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REVIEW



Impact of plant extracts upon human health: A review

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ABSTRACT

With the increase in evidences directly linking diet and health, several foodstuffs, such as phenolic rich fruits and vegetables, have emerged as possessing potential health benefits. Plants, given their fiber and phenolic content (and their intrinsic biological potential), have long been considered as contributing to health promotion. Therefore, the present work aimed to review the existing evidences regarding the various potential benefits of plant extracts' and plant extract-based products' consumption, with emphasis on *in vivo* works and epidemiological studies whenever available. Overall, the information available supports that, while there are indications of the potential benefits of plant extracts' consumption, further human-based studies are still needed to establish a true cause-effect.

KEYWORDS

Health promotion; plant extracts; functional foods; phenolic compounds; dietary fiber

Introduction

Plants have been used by humanity for centuries and, while various applications could be referenced (e.g. food source, raw materials for clothing production, shelter construction or simply decoration), their use as herbal medicine is one of the oldest forms of healthcare known to mankind. In fact, the study of plants goes back hundreds of years and it has permitted them to be explored not only for food, but also to obtain non-food products. From a technical standpoint, a medicinal plant is characterized as possessing pharmacologically active components that allow it to be used, directly or indirectly, in a therapeutic treatment to prevent or cure a certain disorder (Boscolo and de Senna Valle 2008, Briskin 2000, Djeridane et al. 2006). Several works have focused on characterizing the potential medicinal properties of plants which may include anti-inflammatory, anti-tumoral, antidiabetic and antioxidant effects (Jung et al. 2006, Watt and Breyer-Brandwijk 1962, Ekor 2014, Roleira et al. 2015). Moreover, several of the drugs commonly used today in medicine are of herbal origin, with their beneficial/therapeutic effects thought to be due to the presence of several different compounds that can be found in numerous plants, such as terpenoids, alkaloids, flavonoids, phenolics, and some others. The World Health Organization estimates that more than 80% of the world's population relies on traditional medicine using plants to satisfy their primary healthcare needs (Raskin et al. 2002, Farnsworth et al. 1985, Ekor 2014, Who 2013).

The past decades have seen an increase in life expectancy, as well as in the general public's concern with life quality. The connection between health and diet has been reported

by several authors, with some foodstuffs being regarded as more beneficial than others. Nutrition plays a very important role on one's health, with a balanced diet being fundamental to maintain homeostasis and therefore the proper functioning of the human organism. The consumption of fruits and vegetables has been viewed as an important part of a healthy diet, as they have high contents of dietary fiber and phenolic compounds, which are known to exert potentially beneficial effects, such as antioxidant, immunomodulatory and anti-tumoral activity, as described by several different epidemiological studies (Conlon and Bird 2014, Parkar, Stevenson, and Skinner 2008, Rodriguez-Casado 2016, Liu 2013, Slavin 2013, Anderson et al. 2009, Brown et al. 1999, Willcox, Scapagnini, and Willcox 2014, Lopez-Legarrea et al. 2014, Dreher 2018, Ganesan et al. 2018, Veiga et al. 2017).

Additionally, another factor that is perceived has having a great impact upon human health is the intestinal microbiota, with this connection having been shown through several reports (Quigley 2013, Marchesi et al. 2015, Claesson et al. 2012, Sekirov et al. 2010, Round and Mazmanian 2009, Dreher 2018, Alkasir et al. 2017, Holscher 2017). In fact, imbalances in gut microbiota composition, for instance changes in the types and numbers of bacteria in the gut, have been associated with the development of several disorders. This disturbance is known as dysbiosis and may lead to cardiovascular diseases, inflammatory bowel disease and other gastrointestinal disorders as well as mental health disorders. The modulation of the gut microbiota has been studied as a possible alternative to current treatments used, with plant extracts being a focal point due to their constitution (Hu, Wang, and Jin 2016, Morais et al. 2016,

Kashtanova et al. 2016, O'Callaghan and van Sinderen 2016, Finegold et al. 2017, Holscher 2017, Tremaroli and Bäckhed 2012, Million et al. 2013, Marchesi et al. 2015). As such, this review aims to provide some insights into how different plant extracts may have a positive, or a detrimental, impact upon human health and the microbiota, recurring to epidemiological evidences whenever possible.

Plant extracts' composition

Biological active compounds present in plants are not, normally, easily accessible. Therefore, plants have been the target of several works focusing on the extraction of these natural compounds, as well as in the removal of the fractions with lower biological relevance, thus originating extracts which may have several applications, such as medical (for example, extracts have been studied as cancer treatment alternative, treatment of diabetes and dermatological disorders, among others) or agricultural (repellent effects and antifeedant, control of diseases in plants) while being a source of bioactive compounds for the cosmetic and food industries (Djeridane et al. 2006, Hassan et al. 2009, Hilou, Nacoulma, and Guiguemde 2006, Sasidharan et al. 2011, Silva et al. 2013, Seeram et al. 2006, Armendáriz-Barragán et al. 2016, Salem et al. 2015, Ribeiro et al. 2015).

