

# Polyphenols in cancer prevention: New insights (Review)

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**Abstract.** A huge volume of literature data suggests that a diet rich in fruits and vegetables, mostly due to the contribution of natural polyphenols, could reduce the incidence of specific cancers. Resveratrol, epigallocatechin gallate and curcumin are among the most extensively studied polyphenols: The majority of the effects attributed to these compounds are linked to their antioxidant and anti-inflammatory properties. The multiple mechanisms involved include the modulation of molecular events and signaling pathways associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormonal activities, detoxification enzymes and immune responses. Notwithstanding their promising role in cancer prevention and treatment, polyphenols often have a poor bioavailability when administered as pure active principles, representing an important limit to their use. However, the bioavailability and thus the efficacy of these compounds can be improved by their administration in combination with other phytochemicals, with anticancer drugs or in polyphenol-loaded nanotechnology-based delivery systems. The possibility of combining conventional drugs with polyphenols offers very valuable advantages, such as the building of more efficient anticancer therapies with less side-effects on the health of patients. The present review focuses on current knowledge regarding the interactions between natural polyphenols and cancer development in order to gain a clearer comprehension of the potential mechanisms through which individual foods and food components may be exploited to reduce cancer risk.

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## 1. Introduction

Cancer is considered to be one of the most serious issues affecting humanity worldwide and is the second leading cause of mortality after cardiovascular diseases (1). The World Health Organization predicts that by 2050 there will be approximately 27 million cases with an annual mortality rate of 17.5 million individuals (2).

The onset of cancer can be influenced by a number of factors, such as genetic, metabolic, occupational and environmental including benzene, heavy metals, chemicals and mineral fibers (3-5).

These factors can act directly or indirectly, stimulating the expression of the malignant phenotype that regulates its progression. In particular, approximately 30-35% of cancer cases are associated with dietary factors: There is clear evidence suggesting the role of diet in controlling and/or promoting cancer. Combining this evidence, the Mediterranean diet represents one of the most popular dietary models currently under consideration in the field of cancer prevention and treatment outcomes (6). A lower incidence of cancer has been observed in countries where eating habits involve a low intake of meat, moderate intake of dairy and alcohol, and the frequent consumption of fruit and vegetables rich in bioactive nutrients (7). In fact, thousands of phytochemicals with antioxidant, anti-inflammatory, anticarcinogenic, antiviral and antiallergic properties are present in fruits and vegetables; they are classified as carotenoids, vitamins, alkaloids, nitrogen-containing, organosulfuric and phenolic compounds (1). In particular,

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*in vivo* and *in vitro* analyses, as well as human studies, have suggested the protective effects of polyphenols against chronic diseases and have demonstrated an inverse association between the consumption of polyphenols and the risk of tumor development.

A study published in the Cochrane Database of Systematic Reviews assessed possible associations between green tea consumption and the risk of cancer incidence and mortality, as well as safety data and quality of life as secondary outcomes. The authors reviewed 11 experimental studies, including a total of 1,795 participants consuming either green tea extract or a placebo and 131 non-experimental studies (>1,100,000 participants) (8). A beneficial effect due to green tea consumption emerged only for the high-intake subjects at specific cancer sites from randomized control trials and case-control studies; however methodological limitations, such as the low number and size of the studies as well as inconsistency with the results of cohort studies, limit the interpretability of the relative risk estimates.

Phenolic compounds act on carcinogenesis throughout the induction of cell defense systems, including detoxifying and antioxidant enzyme systems, as well as the inhibition of the anti-inflammatory and anti-cellular growth signaling pathways that culminate in cell cycle arrest and/or cellular death. These contributions strongly suggest the anticancer effects of polyphenols, due to their ability to alter the epigenome of cancer cells (2,9-14). Specifically, natural polyphenolic compounds present in the diet can exert their anticancer effects through a variety of mechanisms, including the modulation of cell cycle signaling, the removal of anticancer agents, the activity of antioxidant enzymes, apoptosis and arrest of the cell cycle.

Recent *in vitro* studies have suggested that these compounds modulate Nrf2 and NF- $\kappa$ B activation in cells and can significantly influence MAPK and PI3K function in cells, demonstrating their role in the proliferation of cancer cells (15,16). Moreover, natural polyphenols, e.g., apigenin, resveratrol (RES), genistein, luteolin and quercetin have been shown to induce the apoptosis of several malignant cells (2,17).

