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EXPLORING MICROBIOTA DYNAMICS: FROM TRADITION TO INNOVATION IN HEALTH

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ABSTRACT: The human microbiota, a complex assembly of microorganisms residing in various bodily niches, plays a critical role in health and disease. Historically, traditional medicine implicitly recognized the importance of the microbiota through the use of fermented foods and herbal remedies, which we now understand can influence the gut microbial composition and contribute to a robust immune system and improved metabolic processes. In the contemporary landscape, the role of microbiota has been significantly expanded by modern science. Advancements in genomic and bioinformatics tools have unraveled complex interactions between human health and microbiota, particularly in understanding the impact of modern pharmacological agents. Recent studies have highlighted the dual-edged effects of broad-spectrum antibiotics, which, while combating pathogens, also disrupt commensal microbial communities, potentially leading to dysbiosis and associated health conditions. Furthermore, emerging research into the gut-brain axis suggests profound implications of microbiota management in neurological disorders, signifying a shift towards microbiota-centered therapeutic strategies. This review traces the journey of microbiota research from its historical roots to its current innovations and potential future applications, underscoring its significance in both traditional and modern medical practices. Looking ahead, the future of microbiota research promises revolutionary applications, including the development of microbiota-based diagnostics, personalized probiotic treatments, and engineered bacterial communities capable of precise therapeutic interventions.

INTRODUCTION: The study of human microbiota, encompasses trillions of micro-organisms residing in and on the human body, has become a cornerstone of contemporary biological and medical research. This symbiotic relationship is central to human physiology, influencing everything from metabolic processes to immune system function.

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The traditional usage of microbiota, often mediated through dietary practices and folk medicine, reflects an intuitive understanding of its importance to human health, long before the advent of modern scientific inquiry.

As we advance technologically, this traditional knowledge merges with innovative scientific research to deepen our understanding and application of microbiota dynamics in the promotion of health and the prevention and treatment of diseases. This review aims to explore the evolution of microbiota research from its historical context to its current applications in modern medicine, and to forecast future possibilities that could redefine therapeutic

paradigms. Initially, we investigate into the historical practices that suggest appreciation of the microbiota's role in health, such as the use of fermented food and other traditional medicinal practices across various cultures. We then transition to the present, examining the impacts of modern pharmaceuticals, particularly antibiotics, on the microbiota, illustrating both beneficial and detrimental outcomes. This section also covers how current research leverages cutting-edge technologies like metagenomics and machine learning to decode complex microbiota interactions.

Finally, we project into the future, anticipating innovative approaches that may include microbiota engineering, personalized microbial therapies, and the development of new diagnostic tools that exploit microbiota profiles. Throughout, this review emphasizes the continuous thread from traditional knowledge to innovative practice, illustrating how each era's understanding of microbiota contributes to a holistic view of its potential in advancing human health.

Traditional Practices and Microbiota: Traditional food practices have long recognized the importance of microbial balance for health. Fermented foods have been an integral part of Indian cuisine for centuries and are known for their diverse flavors and health benefits. These foods undergo fermentation by beneficial microorganisms such as bacteria and yeast, which not only enhance their taste but also contribute to their nutritional value and impact on the microbiome. Yogurt is one of the most widely consumed fermented foods in India. It is made by fermenting milk with lactic acid bacteria, primarily Lactobacillus bulgaricus and Streptococcus thermophilus. These bacteria produce lactic acid, which gives yogurt its characteristic tangy flavor. Yogurt is rich in probiotics, which are beneficial bacteria that can help maintain a healthy balance of gut microbiota. Idli and dosa are popular South Indian dishes made from fermented rice and lentil batter. The fermentation process involves soaking rice and lentils, grinding them into a batter, and allowing the batter to ferment overnight. During fermentation, beneficial bacteria such as Lactobacillus spp. proliferate, enhancing the nutritional quality of the batter and making it more easily digestible [1].

Pickles are made by fermenting vegetables or fruits in brine or vinegar. Traditional Indian pickles are typically fermented naturally through the action of lactic acid bacteria present on the vegetables. Dhokla is a savory steamed cake made from fermented batter derived from rice and chickpea flour. The fermentation process involves the growth of lactic acid bacteria, which contribute to the soft, spongy texture and tangy flavor of dhokla [2]. Fecal microbiota transplantation (FMT) offers a promising strategy to restore gut microbiota balance and alleviate chronic pain disorders in traditional chainese population [3].

Kimchi is a traditional Korean fermented vegetable dish, usually made with cabbage, radishes, and a variety of seasonings such as chili pepper, garlic, and ginger. The fermentation process involves lactic acid bacteria, which produce beneficial compounds like vitamins, organic acids, and bioactive compounds [4]. Sauerkraut is a fermented cabbage dish that originated in Germany. It is made by fermenting finely shredded cabbage with salt. Lactic acid bacteria naturally present on the cabbage initiate the fermentation process. Sauerkraut is rich in probiotics and fiber, which can promote digestive health and contribute to a healthy microbiome [5].

Kefir is a fermented milk drink that originated in the Caucasus region. It is made by fermenting milk with kefir grains, which contain a symbiotic culture of yeasts and bacteria. The fermentation process produces a tangy, effervescent beverage rich in probiotics, vitamins, and enzymes [6]. Miso is a traditional Japanese seasoning made by fermenting soybeans with salt and koji and grains like rice or barley. The fermentation process can take weeks to months and involves various microorganisms, including bacteria and fungi. Miso is rich in probiotics, vitamins, and antioxidants [7]. Kombucha is a fermented tea beverage in China. It is made by fermenting sweetened tea with a symbiotic culture of bacteria and yeast (SCOBY). The fermentation process produces a tangy, slightly effervescent drink rich in probiotics, organic acids, and antioxidants [8].

