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Is a higher ingestion of phenolic compounds the best dietary strategy? A scientific opinion on the deleterious effects of polyphenols *in vivo*

Daniel Granato[a,*], Andrei Mocan[b,c], José S. Câmara[d,e]

[a] Food Processing and Quality, Natural Resources Institute Finland (Luke), Tietotie 2, FI-02150, Espoo, Finland
[b] Department of Pharmaceutical Botany, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 400337, Cluj-Napoca, Romania
[c] Laboratory of Chromatography, Institute of Advanced Horticulture Research of Transylvania, University of Agricultural Sciences and Veterinary Medicine, 400372, Cluj-Napoca, Romania
[d] CQM - Centro de Química da Madeira, Universidade da Madeira, Campus Universitário da Penteada, 9000-105, Funchal, Portugal
[e] Faculdade de Ciências Exactas e Engenharia, Universidade da Madeira, Campus Universitário da Penteada, 9000-105, Funchal, Portugal

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ABSTRACT

Background: Phenolic compounds have been studied for a variety number of bioactivities using *in vitro*, *ex vivo*, and *in vivo* protocols. Most of the studies dealing with phenolic compounds deal with *in vitro* antioxidant, antihypertensive, anti-inflammatory, antipyretic, antihemolytic effects in human erythrocytes, hypolipidemic, and antiproliferative activities.

Scope and approach: Companies have used the overall understanding of the beneficial effects of polyphenols to develop "functional" foods and ingredients. However, the main question that arises is still the target of warm discussions: Is the higher ingestion of phenolic compounds the best dietary strategy? Our commentary focuses on this question and we list some examples in which phenolic compounds show deleterious effects *in vivo*.

Key findings and conclusions: Two main conclusions arise: (i) any presumption of "functional effects" based on test-tube studies should be avoided as these results do not represent the real biological effect in humans; (ii) at high concentrations and in specific populations, polyphenols may have several potential adverse health effects presumably associated to their pro-oxidative capacity. All in one, the dietary supplementation containing high doses of polyphenols should be well justified in each case until a consensus is reached supported on medical, nutritional and toxicological data.

1. Introduction

Phenolic compounds are a class of non-nutritional bioactive substances found in millions of species of plants, marine organisms and microorganisms, which have been vastly investigated in the last 20 years for their functional/pharmacological effects in humans (Granato, Santos, Maciel, & Nunes, 2016). Most researches focus on the extraction optimization of these secondary metabolites in addition to their *in vitro* antioxidant, antihypertensive, anti-inflammatory, antipyretic, antihemolytic effects in human erythrocytes, hypolipidemic, and antiproliferative activities, proved by different *in vitro* and *in vivo* pharmacological studies (Chuang, Tan, Tung, & Lin, 2019; Hoskin, Xiong, Esposito, & Lila, 2019; Kim et al., 2018; Nam, Park, Oh, Jang, & Rhee, 2019; Sinrod et al., 2019; Zhang et al., 2019). Their contribution to the unique sensory and organoleptic properties such as flavor, color, astringency and taste of the fruits, vegetables and beverages has been highlighted (Gharras, 2009; Pedan, Popp, Rohn, Nyfeler, & Bongartz, 2019; Soares, Brandao, Mateus, & Freitas, 2017). Although the *in vitro* observations are of pivotal importance, they should be considered as screening studies for further investigations in more complex protocols, such as *in vivo* studies using animals or, preferably, clinical trials (Granato et al., 2018).

2. Is the dietary intake of polyphenols beneficial at high doses?

It is well known that *in vitro* data cannot be directly translated into effectiveness in humans, e.g., a result on chemical antioxidant capacity of a dark chocolate measured by the oxygen radical absorbance capacity (ORAC) or by the ferric reducing antioxidant power (FRAP) – or any other chemical index of antioxidant activity - cannot predict the quantitative antioxidant activity of human plasma. The human organism is rather complex and multiple epigenetic factors, such as age, metabolic dysfunctions and/or chronic diseases, eating habits, smoking and alcohol abuse, and intestinal microbiota composition can influence

* Corresponding author.
E-mail address: daniel.granato@luke.fi (D. Granato).

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the final "bioactivity" of a certain compound or a mixture of compounds. Therefore, any presumption of "functional effects" *in vivo* based on test-tube studies should be avoided as these results do not represent the real biological effect in humans. Finally, as well stated by Martin and Appel (2010), poor bioavailability, rapid metabolism and excretion of polyphenols are reflected in the disparity between *in vitro* and human-based studies.

