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The role of phenolic compounds in metabolism and their antioxidant potential

O papel dos compostos fenólicos no metabolismo e seu potencial como antioxidante

El papel de los compuestos fenólicos en el metabolismo y su potencial antioxidante

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Abstract
The intake of fruits and vegetables rich in nutrients with bioactive properties is associated with the prevention of a range of chronic diseases such as cardiovascular diseases, diabetes, and cancer that originate from physiological disorders, which can be promoted by the accumulation of free radicals in the body. Several chemical compounds with bioactive functions are found in fruits and vegetables. Among these, phenolic compounds stand out for having high antioxidant capacity. These compounds originate from the secondary metabolism of plants, being essential for their growth and reproduction. In addition, they can be more expressed by plants under stress conditions, such as infections by microorganisms, lesions, severe climate changes, nutritional deficiency, among others. The highest concentrations of these phenols are found in fruit and vegetable skins, due to their potential use in protecting against UV rays, pathogens and predators. The search for new sources of natural and/or synthesized antioxidants has been growing due to the wide biological activity observed for these compounds, such as the inhibition of lipid oxidation and its action

against the inactivation of free radicals. These compounds can be synthesized via the shikimate/phenylpropanoid pathway. It is believed that after consumption they are partially degraded in the small intestine, about 5 to 10%, and the rest in the large intestine. Here we review how the plant synthesizes phenolic compounds and their health effects, demonstrating the significant dietary activity of these compounds in metabolic processes.
Keywords: Secondary compounds; Antioxidant activity; Cancer; Free radicals.

Resumo
A ingestão de frutas e hortaliças ricas em nutrientes com propriedades bioativas está associada à prevenção de uma série de doenças crônicas como doenças cardiovasculares, diabetes e câncer que se originam de distúrbios fisiológicos, que podem ser promovidos pelo acúmulo de radicais livres no organismo. Vários compostos químicos com funções bioativas são encontrados em frutas e hortaliças. Dentre estes, os compostos fenólicos se destacam por possuírem alta capacidade antioxidante. Esses compostos são originários do metabolismo secundário das plantas, sendo essenciais para seu crescimento e reprodução. Além disso, podem ser maior expressos pelas plantas sob condições de estresse, como infecções por microrganismos, lesões, mudanças climáticas severas, deficiência nutricional, entre outros. As maiores concentrações desses fenóis são encontradas nas cascas de frutas e vegetais, devido ao seu potencial uso na proteção contra raios UV, patógenos e predadores. A busca por novas fontes de antioxidantes naturais e/ou sintetizados vem crescendo devido a ampla atividade biológica observada para estes compostos, como por exemplo, a inibição da oxidação lipídica e a sua ação frente a inativação dos radicais livres. Esses compostos podem ser sintetizados através da via chiquimato/fenilpropanóide. Acredita-se que após o consumo são parcialmente degradados no intestino delgado, cerca de 5 a 10%, e o restante no intestino grosso. Aqui revisamos como a planta sintetiza os compostos fenólicos e seus efeitos na saúde, demonstrando a atividade dietética significativa desses compostos nos processos metabólicos.
Palavras-chave: Compostos secundários; Atividade antioxidante; Cancer; Radicais livres.

