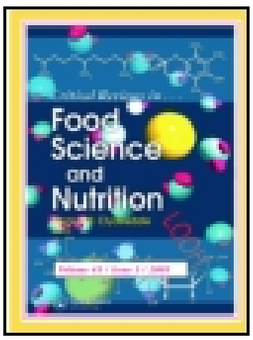

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REVIEW

Interactions of dietary polyphenols with epithelial lipids: advances from membrane and cell models in the study of polyphenol absorption, transport and delivery to the epithelium

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ABSTRACT

Currently, diet-related diseases such as diabetes, obesity, hypertension, and cardiovascular diseases account for 70% of all global deaths. To counteract the rising prevalence of non-communicable diseases governments are investing in persuasive educational campaigns toward the ingestion of fresh fruits and vegetables. The intake of dietary polyphenols abundant in Mediterranean and Nordic-type diets holds great potential as nutritional strategies in the management of diet-related diseases. However, the successful implementation of healthy nutritional strategies relies on a pleasant sensory perception in the mouth able to persuade consumers to adopt polyphenol-rich diets and on a deeper understanding on the chemical modifications, that affect not only their chemical properties but also their physical interaction with epithelial lipids and in turn their permeability, location within the lipid bilayer, toxicity and biological activity, and fate during absorption at the gastro-intestinal epithelium, transport in circulation and delivery to the endothelium. In this paper, we review the current knowledge on the interactions between polyphenols and their metabolites with membrane lipids in artificial membranes and epithelial cell models (oral, stomach, gut and endothelium) and the findings from polyphenol-lipid interactions to physiological processes such as oral taste perception, gastrointestinal absorption and endothelial health. Finally, we discuss the limitations and challenges associated with the current experimental approaches in membrane and cell model studies and the potential of polyphenol-rich diets in the quest for personalized nutritional strategies ("personalized nutrition") to assist in the prevention, treatment, and management of non-communicable diseases in an increasingly aged population.

KEYWORDS

Cardiovascular disease; diabetes; endothelial health; epithelial membranes; LDL; Mediterranean diet; obesity; personalized nutrition; polyphenols; taste perception

1. Introductory perspective and focus

Throughout the 20th century, political, geographic, economic and societal changes were responsible for massive changes to people's lifestyle and eating habits. The inclusion of processed and ready-to-eat foods became routinely consumed in the last century resulting in a sharp rise of fat, salt, and sugar intake. According to the World Health Organization (WHO), there has been a steadily increase incidence of obese, hypertensive and diabetic adults in western developed countries in the past decades, and at present non-communicable diseases (NCDs) account for 70% of all global deaths (Medis et al. 2014) rendering credit to the axiom "we are what we eat" (Lindlahr 1942). The rising prevalence of overweight and obese adults and adolescents (Medis et al. 2014) together with the rise of elder people suffering from two or more chronic conditions is having a detrimental impact on national Health budgets. In face of the continuous rise of diet-related diseases in developed countries governments have implemented educational health campaigns on the benefits of healthy dietary practices and the inclusion of fresh and unprocessed foods rich in polyphenols such as fruits, vegetables, nuts and seeds typical of the Mediterranean and Nordic-style Diets designed to reduce, prevent and manage NCD by 2025 (Medis et al. 2014).

The ingestion of significant amounts of dietary polyphenols (up to 1 g/day) (Karam, Del Mar Bibiloni, and Tur 2018; Paganga, Miller, and Rice-Evans 1999; Pérez-Jiménez et al. 2010) offers great health potential from a nutritional point of view. The health benefits associated with fresh fruits, vegetables, and beverages (fruit juices, olive oil, wine, tea, coffee and chocolate) have long been attributed to polyphenol's ability to complex metal ions and scavenge radical reactions (antioxidant effects) (Perron and Brumaghim 2009), and their ability to bind to proteins in the modulation of hydrolytic enzymes (Kalita et al. 2018; McDougall, Kulkarni, and Stewart 2008; Toda, Kawabata, and Kasai 2001; Yang and Kong 2016). The recognized beneficial health effects of dietary polyphenols as mediators in glucose homeostasis and lipid metabolism (Buchholz and Melzig 2015; Cremonini, Fraga, and Oteiza 2019; Kim, Keogh, and Clifton 2016) and of gut microbiota environment with the release of beneficial polyunsaturated fatty acids with anti-

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inflammatory properties (Ounnas et al. 2014) reinforces the notion that polyphenol-rich diets may serve as a nutritional strategy able to exert protective effects against diet-related pathologies including diabetes, obesity, cardiovascular diseases (CVDs) and metabolic syndrome ("personalized nutrition") and particularly as an alternative to conventional drug-based therapies (statins, ezetimibe, fibrates…) in the treatment and management of NCDs. This concept is gaining increasing popularity in society and is sparking increasing interest by the scientific community considering that cholesterol (Chol)-lowering drugs (e.g., statins) are now routinely and excessively prescribed and their long-term effects are still under scrutiny (Toth et al. 2018).

Despite the concerted efforts by WHO and governments (Inkpen and Ramaswamy 2004), in practice people's dietary choices are mainly ruled by how tasty food is. The axiom "we are what we eat" is equally influenced by "we eat what we like." The bitter and astringent taste associated to polyphenol-rich fruits and vegetables (De Freitas, Carvalho, and Mateus 2003; Joslyn and Goldstein 1964; Soares et al. 2013; Soares et al. 2012) is often a restricting factor to the consumer's daily choices with the exclusion of fresh fruits and vegetables from their diet.

From a technological perspective, the development of innovative tasty food products (*functional foods*) able to: (1) incorporate, fortify and supplement dietary levels of beneficial polyphenols in polyphenol-poor diets (Cirkovic Velickovic and Stanic-Vucinic 2018), and (2) complement the dietary needs imposed by food restrictions (allergies) (Plundrich et al. 2014) is highly desirable alternative strategy able to improve health outcomes. However, the development of functional foods by food biotechnologists is challenging (Moors 2012) due to the fulfillment of certain legislative requirements including: (1) functional foods need to remain foods; (2) be consumed as part of a regular diet; (3) provide the claimed (nutritional, health and risk reduction) beneficial effects supported by prospective and intervention studies. In view of the scarce large cohort studies, the European Union (EU) has imposed tight labeling legislation to protect and support consumers in their healthy food choices (Moors 2012) which at the same time are restricting the appearance of new food products into the market (Lenssen, Bast, and de Boer 2018; Martirosyan and Singharaj 2016; Moors 2012).

In line with the consumer's desire for natural products, consumers are alternatively adopting for the intake of plant-based extracts (pills, tablets or capsules) as a means to supplement and reinforce the daily amount of natural polyphenols. In recent years, the consumption of plant-based supplements has escalated and boosted the Food Supplement Industry. In line with Paracelsus statement in the 17th century ("All substances are poisons…. it is the dose that distinguishes a poison from a remedy") some studies have raised awareness to the adverse effects of high intake of plant-based extracts and the potential for intestinal and liver toxicity (Kapetanovic et al. 2009; Lambert, Sang, and Yang 2007; Mennen et al. 2005). Despite this, at present there is a notorious lack of information advising consumers on the optimal and tolerable upper safe levels of plant-based food supplements (e.g., tea extracts) posing serious food and health safety concerns. Recently, the European Food and Safety Authority (EFSA) issued an opinion article on the safety assessment of green tea catechins (Younes et al. 2018) highlighting caution for the intake of high dosages of plant-based supplements and the need for further evaluation.

For obvious ethical and safety reasons, our current knowledge on the biological and health benefits associated with polyphenol-rich diets is far from complete and to date the beneficial effects of polyphenol-rich foods as nutritional strategies to ameliorate diet-related diseases remain poorly understood. Most of the current knowledge on the biophysical biological properties of plant polyphenols and bioavailability in humans derives from studies with membrane and cell models and humans (De Athayde Moncorvo Collado et al. 2016; Kajiya, Kumazawa, and Nakayama 2001; Lee et al. 2017; Mena et al. 2017; Murase et al. 2011; Phan et al. 2014; Van Rymenant et al. 2017). Membrane and cell models are easy and manageable platforms in research able to deliver improved understanding on the polyphenol's interplay with epithelial lipids and on the molecular mechanisms governing complex in vivo biological processes including modulation of astringency taste perception, gastro-intestinal absorption, plasmatic transport and endothelial absorption.

This review describes the current knowledge on the interactions of polyphenols with epithelia focusing on the polyphenol-lipid interactions in membranes and cell models in the context of physiological processes including taste perception in the oral mucosa, the gastro-intestinal absorption and permeability across the endothelium. Based on the knowledge available, the potential for the development of tasty healthier food by Food Industry (*functional foods*) is discussed as well as the limitations associated with current approaches in models and the therapeutic potential of polyphenol-rich diets (*personalized nutrition*) as alternatives to conventional drug-based therapies in the prevention, treatment, and management of diet-related diseases.

2. Food polyphenols and the journey of ingested polyphenols throughout the human epithelium

2.1. Food polyphenols, ingested polyphenols and circulating polyphenols

From a nutritional point of view, polyphenol-rich foods typical of Mediterranean and Nordic-style diets are obvious and valuable alternatives to be explored in the treatment and management of NCD. Many of the fruits, vegetables and beverages (tea, coffee, hot chocolate, fruit juices, olive oil) included in the Mediterranean and Nordic eating habits are among the Top 100 polyphenol-richest foods (Figure 1) (Pérez-Jiménez et al. 2010).

From the consumer's point of view, pinpointing which fruits and vegetables can help to manage diabetes progression or which are suitable to control the risk of CVDs would be exciting. The answer to this is more challenging as fruits and vegetables do not contain just one class of polyphenols but several classes (Manach et al. 2004; Robards et al. 1999). In addition to this, each class of polyphenols

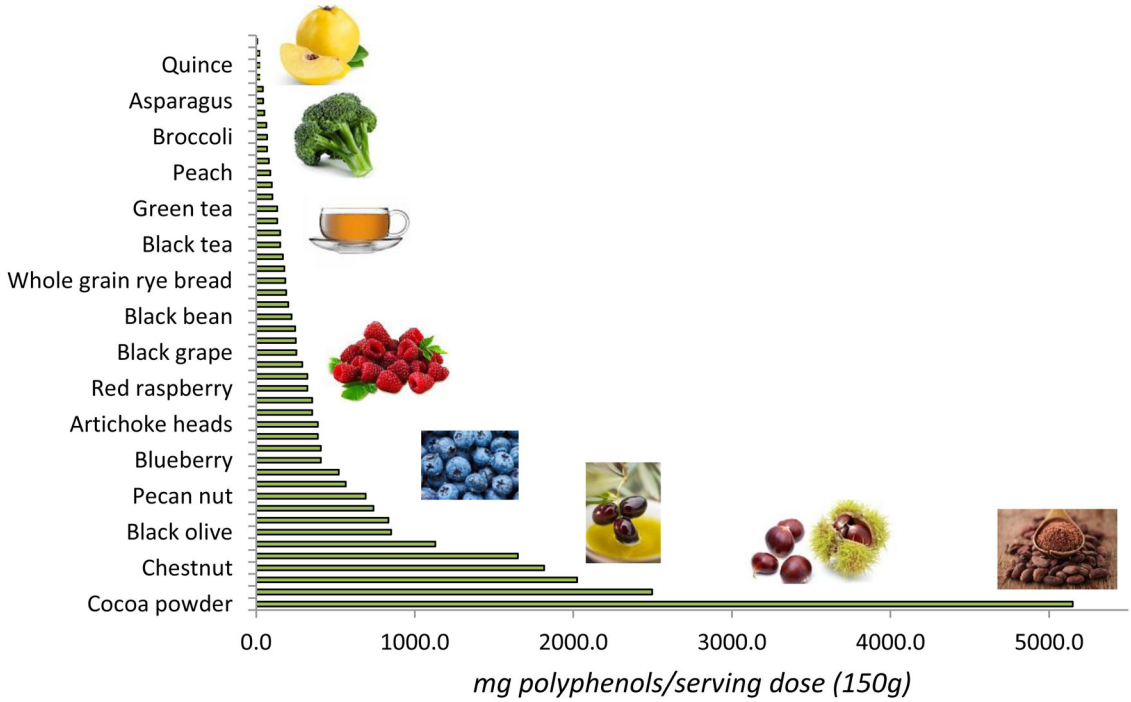

Figure 1. Amount of total polyphenols in fruit, vegetables and seeds (mg) per serving dose (150 g) (adapted from Pérez-Jiménez et al. 2010).

