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OPINION ARTICLE

Gut microbiome-Mediterranean diet interactions in improving host health [version 1; peer review: 3 approved]

Ravinder Nagpal^{1,2}, Carol A. Shively³, Thomas C. Register³, Suzanne Craft⁴, Hariom Yadav^{1,2} 

¹Division of Internal Medicine - Molecular Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA

²Microbiology and Immunology, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA

³Department of Pathology - Comparative Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA

⁴Department of Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, 27101, USA

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Abstract




The gut microbiota plays a fundamental role in host health and disease. Host diet is one of the most significant modulators of the gut microbial community and its metabolic activities. Evidence demonstrates that dietary patterns such as the 'Western diet' and perturbations in gut microbiome (dysbiosis) have strong associations with a wide range of human diseases, including obesity, metabolic syndrome, type-2 diabetes and cardiovascular diseases. However, consumption of Mediterranean-style diets is considered healthy and associated with the prevention of cardiovascular and metabolic diseases, colorectal cancers and many other diseases. Such beneficial effects of the Mediterranean diet might be attributed to high proportion of fibers, mono- and poly-unsaturated fatty acids, antioxidants and polyphenols. Concurrent literature has demonstrated beneficial modulation of the gut microbiome following a Mediterranean-style diet in humans as well as in experimental animal models such as rodents. We recently demonstrated similar positive changes in the gut microbiome of non-human primates consuming a Mediterranean-style diet for long term (30 months). Therefore, it is rational to speculate that this positive modulation of the gut microbiome diversity, composition and function is one of the main factors intermediating the health effects of Mediterranean diet on the host. The present perspective discusses the evidences that the Mediterranean diet induces gut microbiome modulation in rodents, non-human primates and human subjects, and discusses the potential role of gut microbiota and microbial metabolites as one of the fundamental catalysts intermediating various beneficial health effects of Mediterranean diet on the host.


Keywords


fiber, gut microbiota, Mediterranean diet, monkey, non-human primate, short-chain fatty acids, western diet

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1. **Prakash Halami** , CSIR-Central Food Technological Research Institute, Mysore, India

2. **Rajeev Kapila** , ICAR-National Dairy Research Institute, Karnal, India

3. **Raghvendra Kumar Mishra**, Amity University Gwalior, Gwalior, India

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Corresponding author: Hariom Yadav (hyadav@wakehealth.edu)

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Introduction

Diet, gut microbiome and chronic diseases like obesity, diabetes, cancer and aging-related diseases such as Alzheimer's disease are closely associated. Our dietary habits have a strong effect on our gut microbiome and metabolism. Unsolicited perturbations in gut microbiota diversity and composition (gut dysbiosis) are key elements underlying chronic diseases including several low-grade inflammatory disorders of human gastrointestinal tract¹. Specifically, low consumption of dietary fibers is known to induce long-term changes in the gut microbiome that are associated with low production of beneficial microbial metabolites, i.e., short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate involved in the modulation of host immune and inflammatory health status². Epidemiological investigations have reproducibly found that the 'Western-style' dietary habits (typically characterized by low consumption of fruits, vegetables, salads, fish and mono- and poly-unsaturated fatty acids such as fish and olive oil, and high consumption of simple sugars, saturated fat, red meat and processed foods) as one of the main perpetrators for the rising worldwide incidence of chronic diseases³. From that perspective, a dietary-pattern intervention targeting gut microbiome can provide an effective avenue for the prevention and treatment of such chronic diseases.

Mediterranean diet: the intangible cultural and nutritional dietary pattern

Prompted by this evidence, a move towards a Mediterranean-style diet is exemplified as not only a prudent choice of lifestyle but also as a scientifically accepted mechanism that is able to yield the benefits for management of several human disease pathologies and an overall improvement of health and well-being. In 2013, the Mediterranean diet (hereafter, MD) was also enrolled on the "Representative List of the Intangible Cultural Heritage of Humanity" by the United Nations Educational, Scientific and Cultural Organization (UNESCO)⁴. In 406 B.C., Hippocrates, the father of medicine, had already stated: "Let food be your medicine and medicine be your food". Strikingly, this 20-centuries-old statement has been clearly and consistently validated by the ever-mounting literature indicating that the dietary habits can modulate predisposition to various human gastrointestinal,

metabolic, cardiovascular and systemic diseases. A Mediterranean-style diet typifies a nutritionally balanced diet, characterized by intake in high amounts and frequency of important sources of fibers (cereals, vegetables, legumes, fruits and nuts) and chemical ingredients with anti-oxidative properties (vitamins, flavonoids, phytosterols, minerals, terpenes and phenols) (Table 1)⁵. In addition, high proportions of oleic acid, polyphenols and unsaturated fatty acids delivers significant anti-atherogenic and anti-inflammatory properties (Table 2)⁶. Studies have demonstrated that switching to a Mediterranean-style diet demonstrates amelioration in serum inflammation biomarkers as well as their gene expression profile (nutrigenomics), not only in healthy subjects⁷, but also in patients with obesity, type-2 diabetes and Crohn's disease (Table 2)⁸⁻¹⁵. Such dietary habit changes are also accompanied by specific changes in the population level of several gut microbial groups^{6,16-20}. Although the association of diet-microbiome interactions with the host health and disease status remains to be comprehended by means of all-inclusive and mechanistic epidemiological and omics investigations and specific disease related pathologies; however, advancements in novel hypotheses and postulations have already exceeded over and beyond merely a speculation stage. In this context, while concurring that MD represents a promising, efficacious and holistic approach to maintain/restore host health, it is equitable to believe that (many of) these health benefits of MD are mediated via modulation of host gut microbial clades and their metabolic functions (Figure 1).