Fasting has a significant role in Indian tradition, culture, and spirituality, with roots in various religious practices such as Hinduism, Jainism, and

Buddhism. In Hinduism, fasting is observed on specific days dedicated to different deities or during religious festivals. Similarly, in Jainism, fasting is a common practice to purify the body and mind and to attain spiritual growth. The Buddhist tradition also includes fasting as a means of self-discipline and mindfulness. During fasting, the host undergoes metabolic adaptations to cope with limited nutrient availability. These adaptations can influence the gut environment, altering factors such as pH, oxygen levels, and nutrient availability, which in turn shape the composition and function of the gut microbiota. For example, fasting may promote the growth of bacteria capable of fermenting complex carbohydrates or producing short-chain fatty acids (SCFAs), which serve as energy sources for the host and contribute to gut health. Several studies have demonstrated that fasting can lead to changes in microbial diversity, with some beneficial effects such as promoting the growth of beneficial bacteria and reducing the abundance of harmful bacteria. Li *et al.*, investigated the effects of periodic fasting on the gut microbiota in mice. The researchers found that intermittent fasting led to alterations in the composition of the gut microbiota, including an increase in the abundance of certain beneficial bacteria such as Lactobacillus species [9]. Effects of time-restricted feeding, a form of intermittent fasting, on the gut microbiota in humans. The researchers observed changes in the gut microbiota composition after time-restricted feeding, with an increase in the abundance of certain bacteria associated with metabolic health [10].

Certain foods contain prebiotic fibers that serve as fuel for beneficial gut bacteria. These foods stimulate the growth of beneficial bacteria such as Bifidobacteria and Lactobacilli, which can help restore gut health during illness. Some foods and herbs possess antimicrobial properties that can help eliminate pathogenic bacteria in the gut, thereby restoring microbial balance. For example, garlic and ginger have antimicrobial properties against a wide range of pathogens, including bacteria, viruses, and fungi. Garlic is traditionally used to support digestion, respiratory health, cardiovascular function, and immune system strength. Its antimicrobial properties have also been recognized in the management of various infections [11]. Onion is used to stimulate digestion, improve appetite, and alleviate respiratory conditions. Its antimicrobial and anti-inflammatory actions are valued in Ayurvedic formulations for combating infections and promoting overall health [12]. Honey is used internally and externally for its wound-healing, antimicrobial, anti-inflammatory, and immunomodulatory effects. It is often combined with other substances to enhance their efficacy and taste [13]. Herbs like *Zingiber officinale, Curcuma longa, Azadirachta indica,* and *Ocimum sanctum* are commonly used for their antimicrobial, anti-inflammatory, and immune-enhancing properties [14]. Traditional Ayurvedic therapies encompass a wide array of practices, including diet, lifestyle modifications, herbal medicine, and therapeutic techniques such as yoga and meditation.

Present Scenario: Impact of Modern Lifestyle Factors: In the contemporary landscape, the microbiota faces new challenges and opportunities. The ketogenic diet, characterized by high fat and low carbohydrate intake, has garnered interest for its potential impact on microbiota composition and metabolic health. Hydration therapy, intermittent fasting, and stress management techniques also play crucial roles in shaping gut microbiota dynamics. Moreover, the quality of sleep has emerged as a determinant of microbial diversity and function, with disruptions linked to dysbiosis and associated health implications.

The ketogenic diet is characterized by a high-fat, moderate-protein, and very low-carbohydrate intake. This drastic alteration in macronutrient composition shifts the body's metabolism from primarily utilizing carbohydrates for energy to relying on fats as the primary fuel source. This metabolic shift can have profound effects on the gut microbiota, as different microbial species thrive on different substrates. Research suggests that the ketogenic diet may increase the abundance of certain beneficial bacteria, such as Akkermansia muciniphila and Bifidobacterium, while reducing the levels of potentially harmful bacteria like Firmicutes and Proteobacteria [15, 16]. Additionally, the ketogenic diet has been associated with an increase in the production of certain short-chain fatty acids (SCFAs), such as acetate and butyrate, which are metabolites produced by gut bacteria and have important metabolic and immunomodulatory effects. The ketogenic diet alters the availability of

substrates for microbial metabolism in the gut. With limited carbohydrate intake, gut bacteria metabolize dietary and host-derived fats and proteins as energy sources, leading to changes in microbial metabolic pathways. These metabolic shifts can influence the production of metabolites such as short-chain fatty acids, which play roles in host metabolism and immune function [17]. Studies suggest that the ketogenic diet may have beneficial effects on gut barrier function. By reducing carbohydrate intake and stabilizing blood glucose levels, the ketogenic diet can mitigate inflammation and oxidative stress in the gut mucosa, thereby preserving gut barrier integrity and reducing intestinal permeability [18]. The ketogenic diet is known for its metabolic effects, including promoting weight loss, improving insulin sensitivity, and enhancing lipid metabolism. These metabolic changes are influenced by interactions between the gut microbiota, host metabolism, and dietary components. Emerging evidence suggests that the gut microbiota may mediate some of the metabolic benefits associated with the ketogenic diet [19]. The ketogenic diet has been shown to reduce markers of inflammation and oxidative stress, which are implicated in the pathogenesis of metabolic diseases. By modulating gut microbiota composition and metabolism, the ketogenic diet may attenuate inflammatory responses and oxidative damage in the gut and systemic circulation [20].