Resumen
La ingesta de frutas y verduras ricas en nutrientes con propiedades bioactivas está asociada a la prevención de una serie de enfermedades crónicas como las enfermedades cardiovasculares, la diabetes y el cáncer que tienen su origen en trastornos fisiológicos, que pueden ser promovidas por la acumulación de radicales libres en el organismo. Varios compuestos químicos con funciones bioactivas se encuentran en frutas y verduras. Entre estos, los compuestos fenólicos destacan por tener una alta capacidad antioxidante. Estos compuestos se originan en el metabolismo secundario de las plantas, siendo esenciales para su crecimiento y reproducción. Además, pueden ser más expresados por las plantas en condiciones de estrés, como infecciones por microorganismos, lesiones, cambios climáticos severos, deficiencia nutricional, entre otros. Las concentraciones más altas de estos fenoles se encuentran en las pieles de frutas y verduras, debido a su uso potencial en la protección contra los rayos UV, patógenos y depredadores. La búsqueda de nuevas fuentes de antioxidantes naturales y/o sintetizados ha ido en aumento debido a la amplia actividad biológica observada para estos compuestos, como la inhibición de la oxidación lipídica y su acción frente a la inactivación de radicales libres. Estos compuestos se pueden sintetizar a través de la vía del shikimato/fenilpropanoide. Se cree que después del consumo se degradan parcialmente en el intestino delgado, alrededor del 5 al 10%, y el resto en el intestino grueso. Aquí revisamos cómo la planta sintetiza compuestos fenólicos y sus efectos en la salud, demostrando la importante actividad dietética de estos compuestos en los procesos metabólicos.
Palabras clave: Compuestos secundarios; Actividad antioxidante; Cancer; Radicales libres.

1. Introduction

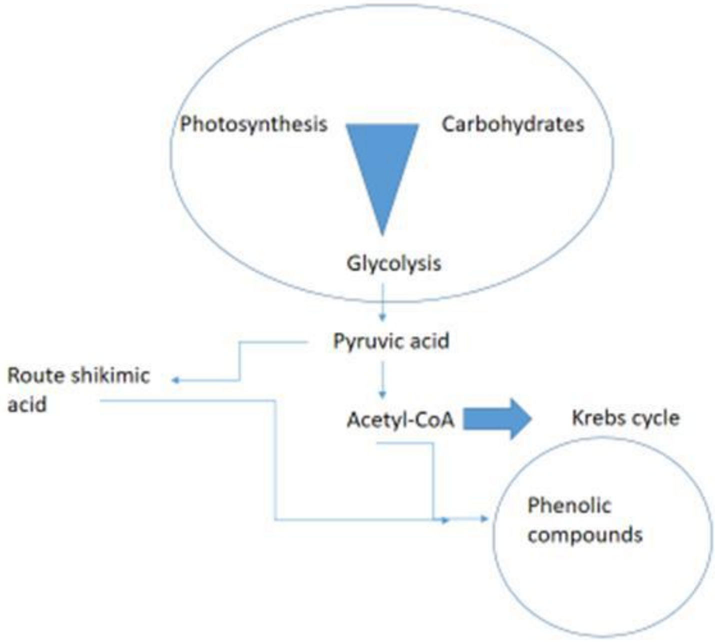
Epidemiological studies indicate that the intake of fruits and vegetables plays a fundamental role in the prevention of chronic and cardiovascular diseases such as diabetes, hypertension, metabolic syndrome, obesity, and cancers, due to the presence of compounds with bioactive functions, highlighting those with antioxidant functions. Based on these properties, the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) has recommended the daily consumption of 400 g of fruits and vegetables (da Silva et al., 2021). Although the Brazilian Ministry of Health has adopted this measure to improve diet and reduce nutritional deficits, daily consumption in Brazil is far below the recommended level, according to data from the Family Budget Surveys (PBS) from 2021 and 2009, showing that less than 10% of the population meets the recommendations for consumption of fruits and vegetables, foods able to improve dietary indices for vitamins A, E, C, D, B1 (thiamine), B2 (riboflavin), B6 (pyridoxine) and B12 (cobalamin), folate, niacin, selenium, zinc, copper, iron, phosphorus, magnesium, and calcium.

During metabolic processes, such as respiration, free radicals are produced naturally by cells as unstable molecules that can easily associate with other molecules. This process is called oxidative stress and is caused by an imbalance between the production and accumulation of reactive oxygen species (ROS) in cells and tissues, which affects damage to healthy cells and promotes premature aging. In addition, these effects can contribute to the emergence of the inflammation process and tumors, Alzheimer's, and cardiovascular diseases (Nardini & Garaguso, 2020; Van Hung, 2014). In this context, exploring new antioxidant compounds (natural and/or synthesized) sources from food with pharmaceutical potential emerges as a good opportunity; however, it is still challenging for research.