(Figure 2) contains dozens of compounds with different substitution patterns and distinct chemical and biological properties (Tsao 2010). For instance, red fruits and berries are rich in glycosylated anthocyanidins (anthocyanins) such as cyanin, whereas citrus fruits are rich in flavanones such as naringenin and soy rich in isoflavones such as luteolin, and green vegetables are rich in flavonols such as quercetin whilst tea, coffee and cocoa beans are rich in flavanols such as epicatechin-gallate (Manach et al. 2004; Robards et al. 1999). Due to their varied substitution patterns and modification traits inserted upon biotransformation, polyphenols can reach several hundreds of different compounds. Polyphenols are a structurally diverse class of compounds and there are different ways to categorize these naturally bioactive compounds (Figure 2).

To complicate matters, the panel and content of polyphenols in foods does not necessarily translate into the panel and content of ingested polyphenols, not only because of people's dietary choices but also because of other external conditions. For instance, the profile and content of polyphenols in fresh fruits and vegetables varies considerably depending on the fruit/vegetable cultivar, seasonal, geographic conditions (soil and altitude) and growth conditions (water, temperature, sun exposure) (Chen, Yang, et al. 2014; D'Archivio et al. 2010; Rodrigues et al. 2010; Rothwell et al. 2016). In addition to cultivar and environmental factors (sun-light, altitude), the introduction of temperature-based processing steps (sun-drying, fermentation, cooking, roasting, frying) and storage conditions also impacts on the overall profile and content of food polyphenols ingested (Chen, Yang, et al. 2014; D'Archivio et al. 2010; Rodrigues et al. 2009; Rothwell et al. 2016).

In overview, the panel and content of dietary polyphenols ingested is influenced by cultivar, geographic and environmental conditions. The panel of ingested polyphenols is influenced by consumer's choices and food processing steps. Finally, the panel and content of circulating polyphenols is mainly driven by genetic factors that regulate the variability of gut microflora and the in vivo biotransformation reactions (Cerdá, Tomás-Barberán, and Espín 2005). As the panel of ingested polyphenols does not necessarily relate to the panel and content of circulating polyphenols, currently, the challenge is to decide which polyphenol-rich food choices translate into a panel of circulating polyphenols tailored to provide the highest health benefits.

2.2. Chemical stability of dietary and circulating polyphenols in aqueous systems: influence of temperature and pH

Dietary polyphenols exhibit high chemical stability at acidic pH solutions but relatively low chemical stability under neutral conditions (Li et al. 2012; Zhou et al. 2003). The poor chemical stability displayed by polyphenols is accelerated when temperature is involved during food preparation or food processing steps (Li et al. 2012; Pace et al. 2018). In boiling water, the content of epigallocatechin-gallate (EGCG) one of the most abundant polyphenols in tea infusions (Chen, Yang, et al. 2014) is degraded over time (Li et al. 2012; Zhou et al. 2003) reaching losses up to 35% within the initial 30 min (Li et al. 2012; Zeng et al. 2017). The degradation reaction is reduced in the presence of metal-chelating agents suggesting that auto-oxidation reactions are involved in the degradation of EGCG (Zhou et al. 2003).

At physiological temperature and under aqueous conditions such as those used in cell culture incubations, EGCG was found to be chemically unstable (Hong et al. 2002; Sang

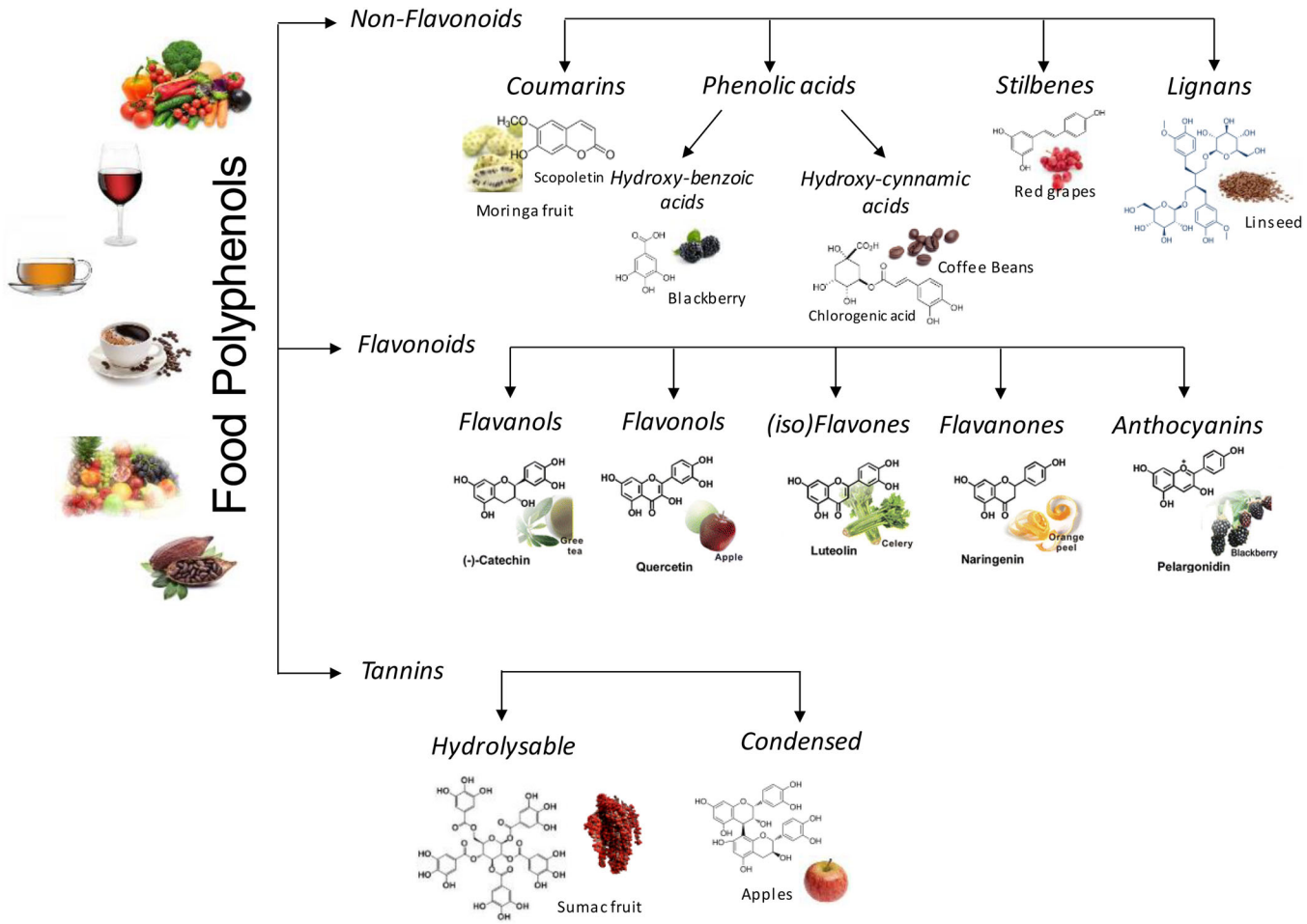

Figure 2. Main classes of polyphenol compounds, chemical structures and some representative compounds of each class as well as food where these classes occur.

et al. 2005; Zhou et al. 2003) namely in Ringers solution (from Braun Medical), in Ham's F12 and RPMI 1640 medium (from Mediatech), in McCoy's 5 A and Hank's Balanced Saline Solution (HBSS) (from Mediatech). More recently, the structure – stability relationship of 53 natural polyphenols was comprehensively investigated under Dubelco's modified Eagle medium culture conditions (DMEM, from Sigma) revealing that catechins and flavonols were particularly unstable when compared to (iso)flavones, flavanones and stilbenoid compounds (Xiao and Högger 2015) with EGCG becoming degraded after 10 min of incubation. Among flavonoids their stability under HBSS culture medium appears to be structure-dependent where baicalein, scutellarein, myrcetin and myrcitrin were the most susceptible to degradation after 1 hour (Tian et al. 2009). Likewise, Goszcz and colleagues reported the degradation of the anthocyanidin delphinidin to gallic acid in M199 medium (from Invitrogen) within the first hour (Goszcz et al. 2017). It should be emphasized that these studies have been conducted under aerobic conditions and not anaerobic conditions such as those found in stomach and intestine. In aerobic conditions, the chemical instability of polyphenols in cell culture media may be related to the extracellular formation of H_2O_2 (Hong et al. 2002) triggered by the supplementation of other cell components such as ascorbic acid (Clément et al. 2001). In the presence of residual transition metal ions such as Fe (II) and Cu (I) present in cell media H_2O_2 form free radicals by the Fenton mechanism triggering the oxidative modification of polyphenols and to significant losses of the parent compound in the early hours of incubation (Goszcz et al. 2017; Hong et al. 2002; Sang et al. 2005; Xiao and Högger 2015). The chemical instability reported for polyphenols in aqueous cell media is apparently not so severe for polyphenol metabolites, as flavan-3-ols metabolites such as γ-valero-lactones exhibited chemical stability for the first hour when incubated in McCoy's 5 A cell medium (Mena et al. 2017) though its sulfated derivatives underwent deconjugation of sulfate moieties afterwards (Mena et al. 2017).

In biological aqueous systems, as is the case of saliva and plasma, the stability of ingested polyphenols in alkalescent conditions appears to be heightened by the interaction of polyphenols with thiol-proteins including serum albumins and glutathione (Latruffe et al. 2014; Lu et al. 2007; Unnadkat and Elias 2012; Xiao and Högger 2015; Zinellu et al. 2015). Although this interaction may stabilize and enable the transport of polyphenols in biofluids under neutral pH conditions without degradation and increase their plasmatic concentration, conflicting results still remain about the impact on their bioavailability and delivery to target tissues (Krook and Hagerman 2012; Unnadkat and Elias 2012; Zinellu et al. 2015).

Based on the reported instability of polyphenol compounds in cell culture media, and the co-existence of several polyphenol species (unmetabolized, metabolized and breakdown products) in cell culture conditions, it is crucial that an accurate and comprehensive characterization is conducted prior to the biological assessment of polyphenolic metabolites in epithelial cell models. Today, one of the key challenges in assessing the in vitro biological activity of polyphenols is how to distinguish whether the observed biological effect is due to the cellular uptake of the unmetabolized polyphenol compound or the cellular uptake of newly formed metabolites resulting from (de)conjugated or breakdown metabolites particularly relevant during long exposure (>24 h) studies (Araújo et al. 2013; Évora et al. 2017; Fernandes et al. 2013; Figueira et al. 2017; González-Sarrías et al. 2017; Hara-Terawaki et al. 2017; López De Las Hazas et al. 2017; Nunes, Figueiredo, et al. 2019).

