

Review article

# Colonic catabolism of dietary polyphenols: Molecule vs Microorganisms

Valentina Garcia Acevedo, Maria Antonia Prieto Vargas, Melissa Ardila Madrigal  
(bachelors' student)

[garciaa.valentina@uces.edu.co](mailto:garciaa.valentina@uces.edu.co)

Research Tutor: Rafael Alvarez Quintero  
CES University-Medellín. Colombia

## ABSTRACT

The aim of this paper is to collect information about polyphenols, knowing how the host reshape the gut microbiota community, and how the host microbiota metabolize these molecules increasing their bioavailability, considering the lack of information in this field, which could help us get a better understanding in whether polyphenols are beneficial or not. **Conclusion:** Polyphenols can reach high bioavailability due to gut microbiota metabolism and therefore symbiosis in gut is essential to provide a beneficial effect of polyphenols, even these molecules can act as nutraceuticals, being effective for prevention of chronic diseases, that nowadays are worldwide problematic.

**KEY WORD:** Polyphenols, Gastrointestinal Microbiome, chronic diseases, metabolism, antioxidant.

## INTRODUCTION

Polyphenols are a group of secondary metabolites in plants, this type of molecules and their different classes are broadly distributed. Major sources are tea, fruit juices, coffee, red wine, also chocolate has been categorized as a rich source of polyphenols, even new commercial products include this ingredient, polyphenols extract, claiming a high content in polyphenols. (1)

Polyphenols present beneficial effects in the human health, such as antioxidants, antihypertensive, anti-inflammatory and cardioprotective properties. Antioxidants decrease the cardiovascular risk; this is related to the neutralization and balance of radical species (2). It's been shown that high consuming polyphenol chocolate, sweetened with sucrose, over an 8-week period decreases cardiovascular risk index by increasing HDL cholesterol without a detrimental effect on glycemic control, insulin resistance, inflammation or weight (3). As well, they may have a pleiotropic effect on cardiometabolic risk factors, due to the action of different subclasses of polyphenols, (see figure 2) (4) like flavonoids, a type of polyphenol, that enhances the nitric oxide (NO) production, acting as a potent vasodilator of the endothelial tissue, preventing platelet aggregation and adhesion, thus increasing the antihypertensive effect. However, in metabolic stress by presence of free radicals, the NO bioavailability decreases (2).

On the other hand, evidence has highlighted that the microbiota plays an important role in diseases such as type II diabetes and obesity, as well in the heart affections, reciprocal interactions between polyphenols and gut microbiota contribute to host health benefits. Dysbiosis of the microbiota tend to oxidative stress, inflammatory activities, thus lead to chronic affections. This interaction requires microbial degradation of polyphenols and modulation of gut microbiota by polyphenols and their

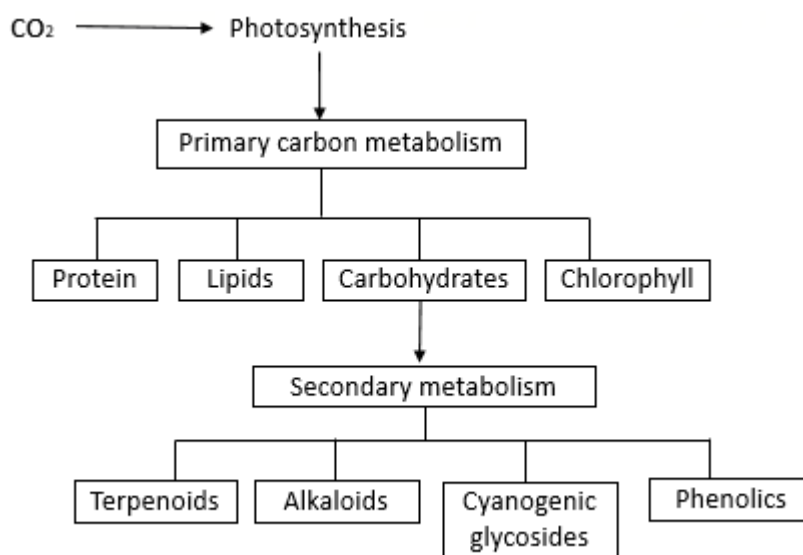
metabolites, which inhibits pathogenic bacteria and stimulates beneficial bacteria, symbiosis.