MD, gut microbiome and host health

The human gut microbiome is comprised of tens of trillions of microbial cells. The association of gut microbiome dysbiosis with various dramatically rising human diseases such as obesity, type-2 diabetes and aging-related diseases like Alzheimer's disease spurs urgent need for devising effective and safe treatments using gut microbiome modulators. Our dietary practices have an immense effect on many features of gut microbes. One of the primary functions of gut microbiome is to metabolize dietary ingredients in a way that the products of this biotransformation (e.g., SCFAs, vitamins, bioactive derivative compounds and modified plant flavonoids) can benefit various aspects of

Table 1. Nutritional characteristics of a typical Mediterranean-style dietary pattern.

Ingredient	Frequency of consumption
Variety of unprocessed or minimally processed whole grains, cereals, and legumes	Regular staple
Variety of fresh fruits, vegetables, and salads	Daily basis (seasonal varieties)
Dry fruits, nuts, seeds, honey	Regular basis (generally as snacks)
Extra-virgin olive oil; fish oil	Principal source of fat (rich in poly- and mono-saturated fatty acids; low in saturated fat)
Poultry (eggs and chicken)	Low to moderate consumption
Sea food (fish, oysters, sea weeds)	Low to moderate consumption
Red and processed meats	Very low consumption
Unprocessed or minimally processed cheese and yogurt	Low to moderate consumption
Wine	Low to moderate (occasionally; particularly with evening meals)

Table 2. Different components of a typical Mediterranean-style diet and their association with various health benefits.

MD ingredient	Positive health effect	Possible mechanism(s)	Reference
Fruits, vegetables, fiber, yogurt, probiotics/prebiotics, vitamins	Gut homeostasis	↑Gut homeostasis ↑Beneficial gut bacteria, SCFAs ↑Gut immune system ↓Gut leakiness, opportunistic pathogens ↓Gut and systemic inflammation	16–19,21
PUFA and MUFA, fruits, vegetables, poultry	Cardiovascular health	↑Gut homeostasis ↑Gut permeability, beneficial gut bacteria, SCFAs ↓Gut dysbiosis ↓Gut leakiness, gut and systemic inflammation -Improved blood lipid and cholesterol profiles, ↑HDL ↓LDL and VLDL ↓Atherosclerosis	22–28
Whole grains, fruits, vegetables, fiber, tea, polyphenols, minerals, vitamins, low-glycemic foods	Liver diseases	↑Gut homeostasis ↑Gut permeability, beneficial gut bacteria, SCFAs ↓Gut dysbiosis ↓Gut leakiness, gut and systemic inflammation ↓Liver toxicity and inflammation ↓Oxidative stress	29,30
Fruits, vegetables, PUFA and MUFA, polyphenols, vitamins C and B ₁₂ and folic acid, carotenoids	Brain diseases	↑Gut homeostasis ↑Gut permeability, beneficial gut bacteria, SCFAs ↓Gut dysbiosis ↓Gut leakiness, gut and systemic inflammation ↓Gut and brain inflammation ↑Enteric nervous system ↑Memory and cognition ↓Stress, depression and hypertension	31–33
PUFA, MUFA, nuts, antioxidants, flavonoids, yogurt, whole milk	Asthma and allergy	↑Immune-potential ↓Systemic inflammation ↓Oxidative stress	34–37
Fiber, vegetables, MUFA, probiotics/prebiotics, antioxidants, low-glycemic foods, vitamins	Diabetes	↑Gut homeostasis ↑Gut permeability, beneficial gut bacteria, SCFAs ↑Gut immune function ↓Gut leakiness ↑Immune-potential ↓Endotoxemia ↓Metabolic syndrome ↓Systemic low-grade inflammation ↓Oxidative stress	11–15,38–40
Fiber, probiotics, PUFA, MUFA	Kidney diseases	↑Gut permeability, beneficial gut bacteria, SCFAs ↓Gut leakiness, gut and systemic inflammation ↑Saccharolytic gut bacteria ↓Proteolytic gut bacteria ↓p-cresol indoxyl sulphate	41–43
Fresh fruits and vegetables, vitamins C and E, β-carotene	Gastric disorders	↑Gastric homeostasis ↓Opportunistic pathogens ↓Chemical contaminants ↓Oxidative stress ↓Ulcers	44

MD ingredient	Positive health effect	Possible mechanism(s)	Reference
Fiber, PUFA/MUFA, probiotics/prebiotics, antioxidants, vitamins, polyphenols	Colorectal cancers	↑Immune-function ↓Low-grade inflammation ↓Oxidative stress	24,44–48
Fiber, probiotics/prebiotics, omega-3 fatty acids, antioxidants, low-glycemic index, polyphenols	Obesity/ Weight loss	↑Gut homeostasis ↑Gut permeability, beneficial gut bacteria, SCFAs ↓Gut leakiness ↑Insulin sensitivity ↑GLP-1, PYY ↑Satiety ↓Colonic transit ↓Fasting glucose, C-peptide ↓IGF-1 ↓Nutrient sensing ↓Oxidative stress	49,50

GLP-1, glucagon-like peptide 1; HDL, high-density lipoproteins; IGF, insulin-like growth factor; LDL, low-density lipoproteins; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; PYY, peptide YY; SCFAs, short-chain fatty acids; VLDL, very low density lipoproteins.

