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RELEVANCE OF GUT MICROBIOTA IN HEALTH, DISEASE AND PRODUCTION OF ANTIMICROBIAL SUBSTANCES

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ABSTRACT

Gut microbiota is the collection of bacteria that inhabit in the gastrointestinal tract producing a diverse ecosystem about 10^{14} microorganisms. The majority of the gut microbiota is composed of five *phyla*, namely *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Cerrucomicrobia*, in which the relative abundance of *Bacteroidetes* and *Firmicutes phyla* is >90%. Numerous diseases are associated with an imbalance in gut microbiota communities, including obesity, type 2 diabetes mellitus, cancer, immune system dysfunction, depression and cardiovascular diseases. The immune system–microbiota alliance allows the induction of protective responses to pathogens and the maintenance of regulatory pathways involved in the innocuous antigens tolerance. The human microbiome gut (HMG) is modulated with prebiotics, probiotics, and postbiotics to potentially aid in diseases treatment. HMG can metabolize not only a variety of chemical synthesis drugs but also many natural products and can be represented as an appropriate ‘druggable’ target. Gut Microbiota intestinal flora could be considered as a new drug target to provide new opportunities for exploring the host-microbiome relationship to develop more effective and safer therapies.

KEYWORDS: Human Gut microbiota, probiotics, diseases, bacteriocin, antimicrobials, druggable’ target.

INTRODUCTION

The relationship between gut microbiota and human diseases has been a major topic of interest for many studies. Microbes that reside in the human gut are key contributors to host metabolism and are considered potential sources of novel therapeutics.[1] The human

microbiome represents an excellent example of such an environmental niche and contains trillions of microorganisms that have co-evolved with the human host, leading to the view that humans can be considered to be super-organisms, constituted by a vast number of symbiotic relationships.[2] It has been demonstrated that the small intestine is of central importance to digestion, nutrient absorption, and immune function, and characterizing its microbial populations is essential for elucidating their roles in human health and disease.[3] Increasing evidence has suggested that gut microbiota plays an important role in diseases[4], including obesity[5,6], type 2 diabetes mellitus (T2DM)[7], cancer[8] and cardiovascular diseases[9], that have been started to be associated with an imbalance in gut microbiota communities.[10,11] Many studies indicated that obesity is associated with a decrease in the number of *Bacteroidetes* and an increase in the number of *Firmicutes*, with the intestinal microbiome of an obese person being less diverse than that of a lean person.[12] In other hand, Gut microbiota can be part of the tumor microenvironment, communicates with tumor cells, and some immune cells, and may be the key factor in the process of High fat diet (HFD)-induced cancer progression.[13, 14] Due to the advent of genetic tools and the metagenomic revolution of the last 15 years that we are now able to characterize the composition and function of microbiomes from different parts of the body and link them to potential diseases, risks or even to the clear onset of clinical symptoms.[15] The composition of the microbiota is largely defined by nutrient requirements of individual bacteria and highly variable at different locations of the intestinal tract.[1] The gut microbiome acts as a barrier against harmful microbes by means of competition for nutrients and ecological binding site occupancies and production of antimicrobial substances.[16] Garcia-Gutierrez et al.[2] reported that gut enabled the development of novel antimicrobials compounds that serve as alternatives to antibiotics (Table 1) and thereby help to prevent antimicrobial resistance. The human microbiota plays an important role in maintaining colonization resistance to multidrug-resistant pathogens and a number of innovative microbiota-based strategies for the prevention of infection with multidrug-resistant bacteria are currently in development.[17] The gastrointestinal (GI) tract is especially suitable for finding novel antimicrobials compounds due to the vast array of microbes that inhabit it and based on the density and diversity of microbial populations present in the gut, it may represent a source of non-ribosomal peptides (NRPs)[18, 19] and ribosomal peptides (bacteriocin) producers.[20, 21] In particular, bacteriocin, address some of the problems described for traditional antibiotics and that is why their range of applications is expanding towards human and veterinary therapeutics development.[22] In the present review, the impact of human gut specific bacteria on host metabolism, human diseases, innate

immune system and as potential sources of novel antimicrobial therapeutics will be discussed.

1. Importance of gut microbiota in obesity

The gut microbiota is now considered as one of the most important environmental factors impacting on host physiology and metabolism. Obesity is a worldwide epidemiologic syndrome and multi-factorial disease characterized by an excessive fat mass accumulation of adipose tissue, mainly visceral fat. Gut microbiota protects gastrointestinal mucosa permeability and control the fermentation and absorption of dietary carbohydrates, which explain its importance in the regulation of fat accumulation and the resultant obesity.[23] Gut microbiota can influence energy extraction from food, lipid metabolism and its profile has shown to differ between obese and lean subjects.[24] Several genetic, metabolic, and inflammatory pathophysiological mechanisms are involved in the interplay between gut microbes and obesity for both in infancy and in adults. Microbial changes in the human gut can be considered a factor involved in obesity development in humans. The modulation of the bacterial strains in the digestive tract can help to reshape the metabolic profile in the human obese host.[25]

Obese patients have a lesser diversity and richness in the bacterial component of gut microbiota than eutrophic subjects[5] and remarkably obese humans showed an increased Firmicutes/Bacteroidetes ratio in the fecal microbiota.[26] The association between the gut microbiota and obesity has been observed in humans. In overweight/obese humans, low fecal bacterial diversity is associated with more marked overall adiposity and dyslipidemia.[27]

Most of bacteria inhabiting the human intestine may be prominent in the genesis of obesity and other non-communicable chronic diseases, such as T2 Diabetes (T2D) and atherosclerosis.[28] Muscogiuri et al.[23] reported that the obesity pathogenesis is mostly related to a high abundance of bacteria that ferment carbohydrates, leading to increased rates of short-chain fatty acid biosynthesis, providing an extra source of energy for the host body that is eventually stored as lipids or glucose.[23] Numerous studies have also shown that endocannabinoid system (ESC) activity is involved in the control of glucose and energy metabolism, and can be tuned up or down by specific gut microbes as *Akkermansia muciniphila*.[29]

It has been demonstrated that dysbiosis, or an imbalance in the microbial community, can initiate a cascade of metabolic disturbances in the host. As known, diet has the potential to balance gut microbiota which is as an important player in body weight regulation and the effective dietary therapeutic strategies (Table 2), such as prebiotics, prebiotics/probiotics and other targeted interventions could contribute to improve health in the body host.[30]

In fact, the majority of the research underlines the role of probiotics and prebiotics for obesity management. The positively altering in the gut microbiota from early life onwards could reduce the burden of obesity worldwide.[31, 32] It has been shows supplementation of overweight and obese adults with lactobacilli and bifidobacteria (Bifidobacterium) reduces bodyweight and improves well-being.[33] Wang et al.[34] reported that *Lactobacillus rhamnosus* I-3690 (renamed as *Lacticaseibacillus rhamnosus)* or *Bifidobacterium animalis* subsp. *lactis* I-2494 (*B. animalis* subsp. *lactis* I-2494) significantly attenuated high-fat diet (HFD)-induced weight gain despite no reductions in food intake in mice. Remarkably, Yoo et al.[35] showed that probiotic supplementation with *Lactobacillus curvatus* HY7601 in combination with *Lactobacillus plantarum* KY1032, newly *Lactiplantibacillus plantarum* KY1032 (species renamed *Lactiplantibacillus plantarum),* effectively suppressed body weight gain and reduced the adipose tissue weight in mice fed a high-fat high-cholesterol diet for 9 weeks.

2. Importance of Gut microbiota in Type 2 Diabetes (T2D)

Type 2 Diabetes (T2D) is a metabolic disease that results mostly from obesity-linked insulin resistance and is considered also as a major risk factor for heart disease and stroke. Most of bacteria inhabiting the human intestine may be prominent in the genesis of non-communicable chronic diseases, such as T2D.[28] It has been demonstrated that the alteration of the gut microbial composition in T2D patients could destroy the gut microbiota balance, leading to functional dysbiosis and an increase in the susceptibility of a host to diabetes.[36] The gut microbiome dysbiosis may reshape intestinal barrier functions and host metabolic and signalling pathways, which are directly or indirectly related to the insulin resistance in T2D. The metabolites derived from gut microbes interact with the epithelial, hepatic and cardiac cell receptors that modulate host physiology.[37] Any change in the gut microbiota can shift the host metabolism towards increased energy harvest during diabetes. The association between the gut microbiota and diabetes T2D was studied and changes in gut microbiota community can be used to identify individuals at high risk for T2D. Numerous studies have

also reported that gut microbiota composition differs between obese and/or T2D individuals and those who are lean and non-diabetic.[28, 29, 36] On humans, a lower proportion of *Bacteroidetes* and a higher proportion of *Firmicutes* were associated with insulin resistance.[36,38] Gut Microbiota increase intestinal permeability to bacterial lipopolysaccharides (LPS), resulting in elevated systemic LPS levels that aggravate low-grade inflammation and insulin resistance.[23] Li et al.[36] reported that an association of microbial tyrosine metabolism in the gut is related to diabetes. Butyrate-producing bacteria such as *Bifidobacterium* and *Akkermansia* were significantly decreased in diabetic patients. The modulation of tyrosine metabolism and butyrate production may be a potential method for improved prevention of T2D. In other hand, it has been showed that intestinal microflora: beneficial intestinal Lactobacilli and *Bifidobacteria* can synthesize bioactive isomers of conjugated linoleic acid that have antidiabetic, anti-atherosclerotic, immunomodulatory, and anti-obesity properties.[39,40] It has been demonstrated that two main strains of probiotics used for health advantages include *Lactobacillus* and *Bifidobacterium* exert positive effects on alleviating diabetes-associated complications through lowering serum cholesterol, producing short chain fatty acids, and increasing bile salt deconjugation.[40,41] Matsuzaki et al.[42] showed that both *Lactobacillus* and *Bifidobacterium* strains inhibit β-cells destruction in the islets of Langerhans and result in an improvement in insulin-binding potential according to animal studies.