## POLYPHENOLS

- **Polyphenols and their classification.**

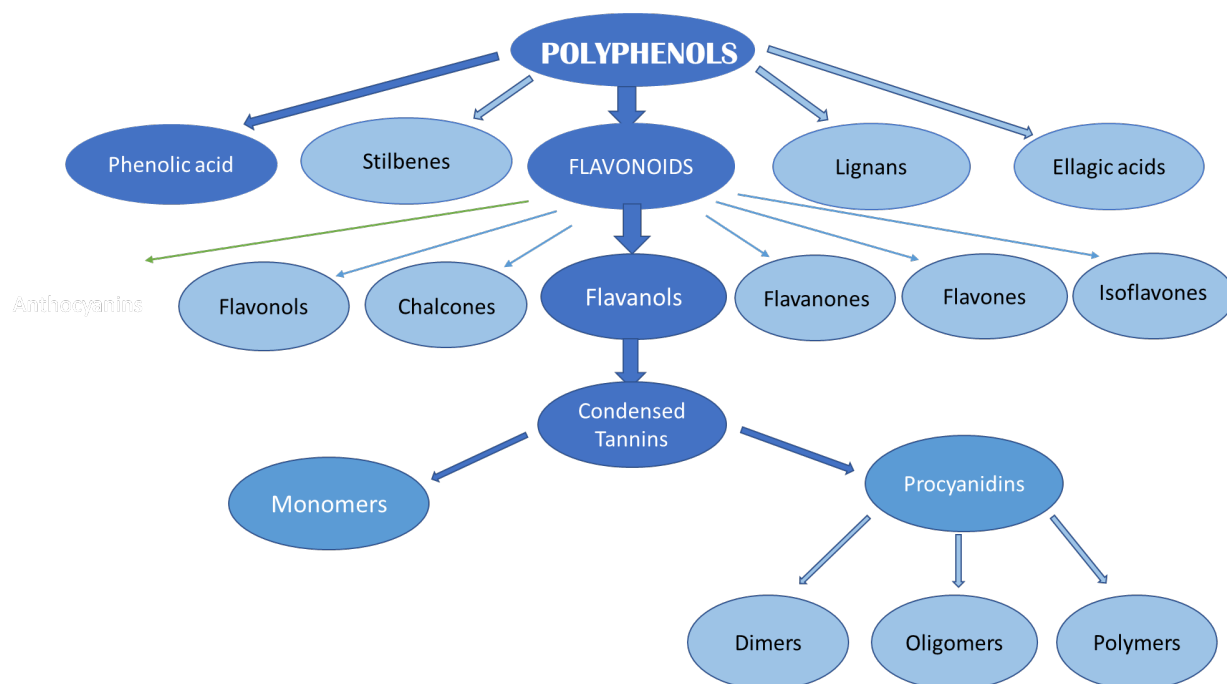
Polyphenols are a large group of heterogeneous compounds characterized by hydroxylated phenyl residues, they are found mainly in plants, including fruits, vegetables, and cereals, as well as in derived beverages such as tea, coffee, and wine. Its structures and chemical products are diverse and contribute the defense mechanism in plants, acting as signaling compounds, attracting pollinators or animals for seed dispersal, in addition, protecting the plant from oxidants and ultraviolet radiation. They also contribute to the color and sensory characteristics of fruits and vegetables.