2.3. Metabolic fate of ingested polyphenols

As part of Mediterranean-based diets, polyphenols are ingested not as single compounds but as complex mixtures becoming nearly impossible to pinpoint which polyphenol predominates in our diet at one given point. Despite the complexity of our daily dietary choices, ingested polyphenols in their journey throughout the human epithelium are exposed to different chemical environments (pH conditions) in the mouth and GI tract, and to different gut microbiota populations responsible for the biotransformation of polyphenols. These 2 factors, together with dietary choices, account for the individual variability of circulating polyphenol metabolites (Bolca, Van de Wiele, and Possemiers 2013; Gheldof et al. 2017).

The mouth has a neutral environment (pH 6.8–7.2) (Aframian, Davidowitz, and Benoliel 2006). The ingestion of acidic fresh fruits and vegetables induces an overall pH drop in the mouth during mastication from neutral physiological values to slightly acidic pH values. For instance, sipping of small volumes of wine has been shown to decrease the oral pH from neutral to values of pH 4–5 (Obreque-Slier, Espínola-Espínola, and López-Solís 2016). Traveling down the gastro-intestinal tract, ingested polyphenols undergo drastic pH changes in the stomach to highly acidic environment (pH 1–2.5). In the stomach, anthocyanins remain stable (Liu et al. 2014) whereas procyanidin oligomers (DP 3–6) under acidic conditions degrade to epicatechin monomers and dimers (Spencer et al. 2000) before reaching the alkalescent conditions (pH 6) in the duodenum and small intestine and terminal ileum (pH 7.4) (Evans et al. 1988).

Our current understanding on the absorption-distribution-metabolization and excretion routes of ingested polyphenols throughout the GI tract is fairly known particularly of flavan-3-ols such as catechin-based polyphenols (Actis-Goretta et al. 2012; Castello et al. 2018; Garcia-Alonso et al. 2009; Ottaviani et al. 2016; Zhang et al. 2018; Zhong et al. 2017). GI tract reactor models (Ekbatan et al. 2016) and in vivo radiolabelled experiments (Czank et al. 2013; Ottaviani et al. 2016) have shown that the biotransformation of polyphenols occurs in a time- and species-dependent manner (Czank et al. 2013; Ekbatan et al. 2016; Ottaviani et al. 2016). In vivo experiments with radiolabelled anthocyanin (^{13}C-cyanidin-3-glucoside) and flavanol (^{14}C-epicatechin) revealed the formation of compounds structurally similar to the parent polyphenol bearing the methyl, sulfate and glucuronide groups attached, which are then metabolized by the gut microflora into smaller compounds by C-ring opening with formation of 5-carbon and 3-carbon ring metabolites (Czank et al. 2013; Ottaviani et al. 2016) including phenolic, hippuric, phenylacetic, phenyl-propenoic acids (Czank et al. 2013), valero-lactone derivatives, hydroxy-phenylacetic, phenylacrilic and hippuric acid derivatives (Ottaviani et al. 2016). These C-ring fission metabolites undergo the entero-hepatic cycle and are released into circulation as methylated, sulfated and glucuronated (Castello et al. 2018; Czank et al. 2013; Espín et al. 2007; Krook and Hagerman 2012; Lee et al. 2017; Mena et al. 2017; Ottaviani et al. 2016; Sasot et al. 2017). Other metabolites such as short chain fatty acids (SCFAs) resulting from breakdown reactions involving flavonoid and non-flavonoids polyphenols were identified in a recent study (Ekbatan et al. 2016). SCFA alter the membrane permeability and the epithelial barrier function (Ohata, Usami, and Miyoshi 2005; Zheng et al. 2017) and are known regulators of immune cells, blood flow, and inflammation (Li et al. 2018; Meijer, De Vos, and Priebe 2010; Ohira, Tsutsui, and Fujioka 2017; Vinolo et al. 2011). The formation of SCFA derived from polyphenols is thus emerging as an additional benefit to the implementation of polyphenol-rich diets in the resolution of chronic inflammatory and metabolic disorders.

Figure 3 briefly depicts the journey of tea (infusion) catechin-based polyphenols and its metabolic fate in humans at various pH environments after oral ingestion.

Because of the distinct polyphenol biotransformation reactions, methylated, sulfated, methyl-sulfated and glucuronidated polyphenol metabolites show plasmatic maxima after 1 h of consumption (Actis-Goretta et al. 2012; Castello et al. 2018; Ottaviani et al. 2016) with predominance of methyl-sulfate conjugates ($MeSO_4$, 59%) and glucuronidated metabolites (Gluc, 41%) (Actis-Goretta et al. 2012; Ottaviani et al. 2016). Ring-fission metabolites such as valero-lactones, hippuric acid, phenyl-valeric acid, phenyl-propionic and phenyl acetic acid derivatives show plasmatic maxima much later between 6 and 24 h after consumption (Bresciani et al. 2017; Castello et al. 2018; Matsui et al. 2007; Mena et al. 2017; Ottaviani et al. 2016). These findings suggest an initial absorption stage at the stomach within the first hour after ingestion followed by a second absorption peak between 6 and 24 h where "surviving" polyphenols entangled in protein and carbohydrate food matrices are metabolized by colonic microbial flora (Czank et al. 2013; Ottaviani et al. 2016). In a study conducted with strawberries, raspberries, walnuts, and oak-aged wines ellagitannins, the authors found that urinary urolithin B-glucuronides resultant from the microbial degradation were related to the variability of colonic microflora populations rather than the amounts ingested (Cerdá, Tomás-Barberán, and Espín 2005).

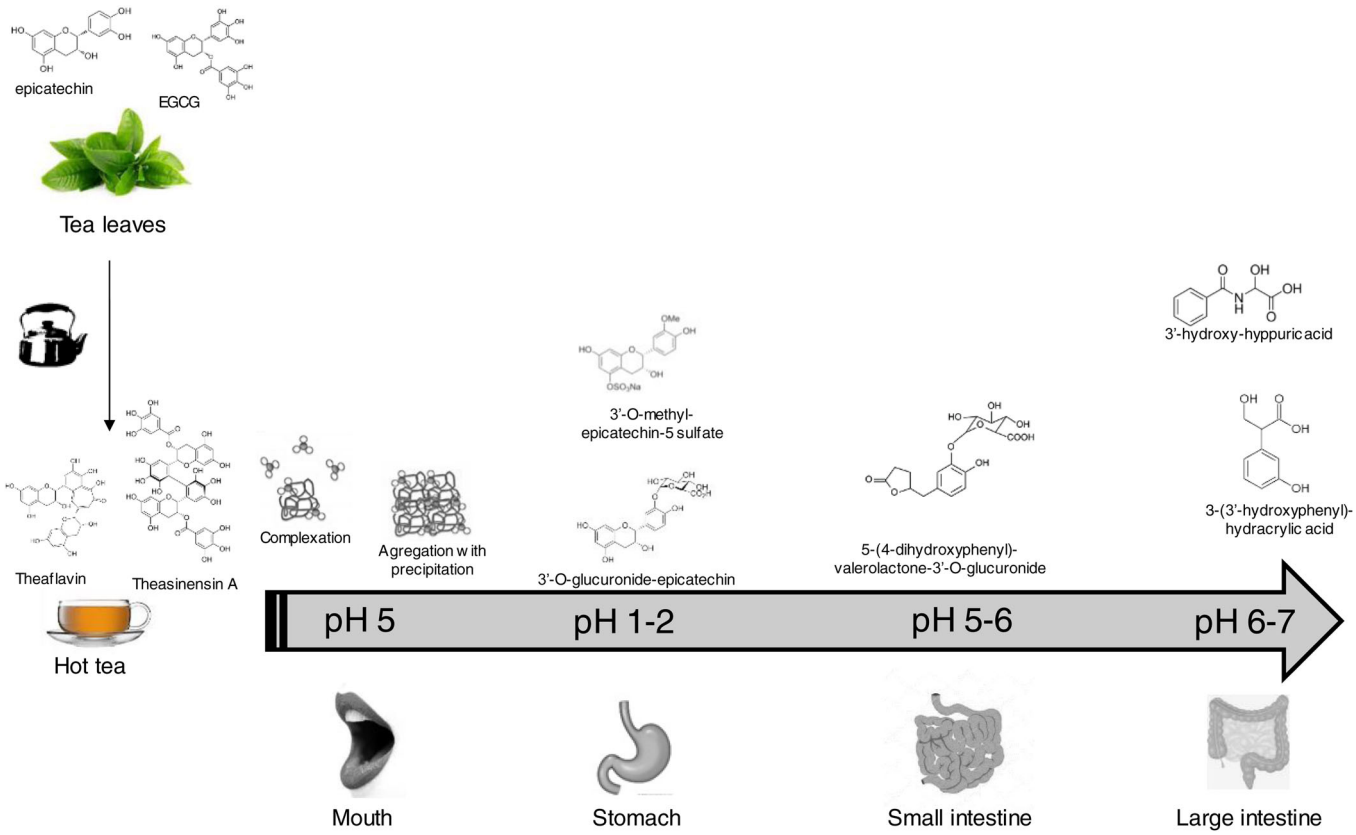

Figure 3. Biotransformation of catechin-based polyphenols present in tea leaves and ingested as tea infusions at various pH environments. Non-glycosilated catechin-based polyphenols found in micromolar amounts undergo oxidation, isomerization and polymerization reactions in hot water and in the mouth interact with salivary proline-rich proteins (PRPs and MUC7) by hydrophobic complexation with formation of insoluble aggregates that precipitate in the oral cavity and contribute to astringency perception (Soares, Mateus, and De Freitas 2007). (Epi)catechin-based polyphenols entangled in protein networks and food matrices that reach the stomach are hydrolyzed and reach the gut where they are metabolized by intestinal microflora with ring fission, reabsorbed and found in circulation as hippuric and γ-valerolactone derivatives in nanomolar amounts (Ottaviani et al. 2016).

Interestingly, most of the ingested polyphenols are excreted in urine, feces and breath (Czank et al. 2013; Ottaviani et al. 2016) and only 2% of ingested polyphenols are released into circulation (pH ~7.2–7.4) occuring at μM range (Castello et al. 2018; Ottaviani et al. 2016). The reasons behind the low bioavailability of polyphenols are not yet fully understood however recent data suggest that the experimental protocols used may be one source of underestimation. Typically, levels of circulating and excreted polyphenol metabolites are estimated by analysis of the parent polyphenol after enzymatic (glucuronidases and sulfatases) hydrolysis (Tulipani et al. 2013; Urpi-Sarda et al. 2009). Curiously, researchers noticed that enzymatic hydrolysis treatment affected the extraction performance and had a negative impact on the recovery of 12 polyphenol (phenolic acids, flavonoids and prenylflavanoids) compounds suggesting that concentrations of polyphenol metabolites in plasma samples were underestimated (Quifer-Rada, Martínez-Huélamo, and Lamuela-Raventos 2017).

In overview, dietary habits, food matrix (water, fiber, protein and fat content) and host related factors (age, gender, ethnicity, (patho)physiological conditions) and other factors such as physical exercise (Beyer et al. 2017; Bowtell and Kelly 2019) may rule the metabolism of ingested polyphenols contributing to a unique panel of polyphenols and metabolites circulating in the body.

