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(Poly)phenols and cardiovascular diseases: Looking in to move forward

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ABSTRACT

Dietary (poly)phenol intake has been associated with a lower risk of cardiovascular mortality and new events. However, no conclusive data can be drawn from clinical trials evaluating the effects of (poly)phenols on cardiovascular risk factors. In addition, the mechanisms of action behind the beneficial association of (poly)phenol intake with cardiovascular health are not completely understood. Therefore, this perspective aimed to highlight the main methodological limitations that might explain the conflicting results obtained so far. In addition, novel insights on local and systemic effects of (poly)phenols were discussed. Finally, some critical issues to take into consideration in future studies were reported.

This more comprehensive approach could represent a strategy to deeply understand the effects of (poly)phenols on human health.

1. Introduction

(Poly)phenols are a huge family of plant-derived compounds with a similar chemical structure (based on one or more phenol rings) that differs for type and number of functional groups attached to the carbon backbone. According to the nutritional classification, (poly)phenols are classified in “flavonoids”, which include anthocyanins, flavonols, flavones, flavanones, isoflavones and flavan-3-ols, and “non-flavonoids”, i.e. phenolic acids, stilbenes, lignans, phenolic alcohols and tannins.

Dietary (poly)phenols are represented mainly by flavonoids and phenolic acids, and their mean total daily intake is ~1 g in general population.

During the last decades, an enormous amount of scientific literature has spread to support the role of (poly)phenols against chronic-degenerative diseases. Indeed, studies in cell, tissue, and animal models deeply endorsed (poly)phenol role in several pathways involved in the development of such diseases, as cell signaling pathways, antioxidant activity and modulation of metabolic and inflammatory response, among others. However, the enthusiasm for their possible cardiovascular health benefits exceeds the current evidence supporting their effects in humans.

Epidemiological studies showed that higher dietary (poly)phenol intake, particularly flavonoids, is associated to lower risk for all-causes and CVD mortality (Tresserra-Rimbau et al., 2014; Zamora-Ros et al., 2013; Wang, Ouyang, Liu, & Zhao, 2014), and new CVD events (Mendonça et al., 2019). Nevertheless, evidence from clinical trials is still lacking, at least for some cardiometabolic risk factors. (Poly)phenols seem to positively affect blood pressure, endothelial function, and some parameters related to blood glucose control (i.e. fasting glucose and insulin, or HbA1c) at least in the short-term (Giacco et al., 2019). Otherwise, less conclusive evidence is available on inflammation, body weight regulation and lipid metabolism. Furthermore, very few data are available on the effects of (poly)phenols on postprandial lipid response, an independent CVD risk factor (Giacco et al., 2019). Overall, the major flaws are related to poor-quality of study design, inadequate sample size, heterogeneity of the clinical characteristics of the participants and huge variability of (poly)phenol amount (Giacco et al., 2019). In addition, most of studies have supplemented native phenolic compounds at pharmacological concentrations (greater than usual dietary intake).

Other issues to point out are related to (poly)phenol amount and bioavailability. Indeed, few studies -both observational and intervention studies- directly assessed the real amount of dietary (poly)phenols consumed by the study population.

Moreover, it is to underline that some phenolic compounds have a low bioavailability and are poorly absorbed, at least in their native form. In fact, only 5–10% of them enter the bloodstream after being metabolized mainly in the intestine by microbiota, and in the liver, - but by no means only in these two sites - prior of their excretion in urine (Vetrani et al., 2016). Nevertheless, recent investigations focusing on the absorption, disposition, metabolism, and excretion (ADME) of (poly)phenols have highlighted some pivotal findings. Briefly, it is evident that many (poly)phenols are highly bioavailable when their

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metabolites and catabolites are included in the overall estimation of ADME (Kay, Pereira-Caro, Ludwig, Clifford, & Crozier, 2017; Ottaviani et al., 2016). Consequently, a detailed ADME of phenolic compounds in humans should take into consideration in the context of feeding trials.

