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Exploring the functional roles of sustainable dietary patterns on gut microbiota composition and optimal health

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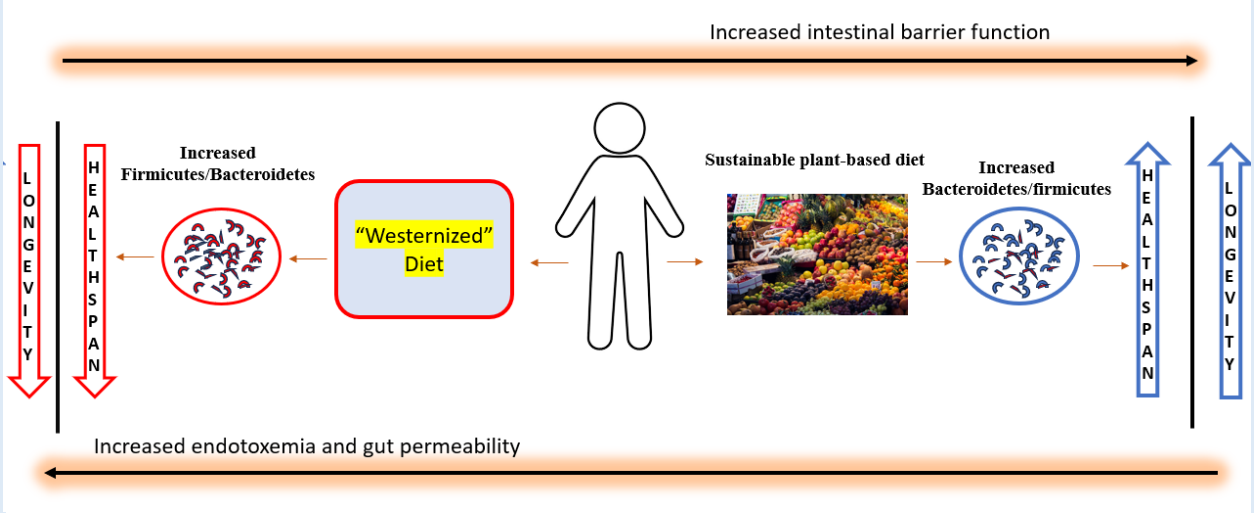
ABSTRACT

The aging population presents a growing global challenge, due to increased risk of age-related diseases, leading to arising burden on healthcare systems and highlighting the need for effective interventions to promote healthy aging. Emerging evidence suggests that certain dietary patterns can influence the gut microbiome favorably, potentially mitigating age-related chronic diseases and metabolic dysfunction such as diabetes, obesity, and cardiovascular diseases. Gut microbiota dynamics, initially stable in early life, are disrupted with age, impacting both prokaryotic and eukaryotic symbionts, resulting in an adaptive response in the gut microbiota defined by an increase in composition and diversity over time. In addition to environmental and genetic factors, the impact of diet has been noted as a critical factor that influences these dynamics. In this review, we propose sustainable dietary patterns like the Mediterranean, vegetarian, ketogenic, and DASH diets as a suitable panacea to counteract deleterious feeding patterns by offering nutritious and environmentally sustainable options, potentially lowering the prevalence of chronic diseases and further explores their functional roles with respect to modulating the gut microbiota composition, and their overall impact on optimal health.

Keywords: Aging; healthy diet; Gut microbiota; Mediterranean Diet; Plant-based diet; dietary intervention



INTRODUCTION

The rise in the elderly population on a global scale has given rise to significant social and healthcare issues, presenting new clinical complexities related to chronic diseases [1-2]. Aging is defined by a gradual loss of physiological integrity, which leads to reduced function and increasing vulnerability to mortality. This degeneration is the key risk factor for major human diseases [3-4]. However, there may be a metabolic clock that regulates aging since various metabolic changes compound with time coupled with a decline in biological fitness. Genetic loci associated with extended longevity affect metabolism, while many inborn abnormalities in metabolic circuits speed up aging. For example, sedentariness and a hypercaloric diet—two hallmarks of the "Westernized" lifestyle—have deleterious metabolic effects that might hasten aging. On the other hand, actions that lengthen lifespan, such as calorie restriction, have positive pleiotropic effects on metabolism.

The hypothesis posits that diet may impact systemic inflammation, insulin sensitivity, and cardiovascular health through alterations in gut microbiota composition, representing a significant focus in aging research aimed at alleviating the negative effects of advanced age and fostering optimal health and longevity [5-6]. Functional foods (FFs) can both help regulate gut flora [7]. Based on the definition provided by the Functional Food Center, FFs are "natural or processed foods that contain biologically-active compounds; which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [8]. Growing body of scientific data indicates the possible health advantages of FFs which has led to their increased attention. Several studies have demonstrated the regulatory roles of antioxidants, usually found in FFs, on redox activities by inhibiting free radicals and suppressing inflammation, conditions known to be consequent to chronic metabolic diseases and cancer [9-10].

Our food system is not sustainable as it stands, making it difficult to meet the goals established by many international organizations, including those included in the Paris Agreement [11]. Sustainable diets, as those that guarantee food security for both current and future generations, provide wholesome and healthy food for

everyone, are culturally acceptable, equitable, and reasonably priced [12]. The Mediterranean Diet (MD) is a recommended nutritional model that is both healthful and ecologically sustainable, compatible with socio-cultural preferences, and has a good influence on local economies [13].