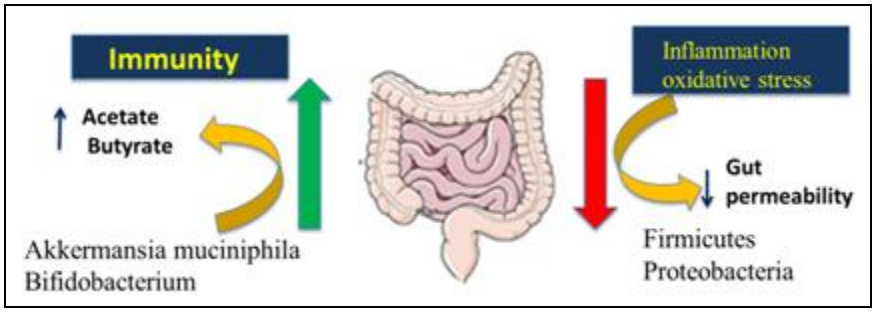

FIG. 1: EFFECT OF KETODIET ON MICRO BIOTA- KETO DIET STIMULATE IMMUNITY BY INCREASING STRAINS SUCH AS AKKERMANSIA AND DECREASE INFLAMMATION BY DECREASING FIRMICUTES

Hydration therapy, which typically involves administration of fluids, electrolytes, and vitamins and minerals, primarily aims to replenish fluids and restore electrolyte balance in the body. Dehydration can increase gut permeability, which allows toxins and harmful substances to pass through the intestinal barrier and enter the bloodstream. Adequate hydration is crucial for maintaining gut health and proper digestive function. Hydration therapy can help optimize hydration status, ensuring sufficient water content in the gut for microbial growth and metabolism. Proper hydration supports gut motility and the transport of nutrients to gut bacteria, which can indirectly influence microbial composition[21].Hydration therapy often includes electrolytes such as sodium, potassium, and chloride, which are essential for various physiological processes, including gut function. Electrolytes play roles in maintaining osmotic balance, fluid secretion, and nerve signaling in the gut, which can indirectly impact microbial communities [22]. Hydration therapy may influence intestinal permeability and preventing the translocation of bacteria and toxins across the intestinal barrier. This could indirectly affect microbial composition by reducing systemic inflammation and maintaining gut barrier function [23]. Adequate hydration can help maintain mucosal immune homeostasis, supporting the production of antimicrobial peptides and immunoglobulins that shape microbial composition [24].

Intermittent fasting (IF), involves cycling between periods of eating and fasting, has been shown to impact microbiota composition. Studies suggest that intermittent fasting may promote microbial diversity by creating fluctuations in nutrient availability and energy intake, which can influence microbial community structure [25]. For example, fasting periods may result in an increase in the abundance of certain beneficial bacteria, such as *Akkermansia muciniphila*, which has been associated with improved metabolic health. Conversely, fasting may decrease the abundance of certain pathogenic bacteria, such as Firmicutes species, which are associated with obesity and

metabolic dysfunction. For example, research has shown that intermittent fasting can increase the abundance of certain beneficial bacteria, such as Lactobacillus and Bifidobacterium, while decreasing the abundance of potentially harmful bacteria [26]. Intermittent fasting can influence microbial metabolism in the gut, leading to changes in the production of metabolites such as short-chain fatty acids (SCFAs). SCFAs, which are produced by gut bacteria through the fermentation of dietary fibers, play a key role in gut health and metabolic homeostasis. Intermittent fasting may promote the production of SCFAs, particularly butyrate, which has been shown to have anti-inflammatory and metabolic benefits. Studies have indicated that intermittent fasting can enhance intestinal barrier integrity by reducing gut permeability. This can help prevent the translocation of harmful bacteria and toxins from the gut lumen into the bloodstream, thereby reducing systemic inflammation and maintaining microbial balance [27]. Intermittent fasting has been shown to improve glucose regulation, insulin sensitivity, and lipid metabolism, all of which can impact the gut environment and microbial communities [28]. Intermittent fasting can promote immune homeostasis by regulating inflammatory responses and enhancing immune cell function. These immune-modulatory effects may contribute to the maintenance of a healthy gut microbiota [29].

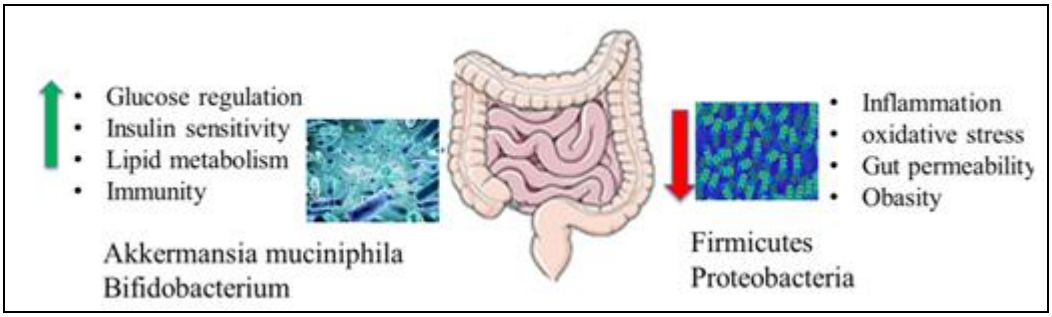

FIG. 2: EFFECT OF INTERNMENT FASTING ON MICROBIOTA- IT INCREASES THE GLUCOSE REGULATION, INSULIN SENSITIVITY AND DECREASES OXIDATIVE STRESS

Stress can have significant effects on microbiota composition through complex interactions between the brain, gut, and microbiota, often referred to as the gut-brain axis. Severe stress has been associated with reduced microbial diversity compared to those with lower stress levels [30].