Polyphenols, divided into flavonoids, phenolic acids, stilbenes, and lignans, are one of the most widely distributed secondary metabolites(5), in fruit, vegetables or food can contain more than a class of polyphenols, for example red wine contain stilbenes, anthocyanin's, and flavanoid like flavanol and flavan-3-ol.(6). Actually, there are characterized more than 8000 phenolic compounds and 6000 of these are flavonoids thus making it a very crucial group to study (7). They can exist in the plant as glycosides, acilglycosides or other conjugated form rather aglycone, these conjugation determinates of molecular weight, polarity, size, also add structural stability during storage in vacuoles and chloroplast (8) (9). Figure 1 illustrates the link between the primary and secondary metabolisms. (It is important to mention phenolic compounds the same term that polyphenols)



**Figure 1.** Primary and secondary metabolism linkage in plants. (10)

Taken and modified of: Vuolo, M. (2019). Chapter 2 - Phenolic Compounds: Structure, Classification, and Antioxidant Power.



**Figure 2.** Structural classification of polyphenols. (9)

Taken and modified of: Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects.

Secondary metabolite is divided, according to the structure, into four main groups: (1) allied phenolic and polyphenolic compounds, (2) terpenoides, (3) alkaloids and (4) cyanogenic glycosides (see figure 2). These are also classified according to their routes and biosynthetic structure. All of these compounds derive from the pentose phosphate, shikimate, and phenylpropanoid pathways in plants. In this review, only structural classification will be

- **Absorption and metabolism of polyphenols.**

The majority of polyphenols are found in the form of esters, glycosides or polymers, preventing direct absorption; hence these molecules suffer metabolism in different levels before being absorbed. Initially Polyphenols are partially hydrolyzed with acid in stomach, and then in the small intestine, these molecules are deglycosylated by human enzymes, forming metabolite absorbable known as aglycone. Aglycone enter epithelial cell by passive diffusion. Unabsorbed molecules must continue until the colon, meanwhile absorbed molecules can arrive to liver by enterohepatic circulation, wherein suffer biotransformation (phase I and II), nevertheless the formed metabolite in the previous process can come back to intestine by transport in bile salts. In the colon, the metabolites and original polyphenols over again are metabolized, but now by gut microbiota action. The metabolites can take different routes, absorbed, metabolize or secreted in urine and feces, it is estimated that 5-10% of polyphenols are absorbed in stomach and small intestine (11)

The absorption, subsequent metabolism or hepatic metabolism known as biotransformation in the host or human individual of different kinds of polyphenols produce several substances known as metabolites, the different kinds of polyphenols and their derivate, metabolites, follow specific absorption kinetics. Bioavailability, or rate of absorption, depends on physiological factors such as pH, bile salts, volume of liquid present, as well as, physicochemical factors like structure, molecule

size and complex formations. As described above, the polyphenols structure is the most important factor to determinate the bioavailability (12), (13). The most absorbed, with simple structures polyphenols are isoflavones and phenolic acids, followed by quercetin, catechins, flavanones and glycosides. The less absorbed polyphenols are proanthocyanidins, galloylated catechins and anthocyanins, due to high molecular weight.

The total variety of polyphenols metabolites is huge, from one type of polyphenol can derive various metabolites, some have been found and are shown in Table 1, with their respective type of study. Some polyphenols have not been yet characterized.

To mention that majority of studies have been performed *in vitro*, due to easier cell manipulation than animal manipulation. *In vivo* model murine is able to transfer microbiota between murine individuals, and observe changes in the microbiota profile; however, this is not possible in human resulting from a complex and lengthy digestive system in humans, interindividual, as well as ethic reasons.