Fruits, vegetals, and cereals have been described as steady sources of chemical compounds, such as vitamins, phenolic compounds, and minerals, with outstanding antioxidant action. These compounds, that can be called as natural antioxidants, have antioxidant properties, which can be composed of several molecules such as phenolic, tocopherols, carotenoids, ascorbic and dehydroascorbic acid, glutathione, and enzymes such as glutathione peroxidase, superoxide dismutase and catalase (Silva et al., 2020; Souza et al., 2022). These compounds can delay and prevent the oxidation of substances from chemical transformations. Natural antioxidants are vitamins C and E, carotenoids, and phenolic compounds, especially flavonoids (Souza et al., 2022). Yu et al. (2022) related to a wide range of natural resources has been used and increased as a source of nutrients essential to human metabolism in recent years. The development of techniques that enhance the extraction of these processes has been applied in food, pharmaceuticals, and cosmetic industries, meeting a demand for natural products by the consumer's search for nutrients.

The plant system is comprised of primary and secondary metabolisms, which both present specific functions. . Primary metabolites are constituted of proteins, nucleic acids, carbohydrates, lipids, and fatty acids and their interaction in plant physiologic metabolism. These metabolites act in the processes of photosynthesis, respiration, and assimilation of nutrients, responsible for the plant's survival. In contrast, secondary metabolites are associated with the defense of the plant (Parida et al., 2018), and also with the main antioxidant natural source, being produced from glucose metabolism. They are divided into three groups: acetate (terpenes), shikimic acid (phenolic compounds), and amino acids (alkaloids) (Figure 1). Phenolic compounds are molecules contenting an aromatic ring linked to at least one hydroxyl, which has been studied in the last years, mainly regarding their bioactive compounds (da Silva, 2021). However, less attention is given to the plant metabolism of these compounds. Therefore, the objective of this work was to demonstrate the plant metabolism of phenolics and their role in the body as antioxidants, demonstrating their numerous benefits for human health. Chen et al., (2022), reports that polyphenols also play an important role in the relationship between T2DM and obesity. On the one hand, obesity is chronic low-grade inflammation that causes insulin resistance, so polyphenols can reduce the risk of T2DM by improving obesity.

Figure 1. Biosynthetic pathway for the production of terpenes, phenolic compounds, and alkaloids.



Source: author himself.

2. Methods

For the development of the research, a tiresome search of data from the last five years was carried out using the main databases. The main scientific bases of searches were PubMed/MEDLINE, Scielo, Sco-pus, Web of Science, google academic, capes periodic and Cochrane Library databases were searched for articles published in English, Spanish, French, and Portuguese of last five years preferably.

3. Phenolic Compounds

The phenolic compounds are substances that have at least one benzene ring in which at least one hydrogen of its structure is replaced by a hydroxyl group capable of donating electrons or hydrogen atoms, neutralizing free radicals and other reactive oxygen species (Monteiro & Brandelli, 2017; Zhang & Tsao, 2016; Souza et al., 2019). They can be obtained from two main metabolic routes: via shikimic acid and mevalonic acid.

