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Review

Current evidence on the effect of dietary polyphenols intake on chronic diseases

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ABSTRACT

Polyphenols are secondary metabolites of plants. They comprise several antioxidant compounds and they are generally considered to be involved in the defense against human chronic diseases. During the last years, there has been growing scientific interest in their potential health benefits. In this comprehensive review, we focus on the current evidence defining the position of their dietary intake in the prevention/treatment of human chronic diseases, including prostate cancer and other types of cancer, cardiovascular diseases, diabetes mellitus and neurodegenerative diseases such as Alzheimer's and Parkinson's disease; we also discuss their ability to modulate multiple signalling transduction pathways involved in the pathophysiology of these diseases. Despite the fact that data regarding the biological functions of polyphenols can be considered exhaustive, evidence is still inadequate to support clear beneficial effects on human chronic diseases. Currently, most data suggest that a combination of phytochemicals rather than any single polyphenol is responsible for health benefit. More studies investigating the role of polyphenols in the prevention of chronic human diseases are needed, especially for evaluating factors such as gender, age, genotype, metabolism and bioavailability.

1. Introduction

Polyphenols are found ubiquitously in plants as secondary metabolites and comprise a large class of compounds classified into flavonoids, phenolic acid and its derivatives, lignans and stilbenes. They derive from phenylalanine and contain an aromatic ring with a reactive hydroxyl group. Over 8000 members have been identified to date (Fenga et al., 2016). Growing evidence from epidemiological studies, *in vivo* and *in vitro* studies, as well as clinical trials and meta-analyses suggest that high intake of polyphenols, largely present in Mediterranean diet, can reduce the risk of chronic diseases, improving human health (Fiorentini et al., 2015).

Numerous studies have attributed several biological and pharmacological activities to polyphenols, including antioxidant, anti-inflammatory, anticarcinogenic, antiviral and antiallergic effects (Bahadoran et al., 2013; D'Archivio et al., 2007; Goutzourelas et al., 2015; Leopoldini et al., 2011; Manach et al., 2004; Martin and Appel, 2009; Sahpazidou et al., 2014). Furthermore, many studies suggest an efficacy of polyphenols to prevent, minimize and possibly treat several pathologies (Carocho and Ferreira, 2013). Due to their biological actions, polyphenols may exert beneficial effects and there is increasing evidence providing a basis for considering the use of phytochemical compounds in the development of novel therapies for the treatment of human diseases. These phytotherapeutic agents are found in several foods, including spices and drinks; most studies investigate the properties of lycopene (predominantly found in tomatoes), green tea (GT; Camelia sinensis) catechins such as EGCG (the major green tea polyphenol accounting for over 50% of total polyphenols), soy (Glycine max) isoflavones (such as quercetin, genistein), CUR from turmeric (Curcuma longa), sulphoraphane, 3,3′- diindolylmethane and indole-3-

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carbinol from broccoli (*Brassica oleracea*), RES from grape skins or Japanese knotweed (Polygonum cuspidatum), pomegranate (Punica granatum) extract (POMx), Silymarin (St Mary's/milk thistle, Silybum marianum), and several types of mushrooms (reishi; Ganoderma lucidum, turkey tail; Coriolus/Trametes, shiitake; Lentinula edodes). (Diaz-Gerevini et al., 2016; Nam et al., 2016; Venigalla et al., 2016; van Die et al., 2016).

Chronic diseases such as cancer, cardiovascular diseases (CVDs), diabetes mellitus (DM) and neurodegenerative diseases (NDGDs) are characterized by slow progression, long duration and leading mortality, accounting for > 60% of death causes worldwide. According to the World Health Organization (WHO), 17 million of deaths are attributed to CVDs, followed by cancer (7.5 million), chronic respiratory diseases (4 million) and DM (1 million) (World Health Organization, 2014). The aetiology of chronic diseases involves several factors including geographical location, ethnicity, gender, age, environmental aspects such as automobile exhaust pollutants, solar ultraviolet (UV) radiation, occupational exposure to carcinogens and mutagens, bacterial/viral infection, genetic susceptibility (Gangemi et al., 2016; Lyman, 1992; Montesano and Hall, 2001) and modifiable risk factors including diet, smoking, alcohol consumption, physical activity and body mass (Costa et al., 2016; Kruk, 2007).

Chronic diseases have a lower incidence in countries where traditional nutritional habits involve the frequent intake of vegetables and fruits (Mazur and Adlercreutz, 2000). According to several reports, dietary polyphenols play a role in limiting the effect of cellular aging, when the damage is induced via metabolic production of reactive oxygen species (ROS) (Khurana et al., 2013b; Queen and Tollefsbol, 2010). Since the major benefit of these food components is their health protecting role, there is a great scientific interest for developing strategies to target numerous cell processes by consuming such components for potentially reducing the risk of chronic diseases (Blade et al., 2013; Weisburger, 2000). In this comprehensive review we focus on the current evidence supporting an association of polyphenol intake with a lower incidence of several human chronic diseases and discuss their ability to modulate multiple signalling transduction pathways involved in the pathophysiology of these diseases.

2. Materials and methods

Medline and Scopus were screened for detecting full text studies conducted on humans and published in English language during the last seven years that correlate dietary intake of polyphenols with the prevention of chronic diseases such as cancer, CVDs, DM, AD and PD. The majority of the citations were detected using the terms: “polyphenols” AND “chronic diseases” OR “cancer” OR “cardiovascular disease” OR “diabetes” OR “Alzheimer's disease” OR “Parkinson's disease”. No restrictions were applied on country of origin, ethnicity or gender. The relevance of the subject and the eligibility of all publications detected was further evaluated based on titles and abstracts. The reference lists of selected articles were further screened for relevance. The literature search results are illustrated in Fig. 1.

3. Results

3.1. Evidence for the efficacy of polyphenols against cancer

3.1.1. Prostate cancer

Prostate cancer (PCa) represents the commonest cancer in men in Europe (excluding skin cancer) (Mottet et al., 2017b), remaining globally the second commonest cancer detected in males (1.1 million diagnoses worldwide in 2012; 15% of all cancers diagnosed) (Ferlay et al., 2015). The frequency of PCa detected on autopsy is roughly similar globally (Haas et al., 2008), with a prevalence increasing by an odds ratio of 1.7 per age decade (Bell et al., 2015). Nevertheless, the incidence of clinical diagnosis varies widely (highest in Australia/New Zealand, Northern America, Northern/Western Europe; lower in Eastern/South Central Asia) (Arnold et al., 2015; Ferlay et al., 2015; Haas et al., 2008), with mortality rates varying relatively less (very low in South-Central Asia) (Ferlay et al., 2015). It has been reported that male Japanese immigrants to California develop an increased risk of PCa that approaches the risk of American men (Breslow et al., 1977).