Consequently, plant-based diets have the added advantage of improving environmental sustainability while lowering risk factors for chronic health problems including diabetes and cardiovascular disease (CVD) [14]. This strategy supports the overarching objective of promoting sustainability on all fronts—social, economic, and environmental. Within this context, MD for instance, can be categorized as a sustainable functional food as it is characterized by a diverse array of bioactive compounds that are renowned for their significant health-promoting properties [15–20]. Thus, this review examines how sustainable healthy diets like the MD, ketogenic diet (KD), vegetarian diet (VD), and dietary approach to hypertension (DASH) diet could positively impact the gut microbiota and promote optimal health.

Age-Related Shifts in Gut Microbiota Influenced by Dietary Factors: The gastrointestinal tract hosts a large and diverse bacteria community commonly referred to as the gut microbiota [21]. This microbial balance crucially supports host health and homeostasis by fostering intestinal immunity, inhibiting pathogenic bacteria growth, aiding food digestion, metabolizing drugs and foreign substances, and synthesizing bioactive compounds [22-23]. Firmicutes and Bacteroidetes, constituting 90% of the microbiota, dominate its predominant bacterial phyla [24]. The gut microbiota's composition and abundance change throughout an individual's life. Analysis of 16S ribosomal DNA sequencing data from fecal samples reveals discernible age-related variations, with microbial composition differences observed between younger and older individuals [25, 26], although certain limitations have been identified based on its applicability to certain genera, genus-level resolution, and nucleotide variations which further complicates the definition of a healthy gut microbiota [27-28].

Dynamic Nature of the Gut Microbiota*:* The dynamic nature of the microbiota is well-established in early life, exhibiting minor fluctuations in diversity until middle age, followed by a period of relative stability [29–31]. However, aging disrupts this stability, affecting both prokaryotic and eukaryotic symbionts collectively known as holobionts [32]. The gut microbiota exhibits a major function by assimilating age-related changes, and while the overall composition and diversity exhibit an upward trend with aging, specific microbial species display increased abundance in higher age groups, while certain health-associated species decline in representation [5]. Researchers suggest that an individual's age has a substantial influence on their gut health, with advancing age correlating with a decline in gut microbiota diversity, marked by a reduction in glycolytic and proteolytic bacteria and an elevated sub-dominant species [33]. This age-related shift is characterized by diminished thick-walled bacteria abundance, in addition to lower abundance of *Bacteroides* and *bifidobacteria* in the elderly, contributing to inflammaging and declining immune function [33-34].

The microbiota of centenarians and very old people is richer and more diverse due to the *Prevotella* enterotype being prevalent, when compared to young individuals, and improved by the elderly's diet, which is high in potatoes and cereals. However, young individuals show a decrease in microbial species' richness and diversity associated with the prevalent *Bacteroides* enterotype, which reveals its high vulnerability to outside influences [35]. In addition, the elderly population have a distinct microbiota characterized by increased production of short-chain fatty acids (SCFAs) compared to young-old adults, with higher levels of *Christensenellaceae*

associated with longevity, normal body mass index (BMI), and reduced CVD risk, while *Bifidobacterium longum* and *Eubacterium coprostanoligenes* increased abundance may mitigate the associated risk [36-37]. However, age-induced microbiota alterations can harm human health [30], although the mechanism remains unclear [38].

Fecal microbiota transplantation (FMT) from young mice to old mice resulted in significant increase in fecal *Akkermansia muciniphila* and improvements in liver damage, glucose tolerance, and inflammation [38]. Additionally, the gut microbiota may serve as an additional aging hallmark based on the existence of gut dysbiosis in patients with neurodegenerative diseases, with indications that the severity of cognitive impairment may be correlated with the extent of dysbiosis, potentially enabling its utilization as a prognostic Alzheimer's disease (AD) biomarker [39]. While microbiota variability is not solely age-dependent, it is also influenced by additional factors associated with aging, such as race, geographic location, lifestyle choices, and genetic distinctions including polymorphism [40–42]. Hirose et al. [43] revealed that specific mitochondrial haplogroups correlate with varying levels of *Bacteroides* and *Prevotella*, though differences are region-specific; however, non-haplogroup-associated single nucleotide polymorphisms lack distinct associations with varying microbial community, partly attributed to the effect of the nuclear genome's variability on gut microbiota composition, while mitochondria DNA mutations resulted in notable variations in microbial species in mice. However, diet emerges as a pivotal factor in shaping microbiota composition by regulating the abundance of distinct species and determining their individual or collective functions [44–49].

Impact of Nutritional Intake on the Gut Microbiota: Nutritional intake plays a pivotal role in influencing both metabolic well-being and the regulation of the immune system [50]. Obesity [51], type 2 diabetes (T2D) [52], and CVD [53] is closely associated with dietary patterns. These maladies are often interconnected with a constellation of metabolic phenotypes, including but not limited to insulin resistance, glucose intolerance, dysregulated lipid metabolism, hypertension, and persistent systemic inflammation [54]. The core objective of introducing a dietary intervention is to reconfigure the equilibrium of bacterial communities within the gastrointestinal tract, transitioning from a state linked to disease to one that is more harmonious and resilient [55].

