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REVIEW

The role of diet in modulating the intestinal microbiota in healthy adults: Is the evidence enough?

Florina Ruta[1], Elena Mardale[2], Andrada Pintea[1], Calin Avram[1*]

1. George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
2. Regina Maria Health Network, Civic Center, Brasov, Romania

The diet is an important factor that can influence the structures and function of the population of germs that compose the intestinal microbiota. This review presents current data on the response of the intestinal microbiota depending on the diet. While many studies have shown that the intestinal microbiota is influenced by macronutrient and micronutrient compounds of the diet, the studies on healthy human subjects were fewer and showed only to a small extent the influence of cooked food on the intestinal microbiota. Additional research is still needed regarding the effect of the way food is cooked can have on the intestinal microbiota, before beneficial dietary recommendations can be made.

Keywords: microbiota, diet, micronutrients, macronutrients, cooked food

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Introduction

The plethora of microbiome research over the last decade has generated various information that contributes to understanding the mechanisms that modulate the functionality and composition of the gut resident microbial flora. In the last two decades, several studies have identified links between the gut microbiota and the risk of health impairment with the occurrence of various diseases [1-4]. The ratio between these cells and the total cells of the body is estimated to be 1:1 [5]. It should be noted that the human microbiome is much more different compared to the human organism cells, and it is important to understand how germs and their metabolites impact the health [6].

The microbes are predominantly present in the large intestine, with the gut microbiota being characterized by changes throughout different stages of human growth. There are a lot of factors that modulate the colonization, composition, growth, and diversity of the gut microbiota. The most important factors in colonization and diversity are age [7], genetics [8-10], how the birth occurred [18,12], way of feeding infants [13,14], use of drugs (antibiotics) [15,16] environment [17] and diet [18,19]. Knowing how the intestinal microbiota is influenced by the mentioned factors represents a valuable tool for innovative strategies to promote human health. The dietary factors illustrated by both micronutrients and macronutrients, are the most important in modulating and shaping the human intestinal microbiota [20]. The understanding of the intestinal microbiota is limited by the fact that a large part of microorganisms, especially anaerobic ones, cannot be cultivated by conventional microbiological techniques. Nevertheless, the development of metagenomic technologies has facilitated the description and evaluation of the intestinal microbiota [21].

The diet appears to be an essential determinant for the structure and function of the population of gut microbes. Nutrition, in addition to supporting homeostasis between the host and microbiota, also bears responsibility for disease susceptibility. The interest in the role of dietary factors on the composition of the intestinal microbiota has intensified in recent years.

Knowledge of the links between the gut microbiota and the human body is essential to understanding its involvement in the biological processes and its contribution to the health status and disease prevention. The impact of the particularities of human nutrition, by combining menus and cooking, must complete the data so far regarding the effect of macro- and micronutrients supplemented in the diet or those obtained on experimental animal models.

Microbial diversity involves the distribution of different bacterial species. Reduced diversity is a condition of dysbiosis of the intestinal level, and species abundance indicates a "healthy gut" [22–24].

The aim of this review was to assess the extent to which scientific studies described the effects of macronutrients from food and cooking methods used, upon gut microbiota composition in healthy individuals.

Material and methods

A descriptive review was conducted to investigate the potential effects of diet on gut microbiota composition.

PubMed, Scopus, and Google Scholar databases were used for research, while the terms entered for the search were the following: diet, microbiota, healthy human subjects, in vitro studies, cooked food.

Using the terms "gut microbiota", article written in the last 5 years were found: 1517 clinical trials, meta-analyses and randomized controlled trials, together with 1148 reviews and systematic reviews. When narrowing the search to include the term 'diet', we found 522 clinical trials,

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* Correspondence to: Calin Avram
E-mail: calin.avram@umfst.ro

meta-analyses and randomized controlled trials, and also 2503 reviews and systematic reviews.