**Table 1.** Metabolites of phenolic compounds *via* gut microbiota *in vivo* or *in vitro* (14)

Polyphenols	Type of study	Metabolites
Balcalin	<i>In vitro</i> study (humans feces)	Baicalein
Epicatechin	<i>In vitro</i> study (humans feces)	(-)-5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactone, 5-(3,4-dihydroxyphenyl)- $\gamma$ -valeric acid, 3-(3-dihydroxyphenyl) propionic acid, 4-hydroxyphenylacetic acid
Apigenin	Animal study (urine)	P-hydroxyphenylacetic acid, P-hydroxycinnamic acid, P-hydroxybenzoic acid
Quercetin	Animal study (urine)	4-ethylphenol, Benzoic acid, 4-ethylbenzoic acid
Catechin	Human Intervention (urine)	(-)-5-(3,4-dihydroxyphenyl)- $\gamma$ -valerolactone (M4), (-)-5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactone
Naringenin	<i>In vitro</i> study (rat feces)	Phenylacetic acid, P-hydroxyphenylacetic acid, Protocatechulic acid
Naringin	<i>In vitro</i> study (humans feces)	3-(4-dihydroxyphenyl)-propionic acid-3-phenylpropionic acid
Rutin	<i>In vitro</i> study (humans feces)	3-(3-dihydroxyphenyl)-propionic acid-3-hydroxyphenylacetic acid
Rutin	<i>Escherichia coli</i>	3,4-dihydroxyphenylacetic acid
Daidzein	<i>In vitro</i> study (rat feces)	Dihydrodaidzein
Anthocyanin	<i>In vitro</i> study (humans feces)	Gallic, syringic and p-coumaric acids
Chlorogenic acid	<i>In vitro</i> study (humans feces)	3-(3-dihydroxyphenyl)-propionic acid
Caffeic acid	<i>In vitro</i> study (humans feces)	Hydroxyphenylpropionic and benzoic acids
Ferulaic acid	<i>Lactobacillus</i> and <i>Bifidobacterium</i>	Coumaric acids and caffeic acids
Ellagic acid	<i>In vitro</i> study (humans feces)	Urolithin(A)

Taken and modified of: Lin, S. et al. (2019). Role of intestinal microecology in the regulation of energy metabolism by dietary polyphenols and their metabolites

- **Antioxidant capacity of the polyphenol.**

Antioxidants possess the capacity to neutralize free radical species. Radical or reactive species are very reactive molecules, due to their unpaired electrons, some reactive species are reactive oxygen species (ROS), reactive nitrogen species (NOS) and reactive species of different halogens (RXS). These are naturally produced in mitochondrial reactions and their excessive accumulation generate an unbalance between reactive species and antioxidants, this is known as the oxidation state (15). Reactive species react with all kinds of macromolecules in the cell: DNA, proteins, RNA, lipids in a way that leads to cellular apoptosis.

Antioxidants can act by various mechanisms; the transfer of an electron to the radical species, another form is the donation of a proton to the radical species. Polyphenols possess antioxidant capacity, due to the presence of OH bonds with low dissociation energy, also because these molecules present a conjugative system with high stability. It's important to mention that the polyphenol antioxidant action is through structure-antioxidant activity (SAR) that is related with the OH position, double bonds, glycosylation and the presence of the substituents in the ring. (10)

Some of the dietary antioxidants, like resveratrol, genistein, s-equol and isoflavone are produced from the biotransformation in the microbiota of soy daidzein. These metabolites have been demonstrated to be effective in the reduction of skin aging. The mechanism of action of these antioxidants is found by activating the  $\beta$ -estrogen receptor, which improves the expression of antioxidant enzymes and inhibits the expression of transcriptional factors, that regulate the proliferation and migration of the keratinocytes, this is another of the benefits that have been granted to antioxidants other than the elimination and acceptance of free radicals. However, it has been shown that interactions of polyphenols with lipid membranes and proteins also initiate the antioxidant effects.

Cardiovascular protection is attributed to flavanol intake, in sources such as cacao, in recent years, several clinical studies have been focused on supporting the fact that there is an inverse relation between flavanol intake and risk cardiovascular, due to antioxidant effect, preventing oxidation of LDL (prone to atherosclerosis) (2). Classically antioxidants where the main mechanism of action of polyphenols, furthermore mechanisms have been attributed to polyphenols, such as molecular signaling.

## **HEALTH**

- **Effect in the health**

A wide diversity of polyphenols provides multiple effects in the human health, we will mention the beneficial effects in the chronic diseases like obesity, diabetes and some cardiovascular conditions.