3. Role of Gut microbiota in chronic kidney disease (CKD)

The intestinal microbiota maintains a symbiotic relationship with the host under normal conditions, but its imbalance has recently been associated with several diseases.[43] In particular, chronic kidney disease is a serious healthcare dilemma, associated with specific changes in gut microbiota and circulating metabolome.[44] It has been showed that from the CKD early stages there is a quantitative and qualitative alteration of intestinal microflora (dysbiosis) and consequently the metabolic activities of microbiota are changed.[43] Among factors potentially impacting on microbiota composition, we find diet changes, prescribed drugs, accumulation of toxins that may alter the gut microenvironment.[45,46] So intestinal microflora generates uremic toxins that are absorbed and accumulate in CKD, and associated with increased oxidative stress and inflammation.[43] It has been demonstrated that also that an increased risk of CKD progression is associated with an accumulation of uremic toxins (or uremic acids) that derived from nutrient processing by gut microbiota, yielding precursors of uremic toxins themselves (such as trimethylamine N-Oxide, p-cresyl sulphate, indoxyl

sulphate and indole-3 acetic acid).[46] During CKD, the impact of an altered intestinal microbiota is resulted on inflammation related to an increased gut permeability of diet-derived nephrotoxic uremic toxins or their precursors or through decreased availability of nephroprotective molecules.[45] The increase in the permeability of the intestinal barrier allows the passage into the systemic circulation of endotoxins and other bacterial products that aggravate the inflammatory state of CKD.[43] In other hand, a depletion of short-chain fatty acids (SCFAs) (as propionic acid, valeric acid, and acetic acid) were observed. Among these SCFAs, propionic acid was significantly decreased at late stages and detected to be highly discriminatory between non-CKD controls and patients with advanced CKD.[44] Castillo-Rodriguez et al.[46] reported a specific change in the gut microbiota community by an increase in bacterial species prone to proteolytic fermentation, such as Clostridium and Bacteroides and/or a decrease in bacteria that may be protective or release potentially nephroprotective molecules (e.g., short chain fatty acids), such as *Lactobacillus.* The availability of nephroprotective molecules has the potential to greatly impact the management of CKD and pave the way for novel therapeutic approaches to control CKD evolution.[46] The changes in diet composition could improve microflora dysbiosis in CKD, reduce uremic toxin levels, or restore intestinal mucosal permeability in CKD patients. Next, the use of probiotics, prebiotics or symbiotics opens an alternative in the treatment of intestinal dysbiosis associated with CKD, and may play a role in slowing the progression of CKD and in preventing relevant associated complications such as mortality and cardiovascular risk.[43] Recently, Wagner et al.[47] have investigated the “real-life” relationship between yoghurt/probiotic intake and inflammation in a CKD population. Results showed that the beneficial effect of yoghurt and probiotic consumption are associated with a reduction of inflammation in CKD patients and apparent for a high level of inflammation (CRP > 6 mg/L).

4. Effect of intestinal microbiota in atherosclerosis and cardiovascular diseases

Atherosclerosis is an inflammatory disease in which, lipids and inflammatory cells are gathered in the intimal layer of arteries. Moreover, it is among the first causes of mortality and morbidity worldwide.[48] Numerous research studies connect gut microbiota community and its metabolites with atherosclerosis. It has been demonstrated that the variation of composition in different phyla as a low level of *Bacteroidetes* and dysbiosis of gut microbiota of pathogens (*Enterobacter*, *Collinsella*, *Desulfovibrio*, and *Klebsiella*) were connected with atherogenesis and atherosclerotic plaques.[49] A variety of metabolites are derived from the gut microbiota, as well as co-metabolism of gut microbiota such as amines methylamines,

polyamines, short-chain fatty acids (SCFAs), secondary bile acids (BAs) and trimethylamine N-oxide (TMAO).

In other hand, the microbiota influence atherosclerosis by promoting plaque development via activation of the immune system, alteration of cholesterol metabolism, and production of bacterial metabolites such as TMAO.[50] TMAO a metabolic product of L-carnitine, choline betaine, and phosphatidylocholine synthetized by gut microbiota, and the inflammation components which are released to the circulation because of gut dysbiosis, contributing to atherosclerosis.[51] BAs are another group of gut microbiota-derived metabolites involved in various metabolic diseases[52], which are stored in the gallbladder and released into the intestine to facilitate the absorption of dietary lipids and fat-soluble vitamins. It has been also reported that microbiota derived secondary BAs play important roles in the development of atherosclerosis through the modulation of various BA receptors.[49] Bacteria-mediated bile-salt hydrolase activity can affect the processes underlying the pathogenesis of atherosclerosis by increasing cholesterol accumulation, foam cell formation, and the size of the atherosclerotic plaque.[53]

This finding highlights the great potential for novel atherosclerosis therapy by targeting gut microbiota.[48] Consequently, gut microbiota-targeted therapy is a promising strategy to treat cardiovascular diseases (CVDs).[54, 55] According to the association of gut microbiota and the development of CVD, different approaches were investigated and have protective or therapeutic actions on CVD by modulating the gut microbiota. The most frequently used approaches to manipulate the gut microbiota include probiotic, prebiotic, natural herbs components, fecal transplantation.[48] DiRienzo[56] reported that *Lactobacillus reuteri* NCIMB 30242 (species renamed *Limosilactobacillus reuteri*) is a probiotic that best meets therapeutic lifestyle change (TLC) dietary requirements by 1) significantly reducing low-density lipoprotein cholesterol (LDL-C) and total cholesterol, 2) improving other coronary heart disease risk factors, such as inflammatory biomarkers, and 3) having “generally recognized as safe” (GRAS) status. Recently, Ahmadian et al.[57] reported that, probiotic supplementation for 6 weeks led to a significant improvement in major CVD-related parameters in populations with T2DM, suggesting the possible beneficial role of probiotics in lowering the risk of future CVDs associated with diabetes.

5. Importance of Gut microbiota in the pregnancy

The relationship between the gut microbiome and the human host is dynamic and we may expect adjustments in microbiome function if host physiology changes. Numerous studies reported that pregnancy is associated with changes in the microbial profiles of the oral cavity, skin, vaginal cavity and the gut.[58] During pregnancy progresses, authors showed a gut microbiota changes include increased abundance of *Proteobacteria*, *Actinobacteria*, opportunistic pathogens, and a decrease in short chain fatty acid producers.[58]

Significant alterations in the gut microbiota between the 1st and 3rd trimesters of pregnancy have been documented, including changes in diversity, certain phyla, and specific genera progresses.[59] During pregnancy, metabolic adaptation takes place in the mother to ensure an adequate supply of nutrients to the fetus. In late pregnancy, the microbiota readjusts the expression of carbohydrate-related functions in a manner consistent with a high availability of glucose.[60] An increase in the relative abundance of *Bifidobacterium* in the 3rd trimester of pregnancy in models of progesterone supplementation was observed. These results demonstrated that progesterone can modulate the pregnancy-associated gut microbial composition, including an increase in the relative abundance of *Bifidobacterium* in order to facilitate both the pregnant mother and perhaps also appropriate transmission of beneficial species to the neonate.[58] Gohir et al.[61] investigated how pregnancy and diet interact to influence the composition of the maternal gut microbiota. Authors showed that pregnancy-induced changes in the female gut microbiota occur immediately at the onet of pregnancy, are vulnerable to modulation by diet, but are not dependent upon increases in maternal weight gain during pregnancy. High fat diet intake before and during pregnancy results in distinctive shifts in the pregnant gut microbiota in a gestational-age dependent manner and these shifts predict significant differences in the abundance of genes that favor lipid metabolism, glycolysis and gluconeogenic metabolic pathways over the course of pregnancy. *Bifidobacterium* may be beneficial for the pregnant mother by moderating weight gain, improving insulin sensitivity and glucose tolerance, and boosting the immune system. *Bifidobacteria* are clearly critical members of the newborn microbiota repertoire, as they are lactic-acid-producing bacteria that have the ability to metabolize human milk oligosaccharides.[62] It has also been shown that *Bifidobacteria* are passed from mother to infant during vaginal birth because specific *Bifidobacterium* species from the mother's prenatal feces have been found in the feces of infants born vaginally but not by cesarean delivery.[63]

6. Microbiota and thyroid interaction in health

The gut microbiome plays a critical role in substance metabolism and influence the essential diagnosis and treatment for various pivotal diseases such as cancer, diabetes and melanoma. Remarkably, the balance of gut microbiome is highly crucial for a healthy human body, especially for endocrine system. The whole thyroid peripheral homeostasis may be sensitive to microbiota changes but there is also evidence that the genesis and progression of autoimmune thyroid disorders may be significantly affected from a changing intestinal microbial composition or even from overt dysbiosis.[64] Zhang et al.[65] reported that both thyroid cancer and thyroid nodules are associated with the composition of gut microbiome and with comparison to healthy controls, *Butyricimonas* and *Lactobacillus* displayed notably lower relative abundance for thyroid cancer and thyroid nodules, respectively. It has been demonstrated also that individuals with hyperthyroidism had significantly lower numbers of *Bifidobacteria* and *Lactobacilli* and significant higher levels of *Enterococcus* species compared to healthy controls.[66] During gut dysbiosis or small intestine bacterial overgrowth, intestinal permeability to bacterial LPS increase, resulting in elevated systemic LPS levels. LPS has been shown to inhibit iodothyronine deiodinase enzyme (IDE) responsible for conversion of T4 (inactive form of thyroid hormone) to T3 (the active form), decreasing the amount of active T3 in circulation.[67] In contrast, metabolism of primary bile acids by the gut bacteria results in the formation of secondary bile acids that increase IDE activity (the main enzyme that converts T4 into T3).[68] The most frequently approaches used to improve thyroid function by manipulating gut microbiota include (**1**) prebiotic as potent endocrine modulators (fermentable fiber), and (**2**) potential probiotics that could facilitate the treatment of thyroid cancer and thyroid nodules (*Lactobacillus reuteri* supplementation).[69,70]

7. How your microbiota affects your mood, sleep and stress level?

Microbiota, beside the expected role in maintaining gastrointestinal homeostasis, metabolic functions in nutrients digestion and absorption, immune functions of the host synthesis, also regulates host sleep and mental states through the microbiome-gut-brain axis. Gut microbiota dysbiosis is associated to sleep loss, circadian misalignment, affective disorders, and metabolic disease and any disruption of the gastrointestinal microbiome might cause or prolong sleep problems.[71] Compared with healthy people, chronic fatigue syndrome patients had significantly reduced *Escherichia coli* and *Bifidobacterium* populations during the acute phase of the disease.[72] The intestinal microbiota plays a crucial role in this bidirectional communication, since it can influence mood and cognitive functions by producing

neurotransmitter precursors that reach the brain through the endocrine and the autonomic nervous systems where they regulate the level of specific neurotransmitters.[73] Reigstad et al.[74] demonstrated that bacterial metabolites (by-products) from fiber digestion increase the levels of the gut hormone as serotonin that can activate the vagus. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. Analysis of microbiome composition revealed that within phyla richness of Bacteroidetes and Firmicutes were positively correlated with sleep efficiency, abstract thinking and interleukin-6 concentrations which is an important player in the sleep-gut microbiome relationship.[75] In conclusion, it's important to regulate and maintain a normal gastrointestinal micro-ecological environment in patients when treating mental disorders such as insomnia and depression. It has been reported that the beneficial effects of probiotics on psychological well-being, as measured by changes in mood (e.g., cognitive reactivity to sad mood, depression, and anxiety), personality dimensions, and quality of sleep.[76]