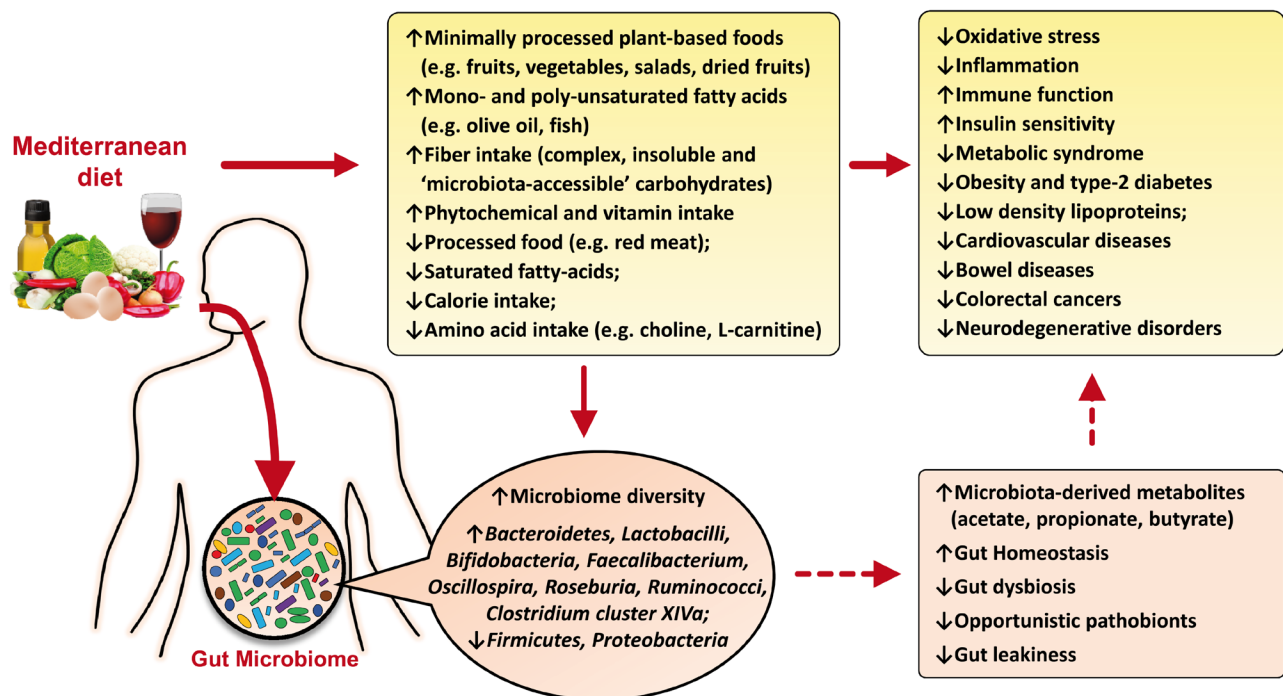


Figure 1. A diagrammatic overview depicting how the various health beneficial effects of Mediterranean diet might be mediated via positive changes in the gut microbiome composition and the gut microbiota-derived metabolites. References are shown in square brackets.

human health and metabolism⁵¹. Mediterranean-style diets are considered nutritionally balanced and scientifically recommended dietary pattern (Table 1)⁵ that are beneficial for the prevention and/or treatment of obesity, type-2 diabetes, inflammatory disorders and cardiovascular diseases (Figure 1 and Table 2)^{8,10,11,22,52–54}. On the other hand, consumption of Western-style diets (mainly

omnivore-type diets) may lead to a gut microbiome composition that is more associated with several diseases⁵⁵. This increasing understanding about the importance of diet-microbiome interactions and their strong influence on human health has led to a novel and timely concept of exploring and developing 'microbiota-directed' foods' that can function by modulating

the functional spectrum of the gut microbial community, providing precursor substratum for microbial biotransformation to bioactive molecules beneficial for the host health, or a combination of both of these approaches⁵⁶. This could provide novel and potential ways for improving host health by fostering/supporting healthy gut microbial communities, restoring the loss of microbial diversity associated with Western-style diets, and ameliorating the structural and functional dysbiosis associated with various human diseases. One example of this microbiota-directed food is 'prebiotic', which is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon/gut⁵⁷. Indeed, a food can include one or more prebiotics (e.g., plant fibers, inulin, chicory, galactooligosaccharides, and others) capable of being processed by selective array of commensal/ beneficial gut microbes, leading to the production of beneficial metabolites like SCFAs. These SCFAs act as key mediators of the beneficial effects of such fibrous diets on host health^{51,58}.