Numerous protein growth factors can induce endothelial cell proliferation and angiogenesis by producing various inflammatory mediators and lipid second messengers, such as prostaglandins and platelet-activating factor (PAF). PAF is a potent mediator of inflammation that is implicated in several pathological conditions, including cancer. In particular, tumor cells, as well as activated endothelial cells expose the PAF receptor on their membrane surface. When PAF binds to its receptor, numerous processes are activated that determine the onset and development of tumor-induced angiogenesis and metastases. The Mediterranean diet provides a dietary profile characterized by the presence of antioxidant substances and PAF inhibitors. Consequently, it can have preventive and protective effects against the development, growth and metastatic manifestations of cancer, through the inhibition of PAF activity and/or its biosynthesis (18,19). The main antiplatelet effect of flavonoids may be due both to the inhibition of thromboxane formation and to the antagonism of the thromboxane receptor (20). In addition, RES and tyrosol have been shown to exhibit biological activity as inhibitors of PAF-induced platelet aggregation (21).

Oxidative stress and DNA damage are the most common triggers activating the mitochondrial apoptotic pathway, which can result in mitochondrial membrane breakage and the release of cytochrome *c* (22).

In addition, other dietary compounds, such as zinc and folate are involved in the DNA repair process, although they do not share an identical mechanism. Some of these have been shown to play a role in epigenetics, while others may interact with genes other than those directly involved in DNA repair and methylation. Some play a protective role against oxidative stress, while others inhibit cell proliferation by modifying the inflammatory process. For example, there is an association between folate deficiency and colorectal cancer, although the risk varies due to genetic interindividual variability (23).

There is increasing evidence to indicate that the consumption of cruciferous vegetables reduces the risk of lung and colorectal carcinoma among subjects with low manifestation of enzymes responsible for the biotransformation of sulforaphane, the actual bioactive compound. These examples are some of the numerous associations between nutrients/genes/cancers (10).

On this basis, the present review focuses on current knowledge regarding the interactions between natural polyphenols and cancer development in order to gain a clearer comprehension of the potential mechanisms through which individual foods and food components may be exploited to reduce cancer risk.

## 2. Literature search

PubMed was searched to identify full text studies conducted on humans and published in the English language over the past year, which associate the dietary intake of polyphenols with the prevention of some prevalent cancer sites. Tumor types included in literature search were selected on the basis of their worldwide incidence. Some studies, although methodologically adequate, were excluded as they were not considered relevant to the study purpose.

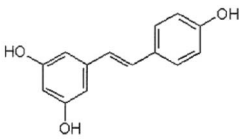
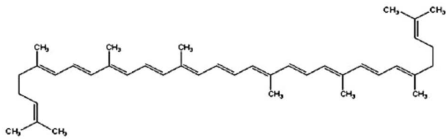
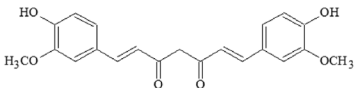
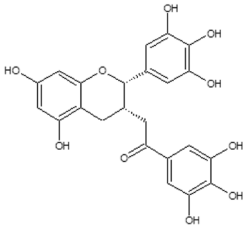
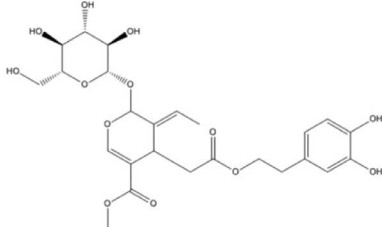
The majority of citations were found using the terms: 'Polyphenols' AND 'Cancer' OR 'Prostate Cancer' OR 'Breast Cancer' OR 'Bladder cancer' or 'skin cancer' or 'blood cancer' or 'colon cancer' or 'lung cancer' or 'pancreatic cancer'. There were no restrictions applied on the country of origin, ethnicity or sex. The relevance of the subject and the admissibility of all the publications retrieved was further assessed on the basis of titles and abstract. Further relevant studies were identified through the manual screening of the reference lists of selected articles and recently published reviews.

