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COMMENTARY

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The role of dietary polyphenols in the control of chronic noncommunicable diseases

Yasmany Armas Díaz[1] | Maria Soledad Ferreiro Cotorruelo[2] | Maurizio Battino[1,3,4]

[1]Faculty of Medicine, Department of Clinical Sciences, Polytechnic University of Marche, Ancona, Italy

[2]Direzione Medica Ospedaliera, Azienda Ospedaliera-Universitaria delle Marche, Ancona, Italy

[3]International Joint Research Laboratory of Intelligent Agriculture and Agri-products Processing, Jiangsu University, Zhenjiang, China

[4]Research Group on Food, Nutritional Biochemistry and Health, Universidad Europea del Atlantico, Santander, Spain

Correspondence
Maurizio Battino, Facolta di Medicina, Dipartimento di Scienze Cliniche Specialistiche, Universita Politecnica delle Marche, Ancona 60131, Italy.
Email: m.a.battino@univpm.it

Abstract

Noncommunicable chronic diseases (NCDs) are among the leading causes of death and disability worldwide. The most common NCDs are cancer, obesity, cardiovascular diseases, and diabetes. Nowadays, they represent one of the greatest challenges health systems face worldwide. The increase in the consumption of polyphenol-rich foods could contribute to the reduction of these pathologies, due to their antioxidant, anti-inflammatory, anticancer, immunomodulatory, and cardiovascular protective properties, among others. This review aims to highlight some studies carried out in recent years to enhance the possible benefits of a diet rich in polyphenols in the prevention or treatment of NCDs.

KEYWORDS
anti-cancer, anti-diabetic, anti-obesity, cardioprotective, chronic noncommunicable diseases, polyphenols

1 | INTRODUCTION

Polyphenols are natural compounds that can be found in fruits, vegetables, cereals, and beverages. The production of these in plants is mainly due to exposure to different types of stress or infections, so they can also be considered secondary metabolites (Abbas et al., 2017).

Polyphenolic compounds are grouped into four main groups, based on their chemical structure, including flavonoids, stilbenes, lignans, and phenolic acids (Figure 1). They are found in abundance in foods such as red grapes, berries, coffee, tea, cereal grains, citrus fruits, soybeans, legumes, and apples, among others. The most studied polyphenols are anthocyanins, ellagitannins, quercetin, resveratrol, and curcumin (Tsao, 2010).

A number of studies at cellular, preclinical, and clinical level have demonstrated the possible biological activity attributed to polyphenols. Anti-inflammatory, immunomodulatory, antioxidant, cardiovascular protective, anticancer, and antimicrobial are some of the properties exerted by these compounds (Figure 1). A short revision on PubMed was conducted to highlight, once again, the positive role of polyphenols in the prevention or treatment of Noncommunicable chronic diseases (NCDs).

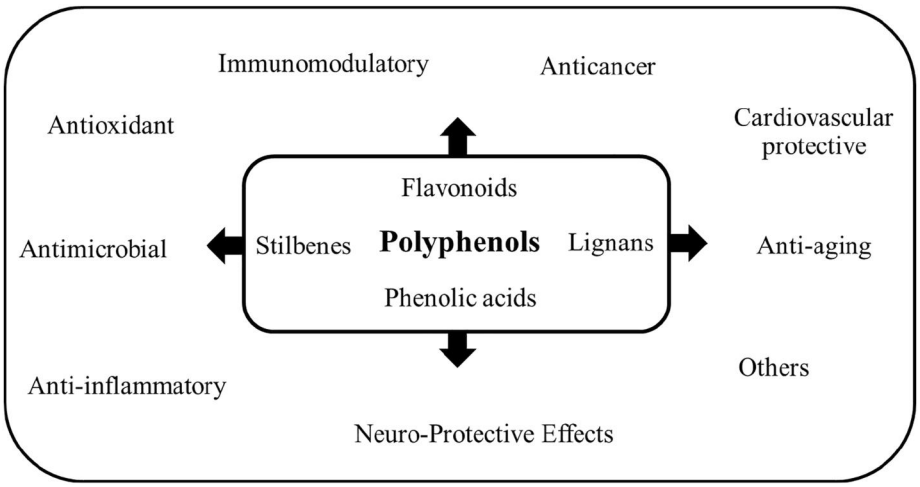

FIGURE 1 Polyphenols classification and health beneficial effects.