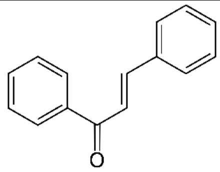
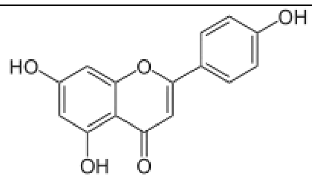
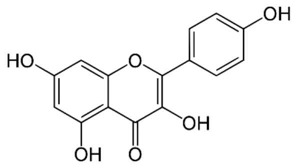
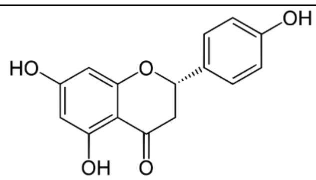
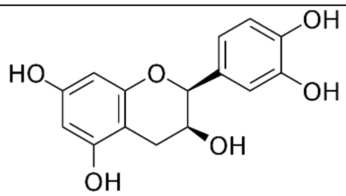
Phenolic compounds may have a single-chain molecule with a well-modified variant and well-modified chains. In the group that is poorly distributed in nature, we have simple phenols, such as the isomers pyrocatechol (ortho), hydroquinone (para), and resorcinol (meta) with molecular formula $C_6H_4\ (OH)_2$. This group also includes aldehydes from reactions of benzoic acids, present in essential oils. The group of polymers comprises tannins and lignins. Finally, the family of those widely distributed in nature includes flavonoids, phenolic acids, and coumarins (Aguiar et al., 2019).

In plants, in addition to acting as a defense against microorganisms and insects, they also contribute to some characteristics, such as color, flavor, and texture (Souza et al., 2022). Additionally, they can act as antioxidants, where their intermediate radicals prevent the oxidation of substances in foods, especially lipids, which can result in the formation of tumors, neurogenerative diseases, diabetes, and proteins that affect enzyme activity, receptors, and membrane transport .Most phenolics occur in nature as bonded forms combined with sugars, organic acids, and esters, although some phenolics occur as aglycones (Parida et al.; 2018). Phenolic acids are found in plant tissues primarily as hydroxyl derivatives of benzoic and cinnamic acids. In plants, these compounds are involved in processes such as bitterness and sour taste and astringent properties (Parus, 2013; Almeida et al.,2020).

Phenolic compounds are divided into flavonoids and non-flavonoids classes (da Silva, 2021). Non-flavonoids have, as their main feature, a benzene ring, a carboxylic group, and one or more hydroxyl or methoxyl groups and derive from hydroxybenzoic acid or hydroxycinnamic acid. Acids derived from hydroxycinnamic acid are the most active and most stable due to their unsaturation, which stabilizes the radical through electron shift resonance (da Silva et al., 2020).

Some of these bioactive compounds are classified according to the number of carbon atoms in a structure or by their degree of unsaturation or oxidation. On the other hand, most flavonoids consist of a carbon skeleton (C6-C3-C6) formed by a chromane ring and an aromatic ring at positions 2, 3, or 4 (Almeida et al., 2020). From the structure, several combinations occur, mainly with hydroxyls and methoxyls, which correspond to flavonoids and are classified into: flavones, chalcones, flavonols, flavanones, flavanols, anthocyanidins, and isoflavones, according to Table 1 (Moon et al., 2006).

Table 1. Examples of flavonoids and their sources.

Class	Structure	Examples	Source
Chalcone	 Chalcone	Chalcone	Hops, beer
Flavone	 Apigenin	Apigenin Luteolin Acacetin Baicalein Chrysine Tangeritin	Parsley, thyme, celery, red pepper, honey, propolis
Flavonol	 Kaempferol	Kaempferol Galangin Morina Myricetin Quercetin	Onion, broccoli, apple, cherry, raspberry, tea, red wine
Flavonone	 Narigenin	Narigenin Eriodctyol Esperetine Homoeriodctyol	Citrus
Flavonol	 Epicatechin	Epicatechin Catechin Proanthocyanidins	Cocoa, green tea, chocolate, red wine, some herbs

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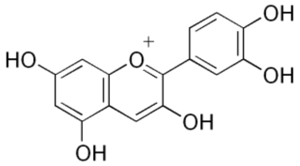
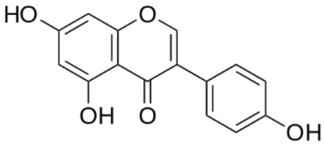
Anthocyanidin	 Cyanidin	Cyanidin	Cherry, grape, raspberry
Isoflavone	 Gynestein	Gynestein Daidzein	Alfalfa, soy,some vegetables

Source: Moon et al., (2006); Almeida et al., (2020); Parus, (2013).