Table 1: Impact of plant-based dietary components on gut microbiota and overall health

Food component	Gut microbiota composition	Overall health outcomes	References
Non-digestible carbohydrates Fructooligosaccharides; Inulin; alpha-linked galactooligosaccharides; beta-linked galactooligosaccharides; xylooligosaccharides from corn cobs and high-fiber sugar cane; beta-glucan from oats	Increase in the abundance of *Prevotella* and *Roseburia,* Bifidobacteria, lactic acid bacteria, *Ruminococcus and Eubacterium rectale;* reduction in *Clostridium* and *Enterococcus* species.	Support the growth of beneficial microbes by acting as prebiotics; Reduction in proinflammatory cytokine secretion, serum triglycerides, total cholesterol, and LDL-c; insulin sensitivity; SCFA propionate generation; Protective effects against CVD and CNS disorders.	[58–60]
Proteins			
Animal protein	Low abundance of dietary plant polysaccharides metabolizing microorganisms which includes *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii, and* butyrate-producing bacteria; increased abundance of *Bacteroides* and	Increased expression of Proinflammatory cytokines; increased risk of colorectal cancer; Increased SCFA production; produces beneficial phenolic acids.	

Food component	Gut microbiota composition	Overall health outcomes	References
	Clostridia, which are examples of bile-tolerant microorganisms; increased microbial diversity.		
Proteins			[59, 61-62]
Animal protein	Low abundance of dietary plant polysaccharides metabolizing microorganisms which includes *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii, and* butyrate-producing bacteria; increased abundance of *Bacteroides* and *Clostridia,* which are examples of bile-tolerant microorganisms; increased microbial diversity.	Increased expression of Proinflammatory cytokines; increased risk of colorectal cancer; Increased SCFA production; produces beneficial phenolic acids.	
Plant protein Whey and Pea protein	Increase microbial diversity and abundance of *Bifidobacterium* and *Lactobacillus;* decrease in *Bacteroides fragilis* and *Clostridium perfringens*	Synthesis of SCFA; enhancement of the intestinal mucosal barrier; reduction of intestinal lipopolysaccharide (LPS) levels; anti-inflammatory and anti-cancer properties.	
Fats			[59, 61, 63-64]
Monounsaturated and polyunsaturated fats	Relative abundance of lactic acid bacteria was increased, in addition to *Bifidobacteria, Akkermansia muciniphila, Ruminococcaceae, Bifidobacteria;* decrease in *Clostridium* sp. cluster XIVa species; increased ratio of Bacteroidetes to Firmicutes	Anti-inflammatory effects; improvement in gut microbiota; reduced generation of T_H17 cells; improved gut mucosal integrity; low intestinal level of LPS; alleviation of chronic disease risk.	
Saturated fats	*Bilophila* and *Faecalibacterium prausnitzii* were increased while there is a relative decrease in *Bifidobacterium*	Heightened pro-inflammatory cytokines levels including IL-1, IL-6, and TNF-α; Promote pro-inflammatory T_H1 immunity; increased blood total and LDL-c; onset of metabolic disorders and risk of CVD.	
Polyphenols: found in seeds and greens, tea, cacao, and fruits	Increased in *Bifidobacterium* and *Lactobacillus-Enterococcus* spp. abundance.	Increased SCFA production; Increased anti-pathogenic, anti-carcinogenic, anti-inflammatory, and antioxidant effects; CVD and obesity-related disorders including diabetes were decreased; improvement in osteoporosis and neuroprotective functions; potential for adverse reactions caused by possible intricate mechanism of action as well as individual diversity; reduction in amyloid formation in humans	[59-60, 65–69]

Despite findings from twin studies suggesting an interplay between host genetics and the intestinal microbiota, environmental factors exert a more significant influence than genetic factors [43, 56]. Numerous population-

based studies have underscored the pivotal role of diet as a primary determinant of the variations observed in the microbiota among individuals [49, 57]. The gut microbiota can modify the host's nutritional status by breaking down dietary components beyond the host's metabolic capabilities, such as extracting energy from foods rich in carbohydrates and lipids [49]. This is exemplified by the interaction between *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii* in sterile mice through increased sugar fermentation and energy absorption, underscoring the substantial influence of gut microbial population on host's digestion and energy acquisition [49].

Fermented black soybean and adlay supplements administered to aging mice mitigated age-induced intestinal dysbiosis and elevated the abundance of beneficial microbes, and inhibited fat deposition in adipose tissues and muscle loss, with a concomitant reduction in pro-inflammatory cytokines [70]. Furthermore, *Agaricus bisporus* displays anti-aging potential via modulation of the gut microbiota by increasing α-diversity, SCFAs, and beneficial microbes, enhanced cognitive and locomotor activities, while decreasing pro-inflammatory cytokines in an aging mice model [71]. Similarly, ellagic acid, a polyphenol largely predominant in medicinal plants, improved plasma, brain metabolites, and cognitive parameters, while also reducing the Firmicutes/Bacteroidota ratio in aging mice [72]. Moreso, certain dietary interventions like the MD and high-protein diets resulted in heightened levels of *Oscillospira* and *Butirycimonas* genus, and enrichment in Firmicutes respectively [49].

