Coffee and Microbiota

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Coffee is one of the most widely consumed beverages in the world, which has important repercussions on the health of the individual, mainly because of certain compounds it contains. Coffee consumption exerts significant influences on the entire body, including the gastrointestinal tract, where a central role is played by the gut microbiota. Dysbiosis in the gut microbiota is implicated in the occurrence of numerous diseases, and knowledge of the microbiota has proven to be of fundamental importance for the development of new therapeutic strategies.

Keywords: coffee ; coffee consumption ; microbiota ; gut microbiota ; microbiome

1. The Gut Microbiota

The human organism operates in concert with trillions of symbiotic microorganisms.

The host and its symbionts are called “holobionts,” and their collective genome is known as the “hologenome” [1].

With the completion of the Human Genome Project, new horizons have opened in microbiome research for a better comprehension of host–microbe interactions in the four major colonization sites of the human body: The gastrointestinal (as headliner), genitourinary, cutaneous, and pulmonary tracts [2].

The plasticity of the holobiont is provided by changes that occur mainly in the human genome and gut microbiome. In the past, characterization of the gut microbiota was done by cultivation methods.

However, most organisms are refractory to cultivation, as many of the colonic bacteria are anaerobic and cannot be cultured under aerobic conditions. Only 30% of intestinal bacteria have been characterized by this method [3].

Metagenomics has been defined as the application of modern genomic techniques to the direct study of microbial communities in their natural environment, bypassing the need for isolation and lab cultivation [4].

Real-time polymerase chain reaction (rtPCR) is the gold standard for detecting known and unknown microbes without cultivation.

Among the different marker genes, 16S ribosomal RNA (16SrRNA) represents the main method to census the community. The 16S rRNA is a part of the small subunit of the 70S ribosome, and it represents the preferred molecule for bacterial identification because it is universally distributed and contains both conserved regions that are identical for all bacteria and nine interspersed regions of short hypervariability that are unique to individual bacteria [5].

In addition to 16SrRNA sequencing, phylogenetic characterization can be performed by shotgun metagenomics. This method comprises the sequencing of the collective genome of the microorganisms present in a sample, after DNA extraction and shearing into small fragments (next-generation sequencing (NGS)). One of the main outcome measures is species diversity, defined as the actual number of different species represented in a dataset, often expressed as species richness (the number of different species represented in an ecological community) and species evenness (the relative abundance with which each species is represented in the community).

Together, they constitute alpha diversity [6].

Gut microbial ecology is dynamic, the more abundant the biodiversity of an ecosystem, the better its ability to resist perturbations from the external environment [7].

In fact, the competitive interactions of increased microbial species promote the stability of the gut microbiome, partially accounting for differences in individual responses to the same diet or drugs [8][9].

A healthy gut microbiome can be defined as the normal individual microbiota that maintains and propagates wellness in the absence of disease [10].

Most gut microbes reside in the colon, where they are present in concentrations of 10^9–10^{12} CFU/mL and include >1000 different species [11].

The collective microbiome is 150 times larger than the human genome, indicating the enormous number of processes in which gut microbes are involved [12].

The gut harbours a complex bacterial community that consists almost entirely of seven major numerical bacterial phyla found in the adult human gut (more than 70% of all microbes in the body): *Bacteroidetes* (Gram-negative anaerobes), *Firmicutes* (Gram-positive), followed by *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Cyanobacteria* [13].

About 90% of bacterial species in adults belong to *Firmicutes* and *Bacteroidetes*. Most species in the phylum *Bacteroidetes* belong to the genera *Bacteroides* and *Prevotella*. Bacterial species belonging to the phylum *Firmicutes* include the genera *Clostridium*, *Eubacterium* and *Ruminococcus* [14].

Alongside the bacteria are members of the Archaea kingdom, predominantly *Methanobrevibacter* species, which produce methane in the gut, and *Eukarya* such as the yeast *Candida*, microbial parasites such as *Entamoeba*, and macroparasites such as *helminths* [15].

Finally, viruses and bacteriophages also play a significant role in maintaining a healthy and balanced gut, contingent on mutualistic interactions between different species and associated substrate availability [16].

Structurally, the microbiota is organized into mucosa-associated microbiota and luminal microbiota. The former contributes more to host cell protection and gut barrier function than the luminal, due to direct interaction with gut-associated lymphoid tissues [17].

The establishment and colonization of the gut microbiota is a complex process. The microbiota begins to develop as soon as a baby passes through the birth canal, with important variables, such as breastfeeding versus artificial feeding, caesarean versus natural delivery, as well as the choice and timing of feeding, and environmental factors, such as hygienic conditions, number of siblings, kindergartens and schools, animals in the home, and rural versus urban lifestyle, being important determinants with long-term effects (including immunity) [18].

The structure of the human gut changes with aging, with a stabilization of the microbiota environment being achieved at around 3 years of age. After this period, the composition of the microbiota begins to differentiate and acquires similarity to that of the adult (50%) [19].