Higher adherence to MD has been found to be associated with reduced incidences of several chronic diseases, such as obesity, type-2 diabetes, metabolic syndrome, gastrointestinal cancer, cardiovascular diseases, fatty liver diseases, chronic kidney diseases and neurodegenerative diseases like Alzheimer's disease (Table 2)⁵⁹⁻⁶³. Based on different studies, the lowering effects of MD against the incidence of these disorders have been attributed to different MD dietary constituents derived from fruits, vegetables, lean meat, nuts and grains, fibers, mono- and polyunsaturated fatty acids, vitamins, polyphenols, and antioxidant (Table 2)⁶⁴⁻⁶⁶. Considering that the pathology of the above-mentioned diseases involves a dysbiotic gut microbiome and that the ingredients of the MD closely interact with gut microbial community, it can be suggested that the mechanisms by which MD drives health effects on the host might be mediated by an integrated interplay between the diet and the gut microbiome (Figure 1). Two main mechanisms underlying these positive effects of MD are (a) beneficial modulation of the gut microbiota (i.e., increased microbial diversity and production of beneficial metabolites like SCFAs), and (b) reduced metabolic endotoxemia by suppressing the growth of gram-negative bacteria and improving the gut barrier integrity by modulating tight junctions and mucus secretion⁶⁷. Both of these mechanisms can help in reducing the systemic inflammation, which is the hallmark of many chronic diseases in the human body. Table 2 presents some of the reported beneficial health effects of Mediterranean-style diets and summarizes how different MD components could prevent/ameliorate these disorders by promoting a homeostatic gut microbiome and permeability to maintain the balanced arrays of the bacterial metabolites and the inflammatory molecules across the gut epithelium.

Microbiome-mediated pro-health effects of MD: purported and speculated mechanisms

Extensive literature is available about the health benefits of MD; however, knowledge concerning the impact of MD on gut microbiota-mediated disease outcomes remain limited. The precise mechanism by which MD confers its beneficial effects on host health such as lowering the risk of cardiovascular, metabolic and gastrointestinal diseases and certain cancers

remains unclear. However, most of these beneficial effects have long been speculated to be mediated by several interrelated and overlapping factors including cholesterol-lowering effect, protection against oxidative stress and inflammation, modification of hormones/growth factors involved in carcinogenesis, and control/inhibition of nutrient-sensing pathways by restriction of specific amino acids⁶⁶. In addition, recent literature suggests that diet has a major impact on gut microbiome and the production of gut microbiota-derived microbial metabolites, which can considerably influence the host metabolic health⁶⁸. Ever-mounting metagenomic studies have suggested that specific nutrients, particularly dietary fiber and proteins, exert strong effects on gut microbiota composition as well as on the production of microbial metabolites that further influence multiple features of the host immune and metabolic health^{69,70}. For example, trimethylamine N-oxide (TMAO), a gut microbial metabolites from dietary choline and L-carnitine, is known to increase the risk of cardiovascular diseases independently of cardio-metabolic risk factors⁷¹. TMAO, at abnormally high levels, can induce vascular inflammation and prothrombosis by exaggerating platelet hyper-responsiveness to multiple agonists, and could be implicated in the pathogenesis of obesity and type 2 diabetes^{72,73}. Given that a typical Mediterranean-style diet contains a proportion of choline and L-carnitine (which are abundant in eggs, red meat, and cheese) that is over 50% lower than a typical Western-style diet, it could be speculated that some of the beneficial effects of MD on host cardio-metabolic health might at least partly be mediated via such microbiome-related mechanisms. On the other hand, studies have shown that a poor adherence to a Mediterranean-style diet is associated with higher urinary TMAO level¹⁶. It is acknowledged that the physiological effects of the gut microbiota on host health are mediated not only by the direct interaction of the microbe with the host but also equivalently by the indirect microbial processes including the production of fermentation metabolites from diet or *de novo*. Thus, the array of microbial metabolites in the host gut from dietary fermentation is a function of not only the gut microbial ecology but also the substrate such as the fermentation of complex carbohydrates (e.g., fiber) or other plant-based foods, which are abundant in a Mediterranean-style diet, that leads to the production of beneficial SCFAs, in contrast to TMAO, which is frequently observed in people consuming Western-style diets poor in minimally processed plant-based foods and rich in processed red meats.

MD is also rich in complex and insoluble fiber content when compared to a typical Western-style diet. A high intake of dietary fiber is well known to promote the beneficial modulation/maintenance of the gut microbiota with a reduced population of Firmicutes, while increasing that of Bacteroidetes, thereby yielding high levels of SCFAs including butyrate in the gut. These microbiota-derived metabolites including acetate, propionate and butyrate are known to protect against the development of several intestinal, inflammatory and allergic disease, and some of these effects are thought to be mediated via binding of these metabolites to specific G-protein-coupled receptors expressed on enteroendocrine and immune cells⁷⁴. Adherence to a Mediterranean-style diet has been shown to reshape the gut microbiota of obese individuals, with increased population of *Bacteroides*, *Prevotella*, *Roseburia*, *Ruminococcus*, and

Faecalibacterium prausnitzii, which are known for their fibrolytic activity, producing SCFAs by metabolizing carbohydrates¹⁸. Notably, *Bacteroides fragilis* and *F. prausnitzii* are also known to confer anti-inflammatory effects via inducing CD4+ T cells, the secretors of the anti-inflammatory interleukin-10^{75,76}. In addition, the high content of vegetables, legumes, and fruit in a Mediterranean-style diet are also found to be associated with increased intestinal levels of short-chain fatty acids. These reports suggest that the Mediterranean-style diet fosters beneficial bacteria in the gut, which subsequently secretes beneficial metabolites.