The production of an extract allows for the removal of the compounds which showcase no relevant benefit to the host. In turn, this leads to the attainment of the bioactive components, in a concentrated form, whose incorporation into other products is easier than the inclusion of the whole plant. However, the extractions usually require the use of organic solvents which may originate some concerns when considering their use/consumption by humans. There are several reports describing the advantages and disadvantages of different extraction methods for different target compounds, ranging from phenolic compounds to carbohydrates and phospholipids (Nicoue, Savard, and Belkacemi 2007, Sasidharan et al. 2011, He et al. 2016, Naczki and Shahidi 2006, Hendrix 1993, Lapornik, Prošek, and Wondra 2005, Escarpa and González 2001, Kolarovic and Fournier 1986, Silva, Costa, Calhau, et al. 2017). Furthermore, the production of plant extracts may be an interesting alternative for waste reduction (particularly at the agro-food level) as these byproducts may function as a low cost, renewable source of biologically relevant compounds and therefore contribute to a more efficient management of resources and the development of circular economy models (Armendáriz-Barragán et al. 2016, Ross 2014, Sasidharan et al. 2011, Hassan et al. 2009, Ribeiro et al. 2015).

Different extracts, obtained from different plants, can exhibit a vast array of potentially beneficial effects such as hepatoprotection, anti-tumoral, antioxidant, antimicrobial, antidiabetic, anti-inflammatory and antimalarial activity among several others. In these cases, it is perceived that the overall activity of the extract results from the synergistic action between its different constituents, particularly as tests performed with only the perceived "active principle" frequently yield poorer results than those observed for the

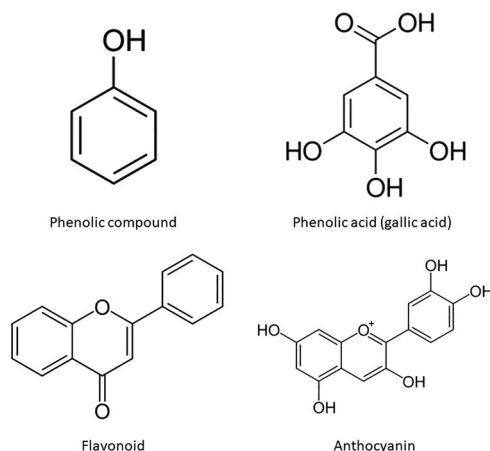


Figure 1. Basic chemical structure of a phenolic compound, phenolic acid, flavonoid and anthocyanin.

complex chemical matrix which is the extract (Jung et al. 2006, Balasundram, Sundram, and Samman 2006, Hilou, Nacoulma, and Guiguemde 2006, Hassan et al. 2009, Islam and Choi 2009, Djeridane et al. 2006, Omoregbe, Ikuebe, and Ihimire 1996).

Plants' bioactive compounds

Diet has long been associated with positive, or negative, impacts upon the health and wellbeing, with foodstuff of plant origin being strongly associated with a healthier status. Fruits and vegetables are generally rich in water, sugar, fiber, several phytonutrients and vitamins, all of which are essential for the body's homeostasis. Most importantly, the potential benefits of their consumption have been frequently associated with their vitamin, phenolic and fiber contents (Fuller et al. 2016, Lv et al. 2015, Nile and Park 2014, Bosscher et al. 2009, Liu 2003, Willcox, Scapagnini, and Willcox 2014, Tiihonen, Ouwehand, and Rautonen 2010, Conlon and Bird 2014, Dillard and German 2000, Raskin et al. 2002, Trinidad et al. 2010).

Phenolic compounds

Fruits and vegetables represent the primary sources of phenolics in the human diet although they can sometimes be found in other organisms, e.g. bacteria, fungi and algae. They are secondary plant metabolites which exert a photoprotective function and several other roles that are crucial for the plants' metabolism and survival, such structural support and protection against pathogen's infection. In nature, ca. 8000 different phenolic compounds have been reported so far. According to their chemical structures, they can be divided into several groups, that range from relatively simple phenolic acids (an example is shown in Fig. 1) to highly polymerized tannins. Moreover, they are also responsible for the pigmentation and some of the organoleptic characteristics showcased by plants, such as flavor and color (Djeridane et al. 2006, Balasundram, Sundram, and Samman 2006, Landete 2012, Cheynier 2012, Lattanzio 2013).

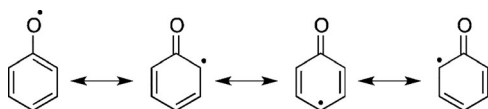


Figure 2. Formation of phenoxyl radicals.