In the elderly, there is a higher proportion of pathogenic enterobacteria and a lower proportion of probiotic *Bifidobacteria* [20].

In centenarians, the lifespan decreases, due to changes in *Firmicutes* enrichment, increased proinflammatory responses (mediated by TNF alpha, IL-6, and IL-8) and decreased abundance of the anti-inflammatory *Faecalibacterium prausnitzii* [21].

Regardless of taxonomic classification, the healthy intestine comprises three enterotypes that are related to dietary habits: *Bacteroides*, *Prevotella*, and *Ruminococcus*, with considerable interindividual variability [22].

Enterotype 1 is characterized by a dominance of *Bacteroides*, which has saccharolytic and proteolytic activities and is involved in the synthesis of biotin, riboflavin, pantothenate, and ascorbate [23].

Enterotype 2 is *Prevotella* dominant, which acts as a mucin glycoprotein degrader, and is involved in thiamine and folate synthesis.

Enterotype 3 is characterized by *Ruminococcus* dominance, which has mucin-degrading activity and transports sugars from the membrane [24].

Regardless of the enterotype, some microbial members serve as the “core microbiota,” while others act as a “flexible pool”. The latter contributes to host adaptation and is generally acquired from ingested food, water, and various components of the environment [25].

The exchange of genetic material between the nucleus and flexible pool confers to the host the ability to adapt to an environment or food habit [26].

Depending on the combination of predominant species, an individual has a specific microbiome fingerprint [27].

Numerous high-quality data from the Human Microbiome Project (HMP) of the United States and the Metagenomics of the Human Intestinal Tract (MetaHIT) of Europe have now demonstrated the beneficial functions of normal intestinal flora on health, down to the genetic level [28].

These include protective (Peyer’s plaques and IgA secretion), metabolic, and structural functions that comprise vitamin production, synthesis of catecholamines from protein catabolism, lipid regulation, and production of short-chain fatty acids (SCFAs) that not only regulate gene expression, but are the fuel for epithelial cells [29].

Specifically, acetate serves as an energy source for peripheral tissues, supporting lipogenesis and cholesterol synthesis. Propionate is metabolized mainly in the liver, and butyrate serves as an energy source for colonocytes, producing ketone bodies with carbon dioxide, and stimulates gut enteroendocrine cells for leptin production from adipocytes, including the production of glucagon-like peptide-1 (GLP-1) in gut cells [30].

Nutritional and lifestyle behaviours are thus crucial players contributing to aging and human diseases, including metabolic (such as, type II diabetes, liver disease, and cardiovascular disease), immunological (such as, inflammatory bowel disease and type I diabetes), and neurological (such as, autism and multiple sclerosis) diseases [31].

The relationship between dysbiosis and disease is bidirectional: the application of gut-modifying therapeutic strategies, including prebiotics (e.g., contained in coffee and other plant foods), probiotics, and faecal microbiota transplantation, can contribute to human–microbiome symbiosis by promoting better health [32].

2. Coffee: The “Longevity Beverage”

Coffee is one of the most popular beverages in the world; it is estimated that more than 2 billion cups are drunk every day [33].

The largest coffee consuming states in the world are Brazil and the United States [34].

Various bioactive compounds are contained in coffee, among which polyphenols, such as the alkaloids contained in caffeine, caffeic acid in roasted coffee beans, and most significantly, chlorogenic acids in green beans, stand out in importance [35].

Caffeine’s mechanism of action operates on several levels in the body, specifically acting as an adenosine receptor antagonist on the nervous system [36].

The universally best-known action of caffeine is that it is a powerful stimulant, being able to increase the user’s attention and ability to concentrate [37].

The safe threshold of caffeine appears to be 400 mg per day [38].

The link between coffee consumption and the onset of diseases, such as Parkinson’s disease, diabetes mellitus type 2, nonalcoholic fatty liver disease (NAFLD), and liver cirrhosis, as well as coffee’s effects on intestinal motility, have also been extensively studied.

A dose-dependent inverse relationship between tea or coffee (including decaffeinated) consumption and the risk of type 2 diabetes has been described [39].

The risk of developing nonalcoholic fatty liver disease (NAFLD) has been shown to be inversely associated with coffee consumption [40].

Coffee consumption is also associated with a lower risk of developing liver cirrhosis [41].

A relationship between coffee intake and a reduced risk of Parkinson's Disease onset is described, although the underlying mechanism remains unclear [42].

Caffeine is a smooth muscle stimulator, and according to some work, its consumption is therefore associated with a reduction in constipation [43].

The most interesting evidence, however, comes from the relationship of caffeine consumption with all-cause mortality.

Coffee consumption is associated with a reduction in mortality from all causes [38].

One reason may be that healthy people use caffeine more than those with disease.

Other studies have shown that caffeine consumption is associated with a reduction in all-cause mortality, regardless of coffee consumption [44].

One of the downsides of caffeine consumption is that it can lead to an addictive condition [45].

In fact, there is a real caffeine withdrawal syndrome, characterized by symptoms such as fatigue, irritability, headache, and difficulty concentrating [46].