More in general, after dietary intake, (poly)phenols undergo several chemical reactions (ie. hydroxylation, methylation, sulphation and glucuronidation) in the mouth, stomach, and upper intestinal epithelial cells. Phenolic compounds that are not absorbed in the small intestine pass to the colon, where they are transformed by the gut microbiota. Then, once in the portal bloodstream, phenolic metabolites reach the liver where they can be further metabolized. In addition, the enterohepatic circulation may yield to some recycling back to the small intestine through bile excretion (Del Rio, Rodriguez-Mateos, Spencer, Tognolini, Borges, & Crozier, 2013).

Therefore, it is changeling to investigate the mechanisms of (poly) phenol action *in vivo* due to the complexity of the metabolic transformations that originate phenolic metabolites and influence their bioavailability.

Several efforts have been made to overcome these methodological limitations. Firstly, Phenol-Explorer (Phenol Explorer) have collected important information about (poly)phenol retention (concentration in processed food/concentration in raw food) after food processing (cooking, freezing, homogenization, etc.) that dramatically affect (poly) phenol content in food and beverages. Thus, when the direct assessment of actual (poly)phenol amount is not feasible, Phenol Explorer might provide a more reliable information about the real amount of (poly) phenols contained in the tested food.

In addition, Phenol-Explorer helped researchers to highlight the importance of phenolic metabolites rather than dietary (poly)phenol subclasses, giving insight on how many and what compounds can exert some biological activities in the host. On the other hand, studies addressing specific *in vivo*-formed phenolic metabolites contributed to improve the knowledge on the most reliable mechanisms of action of (poly)phenols. Finally, it has become more and more apparent that dietary (poly)phenol effects on health are mediated by interaction with the gut microbiota, and by several biological process in different organs and tissues (Fig. 1).

2. Interactions between (poly)phenols and gut microbiota

A clear bi-directional relationship between (poly)phenols and gut microbiota is arising from recent studies, and the convergence of evidence from these types of research is particularly persuasive.

As a matter of fact, gut microbiota plays a pivotal role in (poly) phenol metabolism and their biological activities. Indeed, major chemical changes of phenolic carbon backbone mainly occur in the small intestine and colon, and drastically modify the native form of ingested (poly)phenols. Therefore, new formed phenolic metabolites may be largely different form their dietary precursors and, their biological activities may vary extensively from what expected. As an example, chlorogenic acid and its related compounds are some of the most represented phenolics in the human diet. Through transformations mediated by microbiota, caffeic acid is obtained and it undergoes further metabolism, producing phenylpropionic, phenylacetic, and benzoic acid derivatives that are then absorbed (Bento-Silva et al., 2019).

More recently, several studies have highlighted a dynamic relationship between (poly)phenols and gut microbiota that is mediated by gut–microbial metabolites–host interactions (Fig. 1). According to the majority of studies, some phenolic compounds exhibited an antimicrobial activity (Marin, Miguelez, Villar, & Lombo, 2015; Most, Penders, Lucchesi, Goossens, & Blaak, 2017). On the other hand, a potential prebiotic effect of (poly)phenols has been suggested by several *in vitro* and *in vivo* studies (Etxeberria et al., 2013). As for evidence in humans, a recent study (Vetrani et al., 2020) showed that a (poly) phenol-rich diet (~3 g/day) significantly increased microbial diversity that has been associated with enhanced metabolic health, as reported in three metagenomic studies (Turnbaugh et al., 2009; Cotillard et al., 2013; Le Chatelier et al., 2013). In addition, in this study (Vetrani et al., 2020), an improvement of early insulin secretion, a proxy of good blood glucose control, positively associated to a (poly)phenol-mediated increase in *Clostridium leptum* numbers (clostridial cluster IV according to Collins et al., 1994) in individuals with high cardiometabolic risk.