Exposure to many environmental/exogenous factors, including specific dietary habits, has been suggested to explain these epidemiological observations, considering that these factors may be etiologically implicated in the risk of progression from latent to clinical PCa (Leitzmann and Rohrmann, 2012). Dietary factors that have been evaluated to date include (Mottet et al., 2017a):

1. Alcohol: high intake and total abstention are associated with an increased risk of PCa and PCa-specific mortality (Dickerman et al., 2016)
2. Dairy products and meat: insulin-like growth factor-I levels and high protein intake from dairy products are weakly associated with PCa (Key, 2014); no association with red or processed meat consumption exists (Bylsma and Alexander, 2015)
3. Fat: long-chain omega-3 poly-unsaturated fatty acids intake are not associated (Alexander et al., 2015) but a relation with fried foods intake may exist (Lippi and Mattiuzzi, 2015)
4. Vitamin D: Low and high concentrations are associated with increased risk, especially for high-grade disease (Kristal et al., 2014; Nyame et al., 2016)
5. Selenium/Vitamin E: no association (Lippman et al., 2009)
6. Lycopene (carotenes): a trend towards a favourable effect on PCa incidence has been reported in non-randomized controlled trial (RCT)-based meta-analyses (Chen et al., 2015). However, given the limited number of RCTs and the varying quality of existing studies, it is still impossible to define the role of lycopene (Ilic and Misso, 2012)

Based on the evidence presented above, no definitive recommendation can be currently provided for specific preventive dietary measures to reduce the risk of developing PCa, according to the European Association of Urology (EAU) guidelines; no effective dietary interventions and no food supplements have been approved for PCa prevention to date (Mottet et al., 2017a, 2017b). Nevertheless, the scientific interest for the potential chemopreventive role in PCa of various phytotherapeutic agents found in foods is increasing.

Polyphenols may play a role for PCa prevention and treatment (van Die et al., 2016; Adhami et al., 2012; Davalli et al., 2012; Henning et al., 2011; Nguyen et al., 2012; Patel, 2014). Potential mechanisms by which they exert their anti-cancer activity include proliferation inhibition, apoptosis induction, and cell cycle arrest (Athar et al., 2007; Bhuvaneswari and Nagini, 2005; Cheung et al., 2010; Cipolla et al., 2015; Faria and Calhau, 2011; Juge et al., 2007; Li et al., 2014; Mahmoud et al., 2014; Pandey and Gupta, 2009; Ren et al., 2012; Shehzad et al., 2013). They can modulate signalling pathways and affect epigenetic changes such as DNA methylation and micro RNA expression patterns (Ho et al., 2011; Lall et al., 2015).

More precisely, some polyphenols (lycopene, EGCC, soy isoflavones, indole-3-carbinol and 3,3′- diindolylmethane, CUR), have been reported to act through down-regulation of several signal transduction pathways (in androgen receptor - AR, protein kinase B -Akt, nuclear factor-κB -NF-κB, etc.) (Li et al., 2014). Sulphoraphane has been shown to exert anti-cancer activity both *in vitro* (cancer cell blockage via several mechanisms such as anti-inflammatory, anti-angiogenetic and anti-metastatic activity) and *in vivo* (inhibition of metastatization in transgenic adenocarcinoma of a mouse prostate model (Cipolla et al., 2015). Polyphenols contained in POMx have been reported to act through modulation of B-cell lymphoma 2 (Bcl-2) proteins, upregulation of p21, p27, and downregulation of the cyclin-cyclin-dependent kinase (Cdk) network (Faria and Calhau, 2011). Silymarin (silibinin)

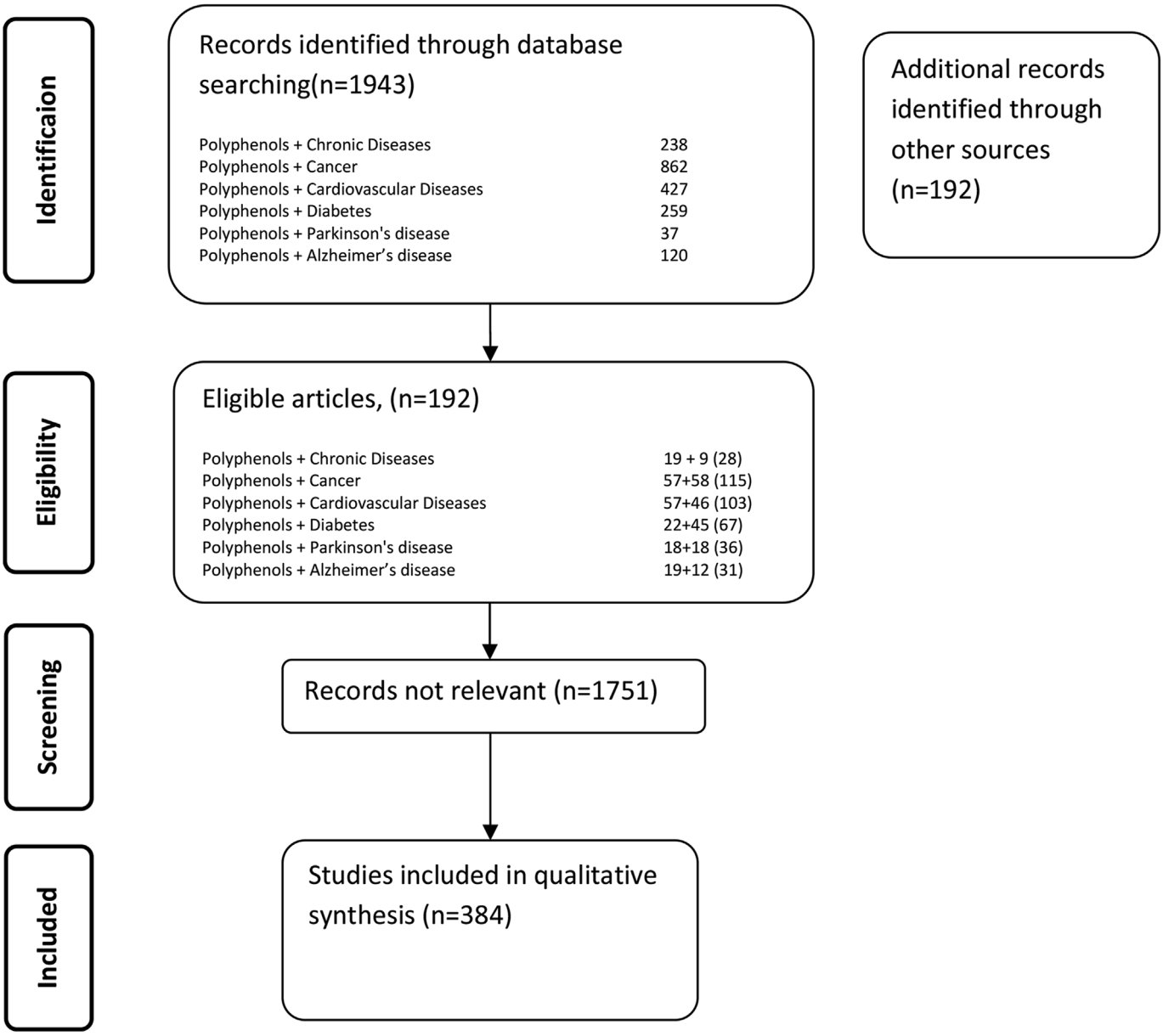

Fig. 1. Results of literature search (2010–2017).

has been reported to enhance IGF-binding protein 3 action, inhibit IGF-1-induced growth or affect AR-regulating gene levels (Cheung et al., 2010). RES has been reported to exert anti-proliferative and apoptotic effect by inhibiting NF-κB signalling pathway (Benitez et al., 2009). CUR and EGCG have been reported to arrest cell cycle both in S and G2/M phases by synergic up-regulation of p21-induced growth arrest in PCa cells (Eom et al., 2015). CUR has also been reported to effectively inhibit cell proliferation by down-regulating the expression of epidermal growth factor and erythroblastosis oncogene B receptors (Thangapazham et al., 2008). Finally, it has been shown that hydroxytyrosols and other polyphenols may inhibit the growth of human PCa cells by decreasing cyclooxygenase-2 overexpression (Adhami et al., 2007), while polysaccharides contained in several types of mushrooms may stimulate responses of the neutrophils, macrophage, T- and B-cells (Ren et al., 2012).