Another reason that could underlie the health beneficial effects of Mediterranean-style diet is the lower intake of processed foods, as the Mediterranean dietary pattern is rich in minimally processed food, unlike a Western-style dietary pattern, which contains a much higher proportion of processed plant- and animal-based foods. This minimized intake of processed plant food with restricted calorie intake through MD is also known to confer positive effects on the gut microbiota diversity and composition by protecting/fostering the homeostasis of population levels of several beneficial bacterial groups⁷⁷. On the other hand, long-term adherence to a Western-style dietary pattern, which has very low content of complex, insoluble, minimally processed, and microbiota-accessible plant-based fibers and carbohydrates, can lead to a dysbiotic gut microbiota, with various subdominant but important bacterial groups vanishing over generations, and may also negatively influence several important features of the host immune system, thereby increasing the predisposition to various gastrointestinal, metabolic and immune diseases^{74,76,78}. Several studies have shown that the healthier and calorie-restricted dietary patterns with a high proportion of minimally processed plant-based foods can reprogram several important gut microbial functions that are crucial for promoting host health and wellbeing^{77,79}.

Emerging evidence shows that the adherence to a MD is associated with higher gut microbial diversity. The CORonary Diet Intervention with Olive Oil and Cardiovascular PREvention (CORDIOPREV) study involving 138 participants with metabolic syndrome and 101 healthy counterparts has reported restoration of the gut microbial dysbiosis in metabolic syndrome patients following long-term adherence to the MD, although the disease persisted⁸⁰. Interestingly, the study demonstrated that the MD adherence could restore the patients' gut microbiota in a similar way to the gut microbiota composition seen in metabolically healthy subjects, by fostering the population of saccharolytic bacterial genera, including *Bacteroidetes*, *Faecalibacterium*, *Roseburia* and *Ruminococci*, all of which are known to be associated with increased fermentation capacity to produce healthy SCFAs in the gut. A long-term adherence to the MD has also been found to increase the population of *Roseburia* sp. and *Oscillospira* sp., in addition to improving insulin sensitivity in obese people⁸¹. Notably, *Roseburia* is a prominent butyrate-producing genus that has been found to confer anti-inflammatory effects and is generally found to be reduced in type-2 diabetes patients^{82,83}. These reports suggest that a MD might be effective in the prevention and management of type-2 diabetes, although more studies are needed to affirm these therapeutic effects in

particular reference to their connection with gut microbiota-associated factors.

Altogether, these reports suggest that the MD modulates gut microbiota profiles (such as higher population levels of *Bacteroidetes*, *Clostridium* cluster XIVa, *Faecalibacterium prausnitzii*, *Lactobacilli*, and *Bifidobacteria*, or lower Firmicutes) and can influence the diversity, activities and functionalities of various gut bacteria, thereby also fostering healthy metabolites (such as SCFAs) that can confer multiple benefits to the host intestinal, metabolic and immune health. Nevertheless, broader and more inclusive clinical and epidemiological studies assessing the temporal changes in the composition and function of gut microbiota enterotypes are still needed to establish a gut microbiome signature as a marker of MD adherence.

Non-human primates (NHPs): an ideal model to elucidate diet-microbiome interactions in human health and disease

Given the profound impact of diet on the diversity and composition of host gastrointestinal microbiome^{68,84–86}, the gut microbiome can be illustrated as a valuable biomarker of long-term intake of healthy or unhealthy diets. Therefore, it is imperative to elucidate whether, how and to what extent these long-term dietary patterns can influence the composition of the gut microbiota and how this could affect the production of beneficial microbial metabolites. As mentioned above, diet shapes the gut microbiome by supplying specific substrates that differentially foster the growth of specific gut microbial communities^{87–89}; this diet-microbiome network is universally consistent in human and animal studies^{85,87,90,91}. Specifically, the majority of diet-microbiome-targeted studies focus on high-fat, high-sugar, low-fiber vs. low-fat, low-sugar, high-fiber diets, with particular reference to nutrition- and gut-related maladies, including obesity, endotoxemia, insulin resistance, type-2 diabetes, and other metabolic syndromes^{92,93}. Several animal models, including those in mice, hamsters, rats, guinea pigs and zebrafish are used for investigating diet-microbiome interactions, but, given the specific and prominent impact of dietary patterns on the gut microbiome, these models might not invariably be truly translatable to human milieu owing to far-reaching dissimilarities in their dietary regimen, age, body size and environmental elements. Accordingly, novel models such as NHPs are being sought for investigations of human diets and their interactions with gut microbiome, to decipher better understanding in human inference^{92,94–100}. In addition, while it is challenging to precisely control and monitor dietary patterns through questionnaires in human interventions, studies performed on small animals are disadvantaged by short-term diet intervention periods. To overcome these limitations, NHPs represent an excellent model for investigating the diet-microbiome interactions and their impact on host health. Their physiological and phylogenetic closeness to humans makes them a perfect and biologically relevant animal model for human context to examine diet-microbiome connections as well as for studying the relation of this network with different nutrition- and gut-related diseases^{95,96,99–102}. In one such endeavor, we recently performed a study wherein we demonstrated the effect of a long-term Western- vs. Mediterranean-style diet intake on the gut microbiome composition in NHPs (*Cynomolgus*

monkeys; *Macaca fascicularis*)²¹. Previous reports have demonstrated that the gut microbiome of NHPs resembles more closely to those of primates than other animals¹⁰³. The human gut largely harbors microbes belonging to nine different bacterial divisions, viz. Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Verrucomicrobia, Fusobacteria, Spirochaetes, Cyanobacteria, and VadinBE97^{104,105}. Interestingly, our NHP data also demonstrated Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, Fibrobacteres, Spirochaetes, Cyanobacteria, and Tenericutes as most abundant bacterial phyla²¹. This again validates that the NHP microbiome studies can yield important indications about specific features of these bacterial clades in the human gut and provide unique opportunities to investigate diet-microbiome interactions.