As for specific food sources, tea flavan-3-ols inhibited the colonization of detrimental microbial species, i.e. *Helicobacter pylori, Staphylococcus aureus, Escherichia coli, Salmonella typhimurium, Listeria monocytogenes, and Pseudomonas aeruginosa* (Duda-Chodak, Tarko, Satora, & Sroka, 2015). Conversely, the intake of (poly)phenols from fruits (mainly flavan-3-ols and anthocyanidins) yielded to an increase of *Bifidobacterium* spp., *Lactobacillus* spp., *Akkermansia muciniphila,* and *Faecalibacterium prausnitzii* (Fraga, Croft, Kennedy, & Tomás-Barberán, 2019). The clinical implications of such modifications are still unknown but this selective activity of phenolic compounds on microbial species warrants further investigations for its potential effect on health.

3. Other relevant mechanisms for health

Much attention has been placed on (poly)phenols and their antioxidant capacity *in vitro* (Ruskovska, Maksimova, & Milenkovic, 2020) and *in vivo* (Annuzzi, Bozzetto, Costabile, Giacco, Mangione, Anniballi, & Rivellese, 2014). However, the hypothesis that their beneficial effects were driven only to the reduction of oxidative process was set aside quickly. Accumulating evidence supports more local – meaning in the gastrointestinal tract - and systemic effects of phenolic compounds (Fig. 1).

Firstly, phenolic compounds may inhibit the activity of digestive enzymes (amylases and lipases) thus reducing dietary carbohydrate and fat absorption in the gut. This activity may explain the influencing effect of (poly)phenols on glucose and lipid metabolism, particularly in the postprandial period (Bladé, Arola, & Salvadó, 2010; Hanhineva et al., 2010; Williamson, 2013). In addition, it has been shown that (poly)phenols may influence lipoprotein composition by regulating important enzymes involved in the dynamic exchange of lipids between the different lipoproteins in plasma (LPL, CEPT) as well as, those related to the metabolic processes that take place in the liver (fat oxidation, lipoprotein secretion, etc.) (Bladé et al., 2010; Della Pepa et al., 2019).

On the other hand, an improvement of insulin sensitivity has been observed after the consumption of (poly)phenols, particularly with anthocyanins and flavan-3-ols (Bozzetto et al., 2015; Vetrani et al., 2017; Costabile et al., 2018). According to *in vitro* studies, this effect may be related to: (1) the reduction of β-cell stress –which might translate into β–cell preservation- and/or (2) the enhanced peroxisome proliferator-activated receptor gamma (PPARγ) expression and activated glucose transporter protein 4 (GLUT-4) -which might yield to an improvement of adipose tissue insulin sensitivity, the modulation of adipogenesis and increased glucose uptake in adipose tissue and muscles (Scazzocchio et al. 2011; Torabi and Di Marco, 2016).

Finally, an anti-obesogenic activity has been ascribed to some (poly) phenols (i.e. catechins and resveratrol). Indeed, there is evidence that they might endorse weight loss and maintenance, likely through increased oxidation in adipocytes, inhibition of lipogenesis, and increased energy expenditure (Cory, Passarelli, Szeto, Tamez, & Mattei, 2018)

4. Conclusion and future perspectives

In conclusion, to improve our knowledge on cardiovascular health benefits of (poly)phenols, future studies should take into account: (a) reliable assessment of (poly)phenol amount in food and beverages, possibly through direct quantification in foodstuff used in the trial, (b) identification of the *in-vivo* formed phenolic metabolites, (c) their bioavailability, and ((d) their mechanisms of action in different tissues, particularly those involving gut microbiota and its role in (poly)phenol