Overall, chemically wise, phenolic compounds may be defined as molecules comprised of at least one phenol unit (an aromatic ring with one hydroxyl substitution, as seen in Fig. 1), with molecules containing more than one of these subunits being conventionally classified as polyphenols. In fruit and vegetables, phenolic compounds are frequently found in glycosylated forms (*i.e.* associated with a sugar moiety) as the free forms often present more toxicity than the glycosylated ones (Das et al. 2012, Hollman and Arts 2000, Landete 2012, Vermerris and Nicholson 2008a, b).

Phenolics have been systematically reported as being beneficial for human health and wellbeing. One of the properties most commonly associated with phenolics is antioxidant activity as, due to the position of the hydroxyl group bound to the aromatic ring, they are efficient proton donors. Moreover, phenol groups can also accept electrons resulting in the formation of relatively stable phenoxyl radicals (Fig. 2). This allows for the disruption of oxidation reaction chains that can be detrimental in biological systems and, when in foods help limit the oxidative damage of the matrix itself (allowing for longer shelf life). Moreover, after ingestion, they may be absorbed by the body and act as local antioxidants. For instance, anthocyanins (seen in Fig. 1) (water soluble flavonoid pigments that are abundant in red and purple fruits) have been described as capable of protecting liver and red blood cells against *in vitro* and *in vivo* oxidative damage and several phenolic rich extracts have been associated with the reduction of plasmatic antioxidant levels and oxidation stress markers. Additionally, these compounds have been used in order to increase functionality of some foods (Duda-Chodak et al. 2015, Youdim, Martin, and Joseph 2000, Liu et al. 2013, Sevgi, Tepe, and Sarikurkcü 2015, Wang et al. 2010, Yan et al. 2018, Silva, Costa, Vicente, et al. 2017, Olas 2017). Functional foods are defined as foodstuff or food ingredients which exert some benefit upon health, helping to prevent or ameliorate the symptoms of certain diseases, including diabetes, osteoporosis, cardiovascular diseases, among many others. Taking into account the possible health benefits shown by phenolic compounds, several studies have demonstrated how their addition or the addition of phenolic-rich extracts to certain foodstuff could be beneficial to one's health (Dissanayake et al. 2018, Quirós-Sauceda et al. 2014, Mohamed 2014, Charalampopoulos et al. 2002, Abuajah, Ogbonna, and Osuji 2015, Çam, İçyer, and Erdoğan 2014). For example, Akhtar et al. (2015) showed how a phenolic-rich pomegranate peel extract could be used as food ingredient and as potential food preservative, contributing to prevent certain diseases as well. Moreover, studies by Junior and Morand (2016) and Gao et al. (2013) showed that supplementation of phenolic-rich mate extracts in rats' diet contributed to prevent endothelial dysfunction and to regulate the expression of lipid metabolic regulators, preventing hepatic fatty deposition.

Additionally, besides the potential health benefits, the use of byproducts also contributes to reduce waste (Putnik et al. 2017, Moncada and Aristizábal 2016).

Dietary fiber

Dietary fiber, found in vegetables, fruits, grains, and legumes has been described as a group of complex non-starch carbohydrates and lignin, which include polysaccharides, oligosaccharides, lignin, and associated plants substances. These compounds are not affected by the digestive process and are not absorbed in the small intestine. However, they may be metabolized in the colon by local microorganisms, resulting in several secondary products that can be absorbed into the bloodstream. The different types of dietary fiber may be categorized according to their sources, solubility (soluble and insoluble dietary fiber), fermentability and physiological effects (Adam et al. 2014, Kendall, Esfahani, and Jenkins 2010).

The intake of fiber has gradually decreased for the past 200 years, regardless of the fact that its consumption has been associated with an array of important health benefits. It binds to substances (such as sugar and cholesterol) preventing or slowing their absorption into the bloodstream therefore contributing to the regulation of blood sugar levels and protecting against cardiovascular problems by lowering the levels of blood cholesterol. For instance, soluble dietary fiber (*e.g.* non-cellulosic polysaccharides, oligosaccharides, β -glucans, pectins and gums) has been described as being responsible for an increase in gut content viscosity and is, therefore, frequently associated with the regulation of blood glucose levels, reduction in serum cholesterol and a delay in bowel movements. Additionally, some dietary fibers may contribute to the modulation of the gut microbiota due to their fermentability, contributing to an increase in beneficial genres, such as *Bifidobacterium* which, in turn, has been associated with colon, stomach, breast and prostate cancer prevention. Furthermore, dietary fiber has been shown to significantly reduce the risk of gaining body weight and fat, notwithstanding the quantity of fat ingested or the amount of physical exercise performed, as it reduces the overall energetic intake. On the other hand, it diminishes some antibiotics' bioavailability. Rich sources of soluble fiber include fruits, vegetables, oats and pulses (Brown et al. 1999, Slavin 2008, Wu et al. 2015, Ye et al. 2015, Adam et al. 2014, Smith and Tucker 2011, Trinidad et al. 2010, Fuller et al. 2016, Tucker and Thomas 2009, Zinman et al. 2015).