Effect of MD on NHP microbiome: similar findings as seen in human and rodent studies

Our data obtained feeding a MD to NHPs also demonstrated that MD boosted the gut microbiome diversity and promoted the carriage of several important bacterial groups, including *Bacteroides*, *Prevotella*, *Lactobacillus*, *Faecalibacterium*, *Clostridium* and *Oscillospira*²¹, again corroborating that the host diet can influence gut microbiome diversity and composition. Notably, similar effects as seen in the NHP cohort have also previously been seen in human studies (Figure 2). For example, diets rich in fiber and unsaturated fatty acids are known to help maintaining a healthy and diverse gut microbiome. Our NHP data also demonstrated higher alpha-diversity in NHPs consuming the MD, an effect that has also been observed in several other studies on humans or animal animals^{68,78,99,106} and can be attributed to a higher proportion of fiber in the MD. In addition, our NHP study also demonstrated higher Bacteroidetes-Firmicutes

ratio and higher abundance of *Clostridium* and *Prevotella* in NHPs on MD. Similar results have been reported by previous studies performed in humans and other mammals reporting that MD (and specifically the higher fiber intake and less intake of high-glycemic index sugars) positively alters the gut microbiota, with an increased *Bacteroides*, *Clostridium* and *Prevotella* population^{8,88,99,107–109} whereas a low-fiber, high-fat and high-sugar diet is linked with increased *Firmicutes* and reduced *Bacteroides* population⁸⁸. Another interesting observation was the increased abundance of genus *Oscillospira* in MD-fed NHPs. *Oscillospira*, a genus from the *Ruminococcaceae* family, is usually found prevalent in the gastrointestinal tract of ruminants consuming diets rich in complex plant fibers and hence is regarded as genus adapted to vegetable-rich diets, such as Mediterranean-style diets^{110,111}.

Another interesting observation from this NHP study was the increased abundance of *Faecalibacterium prausnitzii*, one of the beneficial butyrate-producer previously reported to be found in higher numbers in humans consuming a Mediterranean-style diet^{111–113}. Various human and small animal studies have reproducibly reported fostering of a population of beneficial bacterial groups, including *Lactobacillus* sp^{114–116} and *Faecalibacterium* sp¹¹⁷, following consumption of diets that are rich in complex carbohydrates, such as prebiotics. In addition, omega-3 fatty acids, which are present in higher ratio in Mediterranean-style diet, can also stimulate the intestinal population of several beneficial bacteria including lactobacilli that typically inhabit the distal gut, a primary site for the metabolism of mono- and poly-unsaturated fatty acids^{9,118,119}. Interestingly, in a recent study on these NHPs, we demonstrated that the consumption of MD also leads to an increased *Lactobacillus* abundance and increased

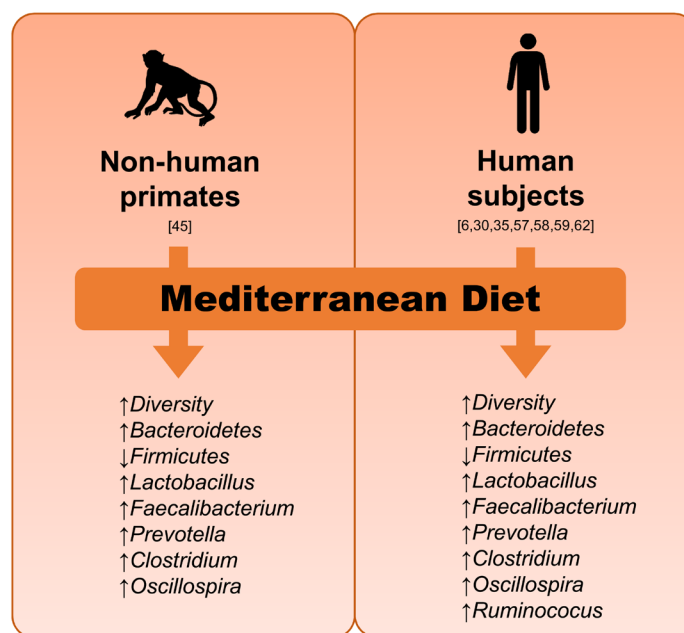


Figure 2. Effects of Mediterranean diet on the population of major gut bacterial groups that have been reported consistently in different studies involving non-human primates and human subjects.

bacterially processed bioactive compounds in the mammary glands compared with Western diet-fed monkeys, clearly indicating that the influence of MD on the microbiome reaches far outside the gut in distal sites such as the mammary glands and could also establish an alternative pathway for breast cancer prevention¹²⁰. Conversely, high-fat diets are also known to reduce the intestinal carriage of lactobacilli^{93,121,122}. In addition, we have recently reported that MD also protects these NHPs against hepatosteatosis while reducing BMI and body fat¹²³. Hence, these common findings between NHP and human studies clearly demonstrate and advocate that NHPs can prove to be an excellent experimental animal model to examine the diet-microbiome interaction in context to human health and disease.