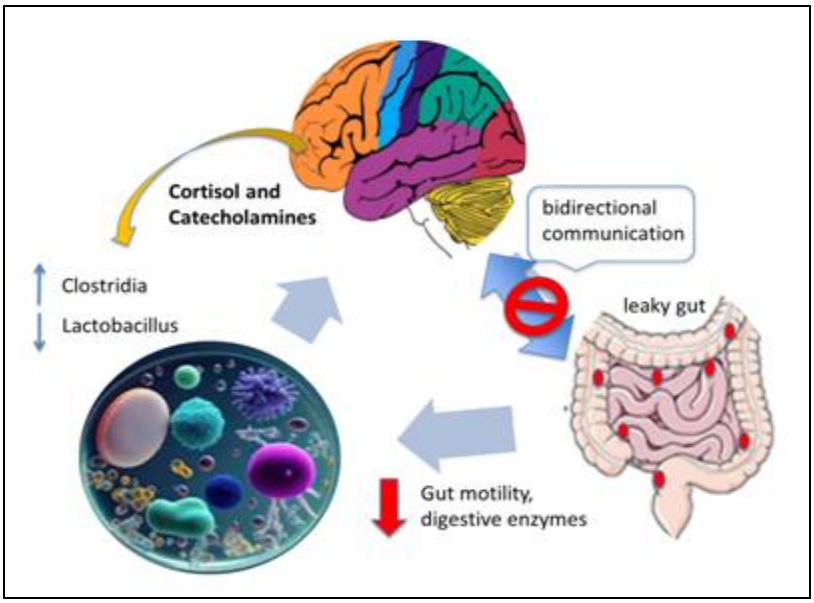

FIG. 3: ROLE OF STRESS ON MICROBIOTA- STRESS INHIBIT BIDIRECTIONAL COMMUNICATION, DECREASES GUT MOTILITY AND ENZYME SECRETION

Stress can lead to alterations in the relative abundance of specific bacterial taxa in the gut. For example, a study by Jiang *et al.* found that stress-induced alterations in gut microbiota composition

were characterized by an increase in the abundance of potentially pathogenic bacteria such as Clostridia and a decrease in beneficial bacteria such as Lactobacillus [31]. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of stress hormones such as cortisol and catecholamine. These stress hormones can directly or indirectly influence microbial composition and function through neuroendocrine signaling pathways. Stress affects the bidirectional communication between the gut and the brain, known as the gut-brain axis. Changes in stress levels can influence gut motility, secretion of digestive enzymes, and gut permeability, which in turn can impact microbial composition and function [32]. Stress can influence dietary habits and food choices, leading to changes in nutrient intake and substrate availability for gut microbes. Stress-induced alterations in diet may favor the growth of certain microbial taxa over others, contributing to shifts in microbiota composition. The gut microbiota plays a crucial role in regulating immune responses, and disruptions in microbial composition can lead to immune dysfunction, inflammation, and increased susceptibility to infections [33].

Alcohol and smoking can both have significant effects on microbiota composition in the gut. Chronic alcohol consumption has been associated with alterations in gut microbiota composition, including reductions in microbial diversity. Chronic alcohol consumption has been associated with reduced microbial diversity in the gut. Studies have shown that individuals with alcohol use disorder or chronic heavy alcohol consumption tend to have lower microbial diversity compared to non-drinkers or moderate drinkers [34]. Alcohol consumption can lead to alterations in the relative abundance of specific bacterial taxa in the gut. For example, a study by Mutlu *et al*. found that alcoholics had higher levels of potentially pathogenic bacteria such as Enterobacteriaceae and lower levels of beneficial bacteria such as Lactobacillus compared to non-alcoholic controls [35]. Alcohol consumption can compromise gut barrier function, leading to increased gut permeability or "leaky gut." This allows bacterial products to translocate from the gut lumen into the bloodstream, triggering systemic inflammation and altering microbial composition [36]. Smoking has also been associated with reduced microbial diversity in the gut. Studies have shown that smokers tend to have lower microbial diversity compared to non-smokers, and this reduction in diversity may persist even after smoking cessation [37]. Smoking can lead to alterations in the relative abundance of specific bacterial taxa in the gut. For example, a study by Biedermann *et al.* found that smokers had higher levels of potentially pathogenic bacteria such as *Fusobacterium nucleatum* and lower levels of beneficial bacteria such as Bifidobacterium compared to non-smokers. Smoking can modulate immune responses in the gut, associated with increased gut inflammation and alterations in immune cell populations in the gut mucosa [38].

An active lifestyle can have significant effects on microbiota composition, positively influencing gut health. Regular physical activity has been shown to stimulate gut motility, aiding in the movement of food and waste through the digestive tract. Enhanced gut motility can contribute to a healthier gut environment by reducing transit time, promoting regular bowel movements, and preventing bacterial overgrowth. Regular physical activity has been associated with increased microbial diversity in the gut. Studies have shown that individuals with higher levels of physical activity tend to have a more diverse gut microbiota compared to sedentary individuals. Increased microbial diversity is often associated with improved metabolic health and reduced risk of various diseases [39]. Physical activity can also lead to changes in the relative abundance of specific bacterial taxa in the gut. For example, a study by Allen et al. found that athletes had higher levels of certain beneficial bacteria, such as Veillonella and Akkermansia, compared to sedentary individuals. These bacteria are known to play roles in enhancing exercise performance and metabolic health [40]. Regular physical activity has been shown to improve gut barrier function, reducing intestinal leaky gut. A healthy gut barrier is essential for preventing the translocation of harmful bacteria and toxins from the gut lumen into the bloodstream, which can trigger inflammation and contribute to various health conditions [41]. Exercise has immunomodulatory effects and can enhance immune function. Studies have shown that regular physical activity can promote a more balanced immune response and reduce inflammation in the

gut. This can help maintain a healthy balance of gut microbiota and reduce the risk of inflammatory diseases [42]. An active lifestyle is associated with improved metabolic health, including better glucose regulation and insulin sensitivity. These metabolic changes can also influence the composition and function of the gut microbiota, creating an environment that is more conducive to the growth of beneficial bacteria and less hospitable to pathogenic species [43].