Flavonoids are of great interest to researchers because they promote the destruction or inactivation of free radicals through two main mechanisms of action: chain breaking, where a hydrogen atom is donated to the free radical, or by removing initiators from species that react to oxygen (ROS) (Souza et al., 2022). In chain breaking, the active hydrogen atom of the antioxidant is more easily abstracted by free radicals than the allylic hydrogens of unsaturated molecules, forming inert species, which are unable to initiate or propagate oxidative reactions (Shrama et al., 2019). Briefly, this is the mechanism of action of phenolic compounds by chain breaking: ROO• + AH → ROOH + A•, where ROO• - free radicals and AH - antioxidant with an active hydrogen atom. In the other mechanism, oxygen is removed from the medium and, therefore, it becomes unavailable for the propagation of autoxidation.

Synthetic polyphenols, such as butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), tert-butylhydroquinone (TBHQ) and propyl gallate (PG), can be classified as biological antioxidants (Messias, 2009). Synthetic polyphenols, BHA, BHT, TBHQ and PG can donate a proton to a free radical, stopping the oxidation process by these radicals and, consequently, becoming free radicals. However, these radicals can stabilize, resulting in the non-propagation of oxidation (Grynkiewicz and Demchuk, 2019). The use of these compounds in Brazil is limited to 0.04 g/100 mL by the Ministry of Health. According to Sharma et al., 2019, on the other hand, tocopherols, natural polyphenols found in plants and some fishes, reduce the oxidation rate of lipid compounds, donating their hydrogens. They can also be synthesized, given their broad applicability to inhibit the oxidation of edible oils and fats (Paraginski et al., 2015), with the use of 0.03 g/100 mL being permitted by law of Brazil.

The tocopheroxyl radical can be regenerated by ascorbic acid (vitamin C) or by reduced glutathione (GSH). Through the use of chromatographic techniques, it is possible to analyze the content of flavonoids in foods, and the highest concentration is found in the skin of fruits and vegetables due to their potential role in protecting against UV rays, pathogens, and predators (Nardini & Garaguso, 2020; D 'Abrosca et al., 2007). The way of cultivation, storage, and preparation directly influences flavonoids' concentration. A higher incidence of UV rays on the plant results in a higher content of phenolic compounds (Sharma et al., 2019).

Over the decades, several studies have been carried out aiming to evaluate the flavonoid content in foods. In 1996, Hollman et al (1995) used liquid chromatography technique (HPLC) to identify and quantify these bioactive compounds in various vegetables, fruits, and beverages. They found the highest concentrations in onions, broccoli, apples, cherries, berries, teas, and red wine. Rietiveld and Wiseman (2003) conducted studies on green and black teas, where both had approximately 200 mg of flavonoid per cup. D'Abrosca et al. (2007), compared the flavonoid content between the pulp and skin of limoncella-type apples, the latter showing a high concentration of total phenols. Thus, the importance and wide variety of flavonoids is clear, being the most studied quercetin, myricetin, rutin, and naringenin compounds in this class (Sharma et al., 2019). For the present study, only the flavonol class will be further explored, with special attention to quercetin and rutin compounds.

3. Mechanisms and Bioavailability of Polyphenols

Phenolic compounds have beneficial effects on health, depending on how they are extracted from food and their intestinal absorption, metabolism, and biological action (Tressera-Rimbau et al., 2017). The speed of absorption of these compounds by the human body varies according to their structure, since the flavonoids linked to sugars have increased solubility, and the functional groups linked to the flavone have a direct influence on this process (Nardini and Garaguso, 2020). Their bioavailability (percentage of utilization) depends on two main factors: chemical structure and differences in the intestinal microbiota (group of bacteria) (Valdés et al., 2015). The chemical structure of these compounds determines the concentration, rate, and extent of absorption, as well as the nature of the metabolites circulating in the plasma (D'archivio et al., 2007 and Sharma et al., 2019).

