Review

Coffee and Microbiota: A Narrative Review

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Abstract: Coffee is one of the most widely consumed beverages in the world, with important repercussions on the health of the individual. Dysbiosis in the gut microbiota is implicated in the occurrence of numerous diseases, and knowledge of it has also proven to be of fundamental importance for the development of new therapeutic strategies. In this narrative review, we thoroughly investigated the link between coffee consumption and its effects on the gut microbiota and their consequences on human health. We have selected the most significant articles published on this very interesting link, with the aim of going deeper in the light of the latest evidence more and more about the relationship that links coffee consumption and its repercussions on the composition of the gut microbiota and on human health.

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: gastrointestinal (as headliner), genitourinary, cutaneous, and pulmonary tract [2].

The plasticity of the holobiont is provided by the 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 genomics techniques to the study of microbial communities directly 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.

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Among 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 its gene represents the preferred molecule for bacterial identification because it is universally distributed and contains both conserved regions that are identical for all bacteria and 9 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 in small fragments (next-generation sequencing called 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 (which refers to the number of different species represented in an ecological community) and species evenness (that refers to 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, competitive interactions of increased microbial species promote the stability of the gut microbiome, partly justifying why different individuals may have dissimilar 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) and *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 that 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].

Establishment and colonization of the gut microbiota is a complex process. The microbiota begins to develop as soon as the 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, rural and urban lifestyle being important determinants with long-term effects (including immunity) [18].

The structure of the human gut changes with aging: a stabilization of the microbiota environment is achieved 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].

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In centenarians, lifespan decreases due to changes in *Firmicutes* enrichment, increased proinflammatory responses (mediated by TNFalpha, IL-6 and IL-8) and lower 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* with saccharolytic and proteolytic activities and is involved in the synthesis of biotin, riboflavin, pantothenate, and ascorbate [23].

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

Enterotype 3 is characterized by *Ruminococcus* dominance with mucin-degrading activity and transport of sugars from the membrane [24].

Regardless of 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 nucleus and flexible pool confers ability to the host 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].

Precisely, acetate serves as an energy source for peripheral tissues, supports lipogenesis and cholesterol synthesis; propionate is metabolized mainly in the liver; butyrate serves as an energy source for colonocytes, produces 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) [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 the 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 turn out to be 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 the most important, namely chlorogenic acids in green beans, stand out in importance [35].

Regarding the mechanism of action of caffeine is to be an adenosine receptor antagonist on the nervous system [36].

Regarding its effects on the body, as known it acts on several levels.

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

Regarding its limits, 400 mg of caffeine per day appears to be the safe threshold [38].

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The link between coffee consumption and the onset of other diseases, including Parkinson's disease, diabetes mellitus type 2, NAFLD and liver cirrhosis, effects on intestinal motility, has also been extensively studied.

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

The risk of developing non-alcoholic fatty liver disease (NAFLD) is 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 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 with caffeine consumption and all-cause mortality.

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

One reason may be that it is precisely healthy people who 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 also 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. Materials and Methods

This narrative review includes about 20 papers published in English in the past 14 years on the topic of the complex interaction between coffee consumption and its effects on the gut microbiota.

We searched PubMed® and Google scholar® with the following keywords, "Coffee and gut microbiota."

We selected the articles that we considered most suitable for this type of work, focusing mainly on the most recent ones, favoring the latest evidence regarding this fascinating topic.

4. Coffee and gut microbiota

We then saw what are the multiple effects of coffee consumption on the human body, so we wondered whether some of these were mediated by alterations in the gut microbiota.

We then collected and selected the studies that we thought were most important in this regard.

We will then present to you the most important studies on this topic, starting with those conducted in animal models and ending with those conducted in humans.

5. Animal models

Most of the studies, as we shall see, have been conducted in animal models.

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

Below we will discuss the most important studies conducted on the topic, 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 it was found that coffee consumption succeeds in changing the gut microbiota of rats fed a high-fat diet [47].

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While in this other work conducted in mouse models, researchers witnessed a reduction in NAFLD in caffeine-consuming mice, accompanied by changes in the gut microbiota [40].

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

Following this supplementation, changes were found in the microbiota, such as an increase in *Akkermansia* and *Dubosiella*, and relook at relative abundance, we document an increase in Alistipes and a decrease in *Turicibacter* and *Bacteroides* [48].