Insoluble fiber is poorly broken down by the gut and absorbed into the bloodstream (such as cellulose, hemicellulose and lignin). However, given their bulking capacity and their (although low) fermentability by gut microbiota, insoluble fiber has often been associated with a reduction of bowel transit time and an improvement of laxation, while their fermentation may also contribute to the modulation of the gut microbiota. Since soluble and insoluble fibers are present in different proportions in food, and considering that both have different biological potentials, it is important to eat a variety of fiber rich foodstuffs in order to ingest both types of dietary fiber at sufficient levels (Brownawell

et al. 2012, Fuller et al. 2016, Kaczmarczyk, Miller, and Freund 2012, Mudgil and Barak 2013, Slavin 2005, Trinidad et al. 2010, Ross et al. 2017, Dreher 2018, Holscher 2017).

Other compounds

All plants exposed to the atmosphere are coated with layers of a lipidic material that helps to reduce water loss and functions as a barrier to prevent pathogens' entry. The main constituents of these coatings are fatty acids polymers (joined by ester linkages) such as cutin, suberin and waxes (Duke et al. 2016, Fich, Segerson, and Rose 2016). Moreover, plants produce a large array of organic, non-phenolic, compounds that have no connection to their development or function but confer them some protection against herbivores, insects and microbes or function as attractants for pollinators and seed-dispersing animals. Terpenes represent the largest class secondary plant metabolites although some have well defined roles in plant growth and/or development and can be considered primary metabolites. The compounds belonging to this class are usually insoluble in water and are biosynthesized from acetyl-CoA or glycolytic intermediates (Duke et al. 2016, Daniel 2016).

Carbohydrates are the basis of the formation of plants. Their complexity varies between a simple monosaccharide to homogeneous and heterogeneous polysaccharides. Some of the biological properties of heterogeneous polysaccharides include a protective action of mucosa and irritated skin, anti-inflammatory effect and immunomodulating activity (Hardy et al. 2015, Hendrix 1993, Duke et al. 2016).

Other compounds of interest that can be found in plants include phytosterols (promising agents in hormonal therapy), salicylates (are used for the development of aspirin), terpenoids (that have anti-inflammatory and antimicrobial activity) and alkaloids (compounds that, despite their pharmacological activity such as anesthetic, antitumoral, antiarrhythmic and antimalarial activity, showcase a high level of toxicity) (Ras et al. 2015, Racette et al. 2015, Malakar 2017, Baye et al. 2017, Tholl 2015, Cushnie, Cushnie, and Lamb 2014, Aniszewski 2015).

Plants' and plant extracts' biological potential

As mentioned previously, plants have been associated with an abundance of epidemiological evidences supporting an array of potential health benefits (Hollman 2001, Neto 2007, Graf, Milbury, and Blumberg 2005, Asif 2015, Jung et al. 2006, Omoregbe, Ikuebe, and Ihimire 1996, Pandey and Rizvi 2009, Ribeiro et al. 2015, Roleira et al. 2015, Runnie et al. 2004, Salem et al. 2015, Sasidharan et al. 2011, Osman et al. 2008, Vendrame et al. 2011, Wang et al. 2010). Therefore, it stands to reason that plant's constituents are, at least in part, responsible for the benefits observed. Dietary fiber and phenolic compounds are two abundant classes of plant components that have been widely recognized as exerting a positive influence upon human health (Cheynier 2012, Maria de Lourdes Reis 2013, Anderson et al. 2009, Kaczmarczyk, Miller, and Freund 2012). For instance,

phenolic compounds have been reported as contributing to the prevention of neurodegenerative diseases (e.g. Parkinson and Alzheimer) as well as with the amelioration and/or prevention of other neurological pathologies such as memory loss, posttraumatic stress disorder (PTSD) and ischemic brain damage. Furthermore, several epidemiological studies have also linked phenolic compound's ingestion to a reduction of the risk of developing diabetes, cancer, cardiovascular and inflammatory diseases (Albishi et al. 2013, Bulotta et al. 2014, Nohynek et al. 2006, Ranilla et al. 2010, Rodríguez-Roque et al. 2013, Selma, Espin, and Tomas-Barberan 2009, Sevgi, Tepe, and Sarikurkcü 2015, Valdés et al. 2015, Wallace 2011). On the other hand, dietary fiber has also been associated with an array of potential health benefits, including a reduction of the risk of developing coronary heart disease, hypertension and of suffering a stroke (due to dietary fiber's potential to aid in the control of blood pressure). Moreover, it has also been reported to help prevent obesity and certain gastrointestinal disorders, such as duodenal ulcer, constipation and hemorrhoids (Anderson et al. 2009, Eswaran, Muir, and Chey 2013, Fuller et al. 2016, Kaczmarczyk, Miller, and Freund 2012, Slavin 2013, Wu et al. 2015, Ye et al. 2015). A concrete example of this biological potential is blueberry, as this fruit has been associated with many health benefits, with existing works reporting on its antioxidant, antimicrobial, antitumoral and anti-inflammatory activity, as well as gut modulating capacity (Bränning et al. 2009, Carey, Gomes, and Shukitt-Hale 2014, Dulebohn et al. 2008, Guglielmetti et al. 2013, Molan et al. 2009, Neto 2007, Piljac-Žegarac, Belščak, and Piljac 2009, Vendrame et al. 2013, Silva et al. 2016, Jo et al. 2015, Vendrame et al. 2014, Taverniti et al. 2014, Ren, Huang, and Cheng 2014).