3. Coffee and Gut Microbiota

There are multiple effects of coffee consumption on the human body, so researchers wondered whether some of these effects were mediated by alterations in the gut microbiota. The most important studies on this topic are presented, starting with those conducted in animal models and ending with those conducted in humans.

3.1. Animal Models

Most of the studies were conducted in animal models.

Starting with the oldest reports, researchers see that they are still quite recent, and that the various research groups have focused on one of the different diseases for which coffee consumption appears to be protective, to better understand the link between consumption of this beverage and the onset of disease.

The most important studies conducted on the topic are discussed, listed by publication date.

Starting from the observation that coffee consumption is negatively correlated with the onset of type 2 diabetes, researchers investigated the link between a high-fat diet and coffee consumption in rats, and found that coffee consumption succeeded in changing the gut microbiota of rats fed the high-fat diet [47].

In another work conducted in mouse models, researchers witnessed a reduction in nonalcoholic fatty liver disease (NAFLD) in caffeine-consuming mice, accompanied by changes in the gut microbiota [40].

In a third study, mice were given caffeic acid, one of the main phenolic acids found in coffee [36].

Following caffeic acid supplementation, changes were found in the microbiota, such as an increase in *Akkermansia* and *Dubosiella*, and in re-examining the relative abundance, an increase in *Alistipes* and a decrease in *Turicibacter* and *Bacteroides* was documented [48].

In this interesting study conducted in rodents, researchers questioned the relationship between coffee consumption and glucose metabolism, studying the effects of chlorogenic acid (CGA), a polyphenol contained in coffee, on the microbiota [36].

The results were surprising. Chlorogenic acid (CGA) led to a change in the microbiota accompanied by an increase in short-chain fatty acid (SCFA) producers with a protective role towards the intestinal barrier [49].

In a recent study in PSD (paradoxical sleep deprivation) rats, there was a change in the gut microbiota after the administration of coffee and decaffeinated coffee [50].

In another interesting study in mouse models, researchers focused on the effect of coffee consumption on aspirin absorption.

Coffee bean extract (CBE) was administered to rodents, which resulted in a change in their gut microbiota such that there was an increase in the populations of *Lactobacillaceae* and *Muribaculaceae* and a decrease in *Bacteroidaceae*, *Proteobacteria*, and *Helicobacteraceae* [51].

Staying with animal models, this recent and very interesting study in mice is mentioned, in which the effect of coffee consumption and subsequent sleep restriction on the composition of their gut microbiota was investigated.

No changes were found in *Bacteroidetes* and *Firmicutes*, but, on the contrary, *Actinobacteria* and *Proteobacteria* were decreased.

So, in this work, caffeine administration resulted in a change in the gut microbiota of mice [52].

3.2. Studies on Humans

Having told you about these important studies conducted in animal models, it is now time to get to those conducted in human models.

Let us start with this study that is somewhat older than the others, with a very small number of participants (16) whose faecal samples were collected before and after a moderate intake of coffee (three cups a day for three weeks). Coffee consumption was found to be associated with an increase in *Bifidobacterium* spp. without affecting the dominant microbiota, however, accompanied by an increase in metabolic activity [53].

This interesting study in which chlorogenic acids is mentioned, the most important bioactive compounds in coffee, were administered in addition to caffeine [36].

The assumptions of this study are that coffee consumption is inversely related to the occurrence of both type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD) [39][40].

In this study, researchers showed that administering caffeine plus chlorogenic acids to a group of patients with diabetes and nonalcoholic fatty liver disease resulted in a reduction in their weight, probably related to an increase in intestinal bifidobacteria [54].

In this work, patients were divided according to their degree of coffee consumption, and it was found that higher levels of *Prevotella*, *Porphyromonas*, and *Bacteroides* were found in heavy coffee drinkers [55].

In a more recent study conducted on a small number (30) of healthy volunteers, it was found that coffee administration led to alterations in the gut microbiota, although this was not significant [56].

In this latest work, scholars focused on chlorogenic acids, the main polyphenols contained in coffee, and it was found that they altered the composition of the microbiota in the healthy volunteers in this important and interesting study [57].

An additional supportive action of coffee could be changes in the composition and metabolic function of the gut microbiota by polyphenols and other undigested prebiotic constituents of coffee (e.g., polysaccharides and melanoidins) [58]. Observational data assessed how dietary fibre is rapidly metabolized into short-chain fatty acids (SCFAs), resulting in up to a 60% increase in the *Bacteroides/Prevotella* bacterial group after consumption of coffee prepared from medium roasted Arabica beans [59].

In another experiment conducted in mouse models, the modulating action of coffee toward the gut microbiota was confirmed; in fact, there was a decrease in *Clostridium* spp. and *Escherichia coli* and an increase in *Bifidobacterium* spp. [60].

Selective metabolism and amplification of some bacterial populations following coffee consumption appear to be mainly due to its richness in polyphenols [61].

In spite of these promising results, much more clinical research is needed to clarify the impact of long-term coffee intake on gut microbiota composition and its health implications.

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