## 3. Classification of polyphenols

Polyphenols (Table I) are mainly classified into flavonoids and non-flavonoids (24). They are natural compounds that are all derived from phenylalanine and contain an aromatic ring with one or more hydroxyl groups. They include a large class of antioxidants such as flavonoids, phenolic acids and their derivatives, lignans and stilbenes.

The principal phenolic acids include hydroxybenzoic acids (e.g., gallic, p-hydroxybenzoic, vanillic and syringic acid) and hydroxy-cinnamic acids (e.g., ferulic, caffeic, p-coumaric, chlorogenic and synapic acid); however, due to their structural

Table I. Most representative polyphenols: Chemical formula and vegetal sources.

Polyphenols	Chemical formula	Vegetal sources
Resveratrol		Red grapes, blueberries, berries
Lycopene		Tomatoes, strawberries, cherries, pomegranate, blood oranges, watermelon, papaya
Curcumin		Turmeric
Epigallocatechin gallate		White, green and black tea, apples, blackberries, raspberries, pecans, hazelnuts, peaches, avocados, pistachios and onions
Oleuropein		Olive, olive oil

similarity, many other polyphenols are considered analogues of phenolic acid, such as capsaicin, rosmarinic acid, gingerol and gossypol. Tea is an important source of gallic acid, whereas the richest sources of hydroxy-cinnamic acids are coffee, lettuce, carrots, berries, sweet potatoes, prunes, peaches, apples, tomatoes and grapes.

Flavonoids are the most abundant polyphenols in diet. They are classified into flavones, flavonols, flavanols, flavanones, isoflavones and anthocyanins. These compounds have the basic skeleton of phenylbenzopyrone consisting of 2 aromatic rings. In nature, flavonoids can occur both in free and conjugated form. Among the predominant flavonols, quercetin is mentioned. The main food sources containing them are onions, cherries, apples, broccoli, cabbage, tomatoes, berries, tea, red wine, cumin and buckwheat.

Flavanones are mainly found in citrus fruits (e.g., oranges, lemons and aurantium), grapes and the medicinal herbs of Rutaceae, Rosaceae and Leguminosae.

Flavanols such as catechin, epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate (EGCG), are also widespread in medicinal herbs and diet plants (e.g., tea, apples, berries, cocoa and catechu). The main sources of flavones (luteolin, apigenin and tangeritin) are leaves, rinds, barks and pollens. Isoflavones include daidzein,

genistein, glycitein, found in soybeans and other legumes. Anthocyanidines are a typically colored group of flavonoids; they are present in flowers and red, blue or purple fruits. Within the subclass of stilbenes, RES has been found in several edible natural products such as grapes, peanuts, berries and rhubarb (25).

#### 4. Prostate cancer

Prostate cancer (PC) represents the second most commonly diagnosed cancer among males worldwide (26). Countries following a Mediterranean-type dietary pattern (Italy, Greece, Spain, Malta and some regions of France) have been documented to have a lower incidence and mortality rate due to PC than northern European regions. In a population-based case-control study conducted in Southern Italy, a total of 118 patients with PC and 238 controls were examined; the controls had a significantly higher adherence to the Mediterranean diet, following correction for confounding factors as age, body mass index, cigarette smoke, alcohol intake and physical activity (27).

The lowest age-standardized incidences of PC worldwide are registered in South Central Asia compared to westernized countries; lifestyle choices, including diet are considered to be involved in the risk of developing PC, as known risk

factors such as age, race and family history cannot explain this geographical variability in incidence. In fact, the risk of developing PC rapidly increases (as much as 20-fold) in Asian immigrants to the United States who reduce their intake of soy, tea, fish, fruits and vegetables, while introducing more red meat and fat (28).

Therefore, dietary components such as vegetables, tomato sauce, fish and vegetable fat are associated with a lower risk of PC progression. In particular, dietary factors that can influence the onset of PC are high intake of alcohol, dairy products, animal fat and meat; lycopene also has a tendency towards a favorable effect on PC incidence. On the other hand, the intake of long-chain omega-3 polyunsaturated fatty acids does not seem to be associated with lower cancer incidence (26). Vitamin D could also play an important role, as both low and high concentrations are associated with an increased risk (29).