Sleep plays a crucial role in regulating the composition and function of the gut microbiome through various mechanisms. The gut microbiome follows a circadian rhythm, with microbial composition and activity fluctuating over a 24-hour period. Disruptions to the sleep-wake cycle, such as irregular sleep patterns or shift work, can disrupt circadian rhythms in the gut microbiome, leading to alterations in microbial composition and function. Sleep deprivation has been shown to affect gut motility and transit time, leading to changes in microbial composition. Studies have shown that sleep disturbances, such as insufficient sleep duration or poor sleep quality, can lead to alterations in gut microbiome composition.

For example, a study by Liang *et al.* found that sleep deprivation in mice resulted in changes in the relative abundance of specific bacterial taxa in the gut, including reductions in beneficial bacteria such as Lactobacillus and increases in potentially pathogenic bacteria [44]. Sleep disturbances have been associated with decreased microbial diversity in the gut. Reduced microbial diversity is often linked to dysbiosis and an increased risk of various health conditions, including obesity, metabolic syndrome, and inflammatory bowel diseases [45].

Sleep is closely linked to the gut-brain axis, a bidirectional communication system between the gut and the central nervous system. These changes may contribute to mood disorders, cognitive impairment, and other neurological conditions [46]. Adequate sleep is essential for maintaining a healthy immune system, and the gut microbiome plays a crucial role in immune function. Sleep disturbances can impair immune function and alter the balance of immune cells in the gut, leading to dysregulation of the gut microbiome and increased susceptibility to infections and inflammatory diseases [47].

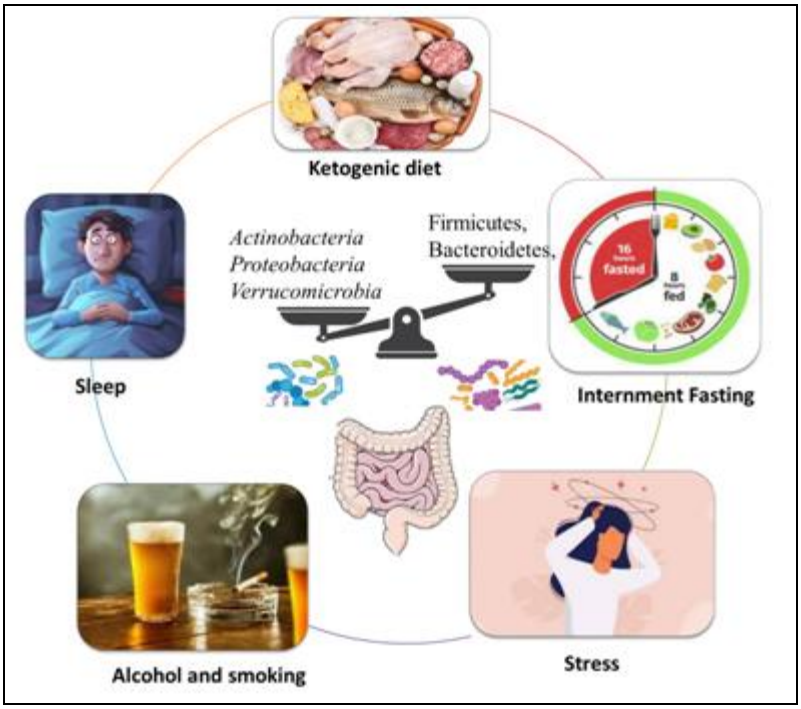

FIG. 4: LIFESTYLE FACTORS SUCH AS SMOKING AND ALCOHOL CONSUMPTION, LACK OF SLEEP, HIGH FAT DIET, STRESS AND FASTING IMPACTS THE COMPOSITION OF MICROBIOTA

Chronic Drug Administration: The widespread use of pharmaceuticals presents another dimension to microbiota modulation. Chronic administration of drugs, such as antibiotics, proton pump

inhibitors, and non-steroidal anti-inflammatory drugs, can disrupt microbial communities, leading to dysbiosis and potential adverse effects on health. In a recent government survey reported in the Data Point article revealed that a significant proportion of hospitalized patients in India are administered multiple antibiotics, over 55% of these antibiotic prescriptions are categorized under the "Watch" group by the World Health Organization (WHO), indicating these medications should be reserved for severe infections only. Resistance rates for several antibiotic-bacterium combinations exceed 75%, indicating a dire public health concern. Specifically, resistance to the ceftriaxone antibiotic in infections caused by *Klebsiella pneumoniae* is particularly high, with 87.4% of such cases showing resistance.