The action of chewing determines the breakdown of cells to release polyphenols weaklier bound to the cell wall structure and those contained in vacuoles. Polyphenols bound to the cell wall are released during the gastro-pancreatic digestive phase as a consequence of the action of the acidic environment of the stomach and the alkaline environment of the intestine (Barros; Maróstica Junior, 2018). About 5 to 10% of polyphenols are absorbed in the small intestine, while the large intestine is responsible for the degradation of the remainder, where the intestinal mucosa does not absorb polyphenols in the glycoside form. For this, they must be released in the aglycone form (Duenas et al., 2015).

This absorption process is mediated by the enzyme lactase-phlorizin hydrolase (LPH), an enzyme present at the edge of the small intestine (Dikmannn et al., 2017). Rhamnoside flavonoids first undergo hydrolysis by lactase-phlorizin hydrolase (LPH) so that they can be absorbed. Otherwise, they are subject to microbial metabolism and long deterioration in the colon (Kumar et al., 2013), resulting in lower bioavailability. Rutinoside flavonoids (rutin hydrolyzed with the enzyme rhamnodiastase) are degraded in the large intestine, depending on the intestinal microbiota for their glycolysis, causing a peak plasma concentration only after 6 hours (Hollands et al., 2008). After being glycolized, the polyphenols leave the enterocytes for the liver through the portal system bound to albumin or through the lymphatic route (Brand et al., 2008). Subsequently, they are conjugated by glucuronidation, sulfation or methylation, or transformed into smaller phenolic compounds (Loomis et al.,2014), becoming more active or being eliminated through feces and urine.

In the gastrointestinal tract (GIT), the biotransformation of the unmodified conjugated forms takes place in the oral cavity, occuring through the beta-hydrolysis of sugar moieties in the flavonoid O-glycosides through phase I (oxidation, reduction and hydrolysis) and phase II (conjugation) enzymatic detoxification pathways. This results in several water-soluble conjugated metabolites capable of crossing the enteric barrier for distribution to organs and, ultimately, excreted in the urine (Santhakumar et al., 2018).

4. Intestinal Absorption of Phenolic Compounds

Before entering the systemic circulation, polyphenols undergo a certain degree of enzymatic phase II metabolism forming sulfates, glucuronides, and methylated derivatives through the action of sulfotransferases (SULTs), uridine-5′-diphosphate glucuronosyltransferases (UGT) and catechol-O-methyltransferase (COMTs), respectively (Del Rio et al., 2013). There is also an efflux of at least some of the metabolites back into the lumen of the small intestine, and this is thought to involve members of the family of adenosine triphosphate-binding (ATP) transporters, including multidrug resistance protein (MRP) and P-glycoprotein (P-gp) (Manzano & Williamson, 2010).

In the bloodstream, MRP-3 and the glucose transporter GLUT2 transport the derivatives to the liver in the efflux of