8. The effect of gut microbiota on drug metabolism

Intestinal microbiota is an aggregate genome of trillions of microorganisms residing in the human gastrointestinal tract.[77] The microbiome possesses a variety of metabolic activities able to modulate the fate of more than 30 approved drugs that are transformed either to bioactive, inactive, or toxic metabolites by microbial direct action or host-microbial co-metabolism.[78] The composition and quantity of intestinal flora varies among individuals, and can be affected by some drug administration (such as antibiotics) or environmental changes (acute plateau hypoxia). Gut microbiota can usually participate in drug metabolism by producing specific enzymes, such as reductase and hydrolytic enzyme, thus affecting the efficacy, toxicity, and bioavailability of drugs.[79] Numerous drugs (such Escin Ia, lactulose, L-DOPA, digoxin and irinotecan) have identified direct relationships between their efficacy and the intestinal microbiome.[80] Yang et al.[81] concluded that Escin Ia is a prodrug and can be metabolited into Desacylescin I by intestinal bacteria to show anti-tumor effect. It has been shown also that lactulose require metabolism by the intestinal microbiome, resulting in their therapeutic metabolites, acetic and lactic acid.[82] Irinotecan are reactivated by the intestinal microbiome via the β-glucuronidase enzyme present in many intestinal bacterial species, resulting in serious side effects in the host such as stage 4 diarrhea and gastrointestinal damage.[83] In terms of drug efficacy and toxicity, the potential of these microorganisms to affect absorption, distribution, metabolism, and excretion (ADME) is clearly worth raising awareness and attention in the drug metabolism. The microbiome

undoubtedly represents a “drugable target”, and there is no doubt that it is possible to modulate both its composition and metabolic activity.[84] Due to the importance of intestinal flora in drug metabolism, intestinal flora could be considered as a new drug target[85] to provide new opportunities for exploring the host-microbiome relationship to develop more effective and safer therapies.

9. Gut microbiota and Immune systems

Gut microbiota plays a fundamental role on the induction, training and function of the host immune system. The small intestine is considered as the major site for immune surveillance in the gut, and compared with the large intestine, it has greater than 100 times the surface area and a thinner and more permeable mucus layer.[86] The relationship between the host immune system and microbiota is bidirectional: in fact, if the immune system of the host is crucial in influencing the intestinal microflora composition, it has been also demonstrated that the microbial community may modulate directly the innate and adaptive host immunity.[64] For neonate, breast milk contains live microbes, metabolites, IgA, immune cells as well as cytokines. These factors synergize to shape the breast-fed infant microbiota and the response of the host to these microbes.[87, 88]

Interestingly, a recent work showed that the commensal microbiota of pregnant mice drives antibody-mediated protective immunity through breastfeeding.[89] Studies on germ-free (GF) animals demonstrated that absence of commensal microbes is associated with significant reduction of αβ and γδ intra-epithelial lymphocytes (IELs) in GF mice compared to conventional colonized animals.[90,91] The ratio between the effector and regulatory lymphocyte concentrations seems to be controlled by the microbiota, through the production of SCFAs and innate signals.[92] It has been demonstrated also that SCFA produced by microbiota through fermentation have direct effects on regulatory T cells (Treg) by regulating their growth and functions, and trigger production of IL-18, which has protective effect for enterocytes.[93]

Gut microbiota is also involved in the activation and differentiation of B cells and the involvement of microbiota in B regulatory (B reg) cells differentiation in spleen and mesenteric lymph nodes was proven.[64, 94] A bacterial polysaccharide derived from the ubiquitous commensal *Bacteroides fragilis* directs the maturation of the developing immune system in mice, including correction of systemic T cell deficiencies and Th1/Th2 imbalances in lymphoid tissues.[95] The large wealth of microbiome-derived metabolites found in high

concentration throughout the gut and in the systemic circulation may offer an opportunity to modulate these potentially bioactive molecules (also called 'postbiotics'). Their supplementation or signaling blockade in defined immune contexts may offer new avenues of microbiome-directed treatments.[90]

10. Gut microbiota as a source of antimicrobials compounds

Antimicrobials are compounds that kill or inhibit the growth of microorganisms. The availability of antimicrobials and antibiotics in particular, has improved the quality of life and increased life expectancy.[2] Gut Human microbiome is a dense and diverse compilation of different microbial ecosystems and extensively is considered as a promising source of novel metabolites. Mousa et al.[96] reported the variety of specialized metabolic compounds produced by this human microbiota and the effects within the human host. These metabolites include lipids and glycolipids, oligosaccharides, terpenoids, polyketides, amino acids, non-ribosomal peptides and ribosomally synthesized post-translationally modified peptides (RiPPs).[2] In general, bacteria develop different antagonism strategies to gain ecological advantages over other bacteria in the gut. The non-peptide antimicrobial activity in the gut is associated with the production of antimicrobials metabolites such H_2O_2, lactic acid, SCFA, diacetyl (2,3-butadione), ethanol, CO_2, ammonia or phenolic compound. It has been suggested that the antimicrobial activity of SCFA or organic acids is due to acidification of the environment and H_2O_2 contributes to maintain a healthy microbiota.[97] Gut Microbiota are also capable of producing antimicrobial peptide compounds including Non-ribosomal peptides (NRPs) that are considered to be target-specific.[19] The microorganisms colonizing the gut produce ribosomally synthesized peptides (Bacteriocins) which distributed throughout the gastro-intestinal tract (GIT) in an attempt to outcompete pathogens. Bacteriocin production in GIT, a harsh and complex environment, may be below minimal inhibitory concentration (MIC) levels.[22] Bacteriocin activity can be enhanced by the presence of other substances, such as lactic acid, that allows the permeabilization of the bacterial membrane. Microcin J25 (MccJ25), is the paradigm of lasso peptides (Class I bacteriocins) formed by 21 amino acids and is produced by *E. coli* AY25 (Enterobacteriaceae) that was isolated from newborn feces.[98] Thuricin CD (Class I bacteriocins) was isolated from a bacterium from the human gut. Produced by *Bacillus thuringiensis* DPC6431, it is particularly important because it has been shown to possess very specific activity against *Clostridium difficile, Bacillus cereus, Bifidobacterium firmus* and *Listeria monocytogenes.*[99] Reutericin 6 (Class II-c bacteriocins) produced by *Lactobacillus reuteri* LA6, renamed as *Limosilactobacillus reuteri*

(*L. reuteri* LA6), is isolated from baby feces and it has been demonstrated that its activity is influenced by the presence of substances on the surface of the target cells and low pH values.[100] Bacteriocin 28b (Class III bacteriocins), isolated from many biotypes of gut symbiotic bacterium *Serratia marcescens*. Its structural analysis showed similarities to colicins (microcins) and it is active against *E. coli*.[101] Bacteriocins are highly promising, due to the variety of advantages that they present. Current limitations in the identification and isolation of these compounds can be addressed by incorporating new techniques like genomic and bioinformatics tools, genome mining and metagenomics.[2]

Table 1: List of different metabolites produced by Human Gut Microbiota (HGM).

Gut Microbiote Producer	Metabolites or end of product	Antimicrobial activity by	References
Lactobacillus johnsoni NCC 533 *Lactobacillus acidophilus*	H_2O_2	Oxidizing effects on pathogenic bacterial cells and their molecular structures	Hertzberger et al.[97] Singh et al.[102]
Lactobacillus ssp and *Bifidobacteria* spp	Organic acids (Lactic acid)	Acidification of the cell bacterial environment.	Mikelsaar et al.[103]
Bifidobacterium spp. *Lactobacillus rhamnosus* GG (LGG), (ATCC 53103) *Lactobacillus gasseri* PA 16/8 *Bifidobacterium longum* SP 07/3, *Bifidobacterium bifidum* MF 20/5	Short chain fatty acids, such as formate, acetate, butyrate	Acidification of the cell bacterial environment.	c, Markowiak-Kope and Sliżewska.[12]
Lactobacillus rhamnosus GG (LGG), (ATCC 53103)	Diacetyl (2,3-butadione)	Inhibition of the amino acid utilization of arginine	Valik et al.[104]
Lactobacillus fermentum *Streptococcus* ssp *Bifidobacterium* ssp *Bacteroides* ssp *Clostridium* ssp *Eubacterium* ssp *Blautia* ssp *Dorea* ssp	Ethanol	Damage the outer cell membrane of pathogenic bacterial cells	Elshaghabee et al.[105] Oliphant and Allen-Vercoe.[106]
Bacteroides ssp *Clostridium* ssp *Eubacterium* ssp *Coprococcus* ssp *Escherichia* ssp	CO_2	Enhanced efficiency in cell destruction	Oliphant and Allen-Vercoe.[106]
Escherichia coli. (pathogens from the human gut that are not normally present in human gut microbiome)	Cereulide, Zwittermicin Tilivalline	Cytotoxic, alongside with colibactin activity, (induce chromosomal instability and DNA damage)	Balskus.[107] Kevany et al.[108]

Escherichia coli LR05 *Blautia obeum* A2-162	Class I bacteriocin*:* Microcin L Nisin O	Binding to lipid II (transporter of peptidoglycan subunits from the cytoplasm to the cell wall) and prevent the correct cell wall synthesis, leading to cell death.	Gaillard-Gendron et al.[109] Hatziioanou et al.[110]
Enterococcus faecium RC714 *Lactobacillus johnsonii* *Lactobacillus reuteri* LA 6 *Lactobacillus rhamnosus* 68	Class II bacteriocin: Bacteriocin RC714 (IIa) Lactacin F (IIb) Reutericin 6 (IIc) Rhamnosin A (II d)	Killing target cells and inducing pore formation on cell membranes by permeabilizing that lead to cell death,	Abee et al.[111] del Campo et al.[112] Toba et al.[113] Dimitrijević et al.[114]
Lactobacillus acidophilus NCFM	Class III bacteriocin: Bacteriocin helveticin J	Sublethal damage on target cells through impairment of cell wall and membrane	Bull et al.[115]