The exclusion criteria used were: studies on microbiota other than gut microbiota, studies that did not include the effect of diet on gut microbiota, and studies conducted on populations with various pathologies and animal studies.

Finally, the results of this review made reference to 52 studies which highlighted the results of in vitro research and in vivo human studies (Figure 1).

Results

Recent studies have shown the association between the dominance of some groups of intestinal microbes and health status (Table I) [25-27].

Effect of diet on the gut microbiota

Important changes throughout human evolution regarding the intestinal microbiota occurred during two periods throughout human history: the transition from the paleolithic age of hunter-gatherers to the agricultural neolithic age (10.000 years ago), with a diet abundant in carbohydrates and the one from the beginning of the industrialized era, having as a feature the richness in carbohydrates, through the consumption of processed flour and sugar (about two centuries ago) [28].

Previous studies have shown differences in the composition of the intestinal microbiota between populations from different areas of the planet probably due to differences in diet, as well as the genetic factor [29]. The gut microbiota of children from the rural part of Africa (Burkina Faso) was compared with that of Italian children from the urban environment, showing that the two populations have significantly different food habits, with European children having a lower fiber intake. The microbiota of African children was dominated by *Bacteroides sp.*, while in the other group, there was a prevalence of *Enterobacteriaceae* and a decrease in *Bacteroides sp.* [29].

Other studies have shown large variations in gut microbiota between Americans, Europeans, and Africans. The gut microbiota of Africans was most similar to that of the South American population, associated with higher consumption of plant polysaccharides, but different from that of North Americans (who mainly have a low-fiber diet). Therefore, dietary carbohydrate intake contributes to the large variation in gut microbiota composition between populations [30]. A diet high in fiber appears to be positively correlated with bacterial diversity. Therefore, lasting changes in the composition of the gut microbiota could be achieved through dietary changes [31,32]. The Western diet, consisting mainly of red meat, animal fats, and foods rich in sugar with a low fiber content was associated with a microbiota dominated by *Bacteroides phyla and Ruminococcus* [33].

The composition of the microbiota has been strongly associated with different long-term dietary patterns. The prevalence of *Actinobacteria* and *Bacteroides* was positively associated with dietary fat intake, but negatively associated with fiber intake, while *Proteobacteria* and *Firmicutes* showed an opposite correlation. The predominance of the *Bacteroides enterotype* was related to the saturated fat and animal protein typical of the Western diet. On the other hand, the predominance of the *Prevotella enterotype* was related to the dietary pattern based on carbohydrates specific especially to vegetarians and agrarian societies [34, 35].

Even a short-term change in diet can alter our body's microbial populations. A diet based on animal products

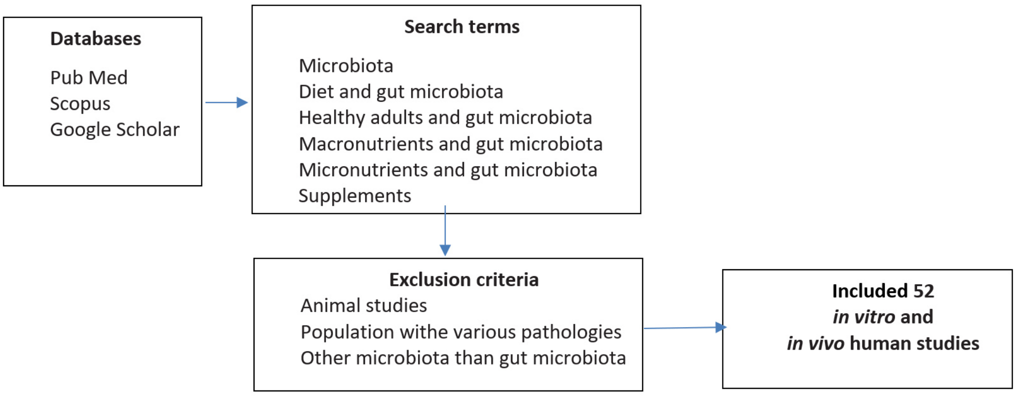

Fig. 1 The organizational chart regarding the selection method

Table I. Classification of the main microbial species according to beneficial vs harmful potential