2 | CARDIOPROTECTIVE EFFECT

Dietary choice plays a central role in the development of cardiovascular diseases (CVD), and their potential mechanisms of action are diverse. The positive effect of polyphenols on CVD is mainly related with their possibility of improving lipid metabolism, decreasing inflammatory signaling, and helping in the regeneration of vascular endothelium. In addition, they reduce the oxidative stress and have a positive effect on survival signaling, calcium homeostasis, and sirtuin (SIRT) activity (Kiyimba et al., 2023; Torres-Fuentes et al., 2022).

Plenty laboratories have focused their effort to elucidate the role of polyphenol extracts or isolated compounds on CVD. Regarding this, the mean systolic and diastolic blood pressure was significantly lower in patients with a diet rich in polyphenols in a study carried out in Italy (Vitale et al., 2018). Ferguson et al. (2022) assayed the effects of a polyphenol-rich dietary supplement containing *Pinus massoniana* bark extract (PMBE) on systolic (SBP) and diastolic blood pressure in healthy Australian adults. SBP reduced significantly in individuals with moderately high SBP at the baseline following 12 weeks PMBE supplementation. The lowering of blood pressure was associated mainly to the fact that polyphenols can decrease the expression of nuclear factor-kB (NF-κB), improving enzymatic activities of catalase, glutathione peroxidase, and superoxide dismutase and activating the redox-sensitive phosphoinositide 3-kinase/Akt pathway (Davinelli & Scapagnini, 2016).

On the other hand, to get deeper on how polyphenols can reduce the incidence of CVD, some studies have been conducted using isolated compounds. For instance, after several studies, it is proposed that flavonoids can specifically act as signaling molecules. This effect seems to be related with the fact that they can interact with some specific cellular receptors or proteins that are involved in regulatory pathways, resulting in physiological responses or regulation of gene expression. These compounds have also been related to the regulation of nitric oxide (NO) levels in the vascular endothelium through the inhibition of superoxide production. These aspects demonstrate their positive action on endothelial function and the regulation of vasodilator processes associated with blood flow (Galiniak et al., 2019; Godos et al., 2019; Zhao et al., 2023).

Furthermore, other clinical and laboratory investigations have confirmed the possible positive benefits of some flavonoids in the regulation of blood pressure and endothelial function (Qian et al., 2017). Administration of cocoa flavanol significantly reduced CVD death by 27% in US healthy adults (Sesso et al., 2022).

Evidence from meta-analyses suggests that anthocyanin-rich foods like berries can improve endothelial function, blood pressure, and arterial stiffness, decrease fasting and postprandial glucose levels and reduce LDL cholesterol (Fairlie-Jones et al., 2017; Giampieri et al., 2023; LiPing et al., 2017; Wood et al., 2019).

Atherosclerotic plaque formation is the key step that underlies cardiometabolic diseases. Several studies have showed that polyphenols treatment reduces atherosclerotic plaque formation (Clark et al., 2022). For instance, gallic acid (GA), a phenolic acid abundant in blackberries, reduced atherosclerosis in male but not in female $ApoE^{-/-}$ mice. Specifically, GA treatment in male mice restored microbiome dysbiosis and reduced serum IL3 and IL12 levels and spleen weight (Clark et al., 2022).

Another effect showed by polyphenols involved the angiotensin II (Ang II) signaling. Activation of Ang II is linked to the onset and progression of CVDs. Polyphenols extract from berries attenuated Ang II-induced senescence through a Nox1-dependent mechanism in vascular smooth muscle cells (Feresin et al., 2016).

Other class of polyphenols that have been extensively studied are stilbenes, in particular, resveratrol. The last one, present in red wine, grapes, and nuts, has also been reported to possess cardioprotective activity, mainly attributed to its anti-inflammatory properties. In vitro and in vivo studies have shown that it can inhibit the enzyme cyclooxygenase, inactivate the gamma receptor, and induce endothelial NO synthase production (Galiniak et al., 2019). In addition, it can also inhibit the NF-κB pathway counteracting the overexpression of the vascular and intracellular

adhesion molecules (VCAM1 and ICAM1) in endothelial cells (Deng et al., 2011).