2.4. Transport of polyphenols and its metabolites in circulation and delivery to the epithelium: impact of lipid remodeling in (patho)physiological conditions

In circulation, polyphenol metabolites are transported by plasma proteins specifically by lipid and protein macromolecular aggregates known as lipoproteins (Covas et al. 2000; Gimeno et al. 2007; Hernáez et al. 2017; Natella et al. 2007; Suzuki-Sugihara et al. 2016). Although polyphenols exhibit affinity to other low molecular weight plasma proteins such as serum albumin (Khan et al. 2011; Latruffe et al. 2014; Lu et al. 2007; Puscas et al. 2018) in vitro addition of resveratrol to plasma proteins revealed that polyphenols are preferentially distributed in the lipoprotein fraction ($d < 1.21$ g/mL) (Belguendouz, Frémont, and Gozzelino 1998). Currently, the exact panel of polyphenol metabolites transported by lipoprotein sub-populations (VLDL, LDL, and HDL), its concentration ranges and the changes associated with age, gender and ethnicity in normolipidemia are not yet known. In addition to this, the permeation of circulating polyphenols may be affected by the ratio of apolar-to-polar (Chol/PL) lipids as reported in normolipidemic lipoprotein sub-populations. The Chol/PL ratio spans from 0.91 in HDL, to 1.56 in VLDL and 2.86 in LDL (Wiesner et al. 2009) evidencing distinct lipid environments in lipoprotein populations which could result in heterogeneous distribution of polyphenol metabolites across lipoprotein sub-

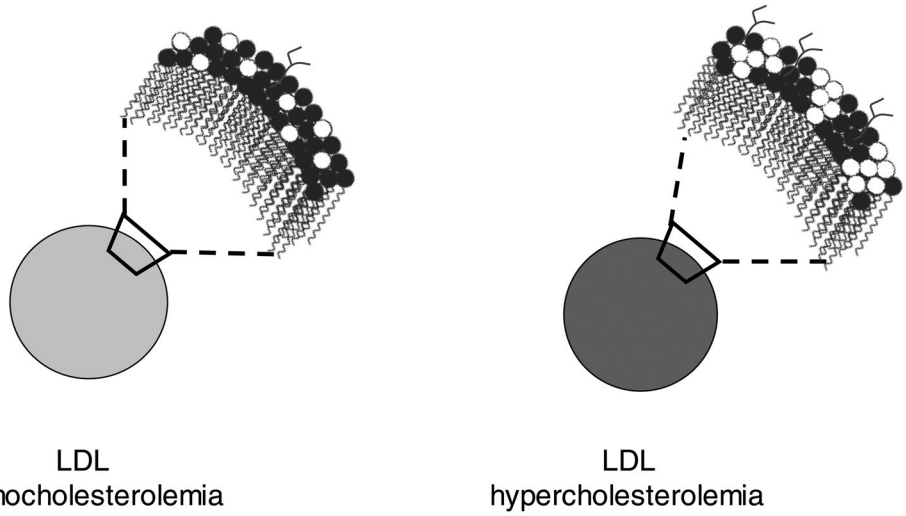

Figure 4. Schematic representation of free cholesterol distribution (white spheres) in LDL particles in normocholesterolemic and hypercholesterolemic scenarios with protrusion of oxidized acyl chains in oxidized phospholipids (oxPC) into the aqueous medium.

populations. Recent spectroscopic studies conducted in membrane models showed that the partition constants (K_p) of catechin-based polyphenols (procyanidin B4, ECG, EGCG) and PGG decreased as the content of Chol increased (Filipe et al. 2018; Leite et al. 2018; Neves, Nunes, and Reis 2015; Reis et al. 2020) suggesting that the permeability of polyphenols in the lipid bilayer was affected by the membrane lipid composition. The distinct behavior of polyphenols' partition observed in Chol-rich environments has huge consequences in hypercholesterolemia conditions such as those found in Chol-rich plasma lipoproteins (LDL). Currently, the changes to the panel and content of circulating polyphenol metabolites in diet-related diseases with associated hypercholesterolemia such as obesity, diabetes and CVD remains unknown. This is particularly relevant considering the associated inflammatory status in NCDs with exacerbated formation of reactive oxygen species (ROS). ROS-mediated reactions are crucial for proper homeostasis but are equally involved in the structural modification of lipids in bilayers (*lipid peroxidation*). At a biophysical level, lipid peroxidation products such as oxidized phospholipids (oxPC) located at the interface of lipid bilayers (Figure 4) are known to increase membrane surface polarity, membrane fluidity and bilayer thickness (Ayee et al. 2017; Borst et al. 2000; Jurkiewicz et al. 2012; Khandelia and Mouritsen 2009; Wong-Ekkabut et al. 2007) while at a biological level oxPC are involved in endothelial barrier gene expression contributing to endothelial dysfunction and vascular inflammation (Birukov and Oskolkova 2019; Fu and Birukov 2009; Gargalovic et al. 2006).

Since oxPC affects the physical and biological properties of membranes it is likely hat the partition and permeability of polyphenols in lipid microenvironments such as lipoproteins is equally affected. Answers to these questions are crucial to improve our understanding on the effectiveness of nutritional strategies in the management of diet-related diseases in an aged population.

Polyphenol and polyphenol metabolites circulating in the blood stream are able to permeate the endothelium. The "classical" approach to polyphenol permeability through the membrane bilayer is via passive diffusion. Measurements of transepithelial/endothelial electric resistance conducted in Caco-2 cells (Tian et al. 2009) and other cell models (Faria et al. 2010; Wong et al. 2012) revealed that small (iso)flavonoid aglycones are able to freely pass the lipid bilayer by passive diffusion whereas more hydrophilic polyphenol glycosides did not diffuse passively across biological membranes. Among 36 flavonoids, formononetin, tangeretin and genistein (iso)flavones were the most permeable in Caco-2 cells (Tian et al. 2009). For higher and more structurally complex polyphenols, permeation occurs via active transport where some polyphenol's structural features appear to be determinant (Figueira et al. 2017; Oliveira et al. 2015). For instance, pentosyl-substituted anthocyanins isolated from artichoke and red grape anthocyanins permeated more readily across gastric NCI-N87 epithelial monolayer cells than hexosyl-substituted derivatives (Sigurdson et al. 2018) evidencing that the polyphenols structural features such as B-ring substitution and glycosylation pattern may be important aspects involved in the transport of polyphenols through the lipid bilayer (Sigurdson et al. 2018). Work with gastric MKN-28 cells, showed that the uptake of glycosylated polyphenols such as anthocyanins across the gastric epithelial cells occurred via membrane glucose transporters (Oliveira et al. 2015) and more specifically GLUT 1 and GLUT 3 transporters (Oliveira et al. 2019). These findings are in agreement with previous bioavailability data on anthocyanins from red grape juice and red wine that suggest a possible synergistic effect of glucose on the transport of anthocyanins across the lipid bilayer and the involvement of GLUT transporters (Bitsch et al. 2004). Other structural details such as sulfate group found in polyphenol metabolites also appear to influence the transport of polyphenol metabolites across the human brain microvascular endothelial cell line (HBMEC) since pyrogallol-2-sulfate (Pyr2Sulf) was detected in the basolateral compartment of the monolayer though the isomer Pyr1Sulf containing the hydroxy groups in vicinal position was not (Figueira et al. 2017).

Table 1. Lipid composition reported in the literature for epithelial cell lines and cells.

Cell phenotype	Chol	Triglycerides	Cer	PL	Chol/PL
Oral (Wertz et al. 1986)	22	15	11	42	0.52
Skin (Wertz et al. 1986)	15	25	19	24	0.625
Small Intestine (Schulthess and Hauser 1995)	17	15	35	34	0.50
Kidney (Sampaio et al. 2011)	25	—	10	60	0.42
Lung (Zehetrofer et al. 2016)	—	20	15	50	—

The differences in the permeability by passive transport observed for polyphenols and their metabolites in various epithelial cell models seem to be related to distinct molecular traits of polyphenol's structure (lipophilicity) and pH environments (Oliveira et al. 2015; Payne et al. 2009; Tian et al. 2009) though the cell's membrane lipid composition may equally be a contributing factor.

In fact, cells collected from different human epithelial tissues contain distinct lipid composition and lipid environments (Table 1) that are likely to affect the permeability of circulating polyphenol metabolites and delivery to tissues. Mammalian epithelia are mainly composed of apolar lipids such as triglycerides, fatty acids, Chol and by less abundant polar lipids such as phospholipids (PLs) of choline and ethanolamine class, and glycosphingolipids (GSLs) (Eiriksson et al. 2018; Kyle et al. 2018; Sadowski et al. 2017; Sampaio et al. 2011; Schulthess and Hauser 1995; Wertz et al. 1986). In spite of the predominance of apolar lipid classes (Chol and triglycerides), the human epithelium exhibits distinct ratio of polar-to-apolar lipids and hence distinct lipid environments within the plasma membrane (Table 1).

The ratio of polar-to-apolar lipids depends on its location (Kyle et al. 2018; Sadowski et al. 2017; Sampaio et al. 2011; Schulthess and Hauser 1995; Wertz et al. 1986) and changes according to age and gender (Kyle et al. 2018; Sadowski et al. 2017). For instance, mammalian primary oral cells collected from different regions of the mouth revealed Chol/PL of 0.35 in the buccal mucosa, and Chol/PL ratio of 0.85 in the palate regions (Wertz et al. 1986). Changes to lipid composition in epithelial cells in the oral cavity and skin were correlated to the increase for the water permeability (Danielsen and Hansen 2008; Sadowski et al. 2017; Squier 1991).The dynamic lipid remodeling reported in epithelial cells appears to be crucial for maintaining proper function particularly the epithelial differentiation and polarization. Remarkably, the brush border membrane (apical domain of enterocyte plasma membrane) in rabbits exhibited higher Chol/PL than basolateral cells due to the contribution of polar glyco(sphingo)lipids (Schulthess and Hauser 1995) which appears to be even more evident during epithelial-to-mesenchymal transition and was associated with the increased contribution of polar lipids (Eiriksson et al. 2018; Guan, Handa, and Hakomori 2009; Sampaio et al. 2011). Changes to other lipids have also been reported in the literature, namely alterations to fatty acid composition in keratinized epithelial cells (Terashi et al. 2000) and GSLs content in intestinal cells (Breimer et al. 2012).

In view of the dynamic adaptation of lipid bilayers to environmental (diet) and (patho)physiological conditions, the interaction of polyphenols with lipids in membrane bilayers may not be so straightforward. The full understanding of the biophysical and biological effects of polyphenols and their metabolites to the epithelial membranes requires an improved knowledge on the lipidome of epithelial cells (epitheliome) and the lipid alterations associated with diet-related diseases. This has been a neglected field of research despite the technological and instrumental advances in past years in chromatographic column performance and mass spectrometry as there is an obvious scarcity of lipidome studies of epithelial cells and tissues (Breimer et al. 2012; Kyle et al. 2018; Sampaio et al. 2011; Squier 1991; Wertz et al. 1986) and the associated changes during (patho)physiological conditions. Once the in vivo lipid alterations to the epithelium are known these should be used to fine-tune the lipid composition of epithelial membrane models in *in vitro* studies.

3. Interaction of polyphenols with lipids in membrane models: biophysical effects

Although most interaction studies of polyphenol with biomolecules has largely focused on proteins, in recent years there has been a devoted interest on the interaction of polyphenols with biological membranes (lipids).