DIETARY PLANS AND OPTIMAL HEALTH

Mediterranean Diet: The traditional MD is characterized by its emphasis on a substantial intake of greens, legumes, fruits, and edible seeds, which are plant-based dietary sources. Primarily in their unrefined state, cereals are also a significant component. This diet features a notable high intake of olive oil while minimizing the consumption of saturated lipids. Fish intake is moderately high, influenced by the proximity to the sea. Dairy products, mainly in the form of cheese or yogurt, are consumed in a low-to-moderate manner. Meat and poultry intake is limited, and there is consistent but moderate consumption of ethanol, predominantly in the form of wine, often enjoyed during meals [73]. During the early 1960s, the dietary patterns characteristic of the traditional MD was prevalent in extensive regions of Greece, Crete, and southern Italy, coinciding with a period when adult life expectancy in these areas was globally among the highest. Remarkably, during this time frame, there were low incidences of CVD, cancers, and chronic metabolic disorders, despite constraints in available medical services [74].

Major composition, impact on gut microbiota and metabolism: The consumption of whole grains is associated with a myriad of health benefits, primarily attributed to the heightened content of dietary fiber in whole grain ingredients in contrast to refined cereal components [75]. Whole grains offer a harmonious blend of both soluble and insoluble fiber, recognized for their potential to lower the occurrence of non-communicable diseases [76]. More specifically, numerous components characteristics of the MD, such as plant foods and red wine, boast nutrient richness in substances like fiber and polyphenols — a noteworthy phytochemical. These elements have been independently linked to a decreased risk of mortality and morbidity associated with non-communicable diseases [77–80]. Dietary fiber and

polyphenols exhibit prebiotic actions, potentially influencing health outcomes [81]. Colonic bacterial fermentation of dietary fiber produces SCFAs which are believed to exert systemic anti-inflammatory effects [82]. The synthesis of SCFAs, such as acetate, propionate, and butyrate, via the fermentative breakdown of non-digestible fiber, serves as a substantial energy reservoir for colonic tissues. This process concurrently contributes to the preservation of gastrointestinal tissue integrity, exerts modulatory effects on inflammatory pathways, and maintains inhibitory control over the proliferation of pathogenic bacteria [83].

Polyphenols undergo initial metabolism by the gut microbiota, leading to enhanced absorption. Following metabolism by host enzymes, various metabolites with a range of physiological effects emerge [84]. Furthermore, specific polyphenols function as antimicrobials, targeting pathogenic bacteria [85]. Alterations in gut microbiome functionality correlate with improvements in cardiovascular and metabolic parameters and immune system modulation and encompass decreased triglyceride levels, enhanced liver function, as well as reduction in C-reactive protein (CRP), which is a biomarker for systemic inflammation, thereby impacting the overall health of the host [50, 86-87]. Furthermore, a systematic review revealed that MD consumption was associated with a lower risk of neurodegenerative diseases including AD and Parkinson's diseases (PD). Specifically, eight genera and two species of bacteria demonstrated an inverse relationship with the MD in the context of AD, while one family, eight genera, and three species of bacteria exhibited a similar inverse relationship in the context of Parkinson's Disease [88]. Selected clinical trials on the age-related effect of MD on gut microbiota are shown in Table 2.

MD, which is high in omega-3 polyunsaturated fats from harvested fruits, vegetables, and oily seafood, also includes omega-6 polyunsaturated fats from nuts and non-olive plant oils [89]. Increased tissue omega-3 polyunsaturated fats levels stimulate the formation of intestinal alkaline phosphatase, causing changes in gut microbiota composition that lower LPS release, gut permeability, and inflammation, eventually easing endotoxemia [90]. While the actions of omega-6 on gut microbiota have received less attention than those of omega-3, rodent-based research reveals the opposite effects of these fatty acids on metabolic endotoxemia and systemic inflammation, which can be eliminated via treatment with antibodies, indicating a possible role for gut microbiota in mediating these effects [91].

Table 2: Selected randomized controlled trials (2019 – 2023) on the effect of mediterranean diet (MD) on gut microbiota in age-related diseases.

Age-related condition	Study/Participants/Duration	Experimental Findings	References
Cardiovascular health	MedDiary; 34 adults aged 45 – 75 years with a risk of CVD; 8 weeks	Increase in *Butyricicoccus* and decreased levels of *Colinsella, Veillonella*, *Lachnospiraceae* and *Streptococcus;* *Oscillospiraceae* and *Ruminococcaceae* decreases.	[50]
Chronic kidney disease (CKD)	Medika study; 60 patients with CKD with mean age of 67 years; 26 weeks	Reduced levels of microbiota metabolites: serum levels of IS and PCS, urinary sodium and potassium levels; increased microbial species-producing butyrate including *Lachnospiraceae, Ruminococcaceae, Prevotellaceae, Bifidobacteriaceae;* decreased relative abundance of *Enterobacteriaceae*.	