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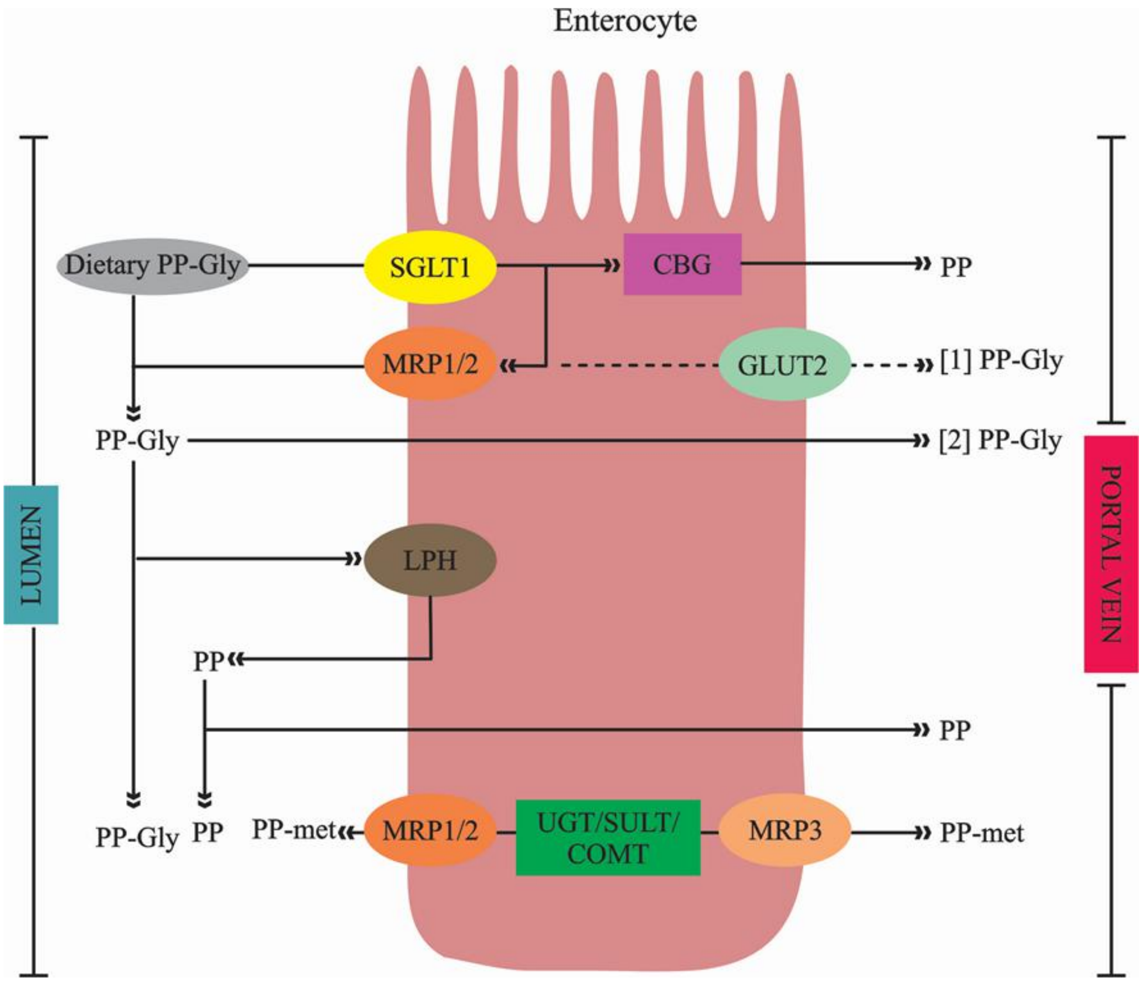
metabolites from the basolateral membrane of enterocytes. In the liver, the derivatives further undergo phase II metabolism, and enterohepatic transport may result in some recycling back to the intestine through the excretion of bile (Viskupicová et al., 2008), as shown in Figure 2.

Figure 2: Proposed mechanisms for the absorption and metabolism of (poly)phenolic compounds in the small intestine. CBG, cytosolic β-glucosidase; COMT, catechol-O-methyl transferase; GLUT2, glucose transporter; LPH, lactase phloridzin hydrolase; MRP1-2–3, multidrug-resistant proteins; PP, (poly)phenol aglycone; PP-gly, (poly)phenol glycoside, PP-met, polyphenol sulfate/glucuronide/methyl metabolites; SGLT1, sodium-dependent glucose transporter; SULT, sulfotransferase; UGT, uridine-5′-diphosphate glucuronosyltransferase.



Source: Author himself.