3.1. Artificial biomembranes

Models of lipid membranes with specific and known lipid composition can be easily mimicked in laboratory environment either as lipid monolayers supported in glass platforms (De Athayde Moncorvo Collado et al. 2016; Olas and Holmsen 2012; Salcedo et al. 2014) or as lipid vesicles in aqueous solutions (Caturla et al. 2003; Cyboran-Mikołajczyk et al. 2017; Fadel, El Kirat, and Morandat 2011; Filipe et al. 2018; Ionescu et al. 2013; Kajiya, Kumazawa, and Nakayama 2001; Longo et al. 2016; Neves, Nunes, and Reis 2015; Phan et al. 2014; Sirk et al. 2009; Tamba et al. 2007; Wesołowska et al. 2009; Yu et al. 2011). Several methods can be found in the literature for the preparation of liposomes suitable for lab setup and scale-up preparations and reviewed elsewhere (Patil and Jadhav 2014). Due to its simplicity, homogeneity of liposome size, low polydispersity and high physical stability upon storage (Caddeo et al. 2008) the most commonly used approach is the hydration-extrusion method described by Hope and colleagues (Hope et al. 1985). Depending on their size, liposomes can be classified as small unilamelar vesicles (SUVs, <100 nm), large unilamellar vesicles (LUVs, $100 < \text{size} < 1000$ nm) and giant unilamellar vesicles (GUVs, >1000 nm). In practice, researchers adopt the use of LUV (Caturla et al. 2003; Cyboran-Mikołajczyk et al. 2017; De Athayde Moncorvo Collado et al. 2016; Filipe et al. 2018; Kajiya, Kumazawa, and Nakayama 2001; Longo et al. 2016;

Neves, Nunes, and Reis 2015; Phan et al. 2014; Sirk et al. 2009; Wesołowska et al. 2009; Yu et al. 2011) or GUV (Phan et al. 2014; Tamba et al. 2007) rather than SUV (Fadel, El Kirat, and Morandat 2011; Ionescu et al. 2013) which are less preferred due to the marked vesicle curvature and low stability over time.

Despite the overall low solubility displayed by polyphenols in water, they interact with membrane lipids affecting the biophysical properties of biomembranes. Spectroscopic and imaging findings in model membranes (Caddeo et al. 2008; Caturla et al. 2003; Huh et al. 1996; Longo et al. 2016; Neves, Nunes, and Reis 2015; Phan et al. 2014; Tamba et al. 2007; Uekusa et al. 2011) have shown that polyphenols affect the lipid hydration layer (Phan et al. 2014), increasing the anisotropy (Ionescu et al. 2013; Salazar et al. 2019), membrane fluidity (Caddeo et al. 2016; Ionescu et al. 2013; Neves, Nunes, and Reis 2016; Yu et al. 2011) and membrane potential (Cyboran-Mikołajczyk et al. 2017; Huh et al. 1996). For instance, hydrophilic EGCG spread over the membrane surface is able to "recruit" water molecules to the water-lipid interface promoting the hydrogen bonding between polyphenol hydroxyl groups and the polar head groups of PLs increasing the hydration layer and membrane fluidity (Ionescu et al. 2013), whereas quercetin, a less hydrophilic polyphenol, was able to modulate the orientation of the water molecules (Ionescu et al. 2013). Polyphenols are also reported to increase membrane packing (Caturla et al. 2003; Cyboran-Mikołajczyk et al. 2017) with decrease of bilayer thickness (Fei et al. 2018; Huh et al. 1996) capable of inducing phase separation (Longo et al. 2016; Phan et al. 2014) and ultimately lead to membrane leakage (Caturla et al. 2003; Fadel, El Kirat, and Morandat 2011; Tamba et al. 2007). Electron density studies have shown that even submicromolar amounts of PGG lead to a decrease of membrane thickness (Huh et al. 1996) due to the partition of PGG into the interfacial region through the accommodation of galloyl residue(s) forcing the rearrangement of acyl chains in order to maintain electronic density (Huh et al. 1996). At higher polyphenol concentrations and in the event of complete coverage of the interfacial surface area, polyphenols may reduce repulsive forces between polar headgroups (Phan et al. 2014) and ultimately contribute to cell-cell adhesion and aggregation events (Huh et al. 1996; Phan et al. 2014).

Based on the reported biophysical properties of polyphenols in lipid bilayers it is also evident that the degree of interaction of polyphenols in lipid bilayers is intimately related not only to the polyphenol's structural features but also to the biomembrane's lipid composition enabling polyphenols to position themselves in different niches of the lipid bilayer and to exert distinct behaviors.

3.2. Lipid composition in artificial membranes and cell membrane leaflet asymmetry

The popularity of model biomembranes derives from their versatility to include different lipids in different ratios thus mimicking to the best cell membranes lipid composition (PL classes and acyl chains). In their endeavor, most research groups use single lipid composition usually glycerophosphatidylcholine (GPC) (Fadel, El Kirat, and Morandat 2011; Filipe et al. 2018; Furlan et al. 2016; Huh et al. 1996; Longo et al. 2016; Phan et al. 2014; Tamba et al. 2007; Uekusa et al. 2011; Yu et al. 2011), as this is the predominant class in mammalian cell bilayers (Quehenberger et al. 2010). The GPC lipids used are typically individual pure synthetic compounds composed of saturated acyl chains or mono-unsaturated acyl chains (De Athayde Moncorvo Collado et al. 2016; Ionescu et al. 2013; Longo et al. 2016; Phan et al. 2014; Wesołowska et al. 2009; Yu et al. 2011). Occasionally commercial mixtures of mono- and polyunsaturated acyl chains (egg- or soybean lecithin) are used (Caturla et al. 2003; Huh et al. 1996; Kajiya, Kumazawa, and Nakayama 2001; Lee et al. 2005; Neves, Nunes, and Reis 2016; Tamba et al. 2007). The inclusion of unsaturated acyl chains in model membranes is more realistic as it reflects the wide diversity of acyl chains in mammalian cells (Quehenberger et al. 2010) nevertheless the use of saturated lipids is preferred, over mixtures of saturated and poly-unsaturated acyl chains, as these are resistant to radical-based reactions and minimize the formation of polar oxidation products occurring even during liposome preparation stage (Reis et al. 2005; Watson et al. 1997) which would mask and alter the final result.

Aside from the predominance of GPC lipids in mammalian lipids and their remarkable acyl chain diversity (Quehenberger et al. 2010), mammalian cells are also abundant in Chol. In fact, Chol is a prominent component of eukaryotic cell membranes, typically associated with sphingo- and glycolipids (Weerachatyanukul et al. 2007) forming nanodomains known as lipid rafts (Simons and Ikonen 1997) that serve as anchoring points for transmembrane proteins and crucial for proper signaling and trafficking mediated events. In biomembranes, Chol seems to be heterogeneously distributed across the lipid bilayer with preferential distribution on the outer membrane leaflet (Liu et al. 2017) and with higher affinity toward regions-rich in saturated acyl chains (Marquardt et al. 2016). At the biophysical level, Chol seems to influence the membrane surface charge by decreasing the zeta-potential (ζ) of membranes (Magarkar et al. 2014) as well as an ordering and condensing effect (Giri, Chakrabarti, and Mukhopadhyay 2017; Róg et al. 2009) with formation of liquid-ordered domains of lower transition temperature fluidifying the membrane bilayer (Brown and Wrenn 2013; Mannock et al. 2010; Silvius 2003).

As an intrinsic component of eukaryotic cells, the inclusion of Chol in model membranes is key to mimic the physicochemical properties of biological membranes and the detergent-resistant nanodomains present in cell membranes (Simons and Ikonen 1997). Remarkably, the number of studies focusing on the behavior of polyphenols in more complex Chol-containing lipid environments are still scarce (Fadel, El Kirat, and Morandat 2011; Filipe et al. 2018; Galiano and Villalaín 2015; Leite et al. 2018; Neves, Nunes, and Reis 2016; Reis et al. 2020; Zhu et al. 2017).

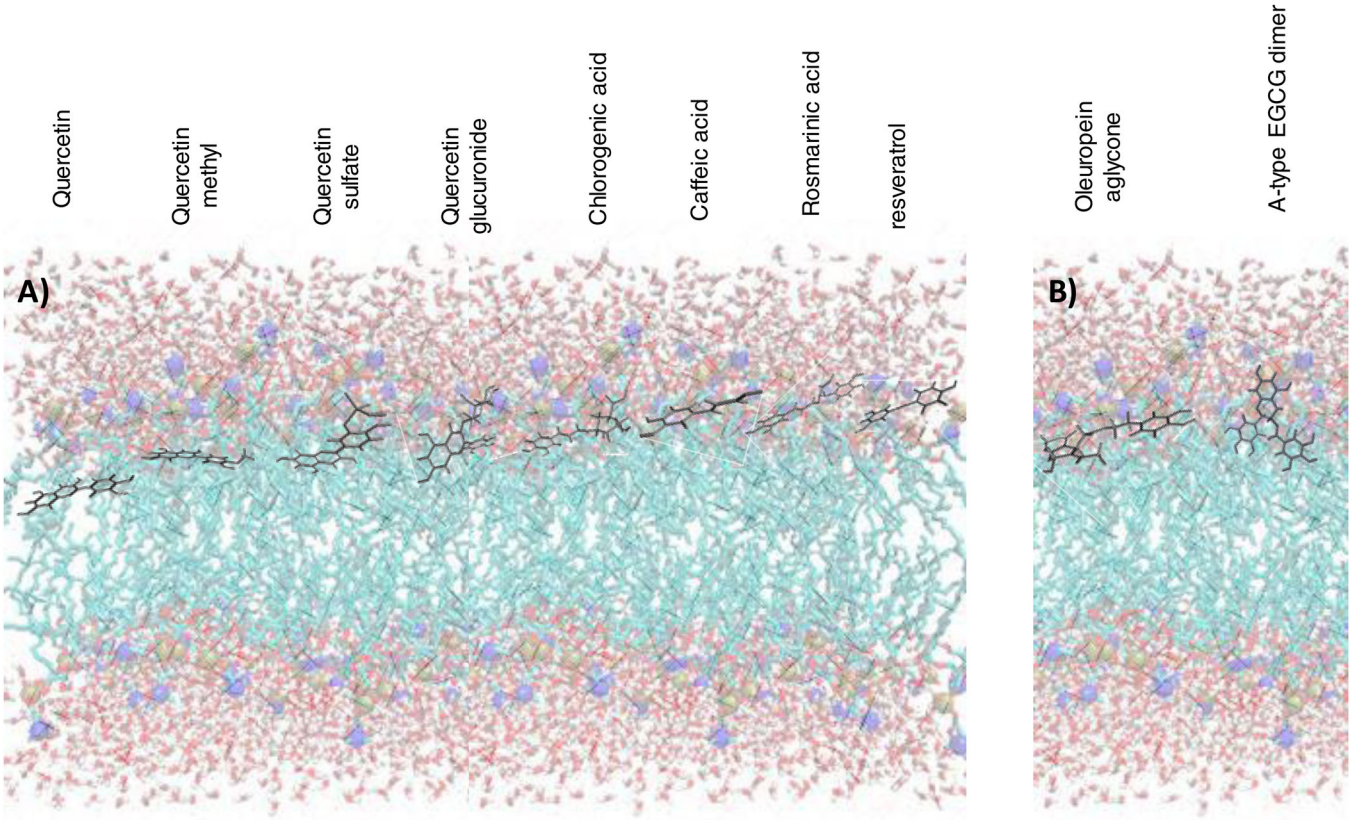

Figure 5. Location of polyphenols in cholesterol-free (A) and cholesterol-rich (B) lipid bilayers based on MD simulations conducted at physiological pH (deprotonated form of polyphenols) and temperature of 25 °C. Quercetin and quercetin metabolites (methylated, sulfated and glucuronide) were conducted in DOPC bilayers (Košinová et al. 2012); caffeic, rosmarinic and chlorogenic acid were conducted in POPC bilayers (Filipe et al. 2018); resveratrol was conducted in DPPC bilayers (Fei et al. 2018); oleuropein aglycone was conducted in POPC/Chol (7:1; Galiano and Villaín 2015); ECG and EGCG A-type dimers were conducted in PC:PE:Chol bilayers (Zhu et al. 2017).