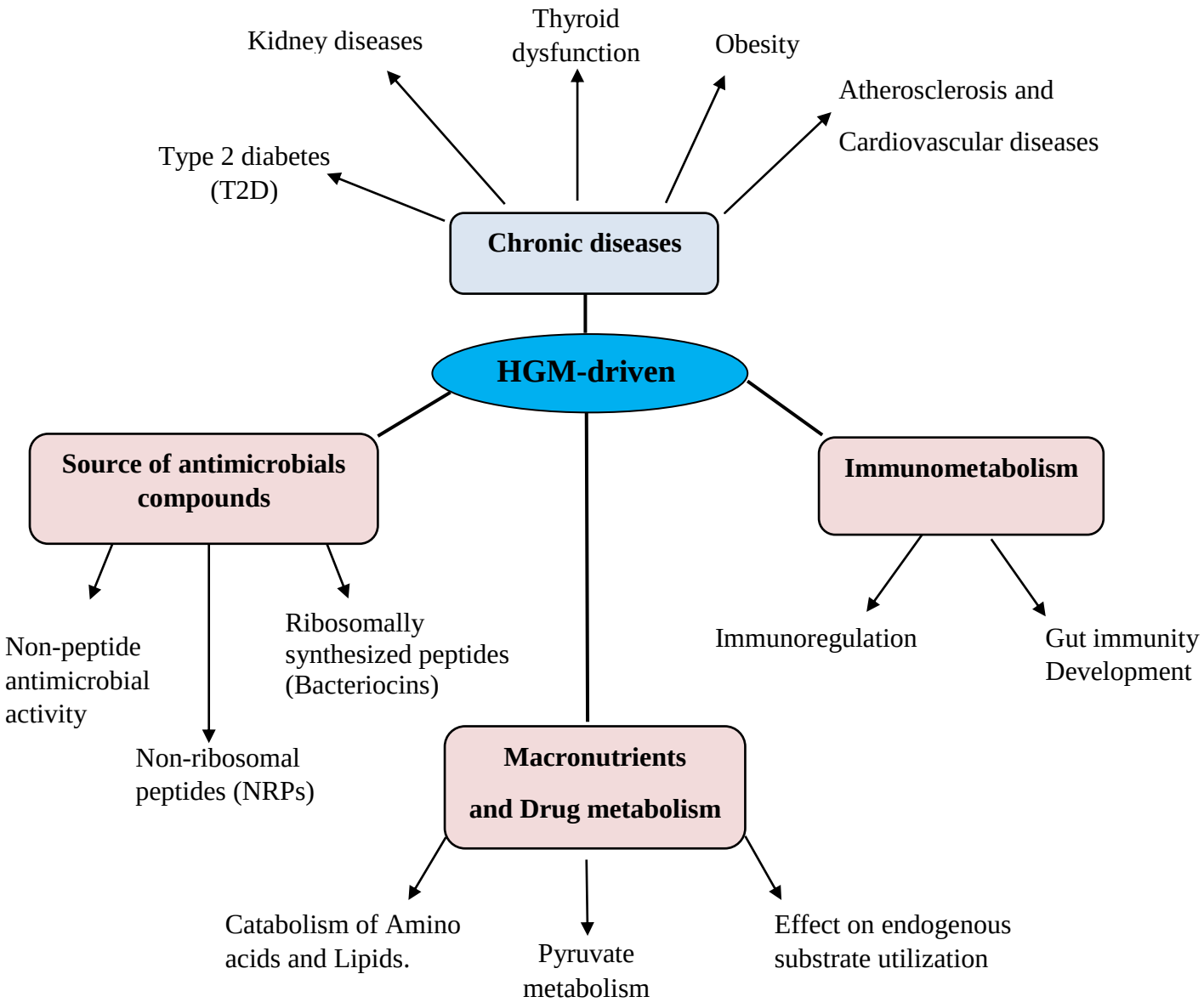

Fig. 1- Schematic representation of Human Gut Microbiota (HGM) function.

Table 2: Probiotic therapeutic strategies for some diseases related to imbalanced intestinal gut microbiota.

Diseases/Disorders	Probiotic Therapeutic Strategies	Effects	References
Obesity and Lipid metabolism disorders	• *Akkermansia muciniphila* • *Hafnia alvei* HA4597®	• Reduce weight gain, adiposity and improves well-being	Muscogiuri et al.[23] Cani et al.[29] Michael et al.[33] Déchelotte et al.[116]
	• *Lactobacillus curvatus* HY7601 in combination with *Lactobacillus plantarum* KY1032	• Reduce cholesterol in plasma and liver	Yoo et al.[35] Kobyliak et al.[40]
	• *Lactobacillus rhamnosus*, *Bifidobacterium breve* and *Lactobacillus paracasei*	• Decrease triacylglycerol content in liver	Plaza-Diaz et al.[117]
	• Bifidobacterium spp. (*Bifidobacterium pseudocatenulatum* SPM 1204, *Bifidobacterium longum* SPM 1205, *Bifidobacterium longum* SPM 1207, *Bifidobacterium adolescentis*, *Bifidobacterium animalis* subsp. lactis I-2494)	• Reduce High fat diet induced weight gain	Wang et al.[34] An et al.[118]
	• *Lactobacillus rhamnosus* GG (LGG)	• Reduce lipid accumulation by stimulating adiponectin secretion	Kim et al.[119]
	• *Faecalibacterium prausnitzii*	• Protective effects and short chain fatty acids production	Breyner et al.[120]
	• *Bacteroides uniformis* CECT 7771	• Improvement in lipid and leptine profiles	Fernández-Murga and Sanz.[121]
Diabetic subjects and Carbohydrates metabolism disorders	• *Lactobacillus rhamnosus* GG (LGG)	• Beneficial effects on glucose homeostasis • Improve glucose tolerance	Kim et al.[119]
	• *Bifidobacterium adolescentis*	• Improved insulin sensitivity	Chen et al.[122]

	• *Lactobacillus curvatus* HY7601 in combination with *Lactobacillus plantarum* KY1032	• Prevented the development of high-fructose diet-induced metabolic syndrome, i.e. lowered plasma glucose, insulin and triglycerides levels	Yoo et al.[35]
	• *Lactobacillus acidophilus* and *Lactobacillus casei*	• Improve the stigmata of diabetes, i.e. hyperglycemia and hyperinsulinemia, in high-fructose induced rat models of diabetes	Yadav et al.[123] Kobyliak et al.[40]
	• *Akkermansia muciniphila*	• Reversed diet-induced fasting hyperglycemia, possibly via a reduction in gluconeogenesis, and reduced insulin resistance in High-fat diet (HFD)-induced obese mice.	Everard et al.[124]
	• *Bacteroides uniformis* CECT 7771	• Improvement in metabolism glucose level.	Fernández-Murga and Sanz.[121]
	• *Bifidobacterium bifidum* • *Lactobacillus acidophilus* • *Streptococcus thermophiles*	• Ameliorating glycemic control of diabetic nephropathy in patients with type 2 diabetes	Jiang et al.[125]
Chronic kidney disease (CKD)	• *Lactobacillus acidophilus* (TYCA06), • *Bifidobacterium longum subspecies infantis* (BLI-02) • *Bifidobacterium bifidum* (VDD088)	• A combination of probiotics might attenuate renal function deterioration in CKD human patients	Wang et al.[34]
	• *Bifidobacterium longum* and *Lactobacillus reuteri*	• Additional beneficial effect on the control and modulation of microbiota-derived and proatherogenic toxins in CKD patients	De Mauri et al.[126] Tian et al.[127]

	• *Lactobacillus delbrueckii subsp. Bulgaricus, Streptococcus salivarius subsp. thermophilus)* and *Bifidobacteria*	• Reduce lower risk of inflammation in patients with CKD	Wagner et al.[47]
	• *Lactobacillus plantarum* • *Lactobacillus casei* • *Lactobacillus Rhamnosus* • *Lactobacillus gasseri* • *Bifidobacterium infantis* • *Bifidobacterium longum* • *Lactobacillus acidophilus* • *Lactobacillus salivarius* • *Lactobacillus sporogenes* • *Streptococcus thermophilus*	• Symbiotic agent significantly decreased plasma p-cresol levels of non-dialysis patients with CKD.	Guida et al.[128]
	• Bifidobacterium and Blautia spp	• Attenuate inflammation patients with CKD, and it modified the gastrointestinal microbiome	McFarlane et al.[129]
Atherosclerosis and cardiovascular diseases	• *Lactobacillus reuteri* NCIMB 30242 *Lactobacillus acidophilus* CHO-220 plus inulin and *Lactobacillus acidophilus* plus fructo-oligosaccharides.	• Reduce low-density lipoprotein cholesterol (LDL-C) and improving other coronary heart disease risk factors, such as inflammatory biomarkers.	DiRienzo.[56]
	• *Bifidobacterium lactis* Probio-M8	• Improve coronary artery disease (CAD)-associated symptoms including a hypolipidemic effects	Sun et al.[130]
	• *Lactobacillus acidophilus* 145 and *Bifidobacterium longum* 913	• Increase HDL-C and reduce LDL:HDL ratio	Kiessling et al.[131]

	• *Streptococcus thermophiles* • *Lactobacillus bulgaricus* • *Lactobacillus acidophilus* LA5 • *Bifidobacterium lactis* BB12	• Reduced Total Cholesterol (TC) and LDL-C,	Madjd et al.[132]
	• Lactobacilli and Bifidobacterium species	• Reduce the risk of atherosclerosis via reducing the serum levels of Trimethylamine N-oxide (TMAO) by improving the gut microbiota. • Diminish the risk of atherosclerosis by inhibiting inflammation and oxidative stress	Abdi et al.[133]
	• *Lactobacillus pentosus* KF923750	• Reduce LDL-C and TC levels in vivo and vitro, but has no effect on HDL-C	Bendali et al.[134]
	• *Lactobacillus plantarum* CUL66	• Significant reductions in plasma total cholesterol levels and suppression of diet-induced weight gain, but no changes in plasma levels of LDL/VLDL	Michael et al.[135]
	• *Lactobacillus acidophilus* ATCC 435639	• Anti-atherosclerotic effects by inhibiting the intestinal absorption of cholesterol	Huang et al.[136]
Depression and anxiety	• *Bifidobacterium lactis* Probio-M8	• Alleviating depression and anxiety in patients with significantly lower serum levels of interleukin-6. • Regulates gut microbiota to alleviate Alzheimer's disease in the	Cao et al.[137]

