, which have been connected to obesity-related metabolic problems, such as lipogenesis, insulin resistance, and raised triglyceride storage [57]. Although, not all gut microbiome components can ferment non-digestible polysaccharides to the same extent. Furthermore, the qualitative and quantitative

generation of SCFAs might fluctuate greatly amongst agents and depending on the substrate type. Finally, the metabolic characteristics of various SCFAs vary. While various bacterial families produce acetate, the synthesis of butyrate and propionate appears to be more conserved and substrate-specific. Few bacterial genera dominate propionate production, the most significant of which is *Akkermansia municiphila.* Propionate is produced when fucose and rhamnose are fermented, whereas butyrate is produced when resistant starch is fermented, primarily by *Ruminococcus bromii. Eubacterium rectale, Ruminococcus bromii, Eubacterium hallii*, and *Faecalibacterium prausnitzii* are among the bacteria that make butyrate[58]. SCFAs, on the other hand, serve as both signaling molecules and energy substrates, impacting metabolism and calorie intake. Increased energy extraction from meals due to gut microbial fermentation is one fundamental process that could explain the variations in body fat between ordinary and germ-free mice. Thus, the gut microbiota may convert complex dietary plant polysaccharides, which are normally unavailable to short-chain fatty acids (SCFAs), monosaccharides, and humans, acetate and butyrate, primarily propionate. SCFAs can contribute up to 70% of everyday energy production in herbivores or 10% in omnivores, making them a substantial source of energy for bodily systems. Under the villus epithelium of the small intestine, the colonic epithelial cells' primary energy source is butyrate, which also improves capillary density. Hepatocytes absorb propionate and acetate, which can be used for glycogenolysis and lipid metabolism.SCFAs, on the other hand, influence energy intake and metabolism as both energy substrates and signaling molecules. The host metabolism may be perfectly alright for the microbiota's secretion of SCFAs, which regulate energy harvest, fat storage, and appetite[59,60].

4.3.2 Activation of metabolic Endotoxaemia:-

Lipopolysaccharides(LPS) are a significant glycolipid part of Gram-negative bacteria's outer membrane, which account for over 70% of the gut microbiota[61]. Moreover, in 2007, researchers found that mice fed a high-fat diet (HFD) had higher blood levels of LPS than mice fed a regular chow diet, which caused inflammation in the liver and adipose tissue, which in turn caused the development of NAFLD and insulin resistance. The researchers named this condition metabolic endotoxemia to describe it. Gut permeability improves when Gram-negative bacteria grow, accompanied by a decrease in Bifidobacterium spp., Lactobacillus spp., and Bacteroides-Prevotella spp., as occurs following a high-fat meal. Several pro-inflammatory pathways as well as increased oxidative stress are triggered by the easily absorbed LPS produced by bacterial lysis[62]. Blood LPS levels are greater in obese people than in healthy people[63]. When obese people's endotoxin-producing Enterobacter cloacae B29 bacteria were transplanted into germ-free mice that were fed a high-fat diet, the mice developed obesity and insulin resistance, which supports the direct link between metabolic endotoxemia and changes in the gut microbiota caused by high-fat diets. Animals on a standard chow diet, on the contrary, showed no signs of metabolic disruption[64].

4.3.3 Bile Acid Metabolism Regulation:-

The activity of microbial enzymes in the gut microbiota deconjugates bile acids. Bacterial bile salt hydrolases (BSH) are generated by bacteria from the Clostridium, Enterococcus, Lactobacillus, and Bifidobacterium, genera, among others[65]. Bile acid has recently been recognized as a signaling molecule for a range of functions mediated by the G protein-coupled membrane receptor 5 (GPCR 5), (TGR5), and farnesoid X receptor (FXR). These receptors, which are typically found in hepatic metabolism tissues but can also be found in peripheral organs, drive the signaling cascade and activate genes associated with bile acid, lipid, and glucose metabolism, as well as energy expenditure and inflammation.