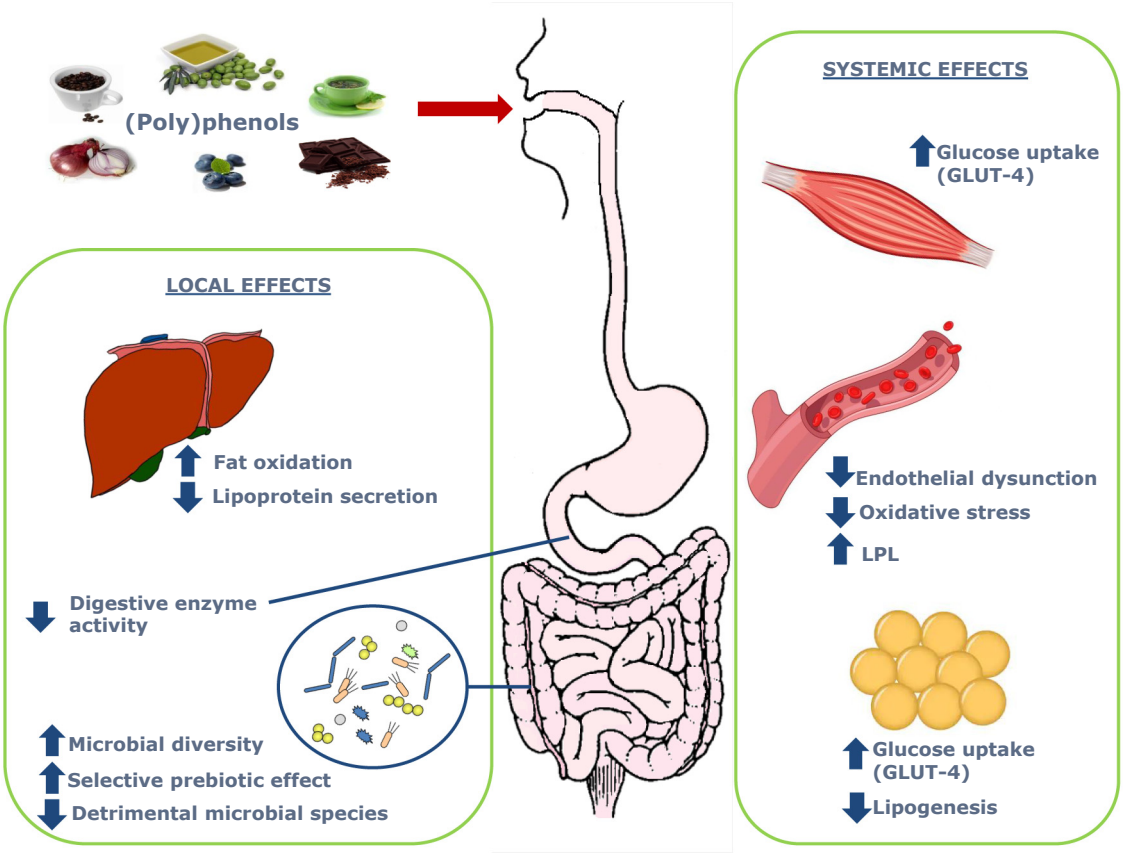

Fig. 1. Main mechanisms of action of (poly)phenols. GLUT-4: activated glucose transporter protein-4, LPL: lipoprotein lipase.

metabolism.

This comprehensive approach represents a key strategy to deeply understand the beneficial effects of (poly)phenols in relation to human health.

In addition, it is well established that other dietary components can influence (poly)phenol bioavailability (Visioli et al., 2011; Fraga et al., 2019). However, additive or synergistic interactions between (poly) phenols and these compounds, as well as negative or neutralizing effects, need more attention in future studies.

Finally, the potential prebiotic effect related to phenolic compounds warrants further investigations since it supports the possibility to specifically modulate microbiota composition. This approach might be a powerful tool in advanced "precision nutrition" strategies for preventing and managing cardiometabolic diseases.

Ethical statement

The research did not include any human subjects and animal experiments.

CRediT authorship contribution statement

Claudia Vetrani: Conceptualization, Writing - original draft, Visualization. **Giuseppina Costabile:** Writing - review & editing. **Marilena Vitale:** Writing - review & editing. **Rosalba Giacco:** Conceptualization, Writing - original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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