		APP/PS1 mouse model	
	• *Lactobacillus brevis* • *Lactobacillus rhamnosus* • *Lactobacillus reuteri* • *Lactobacillus paracasei* • *Lactobacillus plantarum* • *Lactobacillus bulgaricus* • *Lactobacillus helveticus* • *Lactobacillus casei*	• Induce regulatory functions as, impulsivity, learning, motivation, concentration, Psychomotor speed and mood by producing neurotransmitter such Gamma-aminobutyric acid (GABA), Serotonin, Dopamine, Histamine, Acetylcholine, Glutamate and Norepinephrine.	Yong et al.[138]
	• *Ruminococcus flavefaciens*	• Abolish their effects on depressive-like behaviour • Affects gene networks in the brain, suggesting a mechanism for microbial regulation of antidepressant treatment efficiency.	Lukić et al.[139]
	• *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175	• Reducing the symptoms of depression	Romijn et al.[140]
	• *Lactobacillus rhamnosus* HN001	• Prevent postpartum depression and anxiety symptoms.	Slykerman et al.[141]
	• *Lactobacillus acidophilus* • *Lactobacillus casei* • *Bifidobacterium bifidum*	• Improve a lower scores for depression and anxiety	Akkasheh et al.[142]
Immune systems disorders	• *Lactobacillus rhamnosus* (JB-1)	• Modulate the immune system • Regulate inflammation through the generation of regulatory T cells	Bravo et al.[143]

	• *Saccharomyces boulardii* UFMG 905 and *Bifidobacterium* sp.)	• Stimulate and manipulate the gut immune response, inducing intestinal homeostasis.	Vieira et al.[144]
	• *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus reuteri, Bifidobacterium bifidium,* and *Streptococcus thermophilus*	• Stimulate regulatory dendritic cells that express high levels of IL-10 • Induce both T-cell and B-cell hyporesponsiveness and downregulated T helper (Th)	Yan and Polk.[145]
	• *Lactobacillus casei* CRL 431 and *Lactobacillus helveticus* R389	• Increase in IL-6 levels secreted in a TLR2-(Toll Like Receptor 2) dependent manner	Vitini et al.[146]
	• *Lactobacillus acidophilus, Lactobacillus rhamnosus Lactobacillus casei, Lactobacillus delbrueckii* subsp bulgaricus *Lactobacillus plantarum Lactobacillus lactis Streptococcus thermophilus*	• Increase the number of intestinal IgA-producing cells in a dose-dependent manner • Elicit the B cell clonal expansion through IL-6 production in order to release IgAs	Mazziotta et al.[147] Vinderola et al.[148]
	• *Bifidobacterium animalis* NumRes252/-253	• Improve lung function, Immunestimulation	Fanning et al.[149]
	• *Lactobacillus acidophilus* NCFB 1748	• Increased chemotaxis of polymorphonuclear cells	Kourelis et al.[150]
	• *Lactobacillus gasseri* SBT2055	• Induce Immunestimulation by increasing IgA-producing cells	Sakai et al.[151]

CONCLUSION

The gut microbiota has important effects on human health and disease, and an altered composition of the gut microbiota was identified as a factor contributing to numerous diseases listed previously (Fig. 1). It has been demonstrated that it's important to develop potential probiotics that could facilitate the treatment of several diseases such as obesity,

T2DM, cancer, immune system dysfunction, and cardiovascular diseases. Next, intestinal flora could be considered as a new drug target to provide new opportunities for exploring the host-microbiome relationship and to develop novel effective and safer therapies. Metagenomic and metabolomic studies are expected to provide informations on the mechanisms between the gut microbiome, nutrition and chronic diseases, with the final goal to provide guidance for the diagnosis, treatment, and rehabilitation of metabolic disorders.

REFERENCES

1. Cani PD. Human gut microbiome: hopes, threats and promises. Gut, 2018; 67(9): 1716–1725. https://doi: 10.1136/gutjnl-2018-316723
2. Garcia-Gutierrez E, Mayer MJ, Cotter PD, Narbad A. Gut microbiota as a source of novel antimicrobials. Gut Microbes, 2019; 10(1): 1–21. https://doi: 10.1080/19490976.2018.1455790
3. Leite GGS, Weitsman S, Parodi G, Celly S, Sedighi R, Sanchez M, et al. Mapping the segmental microbiomes in the human small bowel in comparison with stool: a REIMAGINE study. Dig Dis Sci, 2020; 65: 2595–2604. https://doi: 10.1007/s10620-020-06173-x
4. Pan C, Guo Q, Lu Na. Role of gut microbiota in the pharmacological effects of natural products. Evid.-based Complement Altern Med, 2019; 2019: 2682748. https://doi: 10.1155/2019/2682748
5. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature, 2006; 444(7122): 1022-1023. https://doi: 10.1038/4441022a
6. Seo DB, Jeong HW, Cho D. Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. J Med Food, 2015; 18(5): 549-556. https://doi: 10.1089/jmf.2014.3265
7. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science, 2018; 359(6380): 1151-1156. https://doi: 10.1126/science.aao5774
8. Guglielmi G. How gut microbes are joining the fight against cancer. Nature, 2018; 557(7706): 482–484. https://doi: 10.1038/d41586-018-05208-8
9. Gentile CL, Weir TL. The gut microbiota at the intersection of diet and human health. Science, 2018; 362(6416): 776–780. https://doi: 10.1126/science.aau5812

10. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol, 2013; 6: 295–308. https://doi: 10.1177/1756283X13482996
11. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut, 2022; 71(5): 1020-1032. https://doi: 10.1136/gutjnl-2021-326789
12. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients, 2020; 12(4): 1107. https://doi: 10.3390/nu12041107
13. Searsand C, Garrett WS. "Microbes, microbiota, and colon cancer". Cell Host & Microbe, 2014; 15(3): 317–328. https://doi: 10.1016/j.chom.2014.02.007
14. Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anti-cancer effects of the microbiome and its products. Nat Rev Microbiol, 2017; 15(8): 465–478. https://doi: 10.1038/nrmicro.2017.44
15. Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev, 2017; 279(1): 70-89. https://doi: 10.1111/imr.12567
16. Dervla K, Liying Y, Zhiheng P. A Review of the oesophageal microbiome in health and disease. Methods Microbiol, 2017; 44: 19-35. https://doi.org/10.1016/bs.mim.2017.08.001
17. Khodamoradi Y, Kessel J, Vehreschild JJ, Vehreschild MJGT. The role of microbiota in preventing multidrug-resistant bacterial infections. Dtsch Arztebl Int, 2019; 116(40): 670-676. https://doi: 10.3238/arztebl.2019.0670
18. Wang G, Li X, Wang Z. APD3: the antimicrobial peptide database as a tool for research and education. Nucleic Acids Res, 2016; 44: 1087-1093. https://doi: 10.1093/nar/gkv1278
19. Donia MS, Fischbach MA. Small molecules from the human microbiota. Science, 2015; 349(6246): 1254766. https://doi: 10.1126/science.1254766
20. Fijan S. Antimicrobial effect of probiotics against common pathogens, probiotics and prebiotics in human nutrition and health. InTech, 2016; Ch.-10. https://doi: 10.5772/63141
21. Hatziioanou D, Mayer MJ, Duncan SH, Flint HJ, Narbad A. A representative of the dominant human colonic Firmicutes, Roseburia faecis M72/1, forms a novel bacteriocin-like substance. Anaerobe, 2013; 23: 5-8. https://doi: 10.1016/j.anaerobe.2013.07.006

22. Dicks LMT, Dreyer L, Smith C, van Staden AD. A Review: The fate of bacteriocins in the human gastro-intestinal tract: do they cross the gut-blood barrier? Front Microbiol, 2018; 9: 2297. https://doi: 10.3389/fmicb.2018.02297
23. Muscogiuri G, Cantone E, Cassarano S, Tuccinardi D, Barrea L, Savastano S, et al. on behalf of the obesity programs of nutrition, education, research and assessment (OPERA) group. Gut microbiota: a new path to treat obesity. Int J Obes Suppl, 2019; 9(1): 10-19. https://doi: 10.1038/s41367-019-0011-7
24. Al-Assal K, Martinez AC, Torrinhas RS, Cardinelli C, Waitzberg D. Gut microbiota and obesity. Clin Nutr Exp, 2018; 20: 60-64. https://doi.org/10.1016/j.yclnex.2018.03.001
25. Abenavoli L, Scarpellini E, Colica C, Boccuto L, Salehi B, Sharifi-Rad J, et al. Gut Microbiota and Obesity: A Role for Probiotics. Nutrients, 2019; 11(11): 2690. https://doi: 10.3390/nu11112690
26. Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, et al. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr, 2013; 98(1): 16-24. https://doi: 10.3945/ajcn.113.058743
27. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. Nature, 2013; 500(7464): 541-546. https://doi: 10.1038/nature12506
28. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA., 2005; 102(31): 11070-11075. https://doi: 10.1073/pnas.0504978102
29. Cani PD, Geurts L, Matamoros S, Plovier H, Duparc T. Glucose metabolism: focus on gut microbiota, the endocannabinoid system and beyond. Diabetes Metab, 2014; 40(4): 246-57. https://doi: 10.1016/j.diabet.2014.02.004
30. Klancic T, Reimer RA.Gut microbiota and obesity: Impact of antibiotics and prebiotics and potential for musculoskeletal health. J Sport Health Sci, 2020; 9(2): 110-118. https://doi: 10.1016/j.jshs.2019.04.004
31. Dahiya DK, Renuka, Puniya M, Shandilya UK, Dhewa T, Kumar N, et al. Gut microbiota modulation and its relationship with obesity using prebiotic fibers and probiotics: A Review. Front Microbiol, 2017; 8: 563. https://doi: 10.3389/fmicb.2017.00563.
32. Jones RB, Alderete TL, Martin AA, Geary BA, Hwang DH, Palmer SL, et al. Probiotic supplementation increases obesity with no detectable effects on liver fat or gut microbiota

in obese Hispanic adolescents: a 16-week, randomized, placebo-controlled trial. Pediatr Obes, 2018; 13(11): 705-714. https://doi: 10.1111/ijpo.12273.