Nevertheless, the evidence of polyphenol-related chemopreventive effects in PCa from human studies (epidemiological studies, clinical trials and meta-analyses), most of which have evaluated GT extracts (Bettuzzi et al., 2006; Brausi et al., 2008; Gontero et al., 2015; Henning et al., 2015; Kumar et al., 2015, 2016; McLarty et al., 2009; Nguyen et al., 2012; Wang et al., 2010) is inconsistent (van Die et al., 2016). Furthermore, studies providing highest level of evidence, namely RCTs (Bettuzzi et al., 2006; Brausi et al., 2008; Cipolla et al., 2015; Gontero et al., 2015; Grainger et al., 2008; Henning et al., 2006, 2015; Kumar et al., 2015; Kumar et al., 2016; McLarty et al., 2009; Nguyen et al., 2012; Paller et al., 2013; Schroder et al., 2005; Thomas et al., 2014; Vaishampayan et al., 2007; Wang et al., 2010) and meta-analyses (Fei et al., 2014; Guo et al., 2017; Lin et al., 2014; van Die et al., 2016; Zhang et al., 2017; Zheng et al., 2011), are highly heterogeneous. Despite the fact that most RCTs provide encouraging results with few exceptions (Gontero et al., 2015; Nguyen et al., 2012), actual effects on disease, dosing, appropriate isoforms and toxicity are not well defined due to a paucity of high quality clinical trials (Taneja, 2015).

A decreased risk of borderline significance has been reported in a meta-analysis of observational studies for Asian men with highest versus none/lowest GT consumption (Zheng et al., 2011), in contrast to two subsequent analogous meta-analyses failing to detect a significant PCa decrease (Fei et al., 2014; Lin et al., 2014). Another recent meta-

analysis of epidemiological studies investigating the role of phytoestrogens concluded that some of them (daidzein, genistein and glycitein) are associated with a PCa risk reduction but others not (total isoflavones, equol, total lignans, coumestrol, secoisolariciresinol, matairesinol, enterolactone) (Zhang et al., 2017). Another meta-analysis evaluated the efficacy/safety of phytotherapeutic interventions in managing biochemically recurrent PCa (van Die et al., 2016). Pooled analysis of five RCTs showed that soy isoflavones, lycopene, sulphoraphane, POMx, and Pomi-T are safe and well tolerated (Cipolla et al., 2015; Grainger et al., 2008; Paller et al., 2013; Thomas et al., 2014; Vaishampayan et al., 2007). However, the authors stressed that high-quality studies in the field are lacking and there is limited evidence that such agents can affect Prostate-Specific Antigen (PSA) dynamics; no recommendation can therefore be made for their use in managing PCa morbidity and mortality until high-quality, fully powered studies are available (van Die et al., 2016). On the other hand a recent meta-analysis (Guo et al., 2017) based on seven observational studies and three RCTs (Bettuzzi et al., 2006; Brausi et al., 2008; Kumar et al., 2015) concluded that higher GT consumption linearly reduces PCa risk with more than 7 cups/day and that GT catechins are effective for preventing PCa.

3.1.2. Other types of cancer

Breast cancer is the leading type of cancer in women (Aiyer et al., 2012) and a role of polyphenols in breast cancer prevention has been suggested (Fenga et al., 2016). The EPIC study investigated the association between pre-diagnostic intake of polyphenols in relation to breast cancer survival, finding a positive association of lignans intake with a lower risk of death (Kyro et al., 2015). Overall the results from other studies are contradictory, highlighting differences probably due to pre- or postmenopausal stage (Dai et al., 2010; Fenga, 2016; Iwasaki et al., 2010). Although some studies show a protective effect, others indicate no clear evidence (Crew et al., 2015; Kapoor et al., 2015; Li et al., 2016; Mocanu et al., 2015; Touvier et al., 2013; Yiannakopoulou, 2014). The consumption of high amounts of bioactive dietary supplements may disrupt the series of harmful events but bioavailability, metabolism and pharmacokinetics may also bias the effects of these compounds. Furthermore, the effect of normal dietary intake of a single component may not be significant without adequate dosing (Khan et al., 2012).

An *in vitro* study reported that treatment of MDA-MB-231 and MCF-7 breast cancer cell lines transfected with human epidermal growth factor receptor 2 (HER2) both with CUR and EGCG caused inhibition of STAT3 phosphorylation with loss of breast cancer stem cell phenotype and arrest of tumour-sphere formation (Chung and Vadgama, 2015; Steelman et al., 2016). RES acts similarly: down-regulation of Bcl-2 expression and suppression of NF-κB activity in MCF-7 breast cancer cells (Pozo-Guisado et al., 2005).

Colorectal cancer is one of the most common malignant diseases in many countries (Macdonald and Wagner, 2012; Santos et al., 2013), representing the fourth cancer diagnosed in the world (Boghossian and Hawash, 2012). Traditionally linked to eating habits, recently attention focuses on the role of polyphenols in this type of cancer. Several studies have been conducted in the field with promising results supporting the protective role of polyphenols in colorectal cancer development, probably due to enhancement of colon mobility and antioxidant status (Henning et al., 2013; Jedrychowski et al., 2010; Pan et al., 2015; Vitaglione et al., 2012; Wang et al., 2013b). On the contrary, others have not detected strong evidence of a beneficial effect (Bobe et al., 2012). The anti-apoptotic effect of EGCG has been investigated in colon cancer cell lines and it has been shown that it induces death in HT-29 cells. Particularly, the growth inhibition is partially blocked by suppressing Akt, p38MAPK, cyclin D1 activator and alternative pathways, increasing phospho-ERK1/2 protein level. EGCG action has also been reported to enhance apoptosis by down-regulating the cellular levels of ErbB2, ErbB3 and EGFR in colon carcinoma cell lines (Cerezo-Guisado et al., 2015; Shimizu et al., 2005). Similarly, RES has shown an apoptotic effect/inhibition of proliferation in colon cancer cell lines (Feng et al., 2016).