Age-related condition	Study/Participants/Duration	Experimental Findings	References
Frailty	NU-AGE; 612 subjects between 65 – 79 years; 12 months	Diet-responsive taxa/markers include *Faecalibacterium prausnitzii, Roseburia (R. hominis), Eubacterium (E. rectale, E. eligens, E. xylanophilum), Bacteroides thetaiotaomicron, Prevotella copri* and *Anaerostipes hadrus* which are enriched with increased adherence to MD while *Ruminococcus torques, Collinsella aerofaciens, Coprococcus comes, Dorea formicigenerans, Clostridium ramosum, Veillonella dispar, Flavonifractor plautii* and *Actinomyces lingnae* were depleted with MD adherence. The diet-responsive taxa had consistent negative associations with Gait Speed Time, hs-CRP, IL-17 levels, and Fried Scores. However, they had a positive association with improved cognitive function, reduced frailty, adiponectin, and sGP130 when compared to the Diet-negative taxa.	[86]
Overweight/Obese	DINAMIC; 82 overweight/obese subjects with a mean age of 43 years; 8 weeks	Increased MD adherence significantly reduced levels of *Ruthenibacterium lactatiformans, Flavonifractor plautii, Parabacteroides merdae, Ruminococcus torques, Ruminococcus gnavus, and Streptococcus thermophilus; Faecalibacterium prausnitzii clade, Roseburia* and *Lachnospiraceae* were enriched at either 4 or 8-week. Low plasma total cholesterol and HDL-c after 4 weeks; increase in urinary urolithins, fecal bile acid breakdown and insulin sensitivity No alteration in other various biochemical parameters tested.	[93]
Mild Cognitive Impairment (MCI)	BEAM; 17 MCI subjects with a mean age of 65 years; MMKD intervention for 6 weeks	Increase in *Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae,* and *Erysipelotriaceae;lacto and Lachnobacterium* decreases Slight reduction in fecal lactate and acetate; increase in propionate and butyrate. Correlation analysis showed a negative correlation between *Tenericutes* and changes in the CSF levels of Aß42, *Enterobacteriaceae,* and Aß42, and *Mollicutes* and tau-p181 in MCI after MMKD. However, there was a positive correlation between *Lachnospiraceae* and Aß42, *Rikenellaeae* and *Parabacteroides* with Aß42 in MCI after MMKD.	[94]
Overweight	CARDIVEG; 23 overweight subjects, low-to-moderate cardiovascular risk with a mean age of 59 years; 3 months	Significant alterations in *Enterorhabdus, Lachnoclostridium,* and *Parabacteroides;* negative correlations between SCFA and VEGF, MCP-1, IL-17, IP-10, and IL-12, only after MD.	[87]
Abdominal Obesity or dyslipidemia	DIRECT PLUS; 90 subjects, abdominally Obese/dyslipidemic with a mean age of 52 years; 6 months	Increased *Akkermansia muciniphila, Bacteroides massiliensis, Alistipes putredinis, Bacteroides vulgatus* and *Paraprevotella clara* abundance, LPS, and two sulfate degradation pathways; decrease in *Lactobacillus ruminis* and the oxidative phase of the pentose phosphate pathway. Altered sugar transport, weight regain, insulin rebound, and waist circumference, after repeated aFMT administration.	[95]

Ketogenic Diet: The KD is a long-standing efficacious dietary strategy for intractable epilepsy that has garnered heightened research focus over the past decade. This surge in attention is attributed to nascent findings that underscores the possible therapeutic efficacy of KD across a spectrum of diseases beyond epilepsy, spanning from obesity to malignancies [96]. KD is marked by an elevated fat level, coupled with reduced levels of carbohydrates, and slightly decreased dietary protein. Despite being labeled a KD, it involves the depletion of one nutrient class (carbohydrates) while introducing an alternative substrate (ketones) to serve as a fuel source for the brain, potentially exerting anticonvulsant effects. The conventional ratio of fats to carbohydrates and protein, measured in grams, typically falls within the range of 3:1 or 4:1 [97]. However, it is noteworthy that lower ratios have demonstrated efficacy in different global contexts, particularly in regions like Asia, where rice constitutes a primary dietary staple [98]. There exist four principal types of KDs with demonstrated efficacy, namely, the classic long-chain triglyceride (LCT) KD, which is the traditional type of the KD, the medium-chain triglyceride (MCT) KD, the modified Atkins diet (MAD), and the low glycemic index treatment [99]. An additional variant, the very low-calorie KD (VLCKD), has recently emerged as an attractive nutritional approach for the management of obesity.

Major composition, impact on gut microbiota and metabolism: The VLCKD possesses a diminished sugar content (<50 g/day), a protein intake of 1–1.5 g per kilogram of ideal body weight, a fat consumption ranging from 15 to 30 g per day, and a daily caloric intake approximately ranging between 500 and 800 calories. Since the KD dietary regimen imposes a stringent limitation on carbohydrate intake, typically below 50 grams per day which concurrently elevates the intake of protein and fat, this instigates an augmentation in circulating ketone bodies through the breakdown of fatty acids and ketogenic amino acids [100]. Ketones, serving as an alternative energy substrate to carbohydrates, induce alterations in physiological adaptations [96]. Under normal physiological conditions, the body predominantly utilizes carbohydrates as the primary source of energy production. Insulin plays a pivotal role in extracting and storing energy derived from glucose. In situations where carbohydrate availability is diminished, insulin secretion is attenuated. Initially, the body utilizes stored glucose in the form of glycogen as a fuel source. However, after a period of approximately three to four days, glycogen reserves are depleted. Subsequently, stored fat emerges as the most readily available fuel, and its breakdown into free fatty acids serves as the precursor for ketone production in the liver [101]. Ketone production is principally evident during instances of starvation, prolonged exercise, and strict adherence to a very low carbohydrate diet, with ketosis hypothesized to elicit beneficial health effects, including reduced hyperglycemia and improved lipid profiles [101].