33. Michael DR, Jack AA, Masetti G, Davies TS, Loxley KE, Kerry-Smith J, et al. A randomised controlled study shows supplementation of overweight and obese adults with lactobacilli and bifidobacteria reduces bodyweight and improves well-being. Sci Rep, 2020; 10(1): 4183. https://doi: 10.1038/s41598-020-60991-7.
34. Wang J, Tang H, Zhang C, Zhao Y, Derrien M, Rocher E, et al. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. ISME J, 2015; 9(1): 1-15. https://doi: 10.1038/ismej.2014.99.
35. Yoo SR, Kim YJ, Park DY, Jung UJ, Jeon SM, Ahn YT, et al. Probiotics *L. plantarum* and *L. curvatus* in combination alter hepatic lipid metabolism and suppress diet-induced obesity. Obesity (Silver Spring), 2013; 21(12): 2571-2578. https://doi: 10.1002/oby.20428.
36. Li Q, Chang Y, Zhang K, Chen H, Tao S, Zhang Z. Implication of the gut microbiome composition of type 2 diabetic patients from northern China. Sci Rep, 2020; 10(1): 5450. https://doi: 10.1038/s41598-020-62224-3.
37. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go? J Nutr Biochem, 2019; 63: 101-108. https://doi: 10.1016/j.jnutbio.2018.10.003.
38. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature, 2012; 490(7418): 55-60. https://doi:10.1038/nature11450.
39. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care, 2010; 33(10): 2277-2284. https://doi: 10.2337/dc10-0556.
40. Kobyliak N, Conte C, Cammarota G, Haley AP, Styriak I, Gaspar L, et al. Probiotics in prevention and treatment of obesity: a critical view. Nutr Metab (Lond), 2016; 13: 14. https://doi: 10.1186/s12986-016-0067-0.
41. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA, 2008; 105(43): 16767-16772. https://doi: 10.1073/pnas.0808567105.
42. Matsuzaki T, Nagata Y, Kado S, Uchida K, Kato I, Hashimoto S, et al. Prevention of onset in an insulin-dependent diabetes mellitus model, NOD mice, by oral feeding of

Lactobacillus casei. APMIS, 1997; 105(8): 643-649. https://doi: 10.1111/j.1699-0463.1997.tb05066.x.

43. Cigarran Guldris S, González Parra E, Cases Amenós A. Gut microbiota in chronic kidney disease. Nefrologia, 2017; 37(1): 9-19. https://doi: 10.1016/j.nefro.2016.05.008.
44. Wu IW, Gao SS, Chou HC, Yang HY, Chang LC, Kuo YL, et al. Integrative metagenomic and metabolomic analyses reveal severity-specific signatures of gut microbiota in chronic kidney disease. Theranostics, 2020; 10(12): 5398-5411. https://doi: 10.7150/thno.41725.
45. Vanholder R, Fouque D, Glorieux G, Heine GH, Kanbay M, Mallamaci F, et al. London GM; European Renal Association European Dialysis; Transplant Association (ERA-EDTA) European Renal; Cardiovascular Medicine (EURECA-m) working group. Clinical management of the uraemic syndrome in chronic kidney disease. Lancet Diabetes Endocrinol, 2016; 4: 360-373. https://doi: 10.1016/S2213-8587(16)00033-4.
46. Castillo-Rodriguez E, Fernandez-Prado R, Esteras R, Perez-Gomez MV, Gracia-Iguacel C, Fernandez-Fernandez B, et al. Impact of altered intestinal microbiota on chronic kidney disease progression. Toxins (Basel), 2018; 10(7): 300. https://doi: 10.3390/toxins10070300.
47. Wagner S, Merkling T, Metzger M, Koppe L, Laville M, Boutron-Ruault MC, et al. Probiotic intake and inflammation in patients with chronic kidney disease: An analysis of the CKD-REIN Cohort. Front Nutr, 2022; 9: 772596. https://doi: 10.3389/fnut.2022.772596.
48. Ma J, Li H. The role of gut microbiota in atherosclerosis and hypertension. Front Pharmacol, 2018; 9: 1082 https://doi: 10.3389/fphar.2018.01082.
49. MantziarisV, Kolios G. Gut microbiota, atherosclerosis, and therapeutic targets. Crit pathw cardiol, 2019; 18: 139–142 https://doi: 10.1097/HPC.0000000000000187.
50. Jonsson AL, Bäckhed F. Role of gut microbiota in Atherosclerosis. Nat Rev Cardiol, 2017; 14: 79-87. https://doi: 10.1038/nrcardio.2016.183.
51. Li DY, Tang WHW. Gut microbiota and atherosclerosis. Curr Atheroscler Rep, 2017; 19(10): 39 https://doi: 10.1007/s11883-017-0675-9.
52. Parséus A, Sommer N, Sommer F, Caesar R, Molinaro A, Ståhlman M, et al. Microbiota-induced obesity requires farnesoid X receptor. Gut, 2017; 66(3): 429-437. https://doi: 10.1136/gutjnl-2015-310283.

53. Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. Annu Rev Pathol, 2006;1: 297–329. https://doi: 10.1146/annurev.pathol.1.110304.100100.
54. Koopen AM, Groen A K, Nieuwdorp M. Human microbiome as therapeutic intervention target to reduce cardiovascular disease risk. Curr Opin Lipidol, 2016; 27: 615–622. https://doi: 10.1097/MOL.0000000000000357
55. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, Shenoy V, et al. Hypertension-linked pathophysiological alterations in the gut. Circ Res, 2017; 120(2): 312-323. https://doi: 10.1161/CIRCRESAHA.116.309006.
56. DiRienzo BD. Effect of probiotics on biomarkers of cardiovascular disease: implications for heart-healthy diets. Nutr Rev, 2014; 72(1): 18–29. https://doi: 10.1111/nure.12084.
57. Ahmadian F, Razmpoosh E, Ejtahed HS, Javadi M, Mirmiran P, Azizi F. Effects of probiotic supplementation on major cardiovascular-related parameters in patients with type-2 diabetes mellitus: a secondary-data analysis of a randomized double-blind controlled trial. Diabetol Metab Syndr, 2022; 14(1): 52. https://doi: 10.1186/s13098-022-00822-z.
58. Nuriel-Ohayon M, Neuman H, Ziv O, Belogolovski A, Barsheshet Y, Bloch N, et al. Progesterone increases Bifidobacterium relative abundance during late pregnancy. Cell Rep, 2019; 27(3): 730-736.e3. https://doi: 10.1016/j.celrep.2019.03.075.
59. Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Bäckhed HK, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell, 2012; 150(3): 470-480. https://doi: 10.1016/j.cell.2012.07.008.
60. Gosalbes MJ, Compte J, Moriano-Gutierrez S, Vallès Y, Jiménez-Hernández N, Pons X, et al. Metabolic adaptation in the human gut microbiota during pregnancy and the first year of life. EBioMedicine, 2019; 39: 497-509. https://doi: 10.1016/j.ebiom.2018.10.071.
61. Gohir W, Whelan FJ, Surette MG, Moore C, Schertzer JD, Sloboda DM. Pregnancy-related changes in the maternal gut microbiota are dependent upon the mother's periconceptional diet. Gut Microbes, 2015; 6(5): 310-320. https://doi: 10.1080/19490976.2015.1086056.
62. Turroni F, Milani C, Duranti S, Ferrario C, Lugli GA, Mancabelli L, et al. Bifidobacteria and the infant gut: an example of co-evolution and natural selection. Cell Mol Life Sci, 2018; 75(1): 103-118. https://doi: 10.1007/s00018-017-2672-0.
63. Nuriel-Ohayon M, Neuman H, Koren O. Microbial changes during pregnancy, birth, and infancy. Front. Microbiol, 2016; 7: 1031. https://doi: 10.3389/fmicb.2016.01031.

64. Virili C, Fallahi P, Antonelli A, Benvenga S, Centanni M. Gut microbiota and Hashimoto's thyroiditis. Rev Endocr Metab Disord, 2018; 19(4): 293-300. https://doi: 10.1007/s11154-018-9467-y.
65. Zhang J, Zhang F, Zhao C, Xu Q, Liang C, Yang Y, et al. Dysbiosis of the gut microbiome is associated with thyroid cancer and thyroid nodules and correlated with clinical index of thyroid function. Endocrine, 2019; 64(3): 564-574. https://doi: 10.1007/s12020-018-1831-x.
66. Zhou L, Li X, Ahmed A, Wu D, Liu L, Qiu J, et al. Gut microbe analysis between hyperthyroid and healthy individuals. Curr Microbiol, 2014; 69(5): 675-680. https://doi: 10.1007/s00284-014-0640-6.
67. Yu J, Koenig RJ. Regulation of hepatocyte Thyroxine 5′-Deiodinase by T3 and nuclear receptor coactivators as a model of the sick euthyroid syndrome. J Biol Chem, 2000; 275: 38296-38301. https://doi: 10.1074/jbc.M004866200.
68. Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature, 2006; 439(7075): 484-489. https://doi: 10.1038/nature04330.
69. Hüser S, Guth S, Joost HG, Soukup ST, Köhrle J, Kreienbrock L, et al. Effects of isoflavones on breast tissue and the thyroid hormone system in humans: a comprehensive safety evaluation. Arch Toxicol, 2018; 92(9): 2703-2748. https://doi: 10.1007/s00204-018-2279-8.
70. Fröhlich E, Wahl R. Microbiota and thyroid interaction in health and disease. Trends Endocrinol. Metab, 2019; 30: 479-490. https://doi: 10.1016/j.tem.2019.05.008.
71. Li Y, Hao Y, Fan F, Zhang B. The Role of microbiome in insomnia, circadian disturbance and depression. Front Psychiatry, 2018; 9: 669. https://doi: 10.3389/fpsyt.2018.00669.
72. Frémont M, Coomans D, Massart S, De Meirleir K. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. Anaerobe, 2013; 50-6. https://doi: 10.1016/j.anaerobe.2013.06.002.
73. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. Neuroscience, 2010; 170(4): 1179-1188. https://doi: 10.1016/j.neuroscience.2010.08.005.
74. Reigstad CS, Salmonson CE, Rainey JF, Szurszewski JH, Linden DR, Sonnenburg JL, et al. Gut microbes promote colonic serotonin production through an effect of short-chain

fatty acids on enterochromaffin cells. FASEB J, 2015; 29(4): 1395-1403. https://doi: 10.1096/fj.14-259598.