Obesity is a metabolic disease characterized in the increase of adipose tissue. It is also related to high free fatty acid levels, diabetes, heart diseases, altered level of adipokines and infiltration of macrophages derivative of cytokines like  $\text{TNF-}\alpha$  and IL-6, for the last obesity is a pathology related to inflammation. This pathology has shown beneficial effects with the intake of dietary polyphenols by enhancing the catabolism of adipose tissue, lowering triglycerides synthesis and promoting adipocyte apoptosis. For example, Resveratrol is a stilbene that has been characterized in multiples

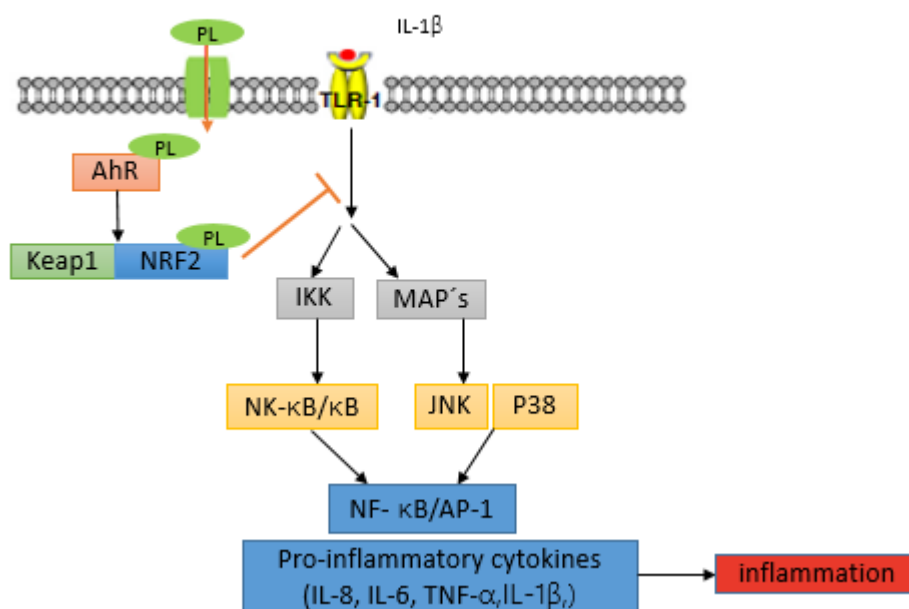
studies as an antiinflammatory, reducing proinflammatory cytokines and thus having an antiobesity effect. (16) (17)

There is a reciprocal relationship between obesity and diabetes, obesity generates an immune response leading to a chronic inflammation process, which results in an insulin resistance as seen in type II diabetes. Whereas diabetic individuals depend more on the lipid metabolism than the carbohydrate metabolism. Type I and II diabetes can occur, nevertheless 90-95% of the clinical cases of diabetes present type II diabetes mellitus (5). This pathology is a worldwide problematic, with a high incidence mortality rate, however it seems to improve and decrease the risk factors associated with diabetes throughout the intake of polyphenol rich foods, these have hypoglycemic effect inhibiting carbohydrate digestion by the inhibition of enzymes involved in that metabolic pathway, salivary enzymes, pancreatic  $\alpha$ -amylase and  $\alpha$ -glucosidase in the intestine. Other mechanisms relate the decreasing  $\beta$ -cell oxidative damage, which preserves  $\beta$ -cell integrity (5), (11). Additionally, *in vitro* studies have shown that dietary polyphenols like epicatechin, epigallocatechin-3-*O*-gallate (EGCG) grape seed-derived procyanidins can stimulate capture glucose throughout GLUT4 transporter mediated by insulin. (11)

Cardiovascular diseases are the number one cause of death each year; in 2012, it was responsible of 17.5 million of all deaths worldwide (18). This disorder includes hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke) and others (19). All these diseases are associated with development of atherosclerosis, which involve an inflammation process in the vessel wall and the infiltration of low-density lipoproteins (LDL), more prone to oxidation LDL (oxLDL), following with an attraction of T-cell, monocytes, macrophages, endothelial activation cells and decreasing the nitric oxide (NO) expression.