Research in system biology and mouse models has revealed a robust link between insulin resistance and major processes in ketosis, demonstrating a direct connection between glucose transporter type 4, acyl-coenzyme A oxidase 1, and hydroxyacy1-CoA dehydrogenase 1[96, 102]. Multiple molecules involved in alleviating hyperglycemia and hyperinsulinemia in ob/ob mice are influenced by KD, with concomitant alterations in O-GlcNAc-modified protein activity [103]. Additionally, KD causes the loss of essential hepatic lipogenesis-related enzymes in ob/ob mice, such as fatty acid synthase and acetyl-CoA carboxylase 1, present in mice fed on a regular diet [104]. It also upregulates fibroblast growth factor 21 and a decrease in glucose transporter type 2 mRNA in the liver of diabetic mice [105] which plays a vital role in glucose-induced pancreatic β-cell insulin secretion, improving insulin sensitivity in T2DM [96].

Clinical trials examining the interplay between KD, insulin resistance and abundance of gut microbial species are currently limited in number. In a recent clinical study, the effects of a 4-month VLCKD regimen, characterized by an undisclosed macronutrient ratio, and a low-calorie meal, were examined in a cohort of 33 Spanish adults with obesity [106]. The study compared the outcomes of VLCKD interventions with and without the supplementation of synbiotics. The results of the investigation revealed that the VLCKD intervention engendered weight loss and induced a beneficial modulation in the composition of gut microbiota, particularly manifesting as an augmentation in microbial diversity. Nonetheless, the study authors reported the absence of a notable discrepancy in microbial richness.

Also, the efficacy of incorporating whey, greens, or proteins from animal sources into a 45-day VLCKD was investigated in a recent randomized pilot study involving 48 obese Italian adults with obesity and insulin resistance, with the VLCKD composition comprising between 40-45% fat and protein, and about 13% sugar [107]. The study revealed significant weight loss across all intervention groups. Furthermore, the findings indicated that all variations of the VLCKD led to a more favorable gut composition, characterized by low Firmicutes and high Bacteroidetes. Notably, whey and vegetable protein groups showed evidence of microbiota modulation. Additionally, the VLCKDs elicited a notable amelioration in metabolic parameters. Consumption of whey protein was associated with a more pronounced enhancement in muscle strength. In contrast, the VLCKD supplemented with animal protein exhibited a substantial decline in renal function compared to baseline. Importantly, VLCKDs devoid of animal protein demonstrated a more favorable safety attribute in addition to healthier gut diversity.