Taking in account the information above, it is notable that the development of CVD is influenced by dietary behavior. Lifestyle is an important risk factor for the development of CVD. Due to the fact that treatment available for CVD can cause side effects, the development of safer therapeutics is necessary, and the intake food rich in polyphenols can be one of them. In summary, foods rich in polyphenols and their isolated bioactive compounds may be effective in reducing cardiometabolic risks and improving lifespan. Important to notice is that effects on clinical cardiovascular events are untested, so more research is needed to understand the mechanism and specific plants' phytochemicals responsible for treating CVD.

3 | ANTICANCER ACTIVITY

The anticancer effect of polyphenols is largely attributed to the possible dynamic regulation of cell death programming pathways, such as apoptosis and autophagy. They also inhibit cell proliferation, interrupting the cell cycle. The anti-inflammatory properties associated with those also favor the inhibition of cancer progression or delay its appearance (Patra et al., 2021; Sharma et al., 2018). Studies have shown the direct participation of polyphenols in the control of the expression of oncogenes and the promotion of tumor suppressor genes for the subsequent inhibition of cancer progression (Patra et al., 2021).

It is well-known that polyphenols may be able to modulate cytokine and chemokine production and immune cell activation. These properties justify their positive action in the chemoprevention, the cytotoxic action against cancer cells, and the induction of greater sensitization to chemoradiotherapies (Mileo et al., 2019). The positive effect of polyphenols has been shown in a plenty number of cancer cells such as colorectal, lung, breast, and ovarian, among others.

The cultivation of polyphenols extracted from Manuka honey on human colon adenocarcinoma (HCT-116) and colon metastasis (LoVo) cell lines demonstrated strong inhibition on cell growth by inducing apoptosis through the upregulation of p53, cleaved-PARP and caspase-3, and the activation of caspase-9 and caspase-8. Also, the treatment caused the arrest in the cell cycle and the reduction of proliferation in a dose-dependent manner (Afrin et al., 2018).

Targeting the metabolic pathways of cancer stem cells (CSCs) could be a possible treatment to increase the survival rate of patients affected by cancer. The application of an extract of Manuka honey polyphenols reduced the entire culture of spheroids deriving from the HCT-116 cell line. The treatment also affected the morphological parameters and induced apoptosis and intracellular accumulation of ROS. In addition, the self-renewal capacity of these cells was affected (Cianciosi et al., 2020).

The application of a strawberry extract rich in polyphenols reduced the survival of the aggressive breast cancer cell (A17), affecting their migration, adhesion, invasion, and the cell cycle. This positive activity was also shown in the female FVB/N mice assay (Amatori et al., 2016). On the other hand, adoption of a Mediterranean diet by a population of Italian women tended to decrease by 30%–50% the incidence of breast cancer (Villarini et al., 2016). Giampieri et al. (2019) and Greco et al. (2023) suggested that strawberry polyphenols could be used in the development of therapeutic and/or preventive supplements for uterine leiomyomas.

Gynecological cancers development has been shown affected by polyphenols treatments. Regarding this topic, El-Kott et al. (2020) demonstrated that kaempferol promote cell apoptosis in A2780 ovarian cancer cells by triggering ER stress-mediated cytotoxic autophagy. The treatment also caused inhibition of the PI3K/Akt signaling pathway, which seems to be the way kaempferol enhances the sensitivity of ovarian cancer cells to chemotherapy.

Kaempferol also showed chemotherapeutic efficacy against nonsmall cell lung cancer (A549 and NCIH460 cell lines). This flavonoid hampered the Nrf2 signaling pathway which induced intracellular accumulation of ROS. Also, it inhibited the proliferation and affected the cell cycle. Taken together, kaempferol induced apoptosis and inhibited the proliferation of these cancer cell lines (Fouzder et al., 2021).

Curcumin also has well-known exerting healing properties and antitumor activity. Its action in controlling cancer development is mainly due to its activities by modulating various cellular processes, including apoptosis, angiogenesis, autophagy, metastasis, and epithelial-mesenchymal transition. Recently, its therapeutic effects have been attributed to alterations of noncoding RNAs, such as circHN1, circ-PRKCA, and circPLEKHM3 (Si et al., 2023; Sun & Fang, 2021; Wu et al., 2022; Xu et al., 2021).