*In vivo* and *in vitro* studies have shown that dietary polyphenols inhibit inflammation process, through enzymatic inhibition of enzymes involved in prostaglandins and leukotrienes pathway like COX-2, COX-1, LOX, PLA-2 (18), (12). Anthocyanins have shown enzymatic inhibition, as well as flavonoids that have a pleiotropic effect on cardiometabolic risk factors (4), enhancing the nitric oxide (NO) production, acting as a potent vasodilator of the endothelial tissue, preventing platelet aggregation and adhesion, thus increasing the antihypertensive effect. However, in metabolic stress by presence free radicals, the NO bioavailability decreases (2). Other mechanism action of polyphenols is the modulation of transcriptional factors; they inhibit the NF-KB pathway and subsequent inflammatory genes expression by silencing of microRNAs.

Figure 3 shows the mechanism of action of polyphenols, enhancing the Keap1 and NRF2 pathway to inhibit inflammation signaling by IKK and MAPs signaling, that normally leading proinflammatory cytokines as IL-9, IL-6, IL1. Furthermore, Keap1 factor regulates expression antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), peroxiredoxin (PRXS). (9), (10)



**Figure 3.** Mechanism action polyphenols. PL: polyphenols. TLR-1: toll receptor type 1(9).

Taken and modified of: Zhang, H. et al. (2016) Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects.

All pathologies mentioned earlier have a great prevalence, and a high cost for the health system, with high mortality rates all over the world. Hence, the aim of therapeutics is not only to focus in pharmacology and pharmaco-therapeutic effects, but in having lifestyle habits that include well round-up nutrition and physical activities. Balanced nutrition includes dietary polyphenols, nevertheless supplementation with different class of polyphenols is most common, therefore more studies are necessary to support matrix, concentration, presentation and stability on this type of products.

- **Profiling of microbiota: health vs diseases.**

Polyphenols and diverse metabolites have a profound influence on the diversity and complexity of the intestinal microflora. Some studies have been carried out to understand the response of the intestinal microbiota, with the administration and addition of polyphenols in the diet, as well as to try to identify the key microorganisms that take part in this process, changes in selective growth of colonic microbiota in humans, suggest probiotic benefits. A large amount of information from experimental and human models have shown that in healthy subjects, *Bacteroidetes* (as *Prevotella*, *Bacteriodes genera*) and *Firmicutes* (as *Clostridium*, *Enterococcus*, *Lactobaccillus*) represent more than 90% of gut microbiota. Also is supported the fact that changing the gut microbiota by increasing the consumption of probiotics and prebiotics can help in the control of several related parameters in the development of metabolic diseases associated with obesity as diabetes and cardiovascular diseases.

The modulation of intestinal microbiota shows an activation of obesity in humans and animals. In obese mice, it has been observed that the reduction on the ratio *Bacteroidetes/Firmicutes*, compared

with non-obese mice, likewise in humans that are undergoing weight loss, the latter two have in common an increase in the relative portion of *Bacteroidetes*. This proved that the relationship between the low rate *Bacteroidetes/Firmicutes* and an obese phenotype.

A microbiota transplantation from obese mice to aseptic mice, result in the formation and development of the obese phenotype in aseptic mice (12). The gut microbiota is very sensitive, even in obese patients fed with high fat content and low fiber content, the gut microbiota changed just in 24 hours. Dietary polyphenols act as a prebiotic and contribute to weight loss, cause of increased rate of *Bacteroidetes/Firmicutes*. (8)