One of the drawbacks of conventional liposome preparation methods is that liposomes have chemically identical bilayer leaflets. In living cells, the two leaflets contain different lipid classes—lipid asymmetry—that is key for cell's proper function. For instance, the outer plasma membrane is enriched with sphingomyelin and PC lipids while the inner leaflet is rich in aminoPLs such as PS and PE. There has an increasing technological effort to develop experimental approaches able to prepare artificial membranes that mimic the lipid asymmetry found in real cell membranes (Doktorova et al. 2018; Drechsler et al. 2018).

3.3. Location of polyphenols in lipid bilayers and the influence of Chol

As mentioned, dietary polyphenols and polyphenol metabolites contain many structural features (section 2.2) that determine their solubility in lipophilic environments and in turn their location within the lipid bilayer. The location of polyphenol's in biomembranes can be inferred experimentally based on the behavior displayed by fluorescent probes (Caturla et al. 2003; Fadel, El Kirat, and Morandat 2011; Kajiya, Kumazawa, and Nakayama 2001; Olas and Holmsen 2012; Sirk et al. 2009; Tamba et al. 2007; Uekusa et al. 2011; Wesołowska et al. 2009) and theoretically by computational molecular simulations (Filipe et al. 2018; Galiano and Villalaín 2015; Košinová et al. 2012; Zhu et al. 2017).

Regardless of the approach adopted there is a general consensus that in biomembranes dietary polyphenols reside just below the lipid-water interface of lipid membranes (Caturla et al. 2003; Fadel, El Kirat, and Morandat 2011; Filipe et al. 2018; Galiano and Villalaín 2015; Ionescu et al. 2013; Kajiya, Kumazawa, and Nakayama 2001; Leite et al. 2018; Neves, Nunes, and Reis 2015; Olas and Holmsen 2012; Phan et al. 2014; Sirk et al. 2009; Tamba et al. 2007; Uekusa et al. 2011; Wesołowska et al. 2009) although more lipophilic polyphenols such as resveratrol and galloylated catechins are reported to penetrate deeper in the lipid bilayer (Caturla et al. 2003; Neves, Nunes, and Reis 2016). Data on molecular dynamics simulations seems to corroborate experimental findings by showing different polyphenols accommodated in specific niches of the lipid bilayer (Fei et al. 2018; Filipe et al. 2018; Košinová et al. 2012; Zhu et al. 2017). Košinová et al. (2012) found that quercetin and methylated quercetin entered the hydrophobic acyl region (Figure 5) whereas polar sulfated and glucuronidated quercetin metabolites remained closer to the polar region (Košinová et al. 2012). Others working with non-flavonoid compounds found similar results (Fei et al. 2018; Filipe et al. 2018). Figure 5 depicts the location of some polyphenols and metabolites (deprotonated forms) based on molecular dynamics (MD) simulations reported in the literature (for additional details see caption). MD simulations have also shown that the precise location of polyphenols is related to the charge state

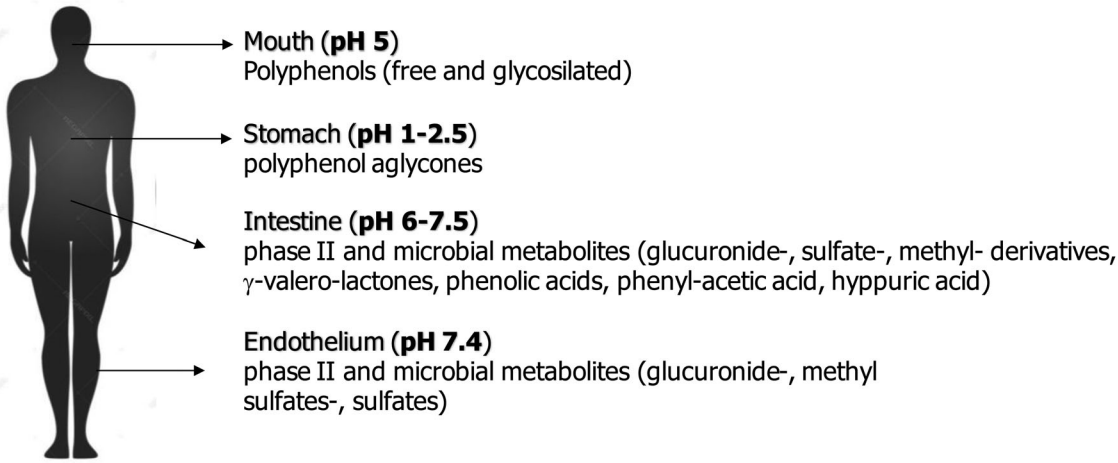

Figure 6. Chemical (pH) environments underwent by polyphenols in the human epithelium.

and the membrane's lipid composition, as observed for oleuropein aglycone (Galiano and Villalaín 2015), and caffeic and chlorogenic acid (Filipe et al. 2018).

However, it should be emphasized that biological membranes contain Chol, preferentially located in the outer leaflet of membranes (Liu et al. 2017) and that this asymmetric distribution inevitably impacts the distribution and organization of polyphenols in Chol-rich model membranes (Marquardt et al. 2016).

There are few biophysical studies conducted with membrane lipids and Chol, but based on literature available several authors reported the decrease of polyphenols partition constants (K_p) with increasing Chol content (Filipe et al. 2018; Leite et al. 2018; Neves, Nunes, and Reis 2015; Reis et al. 2020; Zhu et al. 2017). The findings with Chol-rich membranes also evidence the preferential location of polyphenols at the surface of the bilayer leading to an increased concentration of polyphenols at the water-lipid interface away from the inner lipophilic region (De Athayde Moncorvo Collado et al. 2016; Filipe et al. 2018; Leite et al. 2018; Neves, Nunes, and Reis 2015). This segregatory effect which was consistently observed for resveratrol (Neves, Nunes, and Reis 2015), curcumin (Leite et al. 2018), phenolic acids (Filipe et al. 2018), catechin-based polyphenols and PGG (Reis et al. 2020) in Chol-rich liposomes regardless of the polyphenol lipophilicity is thought to be responsible for the decrease of their antioxidant potential and scavenging capacity against lipid peroxidation modification reactions (De Athayde Moncorvo Collado et al. 2016; Fadel, El Kirat, and Morandat 2011). The preferential location of polyphenols at the surface of membranes seems to be paramount for polyphenol biological activity. Binding studies conducted in complex "lipid-raft liposome" model composed of Chol:GM_1:PE:PC:SPM (Chol:ganglioside:phosphatidylethanolamine:phosphatidylcholine: sphingomyelin; 32:35:14:11:9, %mol) with higher Chol content showed that A-type ECG and EGCG dimers bond to Chol domains (Zhu et al. 2017) while Colin and colleagues using radiolabelled resveratrol found that it accumulated in the rich sphingomyelin- and Chol- (lipid rafts) fractions triggering the signaling cascade and the subsequent biological response (Colin et al. 2011).

3.4. In vitro polyphenol-lipid interactions applied to in vivo processes

Polyphenol-lipid interaction studies in model membranes have been valuable tools to infer on the behavior of polyphenols in the epithelium under distinct pH conditions such as those found in the context of oral astringency, gastro-intestinal absorption and endothelial permeability.

In their journey across the human epithelium, polyphenols (and their metabolites) undergo distinct physiological pH environments (Figure 6) and epithelial lipid environments (Table 1) generating distinct conditions under which polyphenols permeability may be affected. To date, most of in vitro studies with biomimetic membranes have not been adjusted to these changing conditions and so far the inadequacy of experimental conditions in model membranes and their findings has limited translation to oral sensory perception, gastro-intestinal absorption and endothelial permeability.

3.4.1. Oral sensory perception

Polyphenols have long been associated with food sensory properties such as color and taste perception (Ferrer-Gallego et al. 2016; Joslyn and Goldstein 1964; Lu and Bennick 1998; Sun et al. 2013). The interaction of polyphenols with salivary proline-rich proteins is widely accepted in the modulation of oral astringency (Brandão et al. 2017; Soares, Mateus, and De Freitas 2007; Soares et al. 2011) but previous cell-based studies conducted in primary oral cells (harvested from inner cheeks) revealed that grape seed procyanidins bond to membrane lipids (Payne et al. 2009) suggesting for the first time that polyphenol-lipid interactions also contributed to taste sensorial perception (Payne et al. 2009). Recent studies conducted on liposomes (PC/Chol) containing different Chol ratios aiming to mimic distinct amounts of Chol found in the mouth (Wertz et al. 1986) revealed that lipid microenvironment govern polyphenol-lipid interactions and could potentially contribute to the modulation of taste perception in the oral mucosa (Payne et al. 2009; Soares et al. 2016). Data obtained showed that the interaction of tested polyphenols increased with the rise

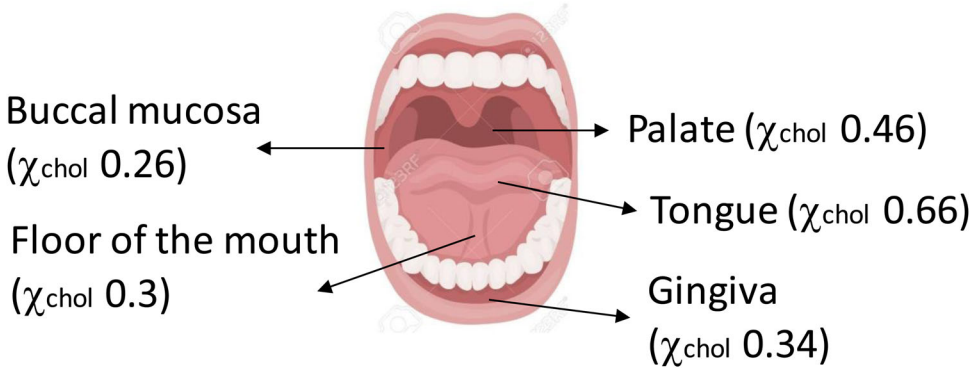

Figure 7. Cholesterol molar fractions (χchol) in mouth regions (adapted from Wertz et al. 1986 and Rabinowitz et al. 1986).

of Chol in model membranes, with PGG displaying a stronger interaction with membranes lipids than catechin-based polyphenols (Reis et al. 2020). Complementary STD data obtained for EGCG and PGG with PC/Chol liposomes displayed strong proton signals between 6.8 and 7.2 ppm confirming that galloyl residues were spatially closer to the lipid bilayer and were the preferential binding sites (Reis et al. 2020). Based on these findings, the authors concluded that lipid environments played a role in the interaction of astringent polyphenols where more polar lipid microenvironments with lower Chol content (χ_{chol}) such as those found in buccal mucosa, floor of the mouth and gingiva (Figure 7) perceived astringent polyphenols with higher affinity than the palate or the tongue with higher χ_{chol} (Reis et al. 2020).