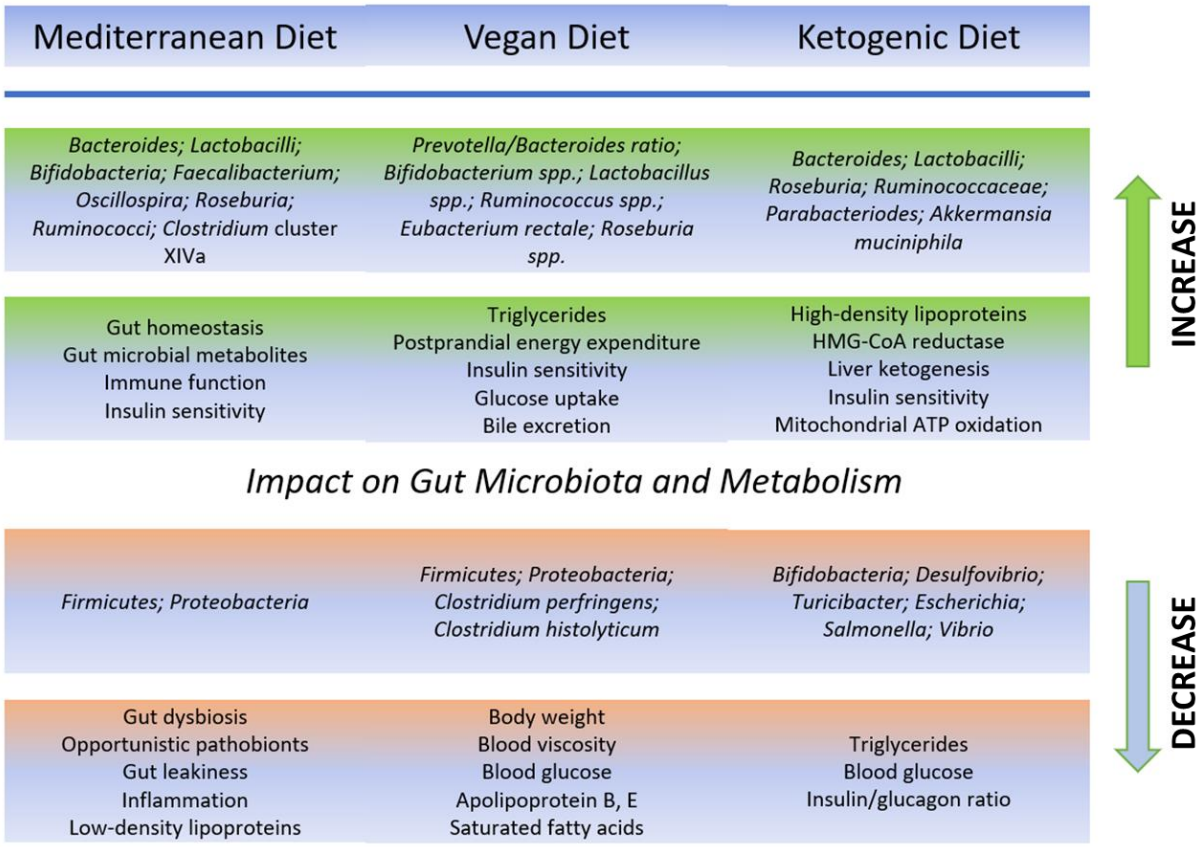


Figure 1: General overview of the potential roles of MD, KD and VD on gut microbiota composition and metabolism [60, 80, 96, 108-109]

Vegetarian Diet*:* Plant-based dietary patterns demonstrate superior environmental sustainability compared to diets characterized by a high intake of animal products. This ecological advantage arises from the reduced demand for natural resources and the markedly diminished environmental impact associated with plant-centric nutrition. Moreover, individuals adhering to vegetarian and vegan lifestyles exhibit a lowered susceptibility to various pathologies. This connection between plant-based diets, environmental sustainability, and favorable health outcomes underscores the multifaceted benefits of embracing such dietary choices [110–112].

Major composition, impact on gut microbiota and metabolism*:* The dietary patterns associated with the VD exhibit considerable diversity owing to the wide array of accessible dietary options and the motivation that lead individuals to embrace the dietary practices. A carefully planned VD encompasses a rich and varied incorporation of plant-based foods [113]. There exist several permutations of VDs, each characterized by distinct inclusions and exclusions. VDs manifest in various forms, each distinguished by their unique dietary components. Vegan involves the complete absence of animal-derived food. Raw vegan shares this characteristic but incorporates food preparation at temperatures below 48°C. Lacto-vegetarians embrace dairy products while excluding eggs, while ovo-vegetarians include eggs with the absence of any milk-based item. Lacto-ovo vegetarians combine milk-based items and eggs. Pesco-vegetarians incorporate fish and seafood but refrain from other animal meats. Across these variations, the commonality lies in the avoidance of animal meat consumption (except for fish in Pesco-vegetarians) and the potential abstention from by-products resulting from animal slaughter [110, 113]. The Academy of Nutrition and Dietetics has earlier provided a comprehensive guide on the nutritional considerations for vegetarians which covers the macronutrients (protein and lipid) and micronutrients composition in addition to their metabolism [110].

A clinical investigation involving 101 adults in Italy revealed discernible differences in microbial composition across dietary groups. Specifically, the vegetarian cohort exhibited higher richness and Bacteroidetes abundance compared to VD and omnivorous groups. This microbial disparity suggests variable role of dietary preferences on gut microbial abundance composition [114]. In a one-month intervention study with six patients with obesity (four with T2D and two with hypertension) following a VD, beneficial changes were reported with respect to the body weight and metabolic parameters. The gut microbiota exhibited changes, including low proportion of Firmicutes/Bacteroidetes, decreased *Enterobacteriaceae*, and increased *Clostridium* species and *Bacteroides fragilis*, indicating potential positive effects on metabolic health and microbiota composition [115].

Similarly, a healthy microbiota was reported in non-diabetic participants including pure vegetarians when compared to omnivores [6]. The vegetarian group exhibited lower Firmicutes and higher Bacteroidetes levels. Specifically, higher microbial populations of *Roseburia* and *Faecalibacterium* within the Firmicutes phylum was shown contributing to higher butyrate levels. Butyrate, a significant energy source for colonocytes, was associated with enhanced intestinal barrier function, low LPS concentration, and reduced CRP and TNF-α/IL-10 ratio in the strict vegetarians [116]. Although classified within the Firmicutes phylum, *Roseburia* and *Faecalibacterium* were associated with a favorable metabolic characteristic in individuals adhering to a VD, marked by reduced body fat and enhanced lipid and insulin resistance markers [117]. In the mixed-diet population, elevated LPS, CRP, TNF-α/IL-10 ratio, and HOMA-IR values suggest manifestations of inflammation and insulin resistance due to high fat diet and may trigger

gut dysbiosis because of intake of animal-based diets, leading to increased LPS and endotoxemia [6, 118]. LPS, found in the external layer of gram-negative bacteria, have been demonstrated to downregulate tight junction proteins, affecting gut permeability, and, when microbiota-derived LPS circulates and binds to Toll-Like Receptor 4 (TLR4), it initiates pro-inflammatory pathways and metabolic dysfunctions [119-120].

Dietary Approaches to Stop Hypertension (DASH): DASH diet is a recognized nutritional regimen employed for the prevention and management of hypertension, as well as the enhancement of cardiovascular health [121]. While sharing similarities with the MD in its emphasis on a plant-based food intake, the DASH diet diverges by placing a heightened emphasis on reducing dietary sodium, limiting the consumption of sweetened beverages and red meats, and excluding alcohol from its recommendations [122].