In this interesting study conducted in rodents, researchers questioned the relationship between coffee consumption and glucose metabolism, thus 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].

Also in this recent study in rats, there was a change in the gut microbiota after the administration of coffee and decaffeinated coffee.

Parabacteroides, Lachnospiraceae and *Oscillospira* were found to be increasing while *Klebsiella* and *Akkermansia* were found to be decreasing [50].

In this interesting study in mouse models, researchers focused on how coffee consumption affects aspirin absorption.

In this regard, coffee bean extract (CBE) was administered to rodents, and it also resulted in a change in their gut microbiota: there was an increase in the populations of *Lactobacillaceae* and *Muribaculaceae* and a decrease in *Bacteroidaceae*, *Proteobacteria* and *Helicobacteraceae* [51].

Let's stay with animal models again, and mention this recent and very interesting study in rats in which they investigated how coffee consumption and subsequent sleep restriction affects the composition of their gut microbiota.

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

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

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

We then mention this interesting study in which chlorogenic acids, the most important bioactive compounds in coffee, were administered in addition to caffeine [36].

The assumptions of this study, as already explained in the introductory part of our article, are that coffee consumption is inversely related to the occurrence of both type 2 diabetes mellitus and NAFLD [39-40].

In this study, researchers showed that administering caffeine plus chlorogenic acids to a group of patients with diabetes and nonalcoholic fat liver disease saw 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 this recent study conducted on a small number (30) of healthy volunteers, it was found that coffee administration led, although not significant, to alterations in the gut microbiota [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].

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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 fiber is rapidly metabolized into SCFAs, resulting in up to a 60% increase in the *Bacteroides*/*Prevotella* bacterial group after medium roasting of Arabica [59].

In another experiment conducted in mouse models, moreover, 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.

As for our narrative review, we saw how the interest of researchers has been steadily increasing in recent years, and how although most of the studies have been conducted in animal models, recently more and more trials have humans as protagonists.

We have also collected all the most important studies and considerations in this summary table (Table 1).

Table 1. The most important studies and considerations on the relationship between coffee consumption and gut microbiota.

Studies conducted on animals		
Author	**Comments**	**Year**
Cowan et al. [47]	Coffee consumption succeeds in changing the gut microbiota of mice fed a high-fat diet	2014
Nakayama et al. [60]	Increase *Bifidobacterium spp.*, decrease *E. coli* and *Clostridium spp.*	2013
Vitaglione et al. [40]	Evidence of reduced NAFLD in caffeine-consuming mice accompanied by changes in gut microbiota.	2019
Wan et al. [48]	Regarding the composition of the rat gut microbiota, an increase in *Akkermansia* and *Dubosiella* was found, and regarding relative abundance, we document an increase in *Alistipes* and a decrease in *Turicibacter* and *Bacteroides*.	2021
Ye et al. [49]	Chlorogenic acid (CGA) administration led to a change in the microbiota accompanied by an increase in short-chain fatty acid (SCFA) producers with a protective role toward the intestinal barrier.	2021
Gu X et al. [50]	Regarding the gut microbiota analysis, *Parabacteroides, Lachnospiraceae* and *Oscillospira* were found to be increasing while *Klebsiella* and *Akkermansia* were found to be decreasing.	2022
Kim et al. [51]	Increased populations of *Lactobacillaceae* and *Muribaculaceae* and a decrease in *Bacteroidaceae, Proteobacteria* and *Helicobacteraceae*.	2022
Song et al. [52]	*Actinobacteria* and *Proteobacteria* decreased.	2022
Studies conducted in humans		
Author	**Comments**	**Year**

Jaquet et al. [53]	Increase in *Bifidobacterium spp*. but without affecting the dominant microbiota	2009
Ludwig et al. [57]	Chlorogenic acids, the main polyphenols contained in coffee, and they were found to change the composition of the microbiota in healthy volunteers in this important and interesting study.	2013
Mansour et al. [54]	By administering caffeine plus chlorogenic acid to a group of patients with diabetes and nonalcoholic fatty liver disease, there was a reduction in their weight, probably related to an increase in intestinal bifidobacteria.	2020
González et al. [55]	Higher levels of *Prevotella, Porphyromonas* and *Bacteroide*s were found in heavy coffee drinkers.	2020
Chong et al. [56]	Coffee administration led, although not significant, to alterations in the gut microbiota.	2020

7. Discussion

We decided to address this fascinating topic for several reasons.