Studies by Borges et al. (2010) showed by urine analysis that absorption occurs in both the large and small intestines, with a utilization of 70 and 30%, respectively. These results were found by comparing metabolites between ileostomized and healthy subjects. Therefore, studies on the metabolism of polyphenols by the intestinal microbiota are crucial to understanding the role of these compounds and their health effects (Duda; Chodak et al., 2015). The concentration of these polyphenols sufficient to have biological activity by the action of digestive enzymes (small intestine) and microbiota (large intestine) bioaccessible in the intestine (Hithamani; Srinivasan 2014).

5. Effect of Polyphenols on the Microbiota

The interaction between polyphenols and microbiota is reciprocal, since different microbial groups are able to change the structure of polyphenols into more absorbable forms and polyphenols can modulate the composition of the microbiota (Santino et al., 2017). Awad et al., (2017), reported that some of these common polyphenols, including quercetin, epigallocatechin gallate (EGCG), genistein, resveratrol, exhibit protective effects on intestinal tight junction barrier functions by increasing TEER through modulation of tight junction protein expression and/or distribution. According to Wan et al (2020), a large proportion of polyphenols are not absorbed along the gastrointestinal tract, and may accumulate in the large intestine, where most of them are extensively metabolized by the intestinal microbiota. The formation of bioactive metabolites derived from polyphenols may benefit the health status of subjects, although the mechanisms have not been delineated. The latter, being determined by a dynamic process of selection and competition. As studies by Ratmanesh (2011) show, after regular ingestion of wine vinegar or fruits rich in polyphenols and green tea, it shows prevalence of Bacteroidetes community due to having more glycan-degrading enzymes.

Anthocyanins have been shown to stimulate the growth of lactic acid bacteria and increase malolactic fermentation. These bacteria can cleave anthocyanin molecules and use the sugar moiety as a carbohydrate source (Duda-Chodak et al., 2015). Pardhi et al., (2019), reports that in the last two decades, given the benefits arising from the bioactive capacity of anthocyanins, drug studies have focused on manufacturing methods, formulation optimization, in vitro physicochemical evaluation (format particle size, solid state behavior, increased solubility and dissolution, physicochemical stability, etc.), solidification and therapeutic applications, as well as in live pharmacokinetics and biodistribution.

Regarding other compounds, such as flavonols, e.g, quercetin and its variations, the bioavailability varies according to the individual, resulting in one of the main reasons for several studies. These variations are not only correlated with lifestyle, but with polymorphisms in the proteins responsible for the degradation of xenobiotics and/or composition of the intestinal microbiota (Guo et al., 2014). The studies by these authors suggest that the bioavailability of quercetin is explained, in part, by the low plasma concentration of vitamin C, which is associated with greater intestinal permeability and inflammation, improving the absorption of quercetin. Specifically, dietary polyphenols have been shown to modulate GM composition and function, interfering with with bacterial quorum sensing, membrane permeability, in addition to sensitizing bacteria to xenobiotics. In addition, it can impact metabolism and gut immunity and exert anti-inflammatory properties (Kumar Singh et al., 2019).

In order to understand drug performance, intracellular fate, or in vivo fate, Shen et al. (2021) explored traces of autofluorescent nanocrystals by tracking the translocation of fluorescence hybridized nanocrystals in biological processes. Their studies described that the smaller the particle size, quercetin (QC), is more easily absorbed, dissolving faster in vivo, leading to greater QC distribution. da Silva et al. (2021) related that quercetin (Q) is a bioflavonoid with biological potential; however, poor solubility in water, extensive enzymatic metabolism and a reduced bioavailability limit its biopharmacological use.

6. Conclusion

Phenolic compounds is of great interest to researchers due to its antioxidative character, may be associated with to prevent diseases caused by free radicals, as well as the inhibition of lipid oxidation, one of the causes of the emergence of neurodegenerative diseases, tumors, and formation of atherosclerotic plaques. Despite the efficacy and safety in its consumption, the limited bioavailability of these compounds continues to be highlighted as a main concern, where factors such as solubility, absorption, and metabolism have a direct influence on this process and its beneficial effects.Use the paragraph as a template.

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