75. Smith RP, Easson C, Lyle SM, Kapoor R, Donnelly CP, Davidson EJ, et al. Gut microbiome diversity is associated with sleep physiology in humans. PLoS One, 2019; 14(10): e0222394. https://doi: 10.1371/journal.pone.0222394.
76. Marotta A, Sarno E, Del Casale A, Pane M, Mogna L, Amoruso A, et al. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. Front Psychiatry, 2019; 10: 164. https://doi: 10.3389/fpsyt.2019.00164.
77. Sun C, Chen L, Shen Z. Mechanisms of gastrointestinal microflora on drug metabolism in clinical practice. Saudi Pharm J, 2019; 27: 1146–1156. https://doi: 10.1016/j.jsps.2019.09.011.
78. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature, 2019; 570(7762): 462-467. https://doi: 10.1038/s41586-019-1291-3.
79. Xie Y, Hu F, Xiang D, Lu H, Li W, Zhao A, et al. The metabolic effect of gut microbiota on drugs. Drug Metab Rev, 2019; 52(1): 139-156. https://doi: 10.1080/03602532.2020.1718691.
80. Nichols RG, Peters JM, Patterson AD. Interplay between the host, the human microbiome, and drug metabolism. Hum Genomics, 2019; 13: 27. https://doi: 10.1186/s40246-019-0211-9.
81. Yang XW, Zhao J, Cui JR, Guo W. [Studies on the biotransformation of escin Ia by human intestinal bacteria and the anti-tumor activities of desacylescin I]. Beijing Da Xue Xue Bao Yi Xue Ban, 2004; 36(1): 31-35. Chinese. PMID: 14970884.
82. Sahota SS, Bramley PM, Menzies IS. The fermentation of lactulose by colonic bacteria. J Gen Microbiol, 1982; 128(2): 319-25. https://doi: 10.1099/00221287-128-2-319.
83. Wallace BD, Roberts AB, Pollet RM, Ingle JD, Biernat KA, Pellock SJ, et al. Structure and Inhibition of Microbiome β-Glucuronidases Essential to the Alleviation of Cancer Drug Toxicity. Chem Biol, 2015; 22(9): 1238-1249. https://doi: 10.1016/j.chembiol.2015.08.005.
84. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl Res, 2017; 179: 204-222. https://doi: 10.1016/j.trsl.2016.08.002.
85. Klaassen CD, Cui JY. Review: Mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metab Dispos, 2015; 43(10): 1505-21. https://doi: 10.1124/dmd.115.065698.

86. Barlow JT, Leite G, Romano AE, Sedighi R, Chang C, Celly S, et al. Quantitative sequencing clarifies the role of disruptor taxa, oral microbiota, and strict anaerobes in the human small-intestine microbiome. Microbiome, 2021; 9(1): 214. https://doi: 10.1186/s40168-021-01162-2.
87. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell, 2014; 157(1): 121-41. https://doi: 10.1016/j.cell.2014.03.011.
88. Marcobal A, Sonnenburg JL. Human milk oligosaccharide consumption by intestinal microbiota. Clin Microbiol Infect, 2012; 4(04): 12-5. https://doi: 10.1111/j.1469-0691.2012.03863.x.
89. Zheng W, Zhao W, Wu M, Song X, Caro F, Sun X, et al. Microbiota-targeted maternal antibodies protect neonates from enteric infection. Nature, 2020; 577(7791): 543-548. https://doi: 10.1038/s41586-019-1898-4.
90. Zheng D, Liwinski T, Elinav. Interaction between microbiota and immunity in health and disease. Cell Res, 2020; 30(6): 492-506. https://doi: 10.1038/s41422-020-0332-7.
91. Umesaki Y, Setoyama H, Matsumoto S, Okada Y. Expansion of alpha beta T-cell receptor-bearing intestinal intraepithelial lymphocytes after microbial colonization in germ-free mice and its independence from thymus. Immunol, 1993; 79(1): 32-7. PMID: 8509140
92. Feng T, Cong Y, Alexander K, Elson CO. Regulation of Toll-like receptor 5 gene expression and function on mucosal dendritic cells. PLoS One, 2012; 7(4): e35918. https://doi: 10.1371/journal.pone.0035918.
93. Ilhan N. Gut microbiota and metabolism. Int J Med Biochem, 2018; 1(3): 115-128.
94. Rosser EC, Oleinika K, Tonon S, Doyle R, Bosma A, Carter NA, et al. Regulatory B cells are induced by gut microbiota-driven interleukin-1β and interleukin-6 production. Nat Med, 2014; 20(11): 1334-9. https://doi: 10.1038/nm.3680.
95. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell, 2005; 122(1): 107-18. https://doi: 10.1016/j.cell.2005.05.007.
96. Mousa WK, Athar B, Merwin NJ, Magarvey NA. Antibiotics and specialized metabolites from the human microbiota. Nat Prod Rep, 2017; 34(11): 1302-1331. https://doi: 10.1039/c7np00021a.
97. Hertzberger R, Arents J, Dekker HL, Pridmore RD, Gysler C, Kleerebezem M, et al. $H(_2)O(_2)$ production in species of the Lactobacillus acidophilus group: a central role for a

novel NADH-dependent flavin reductase. Appl Environ Microbiol, 2014; 80(7): 2229-39. https://doi: 10.1128/AEM.04272-13.

98. Hegemann JD, Zimmermann M, Xie X, Marahiel MA. Lasso peptides: an intriguing class of bacterial natural products. Acc Chem Res, 2015; 48(7): 1909-19. https://doi: 10.1021/acs.accounts.5b00156.
99. Rea MC, Sit CS, Clayton E, O'Connor PM, Whittal RM, Zheng J, et al. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against Clostridium difficile. Proc Natl Acad Sci USA, 2010; 107(20): 9352-7. https://doi: 10.1073/pnas.0913554107.
100. Toba T, Samant SK, Yoshioka E. Itoh T. Reutericin 6, a new bacteriocin produced by *Lactobacillus reuteri* LA6. Lett Appl Microbiol, 1991; 13: 281–286. https://doi.org/10.1111/j.1472-765X.1991.tb00629.x
101. Guasch JF, Enfedaque J, Ferrer S, Gargallo D, Regué M. Bacteriocin 28b, a chromosomally encoded bacteriocin produced by most Serratia marcescens biotypes. Res Microbiol, 1995; 146(6): 477-83. https://doi:10.1016/0923-2508(96)80293-2.
102. Singh AK, Hertzberger RY, Knaus UG. Hydrogen peroxide production by lactobacilli promotes epithelial restitution during colitis. Redox Biol, 2018; 16: 11-20. https://doi: 10.1016/j.redox.2018.02.003.
103. Mikelsaar M, Sepp E, Štšepetova J, Songisepp E, Mändar R. Biodiversity of Intestinal Lactic Acid Bacteria in the Healthy Population. Adv Exp Med Biol, 2016; 932: 1-64. https://doi: 10.1007/5584_2016_3.
104. Valik L, Medvedova A, Liptakova D. Characterization of the growth of *Lactobacillus rhamnosus* GG in milk at suboptimal temperatures. J Food Nutr Res, 2008; 47: 60-67.
105. Elshaghabee FM, Bockelmann W, Meske D, de Vrese M, Walte HG, Schrezenmeir J, et al. Ethanol production by selected intestinal microorganisms and lactic acid bacteria growing under different nutritional conditions. Front Microbiol, 2016; 7: 47. https://doi: 10.3389/fmicb.2016.00047.
106. Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. Microbiome, 2019; 7: 91. https://doi.org/10.1186/s40168-019-0704-8
107. Balskus EP. Colibactin: understanding an elusive gut bacterial genotoxin. Nat Prod Rep, 2015; 32(11): 1534-40. https://doi: 10.1039/c5np00091b.

108. Kevany BM, Rasko DA, Thomas MG. Characterization of the complete zwittermicin A biosynthesis gene cluster from *Bacillus cereus*. Appl Environ Microbiol, 2009; 75(4): 1144-1155. https://doi: 10.1128/AEM.02518-08.
109. Gaillard-Gendron S, Vignon D, Cottenceau G, Graber M, Zorn N, van Dorsselaer A, et al. Isolation, purification and partial amino acid sequence of a highly hydrophobic new microcin named microcin L produced by *Escherichia coli*. FEMS Microbiol Lett, 2000; 193: 95–98. https://doi.org/10.1111/j.1574-6968.2000.tb09408.x
110. Hatziioanou D, Gherghisan-Filip C, Saalbach G, Horn N, Wegmann U, Duncan SH, et al. Discovery of a novel lantibiotic nisin O from Blautia obeum A2-162, isolated from the human gastrointestinal tract. Microbiol (Reading), 2017; 163(9): 1292-1305. https://doi: 10.1099/mic.0.000515.
111. Abee T, Klaenhammer TR, Letellier L. Kinetic studies of the action of lactacin F, a bacteriocin produced by *Lactobacillus johnsonii* that forms poration complexes in the cytoplasmic membrane. Appl Environ Microbiol, 1994; 60(3): 1006-13. https://doi: 10.1128/aem.60.3.1006-1013.1994.
112. del Campo R, Tenorio C, Jiménez-Díaz R, Rubio C, Gómez-Lus R, Baquero F, et al. Bacteriocin production in vancomycin-resistant and vancomycin-susceptible Enterococcus isolates of different origins. Antimicrob Agents Chemother, 2001; 45(3): 905-912. https://doi: 10.1128/AAC.45.3.905-912.2001.
113. Toba T, Samant SK, Yoshioka E, Itoh T. Reutericin 6, a new bacteriocin produced by *Lactobacillus reuteri* LA 6. Lett Appl Microbiol, 1991; 13: 281–286. https://doi: 10.1111/j.1472-765X.1991.tb00629.x
114. Dimitrijević R, Stojanović M, Zivković I, Petersen A, Jankov RM, Dimitrijević L, et al. The identification of a low molecular mass bacteriocin, rhamnosin A, produced by *Lactobacillus rhamnosus* strain 68. J Appl Microbiol, 2009; 107(6): 2108-2115. https://doi: 10.1111/j.1365-2672.2009.04539.x.
115. Bull M, Plummer S, Marchesi J, Mahenthiralingam E. The life history of *Lactobacillus acidophilus* as a probiotic: a tale of revisionary taxonomy, misidentification and commercial success. FEMS Microbiol Lett, 2013; 349(2): 77-87. https://doi: 10.1111/1574-6968.12293.
116. Déchelotte P, Breton J, Trotin-Picolo C, Grube B, Erlenbeck C, Bothe G, et al. The probiotic strain *H. alvei* HA4597® improves weight loss in overweight subjects under moderate hypocaloric diet: A proof-of-concept, multicenter randomized, double-blind placebo-controlled study. Nutrients, 2021; 13(6): 1902. https://doi: 10.3390/nu13061902.