As happened with others NCDs, polyphenols extracted from tea have been studied extensively in cancer treatments. For instance, in Chandrani Fouzder squamous cell carcinoma (KYSE 150), epigallocatechin gallate (EGCG) treatment activated methylation silencing genes and inhibited DNA methyltransferase activity (Ding et al., 2020).

The development of cancer is a microevolutionary and multistage procedure. One of the ways to decrease its incidence or improve life quality of people affected could be the intake of food rich in bioactive compounds, specifically polyphenols. Polyphenols provide a potentially beneficial health-promoting effect by decreasing the growth and development of cancer cells and chemoresistance. Some of these have been well studied, but more research studies have to be conducted to understand the precise molecular basis of the disease and to develop more efficient therapeutic options. Even though this paper shows few results about in vivo studies, several of these have been conducted in animal and human models, but still the information is not enough to be sure about the incidence of polyphenols in the human body.

4 | ANTI-OBESITY EFFECT

The proper lipid metabolism pathway is essential for the prevention of several chronic metabolic diseases such as obesity. Epidemiological evidence suggests the positive effect of polyphenols found in the diet, on overweight and obesity development (Chen et al., 2022).

The AMPK signaling pathway has been widely studied to target lipid metabolism. Regarding this, Wang et al. (2014) reported that polyphenols extracted from tea, curcumin, and resveratrol activated AMPK; therefore, accumulation of fat in adipocytes was diminished. In addition, they noticed the downregulation of some adipogenic genes, such as stearoyl Co-A desaturase-1 and fatty acid synthase. Other studies showed that the application of a strawberry extract in liver cancer cells decreased levels of total cholesterol, LDL, and triglycerides and stimulated the p-AMPK/AMPK expression (Forbes-Hernández et al., 2017). Recently, treatment of a murine 3T3-L1 fibroblast cell line with a mixture of polyphenols and micronutrients reduced lipid accumulation, and this effect was mediated via activation of the AMPK signaling pathway (Pacifici et al., 2023).

Epidemiological studies have shown that tea polyphenols could induce the reduction of waist circumference and body mass index (BMI) (Hiroki T et al., 2017). Similar results were reported by Grosso et al. (2016) where BMI, waist circumference, blood pressure, and triglycerides were significantly lower among people with a high intake of polyphenol-rich foods (Grosso et al., 2016). Polyphenols extracted from berry fruits showed a positive effect on the process related with the dissipation of energy through the production of heat by improving mitochondrial function and the biogenesis of brown adipose tissue (Jiang et al., 2021). Batista-Jorge et al. (2020) conducted a study where resveratrol was orally administrated to obese patients. After 12 weeks of treatment, HDL levels increased, triglycerides decreased 36%, and total cholesterol and VLDL improved.

A double-blind, placebo-controlled, randomized trial with 35 adults with obesity was carried out by Jamar et al. (2020). After 6 weeks of juçara pulp administration, body fat was reduced and HDL increased. Romain et al. (2021) got similar results when they administrated a pull of polyphenols extracted from a Mediterranean diet to overweight and obese but otherwise healthy individuals. Body fat mass decreased and health-related quality of life improved significantly. People with intellectual disabilities seem to be more susceptible to obesity issues. Regarding this matter, Xicota et al. (2020) studied the effect of encapsulated green tea extract, mainly EGCG, on body weight in young Down syndrome. The main results were lower body weight, less increase in BMI, and decrease in plasma lipid concentrations in the treated group compared with placebo.

Finally, in postmenopausal women with normal weight, it was found that the risk of being overweight and obese decreased 35% and 88%, respectively, for women with higher intakes of wine, relative to nondrinkers (Thomson et al., 2012).

To resume, the incidence of overweight and obesity is climbing worldwide at exponential levels which has caused negative effects on human health systems and economic development. Due to these issues, many efforts have been put to elucidate the main metabolic pathways that can regulate the progress of this pathology. In this sense, researchers have looked into the potentials of natural products such as fresh vegetables and fruits for resolving obesity due to their high efficiencies and few undesirable outcomes. Important to notice is that nutrition by itself is not enough to burn out this problem, but it is one of the most important solutions.