Other pathology as diabetes mellitus type 2, patients have shown a high level of the phylum *Firmicutes* and a low level in phylum *Bacteroidetes*, this is explained because phylum *Firmicutes* have more genes for enzymatic activity involved in the metabolism of carbohydrates and lipids than the phylum *Bacteroidetes*. On the other hand subjects with rich diet in carbohydrates possess microbiota high level *Prevotella*, while subjects with rich diet in proteins and saturated fatty acid possess microbiota rich in phylum *Bacteroides*. (6) (11). Dietary polyphenols increase levels of beneficial bacteria in the intestinal tract, including *Bifidobacterium spp*, *Lactobacillus spp* and *Eubacterium rectale* (5). *Bifidobacteria* has been associated with improved glucose tolerance and decreased inflammation responses of interleukins such as IL-6, IL1 $\alpha$ , IL $\beta$ ; therefore, this supports the antidiabetic properties of polyphenols. Other mechanism of antidiabetic effect, have been shown in the oral intake of resveratrol, cause to increase levels of intestinal GLP1 (Peptide similar to glucagon type 1) that stimulates an insulin release. (9) Microbial changes in the gastrointestinal tract have profound effects on host inflammatory and metabolic responses. The intestinal microbiota has essential functions in host metabolism and in directing immune system development (addressed in the next section). Probiotics and prebiotics may have the potential to be effective therapeutics to alleviate the symptoms associated with inflammatory diseases; however, the long-term effects are unknown. As our understanding of the microbiota continues to grow, promoting microbes, which can prevent or control inflammatory-mediated diseases through diet, may represent an exciting therapeutic avenue.