The use of dietary fiber and phenolic compounds as ingredients capable of enhancing technological and nutritional properties of food, thus increasing the functionality of food products has been described by several authors. Furthermore, non-extractable polyphenols, which are not released from the food matrix during the digestive process and therefore manage to reach the colon nearly intact, have been shown to exhibit health promoting properties as well, namely in relation to gastrointestinal health. The gut microbiota converts these compounds into small size phenolics that are better absorbed and that persist in the blood for more than 48 hours, showcasing antioxidant and anti-inflammatory activity (Landete 2012, González-Sarriás, Espín, and Tomás-Barberán 2017, Pérez-Jiménez, Díaz-Rubio, and Saura-Calixto 2013, Yan et al. 2018, Holscher 2017).

Gut microbiota: function and modulation

Polyphenols and fibers, two of the most important plants' constituents, have both been studied regarding their microbiota modulating potential. The human gut harbors a complex microbial community, denominated intestinal microbiota, composed of over 1000 different bacterial species. Its development begins at birth and is strongly

influenced by diverse factors which include immunological factors, antibiotic usage, host genetics and dietary habits. The normal gut flora is constituted by several different genera and species, which range from bacteria known to be beneficial to the host to potentially harmful bacteria such as *Clostridium* and *Salmonella*. The most predominant phylum in the human gut are Firmicutes (which includes genera of bacteria such as *Lactobacillus*, *Enterococcus* and *Clostridium*) and Bacteroidetes (which includes *Prevotella* and *Bacteroides* genera), which together represent 90% of the known phylogenetic categories existing in the gut flora. (Marchesi et al. 2015, Bernalier-Donadille 2010, Boulangé et al. 2016, Claesson et al. 2012, Conlon and Bird 2014).

Gut microbiota is essential for the normal functioning of the body and its health, besides contributing to maximize the absorption of nutrients. In fact, the connection between its composition and the overall health and wellbeing has been widely and systematically reported by the scientific community (I Naseer et al. 2014, Zhao 2013, Alkasir et al. 2017, Boulangé et al. 2016, Carabotti et al. 2015, Claesson et al. 2012, Hu, Wang, and Jin 2016, Mangiola et al. 2016). Overall, the microbiota is responsible for fermenting dietary polysaccharides (that have not been previously absorbed into the bloodstream) which, in turn allows for the removal of calories from indigestible dietary compounds. Therefore, the gut microbiota fermentation results in the production of several metabolites that can be absorbed by the host. In fact, the presence of certain species of bacteria in the gut microbiota fermentative process have been shown to improve the processing and absorption of nutrients. Additionally, there are evidences that the beneficial effects attributed to dietary polyphenols depend on their biotransformation by the gut microbiota. (Boulangé et al. 2016, Carabotti et al. 2015, Quigley 2013, Conlon and Bird 2014).

An imbalance in the normal flora has been described to contribute to intestinal disorders such as chronic inflammatory bowel, cardiovascular diseases, as well as obesity and mental health problems. This imbalance, dubbed dysbiosis, occurs due to a loss of diversity of the species present in the microbiota with a strengthening of the presence of a specie previously not predominant or even due to the depletion of a specie (or several). For instance, the depletion of *Faecalibacterium prausnitzii* (Firmicutes phylum), has been associated with inflammatory bowel disorder even though it is just a single specie (Cardona et al. 2013, Conlon and Bird 2014, Laparra and Sanz 2010, Marchesi et al. 2015, Million et al. 2013).