Two pertinent examples on the "translation" from *in vitro* to clinical trials are reported in literature. The first example is related to chocolate, a well-known source of phenolics, which has shown "high" antioxidant activity *in vitro* (Batista et al., 2016), but results from a double-blind, randomized, placebo-controlled clinical trial indicated that the conventional consumption dose of chocolate does not improve cardiometabolic parameters in humans compared to the negative control (Dicks et al., 2018). Earlier experimental and clinical studies show a protective effect of chocolate against atherogenesis, oxidative stress, and inflammation as well as hypolipidemic and hypoglycemic effects, and modulation of blood pressure (Fernández-Murga, Tarín, García-perez, & Cano, 2011; Leyva-Soto, Chavez-Santoscoy, Lara-Jacobo, Chavez-Santoscoy, & Gonzalez-Cobian, 2018). The other example is related to an umbrella review of systematic reviews of observational and interventional studies (randomized placebo-controlled trials) based on the Grading of Recommendations, Assessment, Development and Evaluation that suggested that still there is no strong evidence for dark chocolate consumption on diabetes and cardiovascular diseases. Authors also concluded that dark chocolate should not be consumed neither with the aim to improve nor prevent metabolic diseases.

The rationale study of natural products, or any bioactive compound, should follow a sequence based on screening *in vitro* chemical and cell-based methods to assess a certain characteristic (e.g., antioxidant or inhibition of some enzymes or even cytotoxicity in normal cells), then animal studies represent a suitable approach to develop and validate markers and study any toxicological effects, in addition to assess the dose-dependence of the functional effects in a living organism (do Carmo, Pressete, Marques, Granato, & Azevedo, 2018; Ochiai, Takeuchi, Nozaki, Ishihara, & Matsuo, 2019; Yan et al., 2019). Obviously, if the polyphenolic-rich matrix is a food, such as apple, berry, tea, dark chocolate or red wine, animal-based investigations can be skipped for certain study targets, such as antioxidant and anti-inflammatory effects, as they are generally recognized as safe for human consumption (Kuebler et al., 2016). However, in most studies meant to ascertain the potential health benefits of a certain food, crude hydrophilic extracts are investigated through several *in vitro* assays (including total phenolics, flavonoids, antioxidant capacity assays, anti-inflammatory and antimicrobial effects, among others) and further chemically profiled by LC-MS (targeted or untargeted profiling) (Granato et al., 2018). While, in most of the cases the used extraction procedure is rather non-selective, the obtained bioactivity is generally ascribed to the identified phenolic compounds, laying back the fact that herbal extracts are complex mixtures and additional steps might be required for the removal of unwanted phenolics or non-phenolic substances such as waxes, fats, terpenes and chlorophylls (Naczk & Shahidi, 2004) or that non-phenolic compounds might be as well partially ascribed for the obtained high level of "total bioactivity" (Shahidi & Zhong, 2015).

The functional effects of phenolic compounds in humans as ascertained by different clinical trials range from antioxidant (Apostolidou, Adamopoulos, Lymperaki, Iliadis, & Papapreponis, 2015; Oliveras-López, Berná, Jurado-ruiz, Serrana, & Martín, 2014), anti-inflammatory (Aziz, Kim, & Cho, 2018), hypolipidemic and antihyperglycemic (Balisteiro, Araujo, Giacaglia, & Genovese, 2017; Valls et al., 2015), gut microflora modulators (Nash et al., 2018), and protective agents against type 2 diabetes (Martin, Goya, & Ramos, 2017), to decreasing the risk of cancer (Rosa, Silva, Soares, Monteiro, & Teodoro, 2016). However, although there are several reports stating the beneficial effects of polyphenols, one question still remains unanswered and is the focus of warm discussions: Is a higher ingestion of phenolic compounds the best dietary strategy? The most appropriate answer was given by Paracelsus in the 17th century "*All substances are poisons, there is none which is not a poison. It is the dose that distinguishes a poison from a remedy*". Furthermore, in the characterization of novel plant-based food matrices or in functional foods development scientists always aim to get a high recovery of phenolics after the extraction procedure, and tend to select the sample/s having the highest values of total phenolics and antioxidant activity. In most cases, this approach is supported by the fact that for several plant matrices, regarded as functional foods as well as herbal drugs, "a good quality" material is translated, for example by the pharmacopoeia monograph, in a high value of total phenolics or flavonoid content or in a certain amount of a specific phenolic compound. However, not always a high concentration of polyphenols in a food matrix is translated into a pharmacologically relevant concentration into the human body of the same compound (Granato et al., 2018). Nonetheless, understanding polyphenol interactions with other food ingredients like dietary fibers or proteins is very important because of the complex reactions that can take place during food processing and digestion. These interactions may affect bioaccessibility, as phenolics linked by covalent bounds differ in their release from the food matrix during absorption in humans (Gleichenhagen & Schieber, 2016; Quiros-Sauceda et al., 2014).