Altogether, these findings from our cohort of the MD-fed NHPs demonstrate that the positive modulation of the gut microbiome is concomitant with the beneficial effects of MD on host health and hint that this microbiome modulation might even at least in part also mediate/underlie the health effects of MD, particularly given that the majority of the MD-induced changes in the gut microbiome including enhanced microbial diversity and fostering of several beneficial bacterial groups are known to be beneficial for host intestinal, metabolic and overall health²¹. However, although the health benefits of MD have been studied extensively, research on MD's impact on microbiome-mediated disease outcomes still remains undetermined. For instance, it is known that MD consumption leads to gut microbiome alterations; however, the magnitude to which these alterations occur may be potentially impacted by multiple factors such as the study duration, host age and lifestyle habits, specific disease predisposition or severity, level of dietary adherence, etc. which otherwise remain to be explicated and hence would be prerequisite to pinpoint the factors contributing to the outcome of MD on gut microbiome and deliver conclusive data on the role of gut microbiome in MD's beneficial health outcomes^{124,125}. As a result, according to the existing literature, the examination of gut microbial composition could not be endorsed as a stand-alone tool for the health effects of MD. To this end, systemic approaches that incorporate gut metagenomics, transcriptomics and metabolomics could help elucidate the complex association of MD-microbiome interrelationship with host health.

Perspectives on the future

Recent evidences from animal and human studies are beginning to elucidate the mechanisms underlying the pro-health effects of the traditional MD. The metabolism and fermentation of plant-based foods packed with complex fibers, a wide variety of vitamins and phytochemicals, could also play an important role in promoting host metabolic health. Although more research is needed, specific dietary patterns (particularly, the Mediterranean-style diet) have been found to have a strong influence on the gut microbiome composition and metabolic function, suggesting that there is an opportunity to prevent and treat various life-style-related disorders based on gut microbiota outcomes. Given the plasticity of the gut microbiota, it can be speculated that such Mediterranean-style nutritional intervention can positively affect host health, either by maintaining a physiologically homeostatic gut microbiota configuration or by reversing the gut dysbiosis state; this positive modulation of the gut microbiome

could be considered as a potential and holistic target for non-pharmacological interventions in a variety of disease states. The potentiality of the gut microbiome is tremendous. It can be easily and rapidly modulated in a natural, non-invasive, non-pharmacologic way, i.e., via diets and other dietary supplements like probiotics and prebiotics. The ever-mounting knowledge of the gut microbiome as acquired by the use of remarkable high-throughput sequencing and omics tools in combination with the data from various *in vitro* and *in vivo* experimental models is shedding a new light on the key mechanisms through which diet-microbiome crosstalk in the gut can modulate potential risk factors of several human diseases. This wealth of knowledge is certainly going to offer potential avenues for decoding the complexities and functionalities of the diet-microbiome interface and for developing personalized dietary strategies to determine the healthiest dietary pattern for the personalized host.

In conjunction with gut microbial composition in response to diets like MD and the Western diet, it is becoming evident that the microbial metabolites produced by gut microbiome and dietary interactions plays an important role to regulate host metabolism and physiology¹²⁶. MD feeding enhances abundance of probiotics or beneficial bacteria like lactobacilli²¹, however, future studies focusing on determining how the increased abundance of lactobacilli benefit host health will be important to conclude the mechanistic views. It is difficult to pinpoint exact molecular mechanism(s) by which diets and ingredients can impact human health; however, several layers of mechanistic studies like systemic, organ- and cell-based mechanism should be the focus of future research. Such studies can provide important information to include the vital ingredients that not only enhance the impact of diets like MD, but can easily be tailored for personalized nutritional approaches. Combining gut microbiome, and metabolic response (like the glycemic index) of diets on individual basis are attractive area of current research, that can extend valuable outcome in the field of diet-microbiome interactions to benefit human health.

Data availability

No data are associated with this article.

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Raghvendra Kumar Mishra

Amity Institute of Biotechnology, Amity University Gwalior, Gwalior, Madhya Pradesh, India

This manuscript describes very timely and important review on how diet and microbiome interactions play a crucial role in maintaining health, especially mental health. This manuscript has been well written, cited all important references properly, and easy to read with nice graphic. I strongly believe that indexing this manuscript on time will provide high readership to the journal.

I find this topic very interesting with well written paper, thus recommend indexing of this interesting manuscript immediately.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: 1. Arachidonic acid production and molecular characterization of *Mortierella alipna* isolates (Filed 02 patents, 01 paper, 01 submitted). 2. Biosynthesis of Nanoparticles from *C. roseus* (01 paper published in *Frontiers in Microbiology* other in pipe line). 3. Development of EST-SSR and ILP data for commercially important plan variety. (03 papers published, one project is

going on)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 July 2020

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Rajeev Kapila 

Animal Biochemistry Division, ICAR-National Dairy Research Institute, Karnal, Haryana, India

In the current perspective, the authors have lucidly briefed that shifting of dietary-pattern from 'Western-style' dietary habits to a 'Mediterranean-style' diet effectively target gut microbiome interactions by diversifying and increasing the richness of gut microbiome which can justifiably help in prevention and treatment of various chronic diseases like obesity, diabetes, cancer and aging-related diseases such as Alzheimer's disease. In a quintessential and step-by-step manner, the authors have well described the usefulness of the Mediterranean-style diet which represents a promising, efficacious, and holistic approach to restore host health.