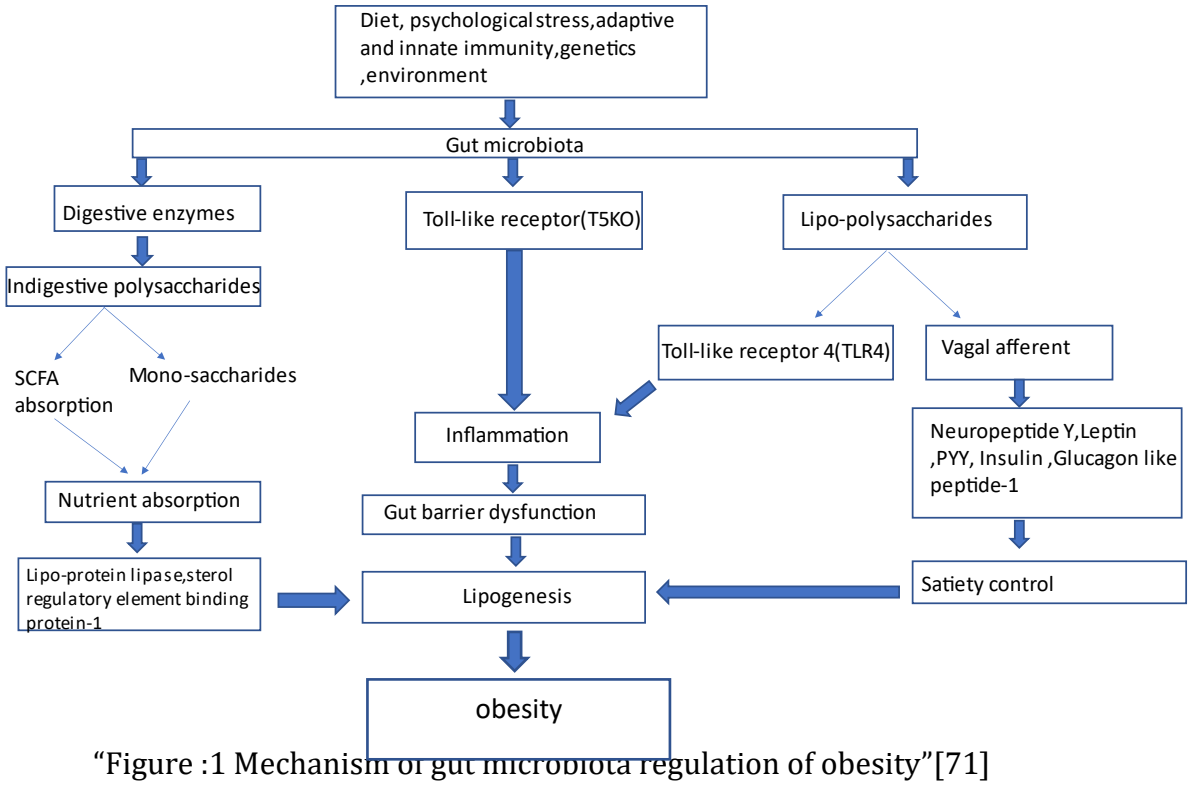
[66,67]. Obese mice have a lower microbial transformation of BAs than lean mice, suggesting a link between body composition and BA metabolism. The role of BA metabolites as microbiome-produced molecular mediators of energy balance should not be disregarded, as it might provide a huge intervention opportunity[68].

4.4 Microbiota and Obesity

The following are some of the hypothesized mechanisms by which the gut microbiota may play a role in the pathogenesis of obesity and other metabolic diseases related to it: (a) a large number of bacteria that ferment carbohydrates, increasing the synthesis of short-chain fatty acids (SCFAs), providing the host with an extra source of energy that is later stored as lipids or glucose; (b) increased susceptibility to bacterial lipopolysaccharides(LPS) in the gut, which leads to raised systemic LPS levels that worsen insulin resistance and low-grade inflammation; (c) enhanced activity of the gut endocannabinoid system[69]. It appears that bacteria can influence the energy balance of the host through a number of mechanisms, including increased fermentation of undigested polysaccharides and obtaining extra energy from the food portion, decreased expression of FIAF (fasting-induced adipocyte factor) in the enterocytes with inhibitory activity towards intestinal lipoprotein lipase, and increased release of peptide YY that slows the gastric emptying[70].