## MICROENVIRONMENT IN THE INTESTINE

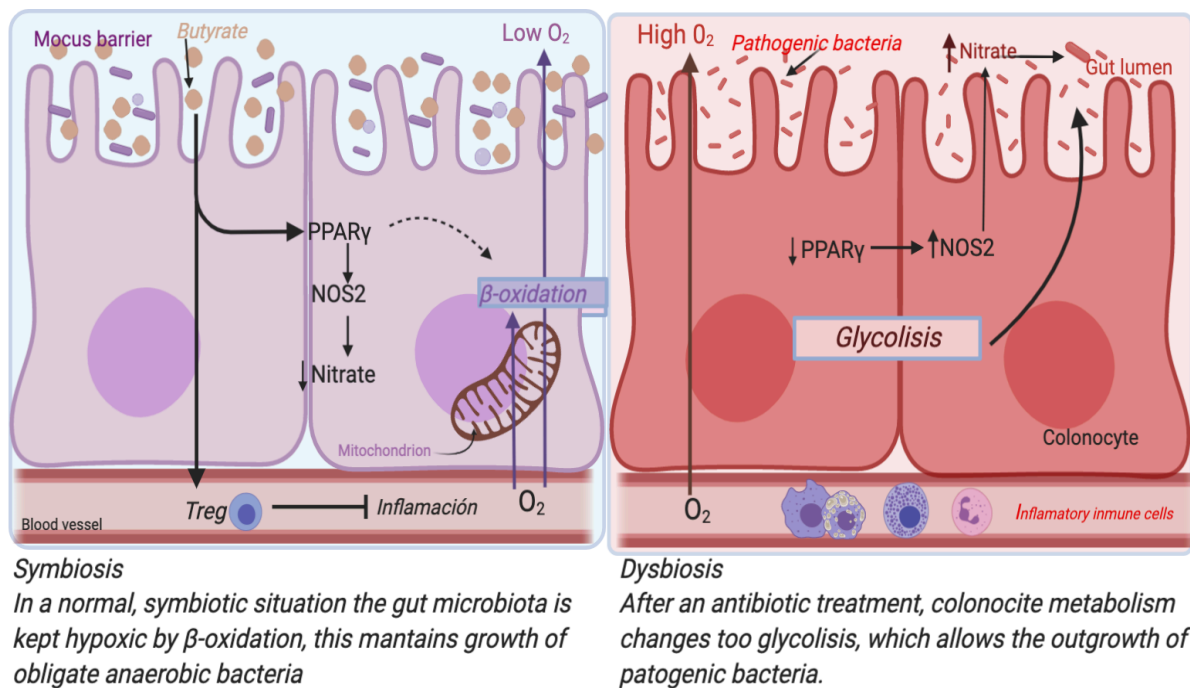
- **Microbiota and its role.**

The human colonic microbiota groups a wide variety of bacteria; at least 500-1000 different species have been identified in the human's gastrointestinal tract. Its composition has a high variation among individuals, due to environmental, epigenetic and genetic factors. The majority of colonic microbiota (96%) can be classified into: *Firmicutes*, *Bacteroides*, *Actinobacteria* (14). These groups of bacteria play a critical role within the metabolism of not absorbed metabolites of polyphenols or original polyphenols. However gut microbiota have other roles such as, vitamin producer, they proportionate a source of energy, modulate the immune responses, as well they regulate the environment of the microbiota when pathogenic bacteria are present, generating a symbiosis. Therefore, it is important to take care the gut microbiota with feeding.

Symbiosis is balance between gut microbiota, colonocytes and immune cells; they have a reciprocal communication, wherein molecules produced by gut microbiota, like short chain fatty acids, can induce antiinflammatory state. The colonocyte cellular metabolism is a condition on the state of the microenvironment, leading to high or low oxygen concentration, thus condition the oxidative state.



Beneficial bacteria are characterized to be obligate anaerobic; they live in low concentration of oxygen, where the colonocyte takes the oxygen to produce energy of beta-oxidation. (See figure 4)



**Figure 4.** In the left Symbiosis and in the right Dysbiosis. (20)  
Taken and modified of: Cani, PD. (2017) Gut cell metabolism shapes the microbiome.

The genome diversity of gut microbiota provides a huge enzymatic capacity to metabolize polyphenols and other molecules, reactions that human enzymes are unable to do, such as esterase activity. Gut microbiota performing transformations throughout deglycosylation, dihydroxylation and demethylation. Desglycosilations are the result of the glycosidase and esterase activities, therefore forming aglycone. As early mentioned aglycone can be absorbed directly by small intestine, nevertheless if aglycone is produced (in colon) by gut microbiota, this molecule can be absorbed or degraded by gut microbiota.

All polyphenols, that arrive into the colon, over different forms, such as bile salts or continue trajectory in intestinal system, can be degraded by gut microbiota. Aromatic rings in polyphenols are sensitive to degradation, resulting in metabolites; for example, flavonoids present a common structure, with two aromatic rings and another ring that connects them, these rings result in hydroxylated aromatic compounds such as benzoic acid, ferulic acid, protocatechuic and phloroglucinol. (21) Table 2 shows metabolite transformation by the intestinal microbiota, the way molecules may unfold until their lineal form, like propionic acid. There is a high diversity of metabolites, even more than original polyphenols. (considering that exist more than 8000 polyphenols compounds characterized.)

Table 2. Colonic metabolism of different polyphenols.

<b>Original polyphenol</b>	<b>Colonic Catabolites</b>
Proanthocianidin	Derivates of phenylvaleric, phenylpropionic, acetic acid
Flavanol, flavanonas, flavonas	Phenilpropionic acid
Flavanol	Phenylvalerolactones
Phenolics acids	Propionic acid

## CONCLUSIONS:

This review was composed to draw attention to the importance of polyphenols. Chemical structures richness confers them the possibility to aid in different metabolic activities and functions, such as it was described, different mechanisms are attribute to the antioxidant activities of polyphenols as molecular signaling, however the mechanisms action to improve or prevent chronic diseases mentioned have not been fully established.

Chronic diseases mentioned have a high prevalence and mortality rate, pharmacological therapy to this affection are expensive and sometimes hard to get. The best option is to have an adequate lifestyle, with exercise and a diet high in polyphenols, because they act as nutraceuticals having long-term non-pharmacologic therapeutic activity.

Despite the possible benefits of polyphenols for human health through modulating the microbiome, studies have been scarce and present several limitations, thus new techniques are being developed, such as epigenotypic or changes in microbiome composition (phylotic) studies, as well as combined with in vitro and in vivo studies, will help reveal more about this field and fill the gap between polyphenol metabolites and their biological activities, thus exploration chronic diseases, their control and further prevention.

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