In order to exert a certain pharmacological effect a bioactive compound needs to be bioavailable. Outside of this concept, the study of the health benefits of dietary phenolics might be seen as redundant if their bioavailability is yet understood and fully elucidated. Bioavailability is a crucial step in the development of functional foods related to phenolic compounds, followed by the elucidation of the circulating metabolites leading to the mechanism of action in relation with the global biological effect (Mckay, Chen, Zampariello, & Blumberg, 2015; Rein et al., 2012). Indeed, although there is a plethora of studies reporting the *in vitro*, *in vivo* or *ex-vivo* bioactivities of polyphenols, still very little is known about the molecular mechanisms of their bioactivity, as they generally have a low oral bioavailability depending on several factors such as physicochemical stability, complex formation, food interactions, gastrointestinal absorption, hepatic and gut metabolization as well as on the composition of the digested food matrix, and the synergism and antagonism that can take place between different components (Heleno, Martins, João, Queiroz, & Ferreira, 2015; Luca et al., 2019; Rein et al., 2012). Indeed, recent studies on polyphenols bioavailability show that metabolites derived from dietary polyphenols trigger important intrinsic bioactivities that could, at least partially, explain the observed global effects on a biological system for the parent compounds (Heleno et al., 2015; Luca et al., 2019; Teng & Chen, 2019). Nonetheless, interpersonal disparateness of gut microbiota modulates differentially the bioactivity of dietary phenolics (e.g., flavanols) (Ho et al., 2019).

Indeed, it is recognized in some recent studies that, at high concentrations and in specific populations, polyphenols may have several potential adverse health effects presumably associated to their pro-oxidative capacity, which generates reactive oxygen (ROS) and nitrogen (RNS) species, which may trigger inflammation processes by the activation of transcription factors, such as nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), tumor protein (p53) and nuclear factor erythroid 2-related factor 2 (Nrf2) (Mao, Gu, Chen, Yu, & He, 2017). Therefore, there is a high association between pro-oxidative effects and inflammation, which may enhance the risk of pathophysiological processes *in vivo* (i.e., animal models). In fact, some reports have claimed that the ingestion of high doses of flavan-3-ols in *Camellia sinensis* teas trigger pro-oxidant effects in normal hepatocytes by collapsing the mitochondrial membrane potential and inducing ROS formation, thus leading to cytotoxicity (Galati, Lin, Sultan, & Brien, 2006; Mazzanti et al., 2009). In addition, high doses of polyphenols have been linked to DNA oxidative damage and overexpression of oxidative stress-relative genes. The safety (i.e., time and dose dependency) and in-depth analysis of high doses of polyphenols in different cell lines should be more

comprehensively studied.

Depending on concentration and free radical source, the same polyphenol compounds could behave either as antioxidants (in dietary physiological doses) (Xu et al., 2017) or as pro-oxidants (in large, pharmacological doses or in presence of metal ions) (de Roos & Duthie, 2015). Experimental and cell-based assays show that higher doses of antioxidants do not present improvements in antioxidant activity (Bragueto Escher et al., 2018; Escher et al., 2020; Macedo et al., 2013). Rather, as shown by Chen, Lin, Ma, Jiang, and Lan (2014), higher concentrations of genistein (up to 400 μmol/L), a typical soy isoflavone, exert pro-oxidant potential in the primary muscle cells through enhancing reactive oxygen species production in a 5-lipoxygenase-dependent manner. Additionally, higher genistein concentrations increased the intracellular content of malondialdehyde, an indicator of lipid peroxidation. These results show an imbalance in the cellular anti- and pro-oxidant system with exposure to high concentrations of genistein. At high concentrations (> 2%) caffeic acid induces the forestomach and kidney tumors in rats and mice (Hagiwara, Hirose, & Takahashi, 1991), may increase the risk of iron depletion in populations of individuals with marginal iron status (Imam, Zhang, Ma, Wang, & Wang, 2017), and may interfere with thyroid hormone biosynthesis (Elnakish et al., 2015; Kokoszko-Bilska, Stepniak, Lewinski, & Karbownik-Lewinska, 2014) in addition to interactions with synthetic drugs (Gerber, Steyn, Kotz, & Hamman, 2018).