In this article, the authors have discussed the nutritional characteristics of a typical Mediterranean-style dietary pattern along with their components having an association with various health benefits. Briefly discussed the adverse effects of TMAO released from Western-style diet over beneficial effects of SCFA released during dietary fermentation of complex carbohydrates present in Mediterranean-diet. Thus authors have also suggested some underlying mechanisms by which the purported health benefits of MD can be exerted. The authors have justified the use of non-human primates as an ideal model to dissect diet-microbiome interactions in human health and disease after drawing evidence from the fact that the diet-microbiome network is universally consistent in human and animal studies. In a nutshell, the manuscript is nicely written with sufficient facts and figures and the following comments are suggested for each section of the manuscript wherever they may apply

Comments:

1. It could be better if a tabular description of Western-style' dietary habits and their components would also be made highlighting the difference in components.
2. Release of metabolites such as SCFA is now well recognised as epigenetic modifiers which could be an alternative underlying mechanism of beneficial effects of Mediterranean-style dietary pattern due to the abundance of prebiotic and polyphenolic components which may also be highlighted in proposed biochemical pathways.
3. Writing "Mediterranean dietary pattern" as rich in minimally processed or unprocessed food, unlike a Western-style dietary pattern appears faulty because cooking and frying used

in these dietary patterns are also a form of food processing hence it is suggested to use different terminology to differentiate between processed / un-processed/ cooked foods.

4. In the introduction section sentence “mono- and poly-unsaturated fatty acids such as fish and olive oil” could be written as mono- and poly-unsaturated fatty acids consumed through fish and olive oil.
5. Under the heading “Mediterranean diet: the intangible cultural and nutritional dietary pattern” the sentence “A Mediterranean-style diet typifies a nutritionally balanced diet, characterized by intake in high amounts and frequency of important sources of fibers” may be modified as “A Mediterranean-style diet typifies a nutritionally balanced diet, characterized by high and frequent intake of important sources of fibres”.
6. It would be better if some references are cited with “Table 1”, if available.
7. In Table 2, Figure 1 and 2, use different yet consistent colours for ↓ ↑ respectively.
8. Under the heading “Microbiome-mediated pro-health effects of MD: purported and speculated mechanisms” the sentence “Thus, the array of microbial metabolites in the host gut from dietary fermentation..... is too long hence better to modify for more clarity.
9. Similarly under the heading “Effect of MD on NHP microbiome: similar findings as seen in human and rodent studies” the sentence “Altogether, these findings from our cohort of the MD-fed NHPs demonstrate that the positive modulation of the gut microbiome..... is very lengthy may be re-written for better understanding

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health validation of nutraceuticals (Probiotics and Bioactive peptides) and their mode of actions

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 15 October 2019

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Prakash Halami 

Department of Microbiology and Fermentation Technology, CSIR-Central Food Technological Research Institute, Mysore, Karnataka, India

In this article the authors have summarized the importance of consuming a Mediterranean-style diet, which is associated with prevention of metabolic and cardiovascular diseases. It is known that a Mediterranean-style diet (MD) contributes to the high proportion of fibre, mono- and poly-unsaturated fatty acids, antioxidants and polyphenols. The authors have also stated the beneficial modulation of the gut microbiome is associated with MD as evident from in-vivo experimental studies.

The consumption of MD has provided many health benefits which is associated with rich microbial diversity, composition and its function. In this review article, the author has discussed, with evidence, the MD in rodent & human subjects, as well as the importance of gut bacteria and microbial metabolites. The article has been well-written with reference to bile, gut microbiota & chronic diseases, where the authors have underlined the benefits of MD. They have also summarised western style of dietary habits associated with chronic diseases.

Further, the authors have provided information on MD, its intangible culture and nutritional dietary pattern along with the ingredients generally used. In subsequent sections, MD and its positive health effects and possible mechanisms is provided in a tabulated form. The authors have presented a diagrammatic overview of the consumption of MD and its effect on gut microbiota, especially on microbiome diversity by minimizing the occurrence of firmicutes and proteobacteria. In subsequent sections the authors have mentioned the microbial mediated beneficial effects of MD and its possible mechanisms. The authors have mentioned the use of Non-human Primates (NHP) for studying diet microbial interaction with reference to human health and diseases. In subsequent sections, the authors have mentioned the effects of MD on the microbial diversity of NHP and its correlation with human subjects, distinct microflora associated with human subjects e.g. *Ruminococcus* is also described.

In the 'Perspectives on the future' section the authors have highlighted the importance of plant based foods and its importance to host metabolic rate etc. The microbiome composition and metabolite production that are required to prevent various lifestyle disorders have been suggested. Authors have also provided information on how probiotics can influence the gut microbiome of the personalized host. Accordingly, authors have prepared the article well and following comments are suggested:

Comments:

1. The use of the acronym MD for "Mediterranean-style diet" should be consistent throughout the MS.
2. In table 2, please change "SCFA" in possible mechanism to "SCFA production".

3. The many repeated MD ingredients mentioned in table 2 could be better represented by combining a few of the rows.
4. In figure 1, it is suggested that the font colour for the increased parameters could be green and the those for decreased one could be red.
5. Authors could include a section for the role of prebiotic compounds that are found in MD.
6. A concern when comparing NHP microbiome with that of the human microbiome is that is all the interaction (enzymatic or hormonal) similar to that of NHP? As any difference in these factors in the two species can result in misleading conclusions.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Probiotics, gut microbiota, antibiotic resistance in lactic acid bacteria & antimicrobial peptides

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