The incidence of skin cancers (melanoma and non-melanoma) has been reported to be increasing during the last decades (Camp et al., 2011; Jensen et al., 2010). One of the most important risk factors of non-melanoma skin cancer development is a persistent skin exposure to solar UV radiation (Afaq and Katiyar, 2011; Candido et al., 2014). Several studies have suggested that polyphenols act as protective factors to contrast UV radiation injuries, supporting their use in skin photoprotection and the prevention of photocarcinogenesis (Clifford and DiGiovanni, 2010; Soltani-Arabshahi and Tristani-Firouzi, 2013). Furthermore, polyphenols such as sulphoraphane and GT modulate DNA methylation status and histone modification via multiple processes and point to additional areas for study of epigenetic mechanisms in skin cancer (Saha et al., 2013).

Potential chemopreventive effects of polyphenols have been reported in hepatocellular (Darvesh et al., 2012; Darvesh and Bishayee, 2013; Stagos et al., 2012), head and neck (Baumeister et al., 2012; Chang et al., 2015; Kim et al., 2010), oral (Ding et al., 2013; Varoni et al., 2015) cervical (Apostolou et al., 2013; Di Domenico et al., 2012; Zou et al., 2010), ovarian (Lee et al., 2013) and gastric cancer (Woo et al., 2014; Zulueta et al., 2015). It has been reported that CUR is able to prevent invasion and proliferation of ovarian and gastric cancer cells by shutting down ErbB2 and cyclin D1 expression and by repressing p21-activated kinase 1 (PAK1) activity, a downstream protein of EGFR (Cai et al., 2009). CUR has also been reported to activate p38 kinase, down-regulate Bcl-2 and modulate Akt signalling, inducing apoptosis in ovarian cell cancer in a p53-independent manner (Watson et al., 2010).

As far as lung and oesophageal cancer are concerned, epidemiological studies have provided unclear results for GT consumption, although evidence from *in vitro* and *in vivo* models support the hypothesis of a protective role of GT polyphenols against tumorigenesis (Khan and Mukhtar, 2015; Yuan, 2011). The effect of the combination of phytochemicals on lung cancer cells enhanced cell cycle arrest at G1 and S/G2 phases; also proteins cyclin D1 and cyclin B1 are remarkably inhibited by the flavanol EGCG (Zhou et al., 2013). CUR has been reported to inhibit proliferation and induce apoptosis in lung and pancreatic adenocarcinoma cells through the regulation of COX-2, EGFR and phosphor-ERK1/2 expression (Lev-Ari et al., 2006), while modulatory activity on the Hedgehog/glioma (HH/GLI)-associated oncogene cascade pathway has been also manifested by genistein (Zhang et al., 2012). No strong evidence emerged from studies on pancreatic cancer and bladder carcinoma although a regular intake of polyphenolic compounds seems to be a preventive factor (Chang et al., 2014; Conde et al., 2015).

The effects of polyphenols on cancer types presented in this chapter are summarized in Table 1.

3.2. Evidence for the efficacy of polyphenols against cardiovascular diseases

CVDs, including heart failure, atrial fibrillation, hypertension and vascular disease, represent the first cause of death in Western countries with an increasing prevalence during the last years (Rangel-Huerta et al., 2015). Non-modifiable risk factors include genetic predisposition, age and ethnicity; whereas other risk factors are modifiable such as high blood pressure, high cholesterol levels, obesity, lifestyle or bad eating habits (Perk et al., 2012; Stone et al., 2014). Conversely a balanced diet, rich in fruits and vegetables, has been related to a minor CVD risk (Sayegh et al., 2014). The prophylactic role of polyphenols has drawn special scientific attention in this respect (Arranz et al., 2013; Basu et al., 2010; Blumberg et al., 2015; Chiva-Blanch et al., 2013; Covas et al., 2015; Riso et al., 2013; Rodriguez-Mateos et al., 2014; Sarria et al., 2015; Tangney and Rasmussen, 2013). Overall, studies have reported a beneficial cardioprotective effect in ischemic heart disease and heart failure (Khawaja et al., 2011; Khurana et al., 2013b;

Table 1
Pathways and mechanisms of polyphenols effect on cancer.

Cancer type	Polyphenols	Signaling Pathways	Antitumoral effects
Breast	Curcumin Epigallocatechin gallate Resveratrol	NF-κB STAT3 HER2	• Inibition of STAT 3 • Inducing apoptosis and cell cycle arrest • Modulation of inflammatory pathways • Interfering microRNA expression
Colorectal	Epigallocatechin gallate Resveratrol	Erb-2 Erb-3 ERK1/2 AKT p38MAPK Cyclin D1 NF-κB	• Enhancing colon mobility and antioxidant status • Inducing apoptosis and cell cycle arrest
Others • Gastric • Ovarian • Cervical • Oesophageal • Lung • Pancreatic • Skin • Liver • Head & Neck • Bladder	Curcumin Epigallocatechin gallate Resveratrol	Erb-B2 Cyclin D1 Cyclin B1 COX-2 ERK1/2 PAK 1 Bcl-2 Akt	• Inhibition Cell proliferation, • Inducing apoptosis and cell cycle arrest • Modulation of inflammatory pathways

Kishimoto et al., 2013; Lecour and Lamont, 2011; Raj et al., 2015; Sung and Dyck, 2015; Tome-Carneiro et al., 2012, 2013; Tresserra-Rimbau et al., 2014; Wang et al., 2013a) but the evidence is neither strong nor consistent (Sayegh et al., 2014; Visioli and Davalos, 2011).

Oxidative stress and ROS are implicated in endothelial damage, progression to atherosclerosis, injury in sustained myocardial infarction and in ischemia reperfusion (Dhalla et al., 2000; Raedschelders et al., 2012; Sugamura and Keaney, 2011). Beneficial effects on vascular system could be exerted through induction of antioxidant defences (Rein et al., 2000a, 2000b; Renaud and de Lorgeril, 1992; Stein et al., 1999; Wan et al., 2001; Yochum et al., 1999), by lowering blood pressure (Desch et al., 2010; Erlund et al., 2008; Grassi et al., 2005; Hooper et al., 2008; Park et al., 2004; Taubert et al., 2007a, 2007b), improving endothelial function (Cuevas et al., 2000; Engler et al., 2004; Grassi et al., 2009; Heiss et al., 2003, 2007, 2005; Hooper et al., 2008; Papamichael et al., 2004; Schroeter et al., 2006; Wang-Polagruto et al., 2006; Widlansky et al., 2007), inhibiting platelet aggregation (Erlund et al., 2008; Keevil et al., 2000; Pearson et al., 2002; Rein et al., 2000c), oxidating low density lipoproteins (Hooper et al., 2008; Mathur et al., 2002) and reducing inflammatory responses (Mao et al., 2002; Schramm et al., 2003).

A suggested mechanism of the polyphenol action on vascular function involves the ability to modulate cell signalling pathways, mainly targeting nitric oxide (NO) produced in a reaction catalysed by endothelial nitric oxide synthase (eNOS). +with kinase signalling pathways such as the PI3-kinase/Akt pathway and intracellular Ca^{+2}, on eNOS phosphorylation and subsequent NO production (Madeira et al., 2009). Secoiridoids are the main phenols in olive oil (Servili and Montedoro, 2002). They are metabolized by hydrolysis in the gastrointestinal tract, producing tyrosol and hydroxytyrosol, respectively from ligstroside and oleuropein. Tyrosol has been implicated in elicited antioxidant defences by increasing of Akt, eNOS and SIRT1 phosphorylation against ischemic stress in rat (Vissers et al., 2002).