4.4.1 4Gut microbiota in energy harvesting:- Enzymes for the utilization of non-digestible carbohydrates, producing vitamins (K and B group), lowering cholesterol, amino acids and, isoprenoids are provided by the gut microbiota (e.g., lysine and threonine). For example, the capacity of the host to extract energy from the food appears to be influenced by the commensal microbiota's use of complex dietary polysaccharides that would otherwise be unavailable to human individuals[71]. Dietary calories may be extracted more easily from the gut microbiota and then either stored as adipose tissue or used as nutrients for microbial development. An individual may be more susceptible to becoming fat if their microbiome is more effective at obtaining energy[72].

4.4.2 Gut microbiota in inflammatory signaling and obesity:- A highly developed mucosal immune system guards the intestine against potentially dangerous pathogens that may be present in the gut microbiota. In fact, the presence of microorganisms in areas where they do not belong is one of the potent causes of inflammation[73]. Recently, research has demonstrated a significant connection between Toll-like receptors (TLR5) and metabolic syndrome. The intestinal mucosa expresses a transmembrane protein called TLR5 that recognises bacterial flagellin. Loss of TLR5 led to changes in the gut microbiota, which is crucial for low-grade inflammatory signaling (T5KO) [74].



"Figure :1 Mechanism of gut microbiota regulation of obesity"[71]

4.4.3 Regulation of brain-gut axis by the gut microbiota:- The key control centers for hunger are the brain stem and hypothalamus. Examples of satiety signals include many hormones, neuropeptides, and the brain-gut axis, or ongoing, bidirectional communication between the stomach and the brain. According to a recent study, gut bacteria may have an impact on brain development. [71]. Thus, it is possible to hypothesize that the host microbiota may have an impact on how the central nervous system regulates hunger and satiety. Through sensory nerves, the gastrointestinal tract sends messages to the brain, such as the classic gastric vagal stimulation or balloon distension-induced satiety[75]. The vagal afferent route is a significant neural system that transmits data from gastrointestinal luminal contents to the brain and affects gastrointestinal motility and eating behavior[76]. To completely comprehend the processes driving this method of microbiota-regulated dietary behaviour, more research is needed. Current research focuses on how the brain-gut axis controls the gut microbiota's regulation of satiety.

4.5 CORRELATION OF INTESTINAL MICROBIOTA IN OBESE AND NORMAL-WEIGHT HUMANS

A series of research in experimental animals first showed a connection between intestinal bacteria and overweight. GF mice were found to be substantially thinner than traditionally bred mice[77]. Furthermore, studies in which adult human gut microbiota was implanted into GF mice revealed that obesity-related microbe traits may be transferred, proving that the gut microbiome is important and play a significant role in influencing overall fat mass deposition [78,79]. The genera *Erwinia, Oscillospira, Bifidobacterium, Alistipes* and *Succinivibrio* on the other hand, were regarded as protective since they were discovered to be more prevalent in normal-weight patients than overweight people[80,81]. *Ruminococcus bromii*, *Blautia hydrogenotorophica, Eubacterium ventriosum,* and *Ruminococcus obeum*, *Coprococcus catus,* on the other hand,