Classification	Representative	Effect
Potentially beneficial microbes	Bifidobacterium, Lactobacillus, Akkermansia, Faecalibacterium, Eubacterium, Roseburia, Ruminococcus and Blautia	part of the neuro-modulatory flora (serotonin and other neurotransmitters) barrier for pathogens, probiotic activity butyrate formers major role in digesting resistant starch shows a significantly negative association in the increase of visceral fat
Potentially harmful microbes	Clostridium, Enterobacteriaceae, Enterococcus, Bacteroides and Ruminococcus	potential for causing wound infections, urinary tract infections, gastroenteritis risk of constipation opportunistic pathogenic effects, inducer of pro-inflammatory cytokines involved in endogenous infections by C. difficile and C. botulinum

can cause bile-tolerant bacteria (*Alistipes, Bilophila and Bacteroides*) to thrive, and the level of *Firmicutes germs* that metabolize the polysaccharides from diet (*Eubacterium rectale, Roseburia bromii and Ruminococcus bromii*) to decrease. The differences between the intestinal microbiota of omnivores and vegetarians are thus confirmed [36].

Influence of diet rich in complex carbohydrates (dietary fiber)

Dietary fibers, divided into complex carbohydrates (digestible and non-digestible) and oligosaccharides, exert a strong influence on the composition of the intestinal microbiota, respectively on the intestinal fermentative metabolism.

The indigestible components of the human dietary intake, including cellulose and pectin (plant cell wall polysaccharides) and inulin and oligosaccharides (storage polysaccharides), pass undigested into the large intestine and are afterward eliminated. The diet can contain four types of resistant starch, which is not completely digested in the small intestine [37,38,39]. The four types are called RS1, RS2, RS3 and RS4. RS1 is mainly found in unprocessed whole grains, seeds and vegetables. Studies have shown changes in the predominance of different bacterial species depending on the type of starch consumed. Prebiotics such as arabinoxylans (AX), arabinoxylan-oligosaccharides (AXOS) and xylo-oligosaccharides (XOS), which are found especially in wheat, influence the growth of beneficial germs, for example *Bifidobacterium* and *Lactobacillus* [41-40, 42-41-43-42].

Diet rich in oligosaccharides.

Fructans, inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and arabinoxylan-oligosaccharides have also been described to have a role in change the intestinal microbiota. Inulin and FOS favor the growth of *Lactobacillus spp and Bifidobacterium spp*, while fructan supplementation reduces the level of *Clostridium spp* and *Bacteroides spp*. [43]. In addition, fructans can lead to the growth of butyrate-producing bacteria (*Faecalibacterium prausnitzii*) [44,45] and galacto-oligosaccharide (GOS) supplementation can stimulate the maturation of *Bifidobacterium* spp. and population growth of *Faecalibacterium prausnitzii* [46,47]. Arabinoxylan-oligosaccharides have a similar effect, increasing the total bacterial population [48].

Different models of dietary intervention determined changes in the intestinal microbiota, in most studies the most frequent increase in *Bifidobacterium spp* was described following the enrichment of the diet with complex carbohydrates (Table II).