In light of these considerations, scientific interest in the potential chemopreventive role in PC of various phytochemicals present in food is increasing. The mechanisms through which they exert their anticancer activity include the inhibition of proliferation, the induction of apoptosis and arrest of the cell cycle. Moreover, they can modulate signaling pathways and influence epigenetic alterations, such as DNA methylation and expression patterns of microRNAs (miRNAs). In particular, some polyphenols (lycopene, EGCG, CUR) act through the downregulation of different signal transduction pathways. Also sulphoraphane seems to exert antitumor effect through several mechanisms, such as anti-inflammatory, anti-angiogenic and anti-metastatic activities (Fig. 1) (10).

Epidemiological studies have indicated that these plant bioactives exhibit multimodal effects on PC cells, and foods such as cruciferous and alliaceous vegetables, tomatoes, red wine, green tea, turmeric and pomegranate have all been linked to a reduced risk of developing PC. For example, red wine and grapes contain RES, which has various biological effects, such as anti-inflammatory, antioxidant and anticancer. RES inhibits the *in vitro* dehydrotestosterone-induced progression of PC, interfering with the AR and CXCR4 pathway. CXCR4 as a chemokine receptor has been found to be upregulated in cancer metastases and has been used as a prognostic marker in various types of cancer, including leukemia, breast cancer (BC) and PC: RES treatment reduced CXCR4, AR, p-PI3K and p-AKT expression (30).

Green tea polyphenols containing EGCG have also been shown to exhibit numerous noteworthy biological activities, including anticancer properties. In particular recent studies on PC have demonstrated that epigenetic mechanisms could represent the main actors in the regulation of matrix metalloproteinases (MMP) and their tissue inhibitor (TIMP) associated with the progression of PC. *In vitro*, GTP/EGCG mediates the epigenetic reactivation of TIMP-3, which acts by inhibiting PC progression. In addition, clinical trials performed on patients undergoing prostatectomy and consuming 800 mg EGCG for up to 6 weeks, compared to matched controls, demonstrate an increase in plasma TIMP-3 levels. These findings confirm that epigenetic induction of TIMP-3 by green tea consumption restores the MMP/TIMP balance suppressing the progression of PC (31).

## 5. Colon cancer

Colorectal cancer (CRC) is the third most common type of cancer worldwide with a high incidence and mortality (32). CRC is recognized as a multifactorial disease that is dependent on environmental variables and individual intrinsic factors. In particular, eating habits have been linked to changes in the intestinal microbiota which could also contribute to the pathophysiology underlying CRC and its metabolic and psychological complications. The intestinal microbiota has a well-defined role in the body's homeostasis, in fact several highly prevalent gastrointestinal diseases have been associated with imbalances in microbiota composition (dysbiosis) and in particular the association with the onset of cancer has been suggested (33).

Among the bioactive compounds of the diet, polyphenols exert favorable effects on the intestinal microbiota, on free radicals and on inflammation (34). Polyphenols are biotransformed by the intestinal microbiota and finally metabolized into relatively simple aromatic carboxylic acids, commonly termed phenolic acids (35). These bioavailable metabolites can be even more bioactive than their precursors. However, only 5-10% of the total intake in polyphenols can be absorbed in the small intestine.

The modification of the composition of intestinal microbiota can significantly influence the bioavailability of polyphenols. In fact, human intestinal microbiota exhibits important hydrolytic activity, therefore when polyphenols reach the colon, their bioavailability can be significantly increased. In addition, polyphenols can decompose into smaller phenolic acids for easy absorption by the intestinal mucosa.

EGCG can be methylated through catechol-*O*-methyltransferase and can exert an inhibitory effect on DNA methyltransferase (DNMT). DNMT inhibition prevents hypermethylation of newly formed DNA strands, leading to a reversal process of silenced genes. EGCG may also suppress DNMT action by activating genes silenced by tumor cells by methylation (36).

An *in vitro* study performed on AK4-knockdown colon cancer SW480 and SW620 cells demonstrated that RES can inhibit the invasion and metastasis of colon cancer cells by reversing the expression of epithelial-mesenchymal transition (EMT) markers through the AKT/GSK-3 $\beta$ /Snail signaling pathway. In fact, AKT1 can be a key regulator of EMT in colon cancer cells and serve as a potential therapeutic target for this disease (37).