Many studies have investigated the possible relationship between dietary intake of phytochemicals with blood pressure reduction. Several authors have demonstrated a certain inverse correlation with diastolic pressure (Biesinger et al., 2016), or both systolic and diastolic (Brull et al., 2015; Medina-Remon et al., 2015, 2013b, 2011; Moreno-Luna et al., 2012), thus reducing one of the most harmful risk factor for CVDs (Barona et al., 2012; Ferri et al., 2015; Grassi et al., 2010; Hassellund et al., 2013; Huang et al., 2013; Hugel et al., 2016; Medina-Remon et al., 2013a; Porteri et al., 2010; Sudano et al., 2012). Conversely, others have not found significant effects (Botden et al., 2012; Hodgson et al., 2014; Ras et al., 2013). A possible effect of RES on patients with atrial fibrillation has been investigated but the evidence is unclear (Baczko and Light, 2015). Moreover, some studies highlight a possible role of polyphenols on endothelial function by decreasing arterial stiffness and platelet adhesion (Dohadwala et al., 2011; Flammer et al., 2012). Unexpectedly a study has demonstrated that RES can blunt the positive effects of physical activity on several cardiovascular parameters in aged men (Gliemann et al., 2013) and another study failed to show any positive impact on exercise performance (Trinity et al., 2014). Coffee consumption can also exert a dual effect: protective due to its antioxidant properties, harmful by increasing the lipid fraction damaging endothelium (Godos et al., 2014).

Another risk factor involved in CVDs progression is plasma lipid level; results regarding the effects induced by polyphenols on HDL- and LDL-cholesterol are controversial. There are reports on the decrease of LDL-cholesterol level under the effect of a polyphenol-rich grape extract supplement as well as a reduction of large LDL particles in obese patients receiving polyphenol supplements; but also contrary data of no correlation between grape seed extracts and LDL-cholesterol levels (Barona et al., 2012; Feringa et al., 2011; Sosnowska et al., 2017; Yubero et al., 2013; Zunino et al., 2014). There are also data from clinical trials and meta-analyses showing that cocoa flavonol consumption is associated with a significant decrease of triglycerides and an increase in HDL levels (Flammer et al., 2012; Lin et al., 2016; Sansone et al., 2015).

It has been demonstrated that phytochemical compounds, especially CUR, RES and EGCG, are implicated in modulation of MAPK signalling via the receptor for advanced glycation end products (RAGE) preventing AGE-related vascular injury and down-regulation transcription factors as NF-κB (Peppa and Raptis, 2008). *In vivo* and *in vitro* studies suggest that CUR suppresses lipopolysaccharide-induced overexpression of inflammatory mediators in vascular smooth muscle cells (Meng et al., 2013), decreases activator protein-1, NF-κB, IL-1β, IL-6, monocyte chemoattractant protein-1, and matrix metalloproteinase-9 in aortic tissue (Parodi et al., 2006); moreover it induces the activation of JAK2/STAT3 pathway (Duan et al., 2012) and inhibits PI3K/Akt/NF-κB signalling pathway (Song et al., 2013). Beside NF-κB decrease, EGCG is also able to modulate the activation of STAT-1 *in vitro* (Townsend et al., 2004). Both signalling pathways, when deactivated, play an important role in the regulation of cell response to inflammatory action. Moreover inducible nitric oxide synthase (iNOS) is inhibited by EGCG reducing oxidative damage (Cheng et al., 2016; Paquay et al., 2000). The inflammatory transcription factor NF-κB expression and the intracellular ROS levels reduction are associated to olive oil and red wine polyphenols dietary intake. These decreases are correlated to reduction of matrix metalloproteinase-9, reducing angiogenesis of cultured endothelial cells (Scoditti et al., 2012); in patients with early atherosclerosis beneficial effects of polyphenol-rich olive oil intake have been demonstrated (Widmer et al., 2013).

It is not entirely clear how polyphenols exert their protective role. They can act on endothelium, improve the effectiveness of vessel smooth muscle function and reduce oxidative stress of vascular microenvironment. Therefore, they may contribute to a good cardiovascular system function maintenance, preventing CVDs (Andriantsitohaina et al., 2012; Das and Das, 2010; Ginter and Simko, 2012; Gormaz et al., 2015; Khurana et al., 2013a; Michalska et al., 2010; Parzonko and Naruszewicz, 2016; Quinones et al., 2013; Yamagata et al., 2015; Yap et al., 2010). Signaling pathways involved in polyphenol effects on CVDs are summarized in Table 2.

Table 2
Pathways of polyphenols effect on cardiovascular diseases.

Polyphenols	Signaling pathways	Effects
Curcumin	AP-1 TLR4-MAPK/ NF-κB JAK2/STAT3 PI3K/Akt	• Suppression of aneurysmal degeneration • Reducing progression of atherosclerosis and plaque instability • Improving post-ischemic cardiac function recovery • Protective effect against CVB3-induced myocarditis
Epigallocatechin gallate	STAT-1 NF-κB MAPK RAGE	• Anti-inflammatory action
Resveratrol	NF-κB MAPK RAGE AMPK NFAT	• Reducing risk of AF, HF and pathological cardiac hypertrophy
Tyrosol	Akt e NOS SIRT1	• Enhancing antioxidant defences
Flavanols and flavonols	ET-1 NO	• No reduction in blood pressure and vasoactive endothelial markers
	PI3K Akt Ca^{+2} e-NOS	• Inducing endothelium-dependent relaxation of coronary arteries

3.3. Evidence for the efficacy of polyphenols against diabetes mellitus

DM is one of the most common metabolic diseases and it is characterized by hyperglycaemia. According to a recent WHO estimate DM will be the seventh leading cause of death in 2030 (World Health Organization, 2016). This pathology is the result of a bad regulation of glucose metabolism triggered by defective insulin secretion, insulin action, or both (American Diabetes Association, 2016); overweight and a sedentary lifestyle can promote its occurrence resulting in harmful cardiovascular complications. The disorder is divided in three categories: DM type 1 (DMT1), DM type 2 (DMT2) and gestational DM (GDM). Most patients are affected by DMT2 (Alberti and Zimmet, 1998; Lopes et al., 2016). Growing evidence supports the anti-diabetic properties of several polyphenol classes (Akaberi and Hosseinzadeh, 2016), suggesting that dietary polyphenols may represent an aid in managing DMT2 (Rasines-Perea and Teissedre, 2017).

DMT2 is associated with development of insulin resistance (IR) and pancreatic β-cell dysfunction; this pathology reduces insulin signaling, bringing to hyperglycaemia and long-term complications involving liver, kidney and heart (Mahler and Adler, 1999; Maradana et al., 2013). When the cells can no longer recompense for IR by increasing insulin production, impaired glucose tolerance occurs and exceeding mitochondrial ROS production causes intracellular oxidative stress. ROS can damage cellular macromolecules as well as inactivate or modulate the insulin receptor and its substrate function (Ceriello and Motz, 2004; Kellerer and Haring, 1995; Rudich et al., 1998). Furthermore, it can also indirectly induce tissue damage by activating a number of cellular stress-sensitive pathways, some of which are related to inflammation. These pathways include NF-κB and p38 MAPK (Evans et al., 2002); each has been identified in the cascade of events promoting the progression and complication of DM.