Table II. Changes in the intestinal microbiota through carbohydrate intake

	Potentially beneficial microbes								Potentially harmful microbes				
Dietary intervention in healthy adults	**Bifidobacterium spp.**	**Lactobacillus spp.**	**Faecalibacterium spp.**	**Roseburia spp.**	**Eubacterium spp.**	**Bacteroides spp.**	**Ruminococcus spp.**	**Prevotella spp.**	**Clostridium spp.**	**Enterobacter spp.**	**Enterococcus spp.**	**Bacteroides spp.**	**Ruminococcus spp.**
Resistant Starch													
The RS2 high-amylose corn starch diet) [49]	↑				↑								
Starch RS3 diet [50]				↑	↑		↑						
Starch RS4 diet [49]					↓		↓						
Diet with arabinoxylan-oligosaccharides (AXOS)													
Diet with wheat bran extract (rich in AXOS) (10 g/day for 3 weeks [50]	↑												
Diet with AXOS (2.2 g for 21 days) [51]	↑												
Diet with AXOS (10 g/d), 3 weeks [40]	↑												
Xylo-oligosaccharides (XOS)													
Diet with XOS (8 g/day, 21 days) [52]	↑												
Diet with XOS (1.4 g/day or 2.8 g/day), 8 weeks [53]	↑												
Lecerf JM, et al. (2012): diet with XOS, (5 g/day), 4 weeks [42]	↑												
Galacto-oligosaccharides (GOS)													
Diet with GOS (9 g/day) and maltodextrins (1 g/day), 5 days [54]	↑												
GOS diet (5.5 g/day, 10 weeks) [55]	↑												
Four-dose GOS diet (0, 2.5, 5 and 10 g/day, 12 weeks (3 weeks each) [56]	↑												
Chocolate chewable diet with GOS (5.0 g and 10.0 g) 3 weeks [57]	↑												
Raffinose-oligosaccharide (RO)													
Canned chickpea diet (200 g/day or 5 g/day), 3 weeks) [58]	↑								↓				
Inulin/inulin-type fructans I/ITF													
Chicory Inulin diet (12 g/day), 4 weeks) [59]	↑												
Inulin diet (10 g/day), 16 days [60]	↑			↑									
High-fiber diet													
Soluble corn fiber diet (21 g/day), 21 days) [61]	↓					↑							
Dietary fiber diet (40 g/day) compared with a dietary fiber diet (10 g/day), 5 days [62]								↑					
Barley bread diet, 3 days [63]								↑					
Dietary fiber formula (19.6 and 18.0 g fiber/day), 14 days) [64]	↑												
Corn-derived whole grain diet (48 g/day), 21 days) [65]	↑												
Polydextrose (PDX)													
PDX diet (8 g/day), 3 weeks) [66]							↑						

Influence of dietary lipids on gut microbiota

A diet high in fats containing ω-6 PUFA reduces the number of *Bacteroides* while enriching, *Actinobacteria, Firmicutes and Proteobacteria* populations [67,68]. Increased intake of MUFA, was associated with reduced levels of *Bifidobacterium* spp. and higher numbers of *Bacteroides spp*. Higher intake of ω-6 PUFA was associated with lower numbers of bifidobacteria [68]. Regular consumption of red meat was responsible for a major concentration of *Bacteroides* [69].

The different models of caloric intake from lipids in the diet have different effects on the intestinal microbiota (Table III). A randomized clinical trial reported that the consumption of 40% calories from fat by healthy young adults was correlated with undesirable changes in gut microbiota, with the intervention increasing harmful *Bacteroides* and *Alistipes species*, which are also abundant in type 2 diabetes (T2DM) and a decrease in beneficial bacteria (*Faecalibacterium*). At a consumption of 20% calories from fat the effect was positive regarding the growth of the intestinal microbiota *Faecalibacterium spp* and *Blautia spp* [70].

The influence of dietary protein on the gut microbiota

Preclinical and clinical studies have suggested that the type and amount of dietary protein consumed per day have substantial effects on gut microbiota (Table IV).

Other researchers have shown that the amount of protein is important through its effect on gut bacterial modulation. A protein supplementation (mixture of 10g whey isolate and 10g beef hydrolysate) of the diet of a group of healthy athletes over a period of 70 days had a negative impact on the gut microbiota by decreasing beneficial species (*Blautia, Roseburia and Bifidobacterium longum*) and an increase in germs of Bacteroidetes species [71]. In the control group, which received maltodextrin, the same effect was not observed.