5 | ANTIDIABETIC EFFECT

Lifestyle and dietary habit changes have cost a high prevalence of diabetes in recent decades. Fruits and vegetables are a good source of bioactive compounds highly recommended in the medical nutrition therapy to prevent or reduce the incidence of type 2 diabetes mellitus (T2DM). During last years, many groups have focused their work on the role of polyphenols in the development of this disease.

As it is well-known, mTORC1 hyperactivation is a key event in the progression of T2DM (García-Aguilar & Guillén, 2022). Several polyphenols, such as resveratrol, curcumin, and EGCG, have been related with the downregulation of mTORC1 through AMPK-dependent and AMPK-independent mechanisms being essential in the survival of pancreatic β cells (García-Aguilar et al., 2021). Furthermore, the administration of curcumin to male rats fed with high-fat diet and streptozotocin for 12 weeks prevented the liver damage induced by hyperglycemia and hyperlipidemia, mainly due to their antiapoptotic and antioxidant activity (Xia et al., 2020).

Also recently, García-Díez et al. (2022) found that epicatechin (EC) was able to decrease lipid accumulation and glucose absorption through AKT and AMPK pathway activation in cardiac H9c2 cells. In addition, the coincubation increased insulin receptor levels and expression of the glucose transporter GLUT-4.

Human gut microbiota are also suggested to be involved in T2DM development, and some authors have found positive effect on the interaction between polyphenols and microbiota. In this sense, it is proposed that phenolic compounds could affect the release of intestinal hormones and the composition of the intestinal microbiota, which, in turn, are directly or indirectly involved in the regulation of metabolic homeostasis (Wang et al., 2021). On the other hand, the digestion of carbohydrates in the small intestine can be reduced by some polyphenols through the lowering of glucose absorption by inhibition of GLUTs, the activity of related enzymes, and enhancing the uptake of glucose by promoting the translocation of GLUTs to the plasma membrane in tissue cells (Chen et al., 2022).

A wide range of human intervention trials and preclinical studies have also shown the possible antidiabetic properties of polyphenols, but evidence is still limited and inconsistent (Menezes et al., 2022). For instance, prospective analysis in the context of the PREDIMED-Plus trial conducted by Menezes et al. (2022) showed that a diet with higher polyphenols lowered the levels of glucose and HbA1c after 1 year in a senior population with T2DM or are at high risk of developing T2DM. In another study carried out by Grabež et al. (2022), they observed that polyphenols extracted from pomegranate peel decreased oxidative stress biomarkers such as O^{-2}, NO^{-2}, TBARS, inflammatory factors (IL-6, TNF-α, hsCRP), and homocysteine in overweight patients with T2DM. Besides, this treatment also increased total antioxidant capacity.

Few years ago, Shoji et al. (2017) also observed that the intake of polyphenols extracted from apples, by the Japanese population between 30 and 60 years, significantly contributed to glucose tolerance by the body. Furthermore, a study conducted in a Polish population between 45 and 69 years old found that a higher intake of a variety

of polyphenols could lower the risk of developing T2DM (Grosso et al., 2017). The main reason attributed to this behavior was the action of flavonoids, which are thought to regulate the biological pathways related to the development of T2DM, by improving endothelial function (Munir et al., 2013).

Even though a lot of effort has to be put to clarify the positive effect of polyphenols in the prevention and treatment of DMT2, it can be concluded that dietary polyphenols might be a good choice to maintain and protect pancreatic beta cells, prolonging its lifespan and avoiding the occurrence of diabetes.

Several years ago, the positive effect of polyphenols in the development and treatment of NCDs was associated mainly to their antioxidant and radical scavenger activity. However, nowadays, it is well stablished that they also eject their action through the up/

TABLE 1 Resume of different ways by which polyphenol-rich extract or isolated compounds exert their positive effect on prevention or treatment of NCDs.