Effect of Antibiotics on Cmposition and Functions of Microbiota: Antibiotics exert selective pressure on microbial communities, killing susceptible bacteria while allowing resistant strains to proliferate. It can reduce microbial diversity in the gut, as they target a broad spectrum of bacteria, including both pathogenic and commensal species. This disruption can lead to alterations in gut microbial composition and diversity. Studies have shown that chronic antibiotic use is associated with decreased microbial diversity and changes in the relative abundance of specific taxa [48, 49]. Antibiotic-induced changes in gut microbiota can also affect host physiology. Disruption of microbial equilibrium may impair important functions of the gut microbiota, such as nutrient metabolism, immune modulation, and maintenance of gut barrier integrity. These changes can contribute to various health conditions, including metabolic disorders, autoimmune diseases, and gastrointestinal disorders [50, 51]. Antibiotics can compromise gut barrier function, leading to increased gut permeability. This allows bacterial products to translocate from the gut lumen into the bloodstream, triggering systemic inflammation and altering microbial composition [52]. SCFAs play important roles in gut health, immune regulation, and metabolic homeostasis. Dysbiosis-induced alterations in SCFA production may contribute to metabolic disorders such as obesity and insulin resistance. Antibiotic-induced dysbiosis can create an environment conducive to the overgrowth of opportunistic pathogens, increasing the risk of gastrointestinal infections such as Clostridium difficile infection (CDI). CDI is a serious and potentially life-threatening condition that commonly occurs following antibiotic treatment. Changes in microbial composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [53]. Chronic antibiotic use can drive the selection of antibiotic-resistant bacteria in the gut microbiota. This can have serious implications for public health, as antibiotic-resistant bacteria may spread within the community and contribute to the global problem of antibiotic resistance [54]. Chronic antibiotic administration has been associated with various long-term health consequences, including increased risk of infections, metabolic disorders, inflammatory bowel disease, and allergic conditions [55].

Proton Pump Inhibitors: Chronic administration of proton pump inhibitors (PPIs), commonly used to treat conditions such as gastro esophageal reflux disease and peptic ulcer disease, can perturb microbial equilibrium in the gut, leading to dysbiosis and potential health consequences. PPIs work by inhibiting the proton pumps in the stomach, reducing the production of gastric acid. While this is beneficial for treating conditions related to excess stomach acid, it can also alter the pH environment in the upper gastrointestinal tract. Changes in gastric pH can impact the survival and growth of bacteria ingested with food, leading to alterations in microbial composition. For example, a study by Jackson *et al.* found that PPI use was associated with changes in gut microbiota diversity and composition, including reductions in bacterial richness and changes in the relative abundance of specific taxa [56]. Similarly, another study by Imhann et al. observed alterations in gut microbiota composition in patients treated with PPIs [57]. PPI-induced changes in gastric acidity can create an environment that promotes dysbiosis by altering microbial survival and growth conditions in the gut [58]. This can allow bacterial products to translocate from the gut lumen into the bloodstream, triggering systemic inflammation and altering microbial composition [59]. The gut microbiota plays a crucial role in regulating immune responses, and dysbiosis resulting from PPI administration can dysregulate immune function. Changes in microbial

composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [60]. PPIs can affect nutrient absorption and metabolism in the gut, which may indirectly influence microbial composition and function. Changes in dietary habits, nutrient availability, and gastrointestinal transit time can impact microbial equilibrium and contribute to dysbiosis [61]. PPIs are known to cause gastrointestinal side effects such as dyspepsia, gastric ulcers, and gastrointestinal bleeding. These side effects can disrupt gut motility, alter nutrient absorption, and create opportunities for dysbiosis [62].

NSAIDs: Chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) can perturb microbial equilibrium in the gut, leading to dysbiosis and potential health consequences. NSAIDs have been shown to directly impact gut microbial composition. For example, a study by Rogers et al. demonstrated that chronic NSAID use was associated with alterations in gut microbiota diversity and composition, including reductions in bacterial richness and changes in the relative abundance of specific taxa [63]. Similarly, another study by Jackson *et al.* found that NSAID use was associated with dysbiosis, characterized by decreased microbial diversity and altered microbial composition [64]. NSAIDs can also exert indirect effects on gut microbiota through alterations in host physiology. For instance, NSAID-induced changes in gut barrier function, intestinal motility, and mucosal immunity can create an environment that promotes dysbiosis [65]. Inflammatory bowel disease may result from dysfunction of the intestinal mucosal barrier and dysregulation of the gut microbiota. Probiotics aid in the targeted delivery and retention of biocompatible artificial enzymes, enabling persistent scavenging of elevated reactive oxygen species and reducing inflammatory factors [66]. The gut microbiota plays a crucial role in regulating immune responses, and dysbiosis resulting from NSAID administration can dysregulate immune function. Changes in microbial composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [67]. NSAIDs can affect nutrient absorption and metabolism in the gut, which may indirectly influence microbial composition and function. Changes in dietary habits, nutrient availability, and gastrointestinal transit time can impact microbial equilibrium and contribute to dysbiosis [68]. NSAIDs are known to cause gastrointestinal side effects such as dyspepsia, gastric ulcers, and gastrointestinal bleeding. These side effects can disrupt gut motility, alter nutrient absorption, and create opportunities for dysbiosis [69]. Substantial evidence shows that gut microbiota plays a crucial role in modulating chronic pain, opening new avenues for understanding its pathogenesis. The gut microbiota acts as a key interface between the neuroimmune-endocrine and microbiome-gut-brain axes, influencing chronic pain directly or indirectly. Signalling molecules like metabolites, neuromodulators, neuropeptides, and neurotransmitters regulate chronic pain by modulating peripheral and central sensitization through specific receptors. Dysbiosis of the gut microbiota has been linked to various chronic pain conditions, including visceral pain, neuropathic pain, inflammatory pain, migraine, and fibromyalgia. Faecal microbiota transplantation (FMT) offers a promising strategy to restore gut microbiota balance and alleviate chronic pain disorders[79].