In addition, the different methods of cooking meat could in turn have consequences on the gut microbiota [72]. An in vitro study of human intestinal microbiota showed that *C. hidrolyticum* (perfringens group), a bacterium that can produce enterotoxins responsible for causing various pathologies, was observed in fermented samples containing fried meat as opposed to those containing boiled meat [73], suggesting that the cooking method and meat type may influence the fermentation profile in human gut microbiota. Adverse effects associated with excessive meat consumption were highlighted at an intake of 380g/day of beef with significant increases of *Bacteroides* [73] and cooking at high temperatures [74,75]. The scientific literature has little similar evidence on human subjects, while the data on the changes of some of the germ populations, namely *Firmicutes*, were contradictory [76,77].

Thus, the need to evaluate the impact of protein quantity and quality on the human microbiota, especially in populations with increased protein intake, remains a subject of interest.

Conclusion

Although there is extensive research in the published literature regarding the role of macronutrients and micronutrients on the composition and/or diversity of the intestinal

Table III. Changes in the intestinal microbiota by lipid intake in healthy adults

	Potentially beneficial microbes								Potentially harmful microbes				
Dietary intervention in healthy adults	**Bifidobacterium spp.**	**Lactobacillus spp.**	**Faecalibacterium spp.**	**Roseburia spp.**	**Eubacterium spp.**	**Bacteroides spp.**	**Ruminococcus spp.**	**Blautia spp.**	**Clostridium spp.**	**Enterobacter spp.**	**Enterococcus spp.**	**Bacteroidetes spp.**	**Ruminococcus spp.**
Fat diet													
Fat Diet (20%, 6 months, healthy young adults) [70]			↑					↑					
Fat Diet (30%, 6 months, healthy young adults) [70]													
Fat Diet (40%, 6 months, healthy young adults) [70]			↓			↑		↑					

Table IV. Changes in the intestinal microbiota by protein intake in healthy adults

	Potentially beneficial microbes								Potentially harmful microbes				
Dietary intervention in healthy adults	**Bifidobacterium spp.**	**Lactobacillus spp.**	**Faecalibacterium spp.**	**Roseburia spp.**	**Eubacterium spp.**	**Bacteroides spp.**	**Ruminococcus spp.**	**Blautia spp.**	**Clostridium spp.**	**Enterobacter spp.**	**Enterococcus spp.**	**Bacteoidetes spp.**	**Ruminococcus spp.**
Protein diet													
Protein diet (20 g/day) 10 weeks) [71]				↓				↓					
Protein group (20 g/day) 70 days [71]				↓				↓					
Oil-free roasted meat (300°C, 15 minutes, then ground, frozen and lyophilized) 48 hours/in vitro fermentation, human faecal sample [72]									↑				

microbiota, the beneficial role of dietary fiber, of supplements with various nutrients, the disadvantage of high-fat diets or high protein intake, studies on healthy human subjects were fewer and showed only to a small extent the influence of cooked food on the intestinal microbiota.

In conclusion, further research on dietary intervention patterns is needed to understand the influence of nutrients from the perspective of the food source, the combination of nutrients in meals and the changes they undergo through cooking.

Further research could extend to:

– elucidation of changes in the microbiota in relation to the consumption of macronutrients according to amounts, sources and in combination with other nutrients and cooking methods;

– researching the purpose of bioactive compounds derived from macronutrients in the context of different eating habits;

– elucidating how some macronutrients (complex carbohydrates) can influence some effects related to the consumption of other macronutrients, such as proteins, mainly from animal sources, and fats, especially saturated ones;

Knowing the changes in the gut microbiota through diet and cooking methods, in healthy subjects, is the way to therapeutic solutions for gastrointestinal and extraintestinal conditions when the sole effect of dietary changes is harder to quantify.

Authors' contribution

FR (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

EM (Data curation; Formal analysis; Funding acquisition; Writing – review & editing)

PA (Data curation; Writing – review & editing)

CA (Formal analysis; Methodology; Software; Supervision; Validation; Writing – review & editing)

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Conflict of interest

None to declare.

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