Major composition, impact on gut microbiota and metabolism: The DASH diet, designed as a comprehensive hypertension prevention and treatment initiative, is centered on the consumption of vegetables, low-fat milk-based products, as well as reduced intake of saturated and overall fat content [123]. Notably effective in substantially lowering blood pressure and recommended for CVD prevention, the DASH diet mirrors the MD in its emphasis on low dietary fat and sodium intake, coupled with a focus on high fiber intake [124]. Furthermore, scientific evidence has indicated that the DASH diet, when implemented, led to reduced circulating propionate levels, and increased acetate and butyrate levels in obese post-menopausal women [125]. The primary distinction between the DASH diet and the MD lies in the former's emphasis on sodium reduction to mitigate blood pressure. Improved adherence to the DASH diet demonstrates significant benefits, including reductions in body weight, blood pressure, serum inflammatory markers, and enhancements in blood glucose and dyslipidemia, contributing to an extended health span [121, 126-127].

While information about the potential impact of DASH on gut microbiota is limited, emerging studies suggest a potential link between gut microbiota dysbiosis and the initiation of hypertension, attributed to decreased microbial richness, diversity, and evenness, along with a heightened Firmicutes/Bacteroidetes ratio observed in hypertensive patients [128-129]. In a cohort of 196 Chinese participants, individuals classified as pre-hypertensive or hypertensive exhibited diminished microbial richness and diversity when compared to their healthy counterparts. Notably, both pre-hypertensive and hypertensive groups showcased a predominant *Prevotella*-dominated enterotype, while the healthy control group displayed a prevailing *Bacteroides*-dominated enterotype [130]. Extended adherence to the DASH diet in older adults is correlates with enhanced cognitive function and decelerated cognitive decline over the long term [131]. However, the role of DASH diet on cognitive and neurological functions has exhibited inconsistency, as evidenced by a prospective longitudinal cohort study revealing no significant association between the DASH diet and mental deterioration in elderly women [132]. Conversely, among overweight individuals with hypertension, the combination of the DASH diet with cardio workout resulted in more pronounced enhancements in learning and memory performance [133]. In addition, a 2018 randomized controlled trial revealed that the standalone DASH dietary intake lacked notable benefits for elderly people with mental decline but enhanced executive functions in participants when supported with aerobic exercise [134].

CONCLUSION

Aging, characterized by a gradual physiological decline resulting in diminished or loss of function and heightened susceptibility to mortality, is underscored by twelve interconnected hallmarks. Aside from their

environmental sustainability, as functional foods, MD, KD, VD, and DASH demonstrate favorable impacts in mitigating metabolic dysfunction and thus preventing or decelerating age-related diseases through several interconnected processes, and in part via the regulation of the gut microbiota. Many of these processes result in enhanced telomerase activity and genome maintenance, a decrease in LINE-1 hypomethylation which is implicated in cancer, activation of autophagy via mTOR and AMPK-dependent mechanisms, regulation of nutrient-sensing pathways, improved cardiovascular health due to balanced protein homeostasis, and enhanced mitochondria function and senolytic properties, overall contributing to optimal health. Hence, this review substantiates the beneficial impacts of these dietary interventions on health and aging, suggesting their potential use as functional foods for studying the mechanistic interplay between nutrition and gut microbiota dynamics during age-related pathological conditions.

Future Perspectives: However, there are still some limitations to what defines a healthy gut microbiome. The establishment of a robust conceptual framework and compelling evidence about the composition of a healthy gut microbiome could serve as an external benchmark for assessing changes in the gut microbiome associated with different dietary patterns. Additionally, heterogeneity across study populations, polymorphism, variations in analysis methods, disparate durations of studies, and divergent characterizations of dietary patterns, lifestyles, and disease stages further complicate the synthesis of the findings reported thus far. To address these limitations and enhance the reliability of outcomes, future investigations can prioritize larger sample sizes, ensure homogeneity, and balance among study groups, and implement rigorous clinical control of variables. Lastly, the pursuit of a more comprehensive understanding of specific gut microbiome profiles associated with each physiological state necessitates future research endeavors. Such studies would aim to identify potential microbial biomarkers and elucidate the implications of these profiles. Therefore, by adopting a more standardized approach and incorporating comprehensive controls, researchers can better unravel the complex connections between dietary patterns, microbial composition in the gut, as well as their consequential impact on optimal health.

Abbreviations: IS: Indoxyl sulfate, PCS: P-cresyl sulfate, hsCRP: High--sensitivity C reactive protein, IL-17: Interleukin 17, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, TMAO: Trimethylamine N--oxide, GLP-1: Glucagon-like peptide 1, PAI-1: Plasminogen activator inhibitor-1 (PAI-1), MMKD: Modified Mediterranean-ketogenic diet, SCFA: Short-chain fatty acids, VEGF: Vascular endothelial growth factor, MCP-1: Monocyte Chemoattractant Protein-1, IP-10: Interferon-gamma inducible protein 10 KD, IL-12: Interleukin 12, aFMT: Autologous fecal microbiota transplantation, LPS: Lipopolysaccharide, Aß42: Amyloid Beta 42 Peptide, tau-p181: Tau phosphorylated at threonine 181, CNS: Central nervous system, CVD: Cardiovascular disease, IL-1: Interleukin 1, T_H1: T helper 1, T_H17: T helper 17 cells, LDL-c: Low-density lipoprotein cholesterol, IL-6: Interleukin 6

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