Coffee is one of the most widely drunk beverages in the world [62], and consequently thoroughly understanding its effects on humans is one of the topics that fascinates multiple researchers.

As we have seen, coffee consumption appears to be implicated in a wide variety of diseases, and its protective role against Parkinson's disease, type 2 diabetes mellitus, NAFLD, and liver cirrhosis is described [39-42].

To be honest, however, what is most striking is how coffee consumption is associated with a reduction in all-cause mortality [38], even though, as explained earlier, currently the most accepted theory is that healthy people are greater consumers of this beverage than unhealthy people.

Since it is difficult to be able to better investigate this important and fascinating relationship, scholars have therefore focused on the link between coffee consumption and the occurrence of the specific diseases.

However, since coffee is a food, according to many authors at its basis there could be a close link with its repercussions on the gut microbiota.

The gut microbiota is one of the most evolving fields of medicine in recent years [63], which is increasingly fascinating researchers worldwide.

There are many reasons for this, starting with the increased technological development that has made it less complicated to conduct studies on this topic.

It is now well known how lifestyle (e.g., smoking) also affects the composition of the gut microbiota [64], and again one of the reasons we have devoted ourselves to this topic is precisely to thoroughly investigate this habit as widespread in the world as coffee drinking.

Knowing the gut microbiota may also prove to be of fundamental importance as a potential new therapeutic strategy, as is the case with Clostridium difficile infection, for example [65].

Scholars are increasingly focusing on the link between gut microbiota and diseases even far removed from the gastrointestinal system [66].

For this reason, we focused on the repercussions that coffee consumption has on the composition of the gut microbiota, precisely because in the future we might try to exploit them as a starting point for new potential therapies.

In most of the papers, researchers have started from an already known hypothesis or link, such as the protective effect of coffee consumption against various diseases such as Parkinson's, type 2 diabetes mellitus, NAFLD, and liver cirrhosis [39-42], to then go on to try to understand its mechanism of action, or whether there was an underlying link or change in the gut microbiota.

We see how the studies we have collected are all recently published, the oldest one having been published in 2009.

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Most were conducted on animal models, probably due to the fact that they are easier to perform than those conducted on a human population.

There is no doubt that coffee consumption leads to changes in the gut microbiota, while regarding the composition of individual species there is no unanimity on this.

In several studies we find a decrease in Proteobacteria [51,52] while there is no unanimity on Akkermansia [48,50].

We then mention this narrative review in which the role of several nutrients, including polyphenols, contained in coffee is analyzed [67].

Polyphenols have demonstrated the ability to modulate the gut microbiota by increasing the concentration of *Faecalibacterium sp.*, *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* associated with SCFA production [67].

This work has several limitations, the most important being that it is a review and therefore not supported by experimental data, and also for several topics there are not enough studies available to state a hypothesis accurately.

The major strength of this paper is that it is up to date with the latest evidence regarding this very complex and fascinating topic.

We have carefully selected the articles that we considered most suitable for this type of coverage, focusing on the topics that are currently attracting the most interest from researchers.

8. Conclusions

In conclusion, we believe that the topic we have just discussed is as fascinating as ever, since it brings together two of the most interesting topics in modern medicine.

On the one hand we have coffee consumption, which we have seen many times as being one of the most widespread habits in the world [68] and therefore involving a very high number of people with important repercussions also from the point of view of the health of the individual.

On the other hand, we have the Gut Microbiota, one of the areas in which there is an increasing interest from researchers all over the world, an ever-expanding field, constantly searching for new therapeutic weapons against various diseases that afflict humans [65].

In this review, we have selected and collected the most important studies conducted on this topic, dividing them between those conducted on animal models and those on humans, going deep into the relationship between coffee consumption and the repercussions on the gut microbiota, and consequently their consequences on human health.

This research has shown how we have only begun to delve into this topic in the last fourteen years, with still too few studies to be able to provide solid evidence in this regard.

Therefore, this work represents a valuable starting point for conducting new and increasingly important studies directed at fully dissecting this very fascinating topic.

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