has been linked to obesity development[82]. This research might have led to the conclusion that the Firmicutes/Bacteroidetes ratio is an indicator of obesity, and that restoring this ratio to normal could help prevent and cure obesity. However, not all human investigations yielded the same results. Although it was shown that a drop in Bacteroidetes abundance and a reduced variety of gut flora were connected with obesity in most cases, other studies were unable to prove this link, or the reverse tendency was discovered[83-88]. By using 16S rRNA gene sequencing, Bacteroidetes relative abundance decreased while Firmicutes relative abundance increased in relation to adult obesity[89]. HFD changes the gut microbiota's makeup, increasing the Firmicutes / Bacteroidetes ratio. Animals fed the HFD have lower levels of Bifidobacterium, Lactobacillus, and Akkermansia muciniphila[90,91]. Different investigations regularly show that the gut microbiota composition differs between slim and overweight animals[92,93]. The Bacteroides–Prevotella group had lower numbers (approximately 1 log unit fewer) in overweight people than in control subjects at baseline, but postsurgical, the numbers grew, according to a study of the fecal microbiota of morbidly obese subjects previous and following Rouxen-Y gastric bypass surgery[94]. At 24 weeks into pregnancy, an investigation of the fecal microbiota of pregnant women found that overweight women had lower counts of Bacteroides than normal-weight women[95]. A microbiome is acquired from the mother's reproductive system during birth. The microbiota and the host eventually form a mutualistic relationship[96].In a comparative genomic sequencing and metaproteomic study of intestinal flora in feces from an overweight and slim adolescence, the phyla Firmicutes was more in numbers than Bacteroidetes in the obese subject, while Bacteroidetes (18.9% total 16S rDNA) was the most active bacterial division (81% percent proteins)[97]. A lifestyle modification focused on calorie reduction and physical activity levels were also found to cause alterations in the gut bacteria structure of obese adolescents, which were linked to weight reduction and BMI z-score decreases[98]. Obesity is brought on by a dysbiosis in the energy homeostasis caused by the gut microbiota. Obese persons have less microbial diversity than thin people in general[99,100]. Lactobacillus Plantarum was given to a group of mice on a high-fat diet, and the results revealed a reduction in final body weight and epididymal fat cell size[101]. Obese patients had a considerable reduction in Bacteroidetes, which resulted in a rise in the relative concentration of Firmicutes, which is linked to plasma glucose levels[102]. Another study in pregnant women found that Bacteroides numbers were higher in obese women than in normal-weight women[103]. Although the microbiome may contribute to obesity, it's also probable that dysbiosis is only a side effect of the body's adjustment to a diet heavy in fat and sugar. [104,105].

4.0 Researches for obesity study by using probiotics strains

Here are some research evidence that shows that altered gut microflora induce obesity which is shown in table:3

" Table 3:(Probiotics-based regulation study for obesity in animals and humans)"

Strain	**Experimental study**	**Dose**	**Result**	**Reference**
P.pentosaceus LP28	Mice	1.25×10^{9} CFU/g for 6 weeks	Reduced liver cholesterols, liver triglycerides, epididymal fat	Zhao et al[106]
Lactobacillus rhamnosus GG	Humans	1×10^{10} CFU/day for 20 weeks	Prevents GDM(Gestational diabetes mellitus) in an	Callaway et al[107]

			obese and overweight pregnant woman	
Lactobacillus casei strain Shirota (LcS)	Rats	10^8-10^9colony-forming units (CFU)776	Prevents weight gain. Decrease fat mass.	Golgi's Karimi et al[108]
L. pentosus L. Plantarum L. fermentum	Rats	1×10^{10} CFU/ml	Reduces, bodyweight, abdominal circumference, BMI	Khanna et al[109]
Bifidobacterium spp.	Rats	10^8-10^9 CFU for 7 weeks	Reduces fat and body weight, reduces the blood serum level	A mi H et al[110]
Dahi containing lactobacillus casei	Mice	>8 $\log_{10}$ CFU/ mL for 8 weeks	Reduces body weight, blood glucose, plasma lipids, and expression level of leptin.	Rather et al[111]
Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032	Humans	2.5×10^9 CFU/ml twice a day for 12 weeks	Probiotic-induced weight loss was linked to a reduction in fat mass as well as oxidative and inflammatory stress in overweight people.	Jung et al[112]
Probiotic fermented soymilk	Mice	10^8 CFU/mL for 6 weeks	Decreases body weight, hyperlipidemia, liver fat accumulation, and reactive oxygen species(ROS)production.	Zhang et al[113]
Lactobacillus gasseri	Humans	1×10^9 CFU/day for 12 weeks	Reduces visceral fat mass.	Kim et al[114]
L. Plantarum LG42	Mice	1×10^9 CFU/day for 80 days	Reduced body weight, serum level, insulin	Park et al[115]
Lactobacillus plantarum Q180	Rats	1×10^9CFU/mL for 8 weeks	Reduces adipocyte size, triglyceride level, and leptin	Park et al[116]
Lactobacillus casei strain Shirota	Rats	(1×10^9CFU/day/ rat) for 12 weeks	Liver weight decreased and triglyceride levels.	Azmi et al[117]
Lactobacillus rhamnosus	Mice	10^8cfu/kg/day for 10 weeks	Obese mice fed an HFD had less body fat gain and liver damage.	Kim et al[118]
Lactobacillus plantarum LMT1-48	Mice	Administered different doses of the extract 10^5 ,10^6,10^7,10^8	Administered at atleast 10^6 reduced body weight and visceral fat.	Choi et al [119]
Lactobacillus sakei ADM14	Mice	10^8–10^9 CFU per 200 μL for 10 weeks	Reduced weight gain, epididymal fat expansion, total blood cholesterol, and glucose levels were all lowered.	Won et al[120]