IR and obesity are correlated with increased incidence of cancer through enhancement in growth signaling, inflammation and perturbations in the tumour microenvironment (Hursting and Dunlap, 2012). Insulin also promotes cancer and cell growth proliferation through mTOR upregulation. Polyphenols such as EGCG, CUR and RES inhibit mTOR and may have therapeutic potential for many disorders connected to mTOR upregulation, including cancer (Zhou et al., 2010).

Several *in vitro* cell culture and *in vivo* animal studies assess the potential mechanisms of action of dietary polyphenols in the regulation of glucose metabolism and insulin sensibility (Aldebasi et al., 2013; Cai and Lin, 2009; Chao et al., 2009, 2010; Du et al., 2006a; Du et al., 2006b; Grussu et al., 2011; Guo et al., 2012; Jayaprakasam et al., 2005; Kim et al., 2016; McDougall et al., 2005; Panchal et al., 2013; Ramana and Srivastava, 2010; Sasaki et al., 2007; Tsuda et al., 2004, 2006; Yang and Kong, 2016). Numerous studies have confirmed that polyphenols improve postprandial glycaemic control and overall glucose homeostasis, in healthy subjects (Bernardo et al., 2015; Jokura et al., 2015), in people with high cardiometabolic risk (Bozzetto et al., 2015), in prediabetic subjects (Butacnum et al., 2017) and in patients with DMT2 (Rostami et al., 2015; Santangelo et al., 2016; Vitale et al., 2016); others do not confirm these results (Clegg et al., 2011).

Polyphenols can inhibit α-amylase and α-glucosidase, inhibit glucose absorption in the intestine by sodium-dependent glucose transporter 1 (SGLT1), stimulate insulin secretion and reduce hepatic glucose output, improve the endothelial dysfunction retarding vascular complications (Schini-Kerth, 2014). Polyphenols may also enhance insulin-dependent glucose uptake, alter the microbiome and have anti-inflammatory effects (Chen et al., 2016; Kim et al., 2016; Roopchand et al., 2015).

In a recent cross-sectional and prospective analysis, it was found that chocolate intake is inversely associated with DMT2 but relation may be bi-directional (Crichton et al., 2017). A prospective investigation suggested an association between some polyphenols (flavanones, flavonols and caffeic acid) and a lower DMT2 risk in short-term follow-up but not during longer follow-up (Sun et al., 2015); moreover, other authors found that a high intake of polyphenols such as flavanones, dihydroflavonols and stilbenes is associated with reduced risk of DM in elderly subjects (Tresserra-Rimbau et al., 2014). It has also been reported that rosmarinic acid may inhibit IR in skeletal muscle cells (Jayanthy et al., 2017). Recently, CUR has been considered helpful for the prevention and amelioration of DM (Maradana et al., 2013; Meng et al., 2013) since it can inhibit α-glucosidase and aldose reductase (Du et al., 2006a, 2006b).

EGCG has also been reported to maintain insulin sensitivity in a rat muscle cell line in inflammatory conditions, increasing the glucose uptake and the GLUT4 translocation by activating phosphoinositide 3-kinase (PI3K) signaling, AMPK and PI3K (Kim et al., 2016). Insulin receptor substrate 2 and AMPK signaling were induced, in pancreatic β-cells treated with EGCG with amelioration of induced glucotoxicity (Cai and Lin, 2009). GT polyphenolic extract may have inhibitory potential against α-glucosidase in DMT2 (Yang and Kong, 2016). Additionally, it has been shown that a unique dark tea produced by post-fermentation technology “Qingzhuan tea”, exhibits the greatest inhibitory effect on porcine pancreatic α-amylase activity *in vitro* (Cheng et al., 2015a). Anthocyanins and anthocyanidins present in fruits can also stimulate glucose-mediated insulin secretion from pancreatic β-cell (Jayaprakasam et al., 2005), modulate adipocytokine gene expression profiles (up-regulated adiponectin and down-regulated inflammatory cytokines) and control the phosphoactivation of AMPK (Tsuda et al., 2004, 2006). Furthermore, recent data support the positive effects induced by RES by improving glycaemic control, reducing fasting glucose and insulin in DM patients, even if there are authors arguing the absence of a significant effect on glucose level. It seems that RES, besides its antioxidant effect, is able to activate AMPK and increase glucose transported expression, thus contributing to lowering of blood glucose (Gencoglu et al., 2015; Goh et al., 2014; Sosnowska et al., 2017; Yao et al., 2015).

Collectively, the data indicate that polyphenol-rich extracts from raspberry show inhibitor activity against α-amylase; in particular, ellagitannins have been identified as inhibitory components and may influence starch digestion having potential implications for

Table 3
Signaling pathways and mechanisms of polyphenols effect on diabetes mellitus.

Polyphenols	Pathways/ Mechanisms	Effects
Curcumin	↓α-glucosidase ↓aldose reductase TLR4-MAPK/ NF-κB	• Suppressing LPS-induced overexpression of inflammatory mediators • Anti-hyperglycemic, anti-oxidant cytotoxic, immunomodulatory, anti-bacterial activity
Anthocyanins and anthocyanidins	AMPK ↑ Adiponectin	• Reducing inflammation cytokines
Ellagitannins	↓α- amylase	• Improving postprandial glycemic control
Epigallocatechin gallate	AMPK PI3K	• ↓α-glucosidase • ↓α- amylase, • ↑ Glucose absorption • Reducing glucotoxicity • Improving glucose homeostasis
Rosmarinic Acid	AMPK PGC-1α SIRT-1 TFAM	• Reducing insulin-restistance in skeletal muscle cells • ↑ Glucose uptake

postprandial glycaemic control (Grussu et al., 2011; McDougall et al., 2005). In the near future polyphenols may represent a novel pharmacological approach to manage hyperglycemia and to prevent life-threatening cardiovascular events considering their proved biological effectiveness, but further studies are needed to formulate new suitable and safe compounds (Solayman et al., 2016; Stull, 2016; Vendrame et al., 2016).

Signaling pathways and mechanisms involved in polyphenol effects on DM are summarized in Table 3.

3.4. Evidence for the efficacy of polyphenols against neurodegenerative diseases

Alzheimer's disease (AD) and Parkinson's disease (PD) are the main NDGDs of the elderly in the western world (Kalia and Lang, 2015; Prince et al., 2013). AD is a progressive and irreversible NDGD that affects the cortical neurons. In the elderly, it is the most common form of dementia and is characterized by a progressive decline of cognitive functions, memory loss, executive dysfunction and visuospatial impairment (McKhann et al., 2011). The key components of neurodegeneration in AD are the extracellular neuritic plaques composed by accumulation of abnormally misfolded Aβ peptide, the intracellular neurofibrillary tangles comprised of the microtubule-associated protein tau and the inflammatory processes (Karran et al., 2011). Current drug therapies to AD tend to stabilize or even slightly improve cognitive performance during the first year but they do not interfere with degenerative processes and eventually they do not change the course of disease (Ashford, 2015). Accumulating evidence supports an important role of dietary compounds in the development and prevention of AD (Luchsinger and Mayeux, 2004). For example, a Mediterranean-type diet has been linked to lower AD prevalence/incidence, lower rate of conversion of mild cognitive impairment to AD and improved survival of AD patients (Dardiotis et al., 2014; Lipnicki et al., 2017; Magklis et al., 2016; Scarmeas et al., 2006, 2007; Tsapanou et al., 2017).