Cardioprotective	Polyphenol-rich extract	Lowering blood pressure	Szczepańska et al. (2022), Haş et al. (2023)
		Improvement of endothelial function	
		Improvement of the lipid profile	
		Reduction of oxidative stress and inflammation	
		Antithrombotic effect	
Lipid metabolism regulation	Polyphenols	Improvements in vascular function through antioxidative and anti-inflammatory properties	Yaskolka Meir and Tsaban (2022), Romain et al. (2021)
		Reduction of lipid peroxidation and adipose tissue lipolysis	Chen et al. (2022)
		Increasing muscle mitochondrial respiration, energy consumption, and fat oxidation	Jiang et al. (2021)
	Stilbenes and flavonoids	Increase of α-diversity of gut microbiome which may mediate the reduction of BMI	Mompeo et al. (2020), Le Roy et al. (2020)
Antidiabetic	Anthocyanin	Improve postprandial insulin and possible glucose response	Solverson et al. (2019)
	Flavonoids	Slows down the absorption of glucose in the intestine	Kerimi et al. (2019)
	Polyphenol-rich extract	Reduction of intracellular ROS and increased survival of pancreatic β-cells	Xu et al. (2018)
		Reduction of β-glucosidase, β-glucuronidase, and β-galactosidase activity	Berendika et al. (2022)
		Decreased α-glucosidase activity in the small intestine	Ramos et al. (2022)
	Cyanidin	Reduction of the formation of AGEs by increasing Glo-1 activity	Suantawee et al. (2020)
Anticancer activity	Resveratrol and curcumin	Regulating of apoptosis genes, such as CASP3, CASP7, and FAS	Chimento et al. (2023)
	Naringenin	Inhibition of cancer progression via apoptosis induction, cell cycle arrest, angiogenesis hindrance, and modification of various signaling pathways including Wnt/β-catenin, NF-κB, and TGF-β pathways	Motallebi et al. (2022)
	Polyphenol-rich extract	Increase in ROS production and apoptosis induction	Trisha et al. (2022)
		Suppressed cell proliferation to increase the sensitivity of chemotherapy drugs	Maleki Dana et al. (2022)
		Activation of tumor suppressor genes, inhibition of angiogenesis, PI3K/AKT pathways, STAT3, transcription factor AP-1, and Nrf2 and also suppressed Wnt/β-catenin signaling	Maugeri et al. (2023)
		Prevention/inhibition of the angiogenesis process	Kim et al. (2023)
	Curcumin	Alterations of noncoding RNAs	Si et al. (2023)
	Kaempferol	Restriction of the inflammation via suppressing the pro-inflammatory cytokines as well as chemokines production	Almatroudi et al. (2023)

downregulation of other cell-signaling pathways that have no connection to ROS production. Overall, the published data available about the effect of dietary polyphenols are not enough and in some cases contradictory. Recent metadata analyses showed that there are still experimental strategies that should be improved. For instance, one of the most important issues to overcome is the metabolic transformation and bioavailability of the polyphenols. During the digestion and absorption, they can suffer some modifications; therefore, the specific metabolites formed in vivo may be different when they reach the specific target tissues.

Despite the need of the improvement of experiments to target the incidence of polyphenols in the development of NCDs, the intake of polyphenols seems to be helpful in their prevention or treatment. Table 1 shows a resume of the positive effect that can be attributed to the intake of polyphenols.

6 | CONCLUSION

In summary, a diet rich in polyphenols is associated with the maintenance of good well-being and with the prevention of many NCDs. Polyphenols stand out due to their possible antioxidant, anticancer, antidiabetic, anti-inflammatory, etc. properties. Although there are numerous studies that demonstrate their benefits, it is necessary to continue with research studies because the nutritional amount for human health is not clear since exposure in the normal diet occurs at lower concentrations than that in the laboratory; their interaction with the intestinal microbiota can affect functionality, and the clinical studies carried out cannot always be generalized to the entire population.

AUTHOR CONTRIBUTIONS

Yasmany Armas Díaz: Conceptualization; Writing – original draft. **Maria Soledad Ferreiro Cotorruelo**: Validation; Visualization. **Maurizio Battino**: Funding acquisition; Project administration; Visualization

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study.

ORCID

Yasmany Armas Díaz https://orcid.org/0000-0003-2772-2225
Maurizio Battino https://orcid.org/0000-0002-7250-1782

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