117. Plaza-Diaz J, Gomez-Llorente C, Abadia-Molina F, Saez-Lara MJ, Campaña-Martin L, Muñoz-Quezada S, et al. Effects of *Lactobacillus paracasei* CNCM I-4034, Bifidobacterium breve CNCM I-4035 and *Lactobacillus rhamnosus* CNCM I-4036 on hepatic steatosis in Zucker rats. PLoS One, 2014; 9(5): e98401. https://doi: 10.1371/journal.pone.0098401.
118. An HM, Park SY, Lee DK, Kim JR, Cha MK, Lee SW, et al. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats. Lipids Health Dis, 2011; 10: 116. https://doi: 10.1186/1476-511X-10-116.
119. Kim SW, Park KY, Kim B, Kim E, Hyun CK. *Lactobacillus rhamnosus* GG improves insulin sensitivity and reduces adiposity in high-fat diet-fed mice through enhancement of adiponectin production. Biochem Biophys Res Commun, 2013; 431(2): 258-263. https://doi: 10.1016/j.bbrc.2012.12.121.
120. Breyner NM, Michon C, de Sousa CS, Vilas Boas PB, Chain F, Azevedo VA, et al. Microbial Anti-Inflammatory Molecule (MAM) from *Faecalibacterium prausnitzii* Shows a Protective Effect on DNBS and DSS-Induced Colitis Model in Mice through Inhibition of NF-κB Pathway. Front Microbiol, 2017; 8: 114. https://doi: 10.3389/fmicb.2017.00114.
121. Fernández-Murga ML, Sanz Y. Safety Assessment of *Bacteroides uniformis* CECT 7771 Isolated from Stools of Healthy Breast-Fed infants. PLoS One, 2016; 11(1): e0145503. https://doi: 10.1371/journal.pone.0145503.
122. Chen J, Wang R, Li XF, Wang RL. *Bifidobacterium adolescentis* supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. Br J Nutr, 2012; 107(10): 1429-34. https://doi: 10.1017/S0007114511004491.
123. Yadav H, Jain S, Sinha PR. Antidiabetic effect of probiotic dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei* in high fructose fed rats. Nutrition, 2007; 23(1): 62-8. https://doi: 10.1016/j.nut.2006.09.002.
124. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA, 2013; 110(22): 9066-9071. https://doi: 10.1073/pnas.1219451110.
125. Jiang H, Zhang Y, Xu D, Wang Q. Probiotics ameliorates glycemic control of patients with diabetic nephropathy: A randomized clinical study. J Clin Lab Anal, 2021; 35(4): e23650. https://doi: 10.1002/jcla.23650.

126. De Mauri A, Carrera D, Bagnati M, Rolla R, Vidali M, Chiarinotti D, et al. Probiotics-supplemented low-protein diet for microbiota modulation in patients with advanced chronic kidney disease (ProLowCKD): Results from a Placebo-Controlled Randomized Trial. Nutrients, 2022; 14(8): 1637. https://doi: 10.3390/nu14081637.
127. Tian N, Li L, Ng JK, Li PK. The Potential benefits and controversies of probiotics use in patients at different stages of Chronic Kidney Disease. Nutrients, 2022; 14(19): 4044. https://doi: 10.3390/nu14194044.
128. Guida B, Germanò R, Trio R, Russo D, Memoli B, Grumetto L, et al. Effect of short-term synbiotic treatment on plasma p-cresol levels in patients with chronic renal failure: a randomized clinical trial. Nutr Metab Cardiovasc Dis, 2014; 24(9): 1043-9. https://doi: 10.1016/j.numecd.2014.04.007.
129. McFarlane C, Krishnasamy R, Stanton T, Savill E, Snelson M, Mihala G, et al. Synbiotics Easing Renal Failure by Improving Gut Microbiology II (SYNERGY II): A Feasibility Randomized Controlled Trial. Nutrients, 2021; 13(12): 4481. https://doi: 10.3390/nu13124481.
130. Sun B, Ma T, Li Y, Yang N, Li B, Zhou X, et al. *Bifidobacterium lactis* Probio-M8 adjuvant treatment confers added benefits to patients with Coronary Artery Disease via target modulation of the Gut-Heart/-Brain axes. mSystems, 2022; 7(2): e0010022. https://doi: 10.1128/msystems.00100-22.
131. Kiessling G, Schneider J, Jahreis G. Long-term consumption of fermented dairy products over 6 months increases HDL cholesterol. Eur J Clin Nutr, 2002; 56(9): 843-9. https://doi: 10.1038/sj.ejcn.1601399.
132. Madjd A, Taylor MA, Mousavi N, Delavari A, Malekzadeh R, Macdonald IA, et al. Comparison of the effect of daily consumption of probiotic compared with low-fat conventional yogurt on weight loss in healthy obese women following an energy-restricted diet: a randomized controlled trial. Am J Clin Nutr, 2016; 103(2): 323-9. https://doi: 10.3945/ajcn.115.120170.
133. Abdi M, Esmaeili Gouvarchin Ghaleh H, Ranjbar R. Lactobacilli and Bifidobacterium as anti-atherosclerotic agents. Iran J Basic Med Sci, 2022; 25(8): 934-946. https://doi: 10.22038/IJBMS.2022.63860.14073.
134. Bendali F, Kerdouche K, Hamma-Faradji S, Drider D. In vitro and in vivo cholesterol lowering ability of *Lactobacillus pentosus* KF923750. Benef Microbes, 2017; 8(2): 271-280. https://doi: 10.3920/BM2016.0121.

135. Michael DR, Davies TS, Moss JWE, Calvente DL, Ramji DP, Marchesi JR, et al. The anti-cholesterolaemic effect of a consortium of probiotics: An acute study in C57BL/6J mice. Sci Rep, 2017; 7(1): 2883. https://doi: 10.1038/s41598-017-02889-5.
136. Huang Y, Wang J, Quan G, Wang X, Yang L, Zhong L. *Lactobacillus acidophilus* ATCC 4356 prevents atherosclerosis via inhibition of intestinal cholesterol absorption in apolipoprotein E-knockout mice. Appl Environ Microbiol, 2014; 80(24): 7496-7504. https://doi: 10.1128/AEM.02926-14.
137. Cao J, Amakye WK, Qi C, Liu X, Ma J, Ren J. *Bifidobacterium Lactis* Probio-M8 regulates gut microbiota to alleviate Alzheimer's disease in the APP/PS1 mouse model. Eur J Nutr, 2021; 60(7): 3757-3769. https://doi: 10.1007/s00394-021-02543-x.
138. Yong SJ, Tong T, Chew J, Lim WL. Antidepressive mechanisms of probiotics and their therapeutic potential. Front Neurosci, 2020; 13: 1361. https://doi: 10.3389/fnins.2019.01361.
139. Lukić I, Getselter D, Ziv O, Oron O, Reuveni E, Koren O, et al. Antidepressants affect gut microbiota and *Ruminococcus flavefaciens* is able to abolish their effects on depressive-like behavior. Transl Psychiatry, 2019; 9(1): 133. https://doi: 10.1038/s41398-019-0466-x.
140. Romijn AR, Rucklidge JJ, Kuijer RG, Frampton C. A double-blind, randomized, placebo-controlled trial of *Lactobacillus helveticus* and *Bifidobacterium longum* for the symptoms of depression. Aust NZJ Psychiatry, 2017; 51(8): 810-821. https://doi: 10.1177/0004867416686694. Epub 2017 Jan 10.
141. Slykerman RF, Hood F, Wickens K, Thompson JMD, Barthow C, Murphy R, et al. Probiotic in pregnancy study group. Effect of *Lactobacillus rhamnosus* HN001 in pregnancy on Postpartum Symptoms of Depression and Anxiety: A Randomised Double-blind Placebo-controlled Trial. EBioMedicine, 2017; 24: 159-165. https://doi: 10.1016/j.ebiom.2017.09.013.
142. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition, 2016; 32(3): 315-20. https://doi: 10.1016/j.nut.2015.09.003.
143. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA, 2011; 108(38): 16050-5. https://doi: 10.1073/pnas.1102999108.

144. Vieira AT, Teixeira MM, Martins FS. The role of probiotics and prebiotics in inducing gut immunity. Front Immunol, 2013; 4: 445. https://doi: 10.3389/fimmu.2013.00445.
145. Yan F, Polk DB. Probiotics and immune health. Curr Opin Gastroenterol, 2011; 27(6): 496-501. https://doi: 10.1097/MOG.0b013e32834baa4d.
146. Vitiñi E, Alvarez S, Medina M, Medici M, de Budeguer MV, Perdigón G. Gut mucosal immunostimulation by lactic acid bacteria. Biocell, 2000; 24(3): 223-232.
147. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells, 2023; 12(1): 184. https://doi: 10.3390/cells12010184
148. Vinderola G, Matar C, Perdigon G. Role of intestinal epithelial cells in immune effects mediated by gram-positive probiotic bacteria: involvement of toll-like receptors. Clin Diagn Lab Immunol, 2005; 12(9): 1075-1084. https://doi: 10.1128/CDLI.12.9.1075-1084.2005.
149. Fanning S, Hall LJ, Cronin M, Zomer A, MacSharry J, Goulding D, et al. Bifidobacterial surface-exopolysaccharide facilitates commensal-host interaction through immune modulation and pathogen protection. Proc Natl Acad Sci USA, 2012; 109(6): 2108-13. https://doi: 10.1073/pnas.1115621109.
150. Kourelis A, Zinonos I, Kakagianni M, Christidou A, Christoglou N, Yiannaki E, et al. Validation of the dorsal air pouch model to predict and examine immunostimulatory responses in the gut. J Appl Microbiol, 2010; 108(1): 274-84. https://doi: 10.1111/j.1365-2672.2009.04421.x.
151. Sakai F, Hosoya T, Ono-Ohmachi A, Ukibe K, Ogawa A, Moriya T, et al. *Lactobacillus gasseri* SBT2055 induces TGF-β expression in dendritic cells and activates TLR2 signal to produce IgA in the small intestine. PLoS One, 2014; 9(8): e105370. https://doi: 10.1371/journal.pone.0105370.