PD is the most common progressive NDGD movement disorder (Dorsey et al., 2007). The main symptoms of PD are bradykinesia, rest tremor, muscular rigidity and postural and gait instability (Hughes et al., 1992). Clinical subtypes of PD include tremor-dominant PD, akinetic-rigid and mixed phenotype that differ in clinical presentation, course and prognosis (Jankovic et al., 1990). PD results from the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and is characterized by abnormal, insoluble, intracellular protein aggregates of α-synuclein called Lewy bodies and Lewy neuritis, in case they are located in the nerve cell body or in the axon respectively (Goedert et al., 2013).

Interventional studies have shown that a number of natural substances including cocoa flavanols, grape juice, blueberry, CUR, Ginkgo biloba, and GT catechins improve cognitive performance (Arab et al., 2016; Krikorian et al., 2010b, 2012; Matias et al., 2016). Vegetables and fruits may have an influence on memory and depression (How et al., 2008; Krikorian et al., 2010a, 2010b; Macready et al., 2009) and analyses on animal behaviour confirm that berries (blueberries and strawberries) are able to reverse age-related deficits in spatial working memory (Barros et al., 2006; Casadesus et al., 2004; Joseph et al., 1998, 1999; Ramirez et al., 2005; Williams et al., 2008), improve object recognition memory (Goyarzu et al., 2004) and modulate inhibitory fear conditioning (Barros et al., 2006; Ramirez et al., 2005). The consumption of an antioxidant beverage, containing extracts of GT leaves and apple was associated with decreased serum levels of the proinflammatory cytokines IFN-γ and TNF-α in AD patients at the initial phase of their disease (Rubio-Perez et al., 2016; Rubio-Perez and Morillas-Ruiz, 2013). Polyphenols seem to be promising therapeutic tools in combination with current approved therapies (Albarracin et al., 2012; Bhullar and Rupasinghe, 2013; Bigford and Del Rossi, 2014; Chao et al., 2012; Cheng et al., 2015b; Davinelli et al., 2012; Lin, 2011; Magalingam et al., 2015; Ngoungoure et al., 2015; Pasinetti et al., 2015; Tellone et al., 2015; Virmani et al., 2013). Some authors have shown that a regular consumption of flavonoid-rich food and drinks has been related to 50% reduction in risk of dementia (Commenges et al., 2000), protection of cognitive performance with ageing (Letenneur et al., 2007), delay in the developing of AD (Morris et al., 2006) and decreased risk of developing PD (Dai et al., 2006). Tea specific polyphenols were found to delay PD onset and to ameliorate the course of the disease (Caruana and Vassallo, 2015). Some studies highlight how EGCG acts on the dopaminergic system responsible for the characteristic degeneration of PD (Renaud et al., 2015).

Natural polyphenols may exert their neuroprotective effects by targeting multiple proteins and mechanisms. Most importantly, it has been shown that polyphenols inhibit the formation of Aβ, hyperphosphorylated tau and α-synuclein misfolded aggregates (Ho and Pasinetti, 2010; Williams and Spencer, 2012). RES was found to reduce accumulation of Aβ and have a dose-dependent action and expression of transthyretin (TTR), a carrier protein that reduces the aggregation and toxicity of amyloidogenic proteins (Bastianetto et al., 2009, 2015; Kumar et al., 2012; Pasinetti, 2012; Pasinetti et al., 2015; Tenore et al., 2016). RES and EGCG may regulate the cytotoxic effects of Aβ via phosphorylation of phosphokinase C (PKC) through the activation of α-secretase. In addition, there are reports regarding the ability of RES to inhibit cAMP phosphodiesterases 4 (PDE4), thus contributing to the reduction of ageing metabolic impairment (Maurice et al., 2014; Park et al., 2012). In a transgenic mice model EGCG has been shown to decrease Aβ concentration and reduce senile plaques *in vivo*, disassembling mature α-synuclein and amyloid-β fibrils into smaller non-toxic protein aggregates (Davis et al., 2009). CUR has been reported to be able to prevent α-synuclein aggregation in PD, and several studies support its clinical application in PD (Kim et al., 2012; Mythri and Bharath, 2012). CUR binding to the N-terminus of Aβ42 monomers constrains fibril formation, disrupts preformed fibrils and binds to plaques *in vitro* and reduces amyloid levels *in vivo* (Hugel and Jackson, 2015).

The second important mechanism mediating the beneficial effects of polyphenols on neurodegeneration is via inhibiting the production of inflammatory cytokines such as IL-1β and TNF-α (Matias et al., 2016). CUR has been shown to reduce mitochondrial dysfunction-induced oxidative stress and inflammatory responses to cytokines such as iNOS and COX-2 (Kim et al., 2012; Monroy et al., 2013). Polyphenols have been reported to protect neurons and decrease inflammation by increasing scavenging of nitrogen and ROS and by inhibiting mitochondrial stress (Sutachan et al., 2012). GT catechins can act as antioxidants,

metal chelators and modulators of intracellular signaling (Mandel et al., 2011, 2012; Ramesh et al., 2010). There is convincing evidence that GT/black tea consumption reduces PD risk, due to its polyphenolic content (Caruana and Vassallo, 2015).

Finally, polyphenols may exert various neuroprotective effects through a number of signaling pathways including the inhibition of NF-κB and MAPK pathways (Spencer et al., 2012; Venigalla et al., 2016; Williams and Spencer, 2012) and the activation of the nuclear factor-erythroid 2-related factor 2 (Nrf2)/antioxidant responsive elements (ARE) (Moosavi et al., 2016). EGCG has been reported to down-regulate the activation of ERK and NF-κB in the Aβ-injected mouse brains and subsequently suppress β- and γ-secretase activities inhibiting the β-site amyloid precursor protein leading to amelioration of cognitive dysfunction (Lee et al., 2009). Activation of Nrf2 pathway by polyphenols results in upregulation of detoxification enzymes such as hemeoxygenase-1, which can explain their neurotrophic activity (Moosavi et al., 2016).

The role of polyphenols in neurodegeneration has been investigated in a number of studies suggesting that polyphenols may exert novel beneficial effects in preventing and improving NDGDs. However, further studies are needed to give additional insight into the specific mechanisms by which polyphenols exert their potential neuroprotective actions. Particularly a better comprehension of their role on signaling pathways is important in order to develop more effective drugs for the management of these diseases. Signaling pathways involved in polyphenol effects on AD and PD are summarized in Table 4.