Bifidobacterium animalis subsp. lactis CECT 8145	Rats	10^{10}cfu/day start from 5 weeks until 17weeks of age	Results show the anti-obesity property of this strain	Carreras et al[121]
Lactobacillus fermentum	Mice	1.0×10^{9} CFU/kg for 8 weeks	Inhibit obesity induced by a high-fat diet	Zhu et al[122]

5.0 Patents

Table 4: Patented instances of probiotics for obesity treatment

Title	Inventor	Patent Number
Probiotics composition and method for the treatment of obesity and obesity-related conditions	Olmstead et al[123]	WO 2014/046804 A1
Probiotics to influence fat metabolism and obesity	Ohlson et al[124]	US 2008/0267933 A1
Bifidobacterium longum for treating obesity and associated metabolic disorder	kiely et al[125]	WO 2017/097987 A1
Probiotics compositions and methods for the treatment of obesity and obesity-related conditions	Olmstead F.S. et al[126]	US2014/0079676 A1
Lactobacillus acidophilus strains of bacteria and compositions thereof	Gorbach et al[127]	0199535 A2
Composition of microbiota and methods related thereto	Kaplan M.L. et al[128]	US 10,149,870B2

Conclusion and future perspective:-Obesity and related diseases have exploded in popularity in recent years, and are now widely regarded as the most serious threat to one's well-being and health. Probiotic, has the ability to fight obesity and related metabolic problems. Obese and lean people exhibit different microbiome components, functioning genes, and enzymatic pathways, showing that gut microbiota is important in these phenotypes. The goal of this study was to look at the corpus of research on probiotics' utility in the treatment of obesity. Probiotics have demonstrated weight reduction properties in both human and animal trials, and a number of explanations have been put out to explain the anti-obesity benefits. Prior to today, gastroenterology was unaware of the importance of microflora in disease and metabolic balance. Since the discovery of the role of microflora in the control of bile salts, SCFAs, metabolic endotoxemia, and obesity study has been done in this review. Finally, research relating gut microbiota to host metabolism could lead to the development of new pharmaceutical techniques for treating or preventing obesity based on gut microbiota modulation. But first, a number of issues must be addressed. It's unclear, for example, which microbial species are most responsible for obesity. A single species was positively affected in certain studies, whereas the converse was true in others. Because of the microbiota's complex structure, this could be the case. The next step is to figure out how many of these dietary modulators to take to improve your health. The question of whether they should be the same across all age categories is a contentious issue, and more research is required. The ability to understand the genetic connection between probiotics and the intestinal microbiota through the exchange of genetic material is a vital part of future research. If

we can successfully change probiotic bacteria, we will be able to produce certain advantageous probiotic strains that are vital for human health. There is a need to look into new strategies that affect the gut microbiota in a good way with no side effects.

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