Modulation of the microbiota towards a perceived beneficial phenotype has been studied as an alternative treatment for some pathologies, including liver conditions and inflammatory bowel disease. This modulation may be caused by, for instance, probiotics, prebiotics or polyphenols, since these can influence the composition and/or metabolic activity of the intestine's normal flora, contributing to reduce pathogenic species such as *Clostridium* (whose reduction has been associated with ameliorating autistic related symptoms), while increasing the presence of others such as *Lactobacillus* and *Bifidobacterium* while also stimulating the

production of beneficial compounds, such as butyric acid, by these bacteria. Prebiotics are food constituents that promote the growth of microorganisms that exert a positive effect on the host. Essentially, they are a specific type of dietary fiber that, when fermented by the gut microbiota, allow for both the selective growth of beneficial bacteria such as bifidobacteria, as well as an increase of the production/accumulation of beneficial metabolites (Dueñas et al. 2015, Faria et al. 2014, Guglielmetti et al. 2013, Pequegnat et al. 2013, Eswaran, Muir, and Chey 2013, Slavin 2013).

Fruit extracts

Fruits are often associated with a healthier lifestyle. For instance, berries are often considered “superfruits”, due to their high anthocyanin and phenolic content. Phenolic compounds have long been regarded as one of the classes of compounds, present in whole plant foods, which are most likely capable of affecting physiological processes that may grant some protection against chronic diet-associated diseases. The gut microbiota plays a very important part in the release of polyphenols that are bound to dietary fiber and that would otherwise not be absorbed into the blood serum. In fact, the majority of polyphenols are not absorbed at the upper gastrointestinal level and, therefore, reach the colon and may be metabolized by the microbiota, altering the original compound's bioactivity and bioavailability. This happens through the enzymatic activity of the gut microbial community (Faria et al. 2014, Marchesi et al. 2015, Cardona et al. 2013, Etxeberria et al. 2013).

Recent studies have shown that the intake of polyphenolic extracts, such as the ones obtained from the consumption of a blueberry powder drink, can help modulate the human gut microbiota, increasing the abundance of *Bifidobacterium* and *Lactobacillus* and diminishing the presence of *Clostridium histolyticum* which, considering that the latter has been associated with inflammatory bowel disease, contributes to a healthier profile of the gut. Moreover, different studies have shown that phenolics can alter the *Bacteroides*/*Firmicutes* balance, with *Firmicutes* being more predominant in people who suffer from obesity and *Bacteroides* being reported as contributing significantly to the reduction of blood pressure and high-density lipoprotein cholesterol. Furthermore, it is thought that *Bacteroides* are the genera mostly involved in the reactions necessary for anthocyanins' metabolization, since they express all the enzymes needed. Likewise, in a 16 weeks long study with mice, the dietary administration of proanthocyanidin-rich extracts led to a shift in the predominance of *Bacteroides*, *Clostridium* and *Propionibacterium* spp. to a predominance of *Bacteroides*, *Lactobacillus* and *Bifidobacterium* spp. In another study, a proanthocyanidin-rich extract from grape seeds given to healthy adults (for 2 weeks) was shown to significantly increase the presence of bifidobacteria in the gut. Thus, polyphenols may be capable of modulating the microbial community present in the gut and potentially improve the health of the host, through host-microbial interactions.

One of the mechanisms involved in the modulation, is due to the presence of microbial enzymes, which can alter phenolics and other compounds through hydrolysis, cleavage and decarboxylation, among others. For instance, the gut microbiota is responsible for hydrolyzing glycosides into their aglycones counterparts and their subsequent degradation into simple phenolic acids. Other possible mechanism involved in the modulation of the gut microflora is thought to be associated with the fact that polyphenols act differently upon distinct microbial colonies, affecting their viability differently. For example, an anthocyanin rich blueberry extract has been shown to have antimicrobial activity against different food pathogens, but no action upon probiotic bacteria. Additionally, phenolic compounds have been reported to exert selective antimicrobial activity against intestinal pathogens such as *Salmonella*, but also against *Staphylococcus*, by generating hydrogen peroxide and by altering the permeability of the cellular membrane. (Selma, Espin, and Tomas-Barberan 2009, Duda-Chodak et al. 2015, Etxeberria et al. 2013, Laparra and Sanz 2010, Marchesi et al. 2015, Puupponen-Pimiä et al. 2005, Cardona et al. 2013, Boulangé et al. 2016, Million et al. 2013, Fernandes et al. 2014, Dueñas et al. 2015, Boto-Ordóñez et al. 2014, Vendrame et al. 2013, Hidalgo et al. 2012, Faria et al. 2014, Valdés et al. 2015).

Anthocyanins have been widely associated not only with gut microbiota modulation, and with strong anti-inflammatory and antioxidant activities, with several epidemiological studies suggesting that the increased consumption of berries and anthocyanin rich berry extracts may lead to a reduction of the risk of developing cardiovascular disease, with anthocyanins exerting a beneficial impact upon related proinflammatory biomarkers and upon endothelial function (Mursu et al. 2008, Wallace 2011, Du et al. 2016, Olas 2017). However, to better support these claims, more studies are needed to assess the involving metabolism of anthocyanins by the gut microbiota and their subsequent impact upon cardiovascular health.