Anti-diabetic Drugs: Chronic administration of diabetic drugs can indeed perturb microbial equilibrium in the gut, potentially leading to dysbiosis and various health consequences. Metformin and sulfonylureas, have been associated with alterations in gut microbiota composition. Metformin, for example, has been shown to reduce the abundance of certain beneficial bacteria such as *Akkermansia muciniphila*, while increasing the abundance of opportunistic pathogens [70], a study by Lee *et al.* observed alterations in gut microbiota composition in patients treated with sulfonylureas [71]. Diabetic drugs can also exert indirect effects on gut microbiota through alterations in host physiology. For example, changes in gut barrier function, glucose metabolism, and immune responses induced by diabetic medications can influence microbial composition and function [72]. Diabetic drugs may impact microbial metabolism in the gut, leading to alterations in the production of metabolites such as SCFAs. SCFAs play important roles in gut health, immune regulation, and metabolic homeostasis. Dysbiosis-induced alterations in SCFA production may contribute to

gastrointestinal disorders and metabolic dysfunction. This can allow bacterial products to translocate from the gut lumen into the bloodstream, triggering systemic inflammation and altering microbial composition [73]. The gut microbial ecosystem influences obesity through various mechanisms, leading to downstream metabolic effects, including changes in systemic inflammation, immune responses, energy harvest, and the gut-host interface. Metabolomics, the systematic study of low-molecular-weight molecules involved in metabolic pathways, provides a valuable approach for understanding the interplay between host metabolism and gut microbiota [74]. The gut microbiota plays a crucial role in regulating immune responses, and dysbiosis resulting from diabetic drug administration can dysregulate immune function. Changes in microbial composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [75]. Diabetic drugs can affect nutrient absorption and metabolism in the gut, which may indirectly influence microbial composition and function. Changes in dietary habits, nutrient availability, and gastrointestinal transit time can impact microbial equilibrium and contribute to dysbiosis [76]. Many diabetic medications can cause gastrointestinal side effects such as diarrhea, constipation, or dyspepsia. These side effects can disrupt gut motility, alter nutrient absorption, and create opportunities for dysbiosis [77]. Research indicates that changes in gut microbiota and metabolites are pivotal in the pathophysiology of immunoglobulin nephropathy. Clinical validation using faecal samples suggests that Actinobacteria may be linked to the onset and poorer prognosis of this condition [78].

Anti-hypertension Drugs: Chronic administration of hypertension drugs potentially leading to dysbiosis and various health consequences. Some hypertension medications, particularly certain classes of antihypertensive drugs such as ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers, have been associated with alterations in gut microbiota composition [80]. Similarly, a study by Kikuchi *et al.* reported alterations in gut microbial composition in patients treated with calcium channel blockers (Kikuchi *et al.*, 2019). Hypertension drugs may influence microbial metabolism in the gut, leading to alterations in the production of metabolites such as SCFAs and trimethylamine N-oxide. Dysbiosis-induced alterations in SCFA and TMAO production may contribute to gastrointestinal disorders and metabolic dysfunction. Hypertension drugs can also exert indirect effects on gut microbiota through alterations in host physiology. For instance, changes in gut barrier function and intestinal motility induced by hypertension medications can create an environment that promotes dysbiosis[45].Changes in microbial composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [81]. Hypertension drugs can affect nutrient absorption and metabolism in the gut, which may indirectly influence microbial composition and function. Changes in dietary habits, nutrient availability, and gastrointestinal transit time can impact microbial equilibrium and contribute to dysbiosis [82]. Many hypertension medications can cause gastrointestinal side effects such as constipation, diarrhea, or dyspepsia. These side effects can disrupt gut motility, alter nutrient absorption, and create opportunities for dysbiosis [45].

Anticancer Drugs: Certain cancer drugs, particularly chemotherapy agents and targeted therapies, have been shown to directly impact gut microbial composition. For example, studies have demonstrated alterations in gut microbiota diversity and abundance following chemotherapy treatment [83]. Additionally, targeted therapies such as tyrosine kinase inhibitors have been associated with changes in gut microbiota composition and function [84]. Cancer drugs can also exert indirect effects on gut microbiota through alterations in host physiology. For instance, chemotherapy-induced gastrointestinal toxicity, such as mucositis or diarrhea, can disrupt the gut environment and create opportunities for dysbiosis [85]. Some cancer drugs may compromise gut barrier function, leading to increased gut permeability. This allows bacterial products to translocate from the gut lumen into the bloodstream, triggering systemic inflammation and altering microbial composition [86]. Metabolites derived from gut microbiota serve as critical links between the gut microbiome and cancer progression by reshaping the tumor microenvironment and modulating key signaling pathways in cancer and immune cells.

Synthetic biology approaches targeting genes involved in microbial metabolism can directly influence microbial metabolite levels, while strategies such as fecal microbial transplantation and phage therapy alter metabolite levels indirectly by modifying the microbiome composition [87]. Chemotherapy induced alterations in microbial composition may affect immune cell populations and cytokine production in the gut, leading to inflammation and immune dysfunction [88]. Cancer drugs can affect nutrient absorption and metabolism in the gut, which may indirectly influence microbial composition and function. Changes in dietary habits, nutrient availability, and gastrointestinal transit time can impact microbial equilibrium and contribute to dysbiosis [45]. drugs, particularly immunosuppressive agents used in chemotherapy, can increase the risk of gastrointestinal infections. Dysbiosis resulting from cancer drug administration may create an environment conducive to the overgrowth of opportunistic pathogens, further increasing the risk of infections and complications [89].