3.4.2. Gastro-intestinal absorption

The gastro-intestinal tract involves a wide pH range (pH 1–6) (Evans et al. 1988; Koziolek et al. 2015) that is likely to affect not just the chemical stability of polyphenols and their metabolites but also their solubility and interaction with the lipids in the membrane and in turn their permeability in lipid bilayers.

At stomachal acidic pH, polyphenols are chemically stable polyphenols such as caffeic acid derivatives immerse deeper into the hydrophobic region of the bilayer as revealed by molecular dynamic simulations with POPC lipids (Filipe et al. 2018). Toward pH 5–6 (similar to those found in ileum) polyphenols are less stable (Krook and Hagerman 2012) and tend to be in their deprotonated form moving toward the lipid-water interface where they remain anchored to the polar head region as previously observed for phenolic acids in POPC bilayers (Filipe et al. 2018). Apart from the theoretical simulations here described, the interaction of polyphenols with membrane lipids under highly acidic conditions are scarce and the partition behavior of polyphenols in lipid bilayers remains poorly known.

3.4.3. Endothelial permeability

In the endothelium, polyphenols circulate under neutral pH conditions as phase II metabolites (Actis-Goretta et al. 2012; Bresciani et al. 2017; Castello et al. 2018; Matsui et al. 2007; Mullen et al. 2010; Ottaviani et al. 2016; Pimpão et al. 2015; Zhang et al. 2018) where they are able to permeate the endothelium. At neutral pH, polyphenol sulfate and glucuronide metabolites are negatively charged favoring electrostatic and H-bonding interactions with water molecules becoming preferentially anchored at the water phase (Košinová et al. 2012).

Many of the interaction studies conducted with artificial membranes at physiological pH have mainly focused on polyphenols (Caturla et al. 2003; Cyboran-Mikołajczyk et al. 2017; De Athayde Moncorvo Collado et al. 2016; Fadel, El Kirat, and Morandat 2011; Fei et al. 2018; Huh et al. 1996; Kajiya, Kumazawa, and Nakayama 2001; Leite et al. 2018; Longo et al. 2016; Neves, Nunes, and Reis 2015; Sirk et al. 2009; Tamba et al. 2007; Uekusa et al. 2011; Wesołowska et al. 2009; Zhu et al. 2017) and not on the expected polyphenol metabolites reported in plasma. To our knowledge, the interaction of polyphenol metabolites with lipid membranes has not yet been conducted and hence the permeability of polyphenol metabolites in the endothelium remains poorly understood opening a promising area of research.

In overview, the biophysical changes induced by polyphenols to lipid bilayers are intrinsically related to the polyphenol's structural details, chemical environment (pH) and to the membrane's lipid composition (lipid environment). However, the inadequacy of experimental conditions used in previous in vitro studies has limited the full potential of liposomes as tools to obtain insightful details on the molecular and biophysical behavior of polyphenols across the epithelium in physiological scenarios. The inclusion of polar lipids (e.g., GSLs) in model membranes and the expansion of interaction studies with polyphenol metabolites may deepen our understanding on physiological role of dietary polyphenols at the gastrointestinal and endothelial level.

4. Interaction of polyphenols with epithelial cells: cytotoxicity and other biological effects

It is consensual that diet supplementation with polyphenol-rich food products leads to an overall improvement of blood lipid parameters, inflammation markers and vascular health (Carrasco-Pozo, Morales, and Gotteland 2013; Fernández-Castillejo et al. 2016; Larrosa et al. 2010; Yang et al. 2017). Most of our knowledge on the biological effects of polyphenols and its circulating metabolites derives from in vitro studies on cultured epithelial cell lines (Colin et al. 2011;

Hara-Terawaki et al. 2017; Mena et al. 2017; Nunes et al. 2016; Oliveira et al. 2015; Sigurdson et al. 2018; Soares et al. 2016; Tian et al. 2009) rather than on cultured primary cells (Chen, Hollborn, et al. 2014; Payne et al. 2009).

4.1. Cytotoxic effects

In vitro cultured cell line studies revealed that at physiological micromolar concentrations (<100 µM) polyphenols do not elicit cytotoxic effects to epithelial cells (Caddeo et al. 2008; Chen, Hollborn, et al. 2014; Évora et al. 2017; Goszcz et al. 2017; Krga et al. 2018; Mena et al. 2017; Oliveira et al. 2015) or to monocytic cells (Amini, Spencer, and Yaqoob 2018; Lee et al. 2017). Anthocyanin's extracted from blackberry and red wine (mlv3glc and cy3glc) showed no effect on the proliferation of HaCaT cells up to 100 µM (Évora et al. 2017) nor did procyanidins to human monocytic THP-1 cells up to 30 µM (Amini, Spencer, and Yaqoob 2018; Lee et al. 2017). Some studies have used grape seed and red wine extracts rich in anthocyanins and oligomeric procyanidins (Nunes, Freitas, et al. 2019; Oliveira et al. 2015; Payne et al. 2009) and found not to affect the viability of MKN-28 cells at 0.05 µg/µL (Oliveira et al. 2015), or HT-29 cells up to 0.6 µg/µL (Nunes, Freitas, et al. 2019; Nunes et al. 2016) and HSC-2 cells up to 50 µg/µL (Payne et al. 2009). The only case reported refers to resveratrol that displayed anti-proliferative effects toward Caco-2 epithelial cells at 1 µM (Storniolo and Moreno 2012) as well as other tissue cell lines (Caddeo et al. 2008; Gheldof et al. 2017) which could be related to its ability to immerse deeper into the lipid bilayer (Neves, Nunes, and Reis 2016). On the other hand, quercetin which equally immerses in the lipid bilayer niche (Figure 5) showed no cytotoxicity to HUVEC cells up to 20 µM (Margina et al. 2013) or to ARPE-19 cells up to 80 µM (Weng et al. 2017).

Similar to polyphenols, polyphenol metabolites revealed no cytotoxic effects toward epithelial cells at micromolar concentrations (<100 µM) as demonstrated for flavan-3-ols gut metabolites such as γ-valero-lactone derivatives (Lee et al. 2017; Mena et al. 2017), protocatechuic acid, 4-hydroxybenzoic acid and phloroglucinaldehyde (Amini, Spencer, and Yaqoob 2018), 4-hydroxy-5-hydroxyphenylvaleric acids and 3-hydroxyphenyl propionic acids (Hara-Terawaki et al. 2017), sulfated derivatives of catechol, pyrogallol and hydroxy-benzoic acid (Figueira et al. 2017) or gallic acid (Goszcz et al. 2017), as well as for methylated anthocyanin metabolites (Fernandes et al. 2013).

Under non-cytotoxic conditions, polyphenols and their metabolites prevented the adhesion of microbial pathogens biofilms to oral cells (Neto et al. 2017) and in bladder epithelial cells (Mena et al. 2017). Also, they were reported to prevent the adhesion of monocytic cells toward endothelial cells (Colin et al. 2011; Krga et al. 2018; Lee et al. 2017) and platelets aggregation (Wright et al. 2010). At higher micromolar concentration values (>100 µM) mimicking acute polyphenol intake, polyphenols displayed some cytotoxicity with anti-proliferative and apoptotic effects (Caddeo et al. 2008; Fernandes et al. 2013; Goszcz et al. 2017; López De Las Hazas et al. 2017; Pace et al. 2018; Weisburg et al. 2013).

The cytotoxic effects displayed by polyphenols may be related not only to their chemical structural features but also to cell phenotypes and the membrane's lipid composition as resveratrol (Colin et al. 2011) and ellagic acid (Weisburg et al. 2013) showed cytotoxicity toward colon cancer cells (Colin et al. 2011) and oral cancer cells (Weisburg et al. 2013) but not to normal cells (Colin et al. 2011; Weisburg et al. 2013). Also, Chen et al. working with retinal pigment epithelial primary cells found that EGCG (flavanol) did not affect the viability and quercetin induced a dose-dependently necrosis (Chen, Hollborn, et al. 2014) whereas in retinal pigment epithelial cell line (ARPE-19 cells) EGCG (Lee et al. 2014) and quercetin (Weng et al. 2017) showed opposite effects. These findings are corroborated by more recent experiments where polyphenol-rich extracts were tested in 5 epithelial cell lines displaying differentiated cytotoxicity (Boncler et al. 2017).

Despite the many studies, the molecular mechanisms by which polyphenols and its metabolites exert a biological response in epithelia remain complex and are still under investigation. An interesting study conducted with radiolabelled resveratrol (^{3}[H]-resveratrol) showed the accumulation of polyphenols in sphingomyelin- and Chol-enriched membrane regions (Colin et al. 2011) which was then responsible for the recruitment of intracellular signaling molecules (Colin et al. 2011) suggesting that the biological response induced by polyphenols in cell membranes may be related to its local lipid composition.

The notion that polyphenol-lipid biophysical interactions may trigger a biological response is an emerging new concept as most of the research in the polyphenol area has focused on the polyphenol's ability to bind to protein chains through hydrogen bonding or hydrophobic interactions with formation of polyphenol–protein insoluble aggregates triggering a biological response. Numerous examples are found in the literature confirming that, from ingestion to excretion, polyphenol-protein interactions are key to physiological processes including taste modulation (Charlton et al. 2002; Ferrer-Gallego et al. 2016; Lu and Bennick 1998; Soares et al. 2011), adherence of bacteria on the dental enamel pellicle (Hannig et al. 2009), cereal gliadin digestion and gastro-intestinal absorption (Kemperman et al. 2010; Pérot et al. 2017; Van Buiten, Lambert, and Elias 2018) reducing cereal intestinal inflammatory response in celiac patients (Romier et al. 2009). A more popular trend of research in polyphenol-protein interactions has been in the regulation of secreted hydrolytic enzymes such as glucosidases (McDougall, Kulkarni, and Stewart 2008; Toda, Kawabata, and Kasai 2001; Yang and Kong 2016) and lipases (Buchholz and Melzig 2015; Rahim, Takahashi, and Yamaki 2015), and other enzymes, hormones and transcription factors involved in Chol metabolism such as plasma cholesteryl ester transport protein activity (Cheuk et al. 2008), sterol regulatory element-binding protein (SREBP) (Murase et al. 2011; Yashiro et al. 2012), leptin signaling (Ibars et al. 2018)

and adipocytes differentiation (Drira, Chen, and Sakamoto 2011; Zhu et al. 2017).

Recent evidences for the active role of polyphenols in the absorption of sugars and fats (Buchholz and Melzig 2015; Kim, Keogh, and Clifton 2016) and in the management of diabetes and obesity is boosting the consumer's desire for the adoption of polyphenol-rich diets. However, advances in these topics have not yet translated into as much of the research on the effect of polyphenols in the modulation of these enzymes has been conducted in cell lines cultured under normolipidemic conditions (Cheuk et al. 2008; Ibars et al. 2018; Murase et al. 2011; Rahim, Takahashi, and Yamaki 2015), and therefore the real effect of ingested polyphenols on these enzymes in dyslipidaemia scenarios typically associated with diabetes, obesity and metabolic disorders (Blumentals et al. 2013; Stegemann et al. 2014) remains elusive.

4.2. Lipoprotein metabolism, endothelial health and CVDs

Advances in polyphenol-protein research and improved understanding on the mechanisms underlying sugar and fat absorption are crucial as in an increasingly aged society, diabetes, obesity and hypertension, are risk factors of CVDs. Evidences for the involvement of polyphenols in the modulation of enzymes involved in Chol metabolism (Cheuk et al. 2008; Drira, Chen, and Sakamoto 2011; Murase et al. 2011; Zhu et al. 2017) similar to statins in the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) in the biosynthesis of Chol opens promising topics of interest in polyphenol area of research.