In most cases, the administration of drugs and a high dietary intake of polyphenols (mainly seen as a dietary supplementation – capsules, powders, among others) is expected to lead to undesirable clinical consequences (Basheer & Kerem, 2015). As example, one the most representative polyphenols, resveratrol is known to act as an inhibitor or inductor of drug metabolizing enzymes as well as a modulator of transporters (Brantley, Argikar, Lin, Nagar, & Paine, 2014). CYP3A4, one of the main enzymes known to be involved in metabolizing drugs and other xenobiotics, interacts with polyphenols, which are known to alter its expression and activity (Basheer & Kerem, 2015). These interactions are highly clinically relevant especially when they target narrow therapeutic index drugs such as anticoagulants, anticancer agents, antibiotics, among others.

Another study conducted by the European Food Safety Authority (Younes et al., 2018) concluded that the regular consumption of green tea (90–300 mg/day of epigallocatechin-3-3-gallate, EGCG) is considered safe from the toxicological standpoint, but the consumption of capsules of EGCG (≥800 mg/day) have been shown to induce a significant increase of serum transaminases and bilirubin (hepatotoxicity) in treated subjects compared to control (Galati et al., 2006). Interestingly, repeated oral administration of high doses (a 6% punicalagin-containing diet) of punicalagin (one of the most important tannins from pomegranate) in rats showed the absence of any liver or kidney toxicity (Cerdá, Cerón, Tomás-Barberán, & Espín, 2003).

Galati et al. (2006) have reported that treatment of rat hepatocytes with 200 μmol/L EGCG reduced cell viability, associated with increased production of ROS and depletion of reduced glutathione (GSH). Furthermore (Yamamoto et al., 2003), showed that EGCG exhibits pro-oxidant activity, produces ROS and hydrogen peroxide, and leads to oxidative stress and *in vitro* cytotoxicity, whereas (Ishii et al., 2011) reported that EGCG causes protein carbonylation and forms covalent cysteinyl adducts with proteins. These pro-oxidant mechanisms may result in disturbance of redox homeostasis and lead to redox stress and toxicity, namely gastrointestinal toxicity, hepatotoxicity and nephrotoxicity (Galati et al., 2006; Inoue et al., 2011; Isbrucker, Edwards, Wolz, Davidovich, & Bausch, 2006; Lambert & Yang, 2003). These data clearly show that high concentrations of polyphenols, pH, presence of iron or copper ions, play an important role for polyphenols behave as pro-oxidants and toxic agents *in vivo*.

The major problem related with high doses of polyphenols is based on polyphenols rich supplements, easily available on internet or dietetic shops, which tend to provide much higher quantities (up to 100 times higher), than those typically found in polyphenols-rich foods, causing harmful effects. In addition, the polyphenols supplements may have modified bioavailability and can discourage the consumption of a "healthy" diet in favour of supplementing a poor diet. Despite several human studies that showed no toxicity of tea polyphenol preparations and that the major adverse effects associated with consumption of high doses of tea preparations are due to gastrointestinal irritation, there have been a number of recent case reports of hepatotoxicity related to the consumption of high doses of tea-based dietary supplements (10–29 mg/kg/day) (Bonkovsky, 2006; Chu et al., 2006).

A review of observational and randomized clinical trials conducted by (Bjelakovic, Nikolova, & Gluud, 2014) concluded that "antioxidant supplements do not possess preventive effects and may be harmful with unwanted consequences to humans, especially in well-nourished populations". With that in mind, it is very usual to find authors stating that a food matrix or a beverage is rich in bioactive compounds and by using one or several test-tube assays (e.g., DPPH, ABTS, ORAC, FRAP) state that the material has "a high antioxidant activity". This statement should be avoided as there is no standard to classify one matrix into "high" or "low" in antioxidant activity. Results of assays such as total phenolic, total flavonoids and antioxidant capacity should be seen at most as rapid tools used to verity or certify certain quality parameters of the investigated food matrix, as well as a chemical index in comparing similar samples.

3. Final remarks

Considering all the factors involved in human metabolism and assessing previous published results, it is obvious that more in-depth studies on the potential adverse effects of dietary phytochemicals are required in order to assess the potential toxicities and to determine their potential usefulness as disease preventive and/or treatment agents. The underlying cytotoxicity of high doses of polyphenols should be comprehensively studied using different normal cell lines to assess time and dose dependency of the deleterious effects. All in one, the dietary supplementation containing high doses of polyphenols is, at this time, questionable and should be well justified in each case until a consensus is reached using medical, nutritional and toxicological data.

Author's contributions

D. Granato conceived the idea and wrote the manuscript, while A. Mocan and J. S. Câmara helped in drafting the manuscript and revised it critically. All authors read the final version and approved its submissions.

Declaration of competing interest

The authors declare no conflict of interest.

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