Citrus fruits have lower phenolics content than berries, possessing mainly flavonoids as well as fiber, pectins, vitamins and sugar. While citric extracts have been studied mainly for their antioxidant potential, reports on their potential antimicrobial, anti-diabetic, anti-inflammatory and cardiovascular protective effects have been published. Additionally, two phenolic compounds present in citrus peels (polymethoxyflavones and hydroxypolymethoxyflavones) have shown anti-obesity potential in studies conducted *in vitro* and *in vivo*, by decreasing lipid accumulation as well as showing gut modulating capacity (Zou et al. 2016, Ghasemi, Ghasemi, and Ebrahimzadeh 2009, Lv et al. 2015, Gorinstein et al. 2001, Goulas and Manganaris 2012, Park et al. 2015, Alu'datt et al. 2017, Tung et al. 2018).

Leaf extracts

Although fruits are known to be rich in several bioactive compounds, leaves also represent a rich source of potentially beneficial compounds, with some authors reporting that

leaves possess a significantly higher amount of total phenolics than the fruit (Jiménez-Aguilar and Grusak 2017, Salem et al. 2015, Piljac-Žegarac, Belščak, and Piljac 2009, da Silva et al. 2013). This difference may be due to the function of leaves, since these are responsible for the photosynthetic pathway and consequent O₂ production, which also lead to the production of reactive oxygen species that are detrimental to tissues. As such, taking into account the known antioxidant activity of phenolic compounds, these may be present in larger amounts in leaves to exert a protective effect upon its tissues, as well as to protect against the stress caused by solar exposure. For instance, aqueous and ethanolic extracts of passion fruits' leaves have been shown to possess higher antioxidant activity than the fruit itself, with this also happening with the leaves of berry bushes when comparing with the fruit themselves, including berries such as blackberry and strawberry. Chlorophyll is responsible for the leaves' usually green color, while carotenoids and flavonoids (such as anthocyanins) can also be present contributing to leaves' red/orange color during autumn. Additionally, some leaves extracts have been shown to possess some antimicrobial activity due to the presence of flavonoids (Jaakola et al. 2004, Riihinen et al. 2008, Ehlenfeldt and Prior 2001, Bendini et al. 2006, da Silva et al. 2013, Wang and Lin 2000).

Moreover, leaf extracts have also been studied for their microbiota modulating capacity. A particular example is the strong link existing between leaves extracts and obesity amelioration. Obesity has been shown to be connected to an imbalance in the gut microbiota, with reports showing predominance of the phylum *Firmicutes* in obese people. Previous works have shown that green tea extract may not only contribute to an amelioration of obesity related complications through gut microbiota modulation, but also exert a beneficial effect upon lipid metabolism. Moreover, rats fed a green tea powder in association with a *Lactobacillus* strain exhibited an increased presence of *Lactobacillus* genera in the gut and attenuated the inflammation resulting from the high fat diet given to the mice in the experiment. Additionally, black tea led to changes in a gut model microbiome, shifting the Firmicutes/Bacteroidetes ratio, and showing the possible modulation of select bacteria genera of the intestinal flora (Seo et al. 2015, Million et al. 2013, Zhao 2013, Axling et al. 2012, Kemperman et al. 2013).

Rosemary extracts have been investigated for their metabolism and inflammation regulatory properties in animal models, with some extracts leading to changes in rat's microbiota composition of rats, that translated into an increase of *Bifidobacterium* and short chain fatty acids' levels. Rhubarb extract has been shown to have interesting microbiota modulating properties. The supplementation of mice's diet with this extract led to an increase of the Verrucomicrobia phylum, associated with potential health benefits (although further studies are still required), in detriment of the Firmicutes phylum. Additionally, besides the gut microbiota modulating effect, rhubarb has shown renal-protective and hepaprotective effects in several *in vivo* experiments, as well as potential as acting as an

antiproliferative compound against pancreatic cancer cells (Neyrinck et al. 2017, Arosio et al. 2000, Wang et al. 2009, Cai et al. 2008, Clementi and Misiti 2010, Romo-Vaquero et al. 2014, Vallverdú-Queralt et al. 2014). On the other hand, da Silva et al. (2013) described how passion fruit leaves promoted an increase in the total bacteria found on gut without being selective, unlike what has been described about some leaf extracts, which are able to inhibit pathogenic bacteria growth, while augmenting the presence of potentially beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* (Cueva et al. 2010, Puupponen-Pimiä et al. 2005, Nohynek et al. 2006, Silva et al. 2013).

Olive leaves are the byproducts of olive production, with its extracts showing high potential for incorporation into different matrixes. As olive leaves possess high amounts of phenolic compounds, their potential health benefits have been studied, with authors describing olive leaf extracts as having antimicrobial, antioxidant and antidiabetic activity, as well as exerting cytotoxicity activity against breast cancer cells. Olive leaves possess phenolics belonging to the secoiridoids family, such as secoiridoid oleuporein, a bioactive compound which is thought to contribute to the leaves' potential health benefits (Paiva-Martins et al. 2007, Ribeiro et al. 2015, Pereira et al. 2007, Talhaoui et al. 2015, Taamalli et al. 2012, De Marino et al. 2014).