However, the impact of ingested polyphenols on CVD risk may not be so straightforward and may involve a concerted interplay between understanding how polyphenols permeate and are transported by circulating lipoproteins, their action on secreted lipases by endothelial cells and their effects on other circulating cells.

Studies with purified lipoproteins populations have shown that food polyphenols are able not only to improve antioxidant capacity of circulating LDL (Gimeno et al. 2007; Natella et al. 2007; Suzuki-Sugihara et al. 2016) through a synergism with lipophilic vitamins (Fabre et al. 2015; Milde, Elstner, and Grassmann 2007) protecting lipoproteins against damaging radical-mediated modifications (Ivanov, Carr, and Frei 2001; Milde, Elstner, and Grassmann 2007), but also to change ApoB-100 protein's conformation increasing its affinity for the LDL receptor facilitating its clearance from circulation (Atrahimovich et al. 2016). Atrahimovic and colleagues described that punicalagin, a polyphenol abundant in pomegranate, bound to ApoB-100 protein at micromolar concentrations (up to 4 μM). The binding of polyphenol close to the LDL-receptor binding site (region ^{3359}Arg-^{3369}Ala) changed the ApoB-100 protein conformation and enhanced the affinity to LDL receptor (Atrahimovich et al. 2016). Presently, any studies able to show the effect of polyphenol metabolites in lipoprotein metabolism either by reduction of atherogenic LDL or enrichment of atheroprotective HDL would have a significant impact on the management of CVD risk. Recently, Hilvo and colleagues reported that the inhibition of proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme responsible for lowering LDL Chol (Peterson, Fong, and Young 2008) altered lipid plasma profile (Hilvo et al. 2018) suggesting the potential of PCSK9 inhibition therapies on CVD. Similarly, the inhibition of endothelial and hepatic lipases is reported to lead to an increment of atherogenic HDL (Broedl et al. 2004; Escolà-Gil et al. 2013) and although preliminary studies conducted with gallic acid and catechin-based polyphenols revealed that these dietary polyphenols inhibited pancreatic lipase (Rahim, Takahashi, and Yamaki 2015) the inhibitory effect of circulating polyphenols on other triglyceride lipase gene subfamily members, including endothelial and lipoprotein lipases, or on PCSK9, remains unknown.

Polyphenols transported by circulating lipoproteins are in close contact to other cells circulating in the bloodstream including monocytes and platelets, and endothelial cells, and in general their presence attenuates the adherence of cells preventing cell aggregation (Krga et al. 2018; Lee et al. 2017; Xu et al. 2017). Circulating platelets contribute to homeostasis but under pathological conditions platelets secrete adhesion molecules that could lead to thrombus formation with restriction of blood flow and endothelial damage (Ludovici et al. 2018). In vitro studies have shown that polyphenols and polyphenol metabolites are strong inhibitors of aggregation mediated by arachidonic acid, collagen or phosphoinosite-3-kinase pathway conferring them with anti-aggregation properties which have been extensively detailed by other authors (El Haouari and A. Rosado 2011; Faggio et al. 2017; Ludovici et al. 2018). The anti-aggregation properties of polyphenols have also been reported in circulating immune cells. In vitro cell culture incubations of di-hydroxyphenyl-γ-valerolactone efficiently attenuated the adhesion of THP-1 monocytes to endothelial cells when compared to other metabolites and its procyanidin precursors (Lee et al. 2017). Upon stimulation with inflammatory lipopolysaccharide (LPS) phloroglucinaldehyde and protocatechuic acid inhibited the production of inflammatory cytokines (IL-6) in cultured THP-1 monocytes and macrophages at submicromolar concentrations (Amini, Spencer, and Yaqoob 2018). In another study, low concentrations of gallic acid (100 nM–1 μM) a metabolite of anthocyanins increased glutathione release in HUVEC cells (Goszcz et al. 2017). Also working with HUVEC cells, Warner and colleagues found that among 20 tested polyphenols and polyphenol metabolites (conjugates), protocatechuic acid was the most efficient in inhibiting the secretion of pro-inflammatory marker vascular cellular adhesion molecule 1 protein in a concentration-dependent manner (Warner et al. 2016). At the tissue level, polyphenols exhibited a vaso-relaxating effect in a concentration-dependent manner as observed in ex vivo mouse arteries (Van Rymenant et al. 2017) as well as potentiating vascular function by the activation of endothelial NO synthase (Rocha et al. 2014) and preservation of tight junctions integrity by promoting the expression of tight-junction

proteins even under inflammatory conditions and averting the expression of claudin-2 by inflammatory cytokines (Nunes, Freitas, et al. 2019).

5. Achievements and challenges in polyphenol research: future directions toward personalized nutrition in diet-based diseases

Based on the literature here described, much is now known about the polyphenol food composition, their fate from ingestion to excretion, and the biological effects corroborating to the health benefits associated with polyphenol-rich diets. In recent years, with the increasing incidence and prevalence of diet-related diseases governments are investing heavily in promoting Healthy Diets for a Healthy Life (https://www.healthydietforhealthylife.eu) and the research behind it toward a more sustainable society. Despite the effort to improve our understanding on the relationship between dietary choices and health outcomes a direct casual effect between polyphenol-rich diet intake and the health benefit is yet to be shown and to date the potential of polyphenol-rich diet strategies as therapeutic strategies complementary to conventional drug-based therapies in the prevention, management and treatment of NCDs is yet to be established.

The effective implementation of polyphenol-diet strategies relies on a deeper understanding of its players at the physiological level, including knowledge on the plant/fruit polyphenol metabolome (Yang et al. 2018), how this translates into the human circulating polyphenol metabolome (Actis-Goretta et al. 2012; Castello et al. 2018; Mena et al. 2017; Mullen et al. 2010; Nuñez-Sánchez et al. 2014; Pimpão et al. 2015) and the inherent biophysical and biological effects on circulating cells (monocytes and platelets) and endothelial cells.

At the moment, the polyphenol metabolome in food and clinical samples remains poorly explored despite the technological advances in chromatographic column performance and user-friendly mass spectrometers equipped with high sensitivity and resolution, fast scan rates and polarity switching modes ideally suited for the high-throughput of complex biological samples. One of the bottlenecks in the analysis of polyphenols relates to the enormous complexity of structural features present in polyphenol sub-classes and their metabolites (discussed in section 2.2). Polyphenols are usually analyzed by reversed-phase liquid chromatography (RPLC) (Álvarez-Fernández et al. 2014; Cerdá, Tomás-Barberán, and Espín 2005; Pimentel et al. 2010; Robards et al. 1999) but the comprehensive screening of polyphenols is not possible in one-single injection. Recent developments in two dimension chromatography (2 D-LCxLC) were crucial to the comprehensive profiling of polyphenol metabolome in aged wines, apples, cocoa, green tea and other drinks (Kalili et al. 2014; Montero et al. 2013; Venter et al. 2018; Willemse et al. 2015). Interestingly, the use of hydrophilic interaction liquid-chromatography (HILIC) already applied to the simultaneous separation of small and large (a)polar ionized compounds in complex biological samples (Fu et al. 2013; Reis et al. 2015; Zhao et al. 2013) together with RPLC (2D HILICxRP) holds great potential in disclosing the polyphenol metabolome signature in biological samples given the solvent compatibility between the 2 chromatographic approaches and the advantage of polarity switching acquisition modes in high resolution mass spectrometers.

Currently, consumers are opting for supplementation, reinforcement or addition of supplements of polyphenol extracts in the form of pills, capsules, or tablets as an alternative to boost the levels of circulating polyphenols. However, the regulation and legislation surrounding the health benefits of polyphenol-rich extracts and supplements commercially available is not yet conclusive. In a recent report, the EFSA was unable to identify a safe dose based on data available on the safety of green tea catechins, and asked for more research to be carried out (Younes et al. 2018). Currently, for obvious safety and ethical reasons, clinical trials with polyphenol supplement in humans are limited, and most of the knowledge on the anti-inflammatory, antithrombotic, hypoglycemic and hypocholesterolemic effects of polyphenols and their metabolites (D'Archivio et al. 2010; Zanotti et al. 2015) comes from in vitro membrane and cell models (discussed in sections 3 and 4).

Until now, *in vitro* membrane and cell models have had a pivotal role in improving our understanding on the molecular mechanisms regulating absorption, transport and permeability of ingested polyphenols and our understanding on physiological processes including oral taste perception, gastro-intestinal absorption and endothelial permeability. However, the conclusions achieved and reported in the literature have not yet translated to an improved understanding of polyphenols in in vivo processes mainly due to the poor knowledge of polyphenols physiological concentration range (discussed in section 2.2) and inadequacy of experimental in vitro conditions in model studies that are often far from real physiological in vivo conditions (discussed in sections 3.2 and 4.1). The inadequacy of experimental parameters and models used in polyphenol research were recently highlighted in an opinion article by Ávila-Gálvez, González-Sarrías, and Espín (2018) reinforcing the need to adopt a "first *in vivo* and then *in vitro*" approach to avoid the speculation of "potential effects" linking polyphenols to health (Ávila-Gálvez, González-Sarrías, and Espín 2018).

Aligned with the "first *in vivo* and then *in vitro*" approach, additional studies aimed to deepen our knowledge on the human epithelium lipidome are needed, not only to help and fine-tune the lipid composition in epithelial membrane models (Essaid et al. 2016) but particularly crucial to explore the preliminary evidences that the biological effects elicited by polyphenols appear to be triggered at Chol- and sphingolipid-rich domains (discussed in section 3.3 and 4.1). In addition to this, the various in vitro liposome and cell models have yet to include the in vivo lining by viscous mucin proteins in the oral (MUC5B and MUC7), stomachal (MUC5AC) and intestinal epithelium (MUC2) that "coat", hydrate and protect the human epithelium (McGuckin et al. 2011). The interaction of polyphenols with heavily glycosylated mucins and how this interaction affects the tight

junctions in epithelia may provide valuable clues to the overall health effects of polyphenol-rich foods to diet-related diseases.

In overview, the pursuit of dietary guidelines and the implementation of polyphenol-rich nutritional recommendations suitable for the prevention and management of diet-related diseases in an aging population would clearly benefit from the identification of diet-specific markers able to deliver a specific biological effect. The search for diet-specific markers will in turn have to take into account the variability of gut microbiota within the population (microbiome) and its evolution within the host. This aspect has remained overlooked and the relationship between diet, microbiome and diseases is only now being addressed (Clemente et al. 2012). This can only be achieved through a holistic and integrative Omic approach. At the moment, the use of Omic approaches to identify diet- and metabolic-based markers are becoming popular with the emergence of sophisticated areas of research such as FoodOmics (Capozzi and Bordoni 2013) and NutrimetabolOmics (Rangel-Huerta and Gil 2016; Ulaszewska et al. 2019). Unfortunately, these are constrained by the limited panel of commercially available synthetic metabolite standards, the improvement of commercial and open-source metabolite databases (PhenolExplorer [www.phenol-explorer.eu], FooDB [www.food.ca], and HMDB [www.hmdb.ca]) and most importantly the development of user-friendly bioinformatics tools able to handle large datasets and deliver useful information. Once this is achieved information on the basal values of circulating polyphenols metabolites, the safe and tolerable levels, the changes with age, gender, ethnicity and diet, in health and in disease which are lacking to date, is valuable in the pursuit of personalized dietary recommendations suitable for disease prevention, treatment and management contributing to a sustainable Health in an increasingly aging population.

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