TABLE 1: ANTICANCER ANTIBIOTICS PRODUCING MICROORGANISM AND ITS MEDIA REQUIREMENTS

Antibiotic	Micro-organism	Culture maintenance
Bleomycin	Streptomyces verticillus	The spores of Streptomyces verticillus can be preserved on ISP4 solid medium. ISP4 solid medium contains 0.5 g/L yeast extract and 1 g/L tryptone
Mitomycin	Streptomyces caespitosus / Streptomyces lavendulae.	Streptomyces caespitosus can grow in YEME liquid medium containing glycine.
Dactinomycin	Streptomyces strains	Most Streptomyces species sporulate well on the Oatmeal-agar, MYM-agar, ISP4-agar.
Daunorubicin	Streptomyces peucetius subsp. caesius	R2YE medium: Used for inoculating peucetius strains. APM production medium: Used after two days of growth in R2YE medium. ISP4 medium: Used for growing S. peucetius strains. R2YE agar medium: Used for transformation experiments.
Doxorubicin	Streptomyces peucetius	NDYE medium
Plicamycin	Streptomyces plicatus	Buffered culture medium (pH 8.0) containing chitin, sucrose, and calcium nitrate as carbon and nitrogen sources.
Dactinomycin	Streptomyces strains.	Most Streptomyces species sporulate well on the following media: Oatmeal-agar, MYM-agar, ISP4-agar.

Antipsychotics Drugs: Chronic administration of psychotropic drugs can perturb microbial equilibrium in the gut through various mechanisms, including direct effects on gut microbiota composition, alterations in gut-brain axis signaling, immune modulation, changes in nutrient absorption and metabolism, and gastrointestinal side effects. Psychotropic medications, such as antidepressants and antipsychotics, have been shown to directly impact gut microbial composition [90]. Jiang *et al.* found that chronic treatment with fluoxetine, a commonly prescribed antidepressant, led to changes in gut microbial composition in mice, including reductions in Lactobacillus and Bifidobacterium species. Stress-induced alterations in the gut microbiota have been reported in both animal and human studies [91]. The study by Chen et al. demonstrated that Actinobacteria, Bifidobacterium, and Ruminococcus have a protective effect, while Streptococcaceae may have a potentially anti-protective role in the pathogenesis of major depressive disorder [92]. Dysbiosis resulting from psychotropic drug administration may disrupt the gut-brain axis, affecting neurotransmitter production, immune responses, and neuroinflammation in the gut. The gut microbiota has been implicated in various psychiatric disorders, and alterations in microbial composition have been associated with changes in mood and behavior [93]. The gut microbiota plays a crucial role in regulating immune responses, and alterations in microbial composition have been linked to immune dysfunction and inflammatory conditions [94]. Many psychotropic medications can cause gastrointestinal side effects, such as constipation, diarrhea, or dyspepsia, which can disrupt gut microbiota composition and function. Gastrointestinal disturbances induced by psychotropic drugs may alter gut motility, nutrient absorption, and create opportunities for dysbiosis [95].

Future Perspectives: Harnessing Microbiota for Metabolic Health: Harnessing the microbiota for metabolic health represents a promising avenue for

future research and therapeutic interventions. Advances in microbiome sequencing technologies and computational analysis techniques are enabling the development of precision microbiome therapeutics. Personalized interventions targeting specific microbial taxa or metabolic pathways could be tailored to individual patients based on their unique microbiome composition and metabolic profile.

The gut microbiota composition has been linked to various metabolic disorders, including obesity, type 2 diabetes, and metabolic syndrome. Future developments in microbiota-based diagnostics could leverage this association to develop non-invasive biomarkers for early detection, risk stratification, and monitoring of metabolic health. Strategies aimed at modulating the gut microbiota composition and function hold promise for improving metabolic health. This may include dietary interventions, prebiotic and probiotic supplementation, fecal microbiota transplantation (FMT), microbial metabolite supplementation, and microbial gene editing techniques.

Synthetic biology approaches could be employed to engineer microbial consortia with specific metabolic functions tailored for improving metabolic health. This could involve designing probiotic strains with enhanced capacity for producing beneficial metabolites such as short-chain fatty acids (SCFAs) or engineering commensal bacteria to deliver therapeutic payloads to the gut. Future research efforts may focus on identifying key microbial metabolites involved in metabolic regulation, elucidating their mechanisms of action, and exploring their therapeutic potential. Personalized recommendations tailored to an individual's microbiome composition and metabolic profile could optimize the efficacy of these interventions. Translating microbiota-based therapies from preclinical research to clinical practice will require rigorous evaluation in well-designed clinical trials. Large-scale longitudinal studies are needed to establish the safety, efficacy, and long-term effects of microbiota-based interventions for metabolic health. Looking ahead, the future holds promise for leveraging microbiotabased interventions in the management of metabolic diseases. Innovations in microbiome research, coupled with advances in precision medicine, offer novel strategies for personalized interventions aimed at restoring microbial balance. From targeted dietary interventions to the development of microbial therapeutics, the potential for drug-free treatments rooted in microbiota modulation is vast.

CONCLUSION: This review underscores the intricate relationship between traditional practices, modern lifestyle factors, medical interventions, and the microbiota. By understanding and harnessing these interactions, we stand poised to unlock new avenues for promoting health and well-being through microbiota-centric approaches. From the past to the present and into the future, the journey towards enriching microbiota for a healthy life continues to unfold, offering hope for transformative advancements in healthcare.

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