Root and tuber extracts

Root and tuber crops have been studied for their potential health benefits and as a source of functional ingredients. Some of their potential health benefits include antioxidant, hypoglycemic, antimicrobial and immunomodulatory activities, which are thought to be associated to the presence of phenolic compounds, some proteins, phytic acids and glycoalkaloids, their usually high fiber content that may help modulate microbiota composition and consequently ameliorate metabolic disorders in obese people, as well as cardiovascular diseases and other maladies (Delzenne, Neyrinck, and Cani 2011, Holscher 2017, Eswaran, Muir, and Chey 2013, Slavin 2013, Anderson et al. 2009).

Solanum jamesii tuber extracts have been shown to exert antiproliferative activity upon intestinal cancer cells. When the main components of the extract were tested for their antiproliferative activity, they did not prove to be effective, corroborating the hypothesis that the compounds present in extracts possess higher biological activity when interacting synergistically among themselves (Chandrasekara and Josheph Kumar 2016, Imam et al. 2014, Nzaramba et al. 2009).

A popular plant in India, nagarmotha (*Cyperus rotundus*) has been described as having diuretic, anti-inflammatory, antimicrobial, analgesic and anti-dysenteric activities, among several others, with essential oils being prepared from the tuber of the plant. Infusions of these tubers, as well as extracts prepared from the plant, have also been associated with antimicrobial, antioxidant, apoptotic and cytotoxicity activities. Additionally, reports have shown that when nagarmotha extracts were administered to obese mice, it

prevented weight gain. However, reports connecting the gut microbiota modulation and this plant are still scarce, with results being inconclusive (Imam et al. 2014, Kilani et al. 2008, Lemaure et al. 2007, Torres-Fuentes et al. 2015).

Yacon tubers, rich sources of fructooligosaccharides and phenolic compounds, have shown potential to treat hyperglycemia, kidney problems, as well as reduce the risk of colon cancer. Yacon tuber extracts have also been studied regarding their potential prebiotic effect and gut modulating properties, since they are able to increase numbers of health promoting bacteria while decreasing the levels of potentially pathogenic bacteria. For instance, the prebiotic effect of yacon extract has been assessed with a guinea pig model, with yacon enhancing beneficial bacteria such as *Lactobacillus* and promoting the production of short chain fatty acids. Furthermore, yacon sirup, when administered for a period of 120 days led to increased satiety levels and a decrease in body weight. As such, yacon roots are considered to be potential dietary supplement that may prevent and/or ameliorate some diseases (Sousa et al. 2015, Campos et al. 2012, Delgado et al. 2013, Caetano et al. 2016, Valentová and Ulrichová 2003, Delzenne, Neyrinck, and Cani 2011).

Inulin extracted from Jerusalem artichoke (*Helianthus tuberosus* L.) tubers was shown to have a higher prebiotic capacity than a commercial prebiotic with inulin having been associated with colorectal cancer inhibition and a decrease of intestinal pH (Rubel et al. 2014, Shoaib et al. 2016). An extract of Chinese yam flour (*Dioscorea batatas*) was tested to evaluate its effects upon the gastrointestinal tract of rats, with results showing it appeared to improve digestive capacity, but it did not affect the growth of bacteria belonging to the gut. However, other reports have shown an increase of butyrate, acetate and propionate after the administration of Chinese yam polysaccharide to rats and there was shift in the predominant groups of bacteria of the gut microflora, with *Lactobacillus* and *Ruminococcus* species increasing and *Salmonella typhimurium* and *Clostridium perfringens* decreasing after 21 days of supplementation (Jeon et al. 2006, Kong et al. 2009).

Conclusion

A healthy diet is considered to be rich in fruits and vegetables, with these foodstuffs being strongly associated with overall wellbeing mainly due to the presence of phenolic compounds and fiber. As such, the addition of extracts rich in potentially biologically active compounds might confer some added benefits to certain foodstuffs, contributing to an improvement of the overall health and wellbeing. For example, the supplementation of phenolic compounds in the diet, either through fruits or leaves extracts, might lead to an increase of *Bacteroidetes* and a reduction of *Firmicutes*, as well as an increase in *Bifidobacterium* and *Lactobacillus* species, changes considered positive for one's health and associated with the amelioration of obesity, inflammation and other disorders, and also contributing to the prevention of cardiovascular and neurological problems.

Although several studies have shown the biological potential of the extracts consumption, mostly extracts derived from fruits, further human based studies are still needed to establish a true cause effect, with roots and tubers extracts impact upon health being the least explored.

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