3.5. Evidence for the efficacy of polyphenols against other chronic diseases

Particular attention is paid to the effect that polyphenols have on allergic diseases, particularly atopic eczema, food allergy and asthma. Some studies show that dietary polyphenols can prevent the onset of allergic diseases. Polyphenols can activate T-helper 2 cells, resulting in attenuation of allergic symptomatology. Moreover, T-regulatory cells may represent the target of polyphenol activity. The anti-inflammatory role played by these substances could be based on the activation of immune cells of the skin interacting with proteins responsible of the allergic sensitization process and with mast cells, so as to inhibit the release of mediators and reduce the symptoms (Akiyama et al., 2014; Magrone and Jirillo, 2012; Singh et al., 2011). Some authors have reviewed the role of polyphenols in the treatment of major depression, because they may act modulating the monoaminergic neurotransmission in the brain exerting antidepressant functions (Pathak et al., 2013). Farzaei et al. suggest that a significant intake of polyphenols through the diet or as supplements to conventional therapy could be helpful in the treatment of peptic ulcer (Farzaei et al., 2015a) and in the management of the inflammatory bowel diseases decreasing the levels of inflammatory cytokines, stimulating antioxidant processes and modulating signaling pathways (Farzaei et al., 2015b).

4. The issue of inter-individual variability in response after consumption of plant food bioactive compounds

Numerous human intervention studies investigating the health effects of dietary polyphenols have revealed important interindividual variability in the response.

An aspect to consider is the concentration of the bioactive compounds present in the foods eaten by study subjects. Specific polyphenol content is often unknown because of lack of titration, but it is also extremely variable due to food processing or storage, seasonal effects, climate, variety.

A limitation of many epidemiological studies is assessment of dietary exposure; it is usually based on diaries or questionnaires, which represent a significant source of error. To provide a more reliable assessment, some products of polyphenol metabolism have been recently suggested as biomarkers of polyphenol intake, but they are still far from validation. Indeed, their bioavailability presents substantial differences between specific compounds and there is also great interindividual variability in their kinetics after ingestion. Polyphenol glycosides can be hydrolyzed by saliva in the oral cavity, although most reach the small; here they are hydrolyzed by enzymes located in the brush border of epithelial cells (lactase phloridzin hydrolase) or in the cytosol (β-glucosidase) with consequent release of the aglycone, and thereafter conjugated before entering the systemic circulation and/or being excreted. A substantial quota of both metabolites and parent compounds, including conjugates with sugar moieties resistant to enzymatic cleavage, reach the colon, where resident microflora determines further hydrolization generating low molecular weight molecules, which are easily absorbed; nevertheless, a number of small phenolic acid and aromatic catabolites are excreted, in amounts largely exceeding those absorbed in the small bowel. Some classes of polyphenols, as anthocyanins and flavones, are characterized by very scarce absorption and biotransformation rate. Genes and enzyme polymorphisms can influence the metabolism of compounds; for example caffeine is usually metabolized by CYP1A2 and subjects with the variant CYP1A2*1F have a slower metabolism; polymorphism of CYP7A1, cathecol-*O*-methyltransferase (COMT) or apolipoprotein E (APOE) genes may add between-subject variability in response (Del Rio et al., 2013; Rodriguez-Mateos et al., 2014; Manach et al., 2017).

Recent advances have focused on the effects of gut microbiota on polyphenol uptake and efficacy, as well as on how polyphenols can reciprocally affect the composition and activity of microbiota. Microbial status of the intestine seems to have great relevance for the individual response to these compounds, endowing each subject with a specific metabotype. A common example is the biotransformation of some isoflavones, lignans and ellagitannines into equol, suggested to have higher efficacy than the parent compound; only ~30% of Western population and ~60% of Asian subjects can produce equol and have more beneficial health effects from soy consumption, due to the presence of specific bacteria in the gut (Tomás-Barberán et al., 2014).

Another factor to consider is represented by gender. For example

Table 4
Pathways of the effects of polyphenols on Alzheimer's disease and Parkinson's disease.

Neurodegenerative diseases	Polyphenols	Signaling pathways	Effects
Alzheimer's disease	Epigallocatechin gallate Curcumin Resveratrol	SIRT1 NF-κB eNOS MAPK's HSP	• Decreasing risk of age-associated neurological dysfunction • Chelate metal ions • Neuroprotective effects
Parkinson's disease	Epigallocatechin gallate	ERK NF-κB	• Suppresses β- and γ-secretases activities
	Curcumin	NF-κB	• Attenuation of mitochondrial dysfunction-induced oxidative stress and inflammatory responses to inflammatory cytokines, COX-2 and nitric oxide synthase (iNOS)

sex hormones regulate UDP-glucuronosyltransferase isoenzyme expression profiles affecting resveratrol glucuronidation. (Manach et al., 2017). Probably other factors can have a role in the mechanism by which polyphenols are conversed into active compounds, such as age, health and metabolic status, but to date evidence is still lacking to assert with sureness. It is necessary to design trials with adequate statistical power with subject stratification based on factors influencing individual response, assessing qualitatively and quantitatively that specific active compounds reach their target tissue in sufficient time and concentration, with appropriate control.

5. Conclusions

Several studies support the perception that a polyphenol-rich diet may directly benefit human health and be associated with reduced chronic diseases risk thereby promoting optimal aging. Research has been directed towards the potential benefits of polyphenols on cancer, with particular attention to PCa, while studies on other cancer types are fewer. The most studied compounds are EGCG, RES and CUR, abundant in the Mediterranean diet that exert antioxidant, antiproliferative and apoptotic effects. Polyphenols may play an important role in preventing/treating cancer but further studies are needed to support this notion. The protective role of polyphenols on CVDs is not entirely clear. They can act on endothelium, improve the effectiveness of vessel smooth muscle function and reduce oxidative stress of vascular microenvironment. Therefore, they may contribute to a good cardiovascular system function maintenance preventing CVDs. Studies have also shown that polyphenols can act on glucose homeostasis, supporting the hypothesis of their use in association with standard therapies. In the near future they may represent a novel pharmacological approach to manage hyperglycemia and prevent life-threatening cardiovascular events considering their proved biological effectiveness but more studies are needed to formulate new suitable and safe compounds. Finally, polyphenols may have a beneficial effect in patients with NDGDs such as AD and PD. However, more studies are needed to give additional insight into the specific mechanisms by which polyphenols exert their potential neuroprotective actions, particularly a better comprehension of their role on signaling pathways is important in order to develop more effective drugs for management of these diseases.

Despite the fact that data for the biological functions of polyphenols are exhaustive, evidence is still inadequate to support clear effects on human health. The main weaknesses of the studies conducted so far are the inaccurate concentration of polyphenols in the tested food or drinks, the poor awareness about their absorption and metabolism, and to assess which specific compound is responsible of a specific action, since they contain several classes of polyphenols. Therefore, most data suggest at present that a combination of phytochemicals rather than any single polyphenol is responsible for a health benefit.

There is a number of factors, such as gender, age, genotype, metabolism and bioavailability, potentially inducing interindividual differences in response; e.g., polyphenol bioavailability and efficacy may be greatly influenced by gut microbiota (Cardona et al., 2013 #1). Therefore more studies investigating the real role of polyphenols in the prevention of chronic human diseases in relation to these variables are needed.

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