Djulius, a cereal crop rich in polyphenols and dietary fiber, can also prevent CRC. Indeed Lee *et al* carried out a study on rats showing that polyphenols can protect rats from oxidative stress and regulate proteins related to anti-apoptosis, proapoptosis and proliferation to prevent CRC progression. Therefore, djulis may prove to be a promising CRC chemopreventive product in the future (32).

Inflammation-induced carcinogenesis has been shown to be associated with oxidative stress, genomic instability, immune effectors, cytokine dysregulation and the modulation of the NF- $\kappa$ B signaling pathway. Foods such as strawberries and black raspberries have been shown to play a synergistic role in multiple molecular events, including the suppression of cytokine release, the reduction of oxidative stress, the

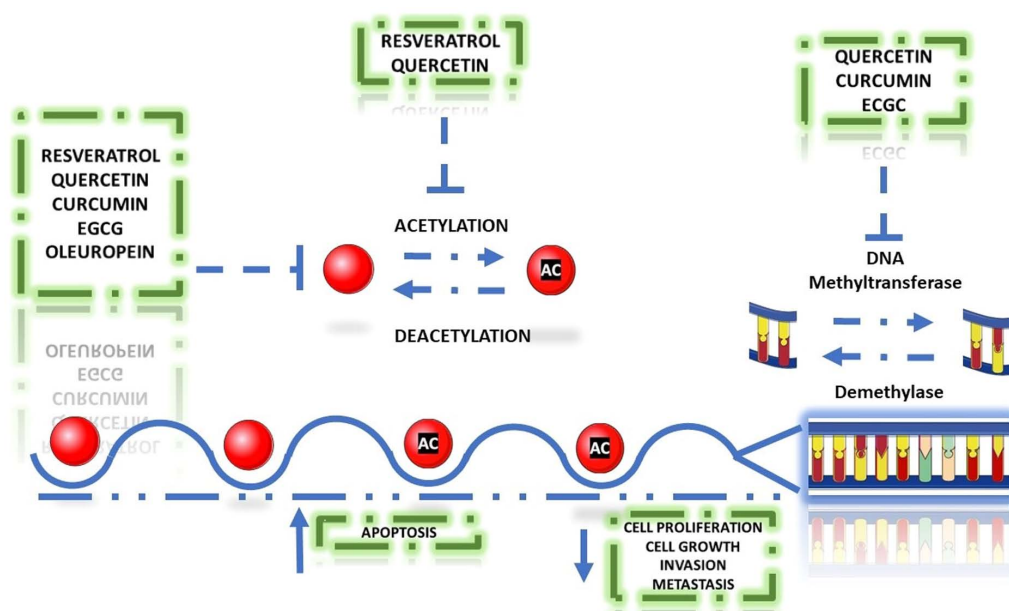


Figure 1. Polyphenols act on the epigenetic mechanism by inhibiting the methyltransferase activities of HDAC, HAT and DNA which are deregulated in cancer cells.

reduction of genomic instability and the inhibition of NF- $\kappa$ B and related pathways (38).

A study carried out by Hu *et al* demonstrated a synergistic action of ginkgetin and RES in preventing VEGF-mediated angiogenesis in several experimental models, suggesting that this combination may play a role in anti-tumor treatment. The reduced formation of sub-intestinal vessels was shown in zebrafish embryos and microvascular sprouting in rat aortic ring; the reduced phosphorylation of VEGFR2, Akt, eNOS and Erk, as well as the expression of matrix metalloproteinases (MMPs) was found in human umbilical vein endothelial cells (HUVECs). The combination of ginkgetin and RES was also effective on HT-29 colon cancer xenograft nude mice and relieved the 5-fluorouracil-induced inflammatory response by suppressing expression levels of COX-2 and inflammatory cytokines (39).

## 6. Breast cancer

BC is the second most frequent type of cancer worldwide; in particular, among women, it is considered the most commonly diagnosed type of cancer, constituting approximately 25% of all diagnosed tumors (7).

The risk of developing BC is affected by non-modifiable factors, including age and genotype, as well as modifiable factors, such as smoking, alcohol, nutrition and occupational exposure (40). It has been observed that obesity, a sedentary lifestyle and unhealthy diet are known to increase the mortality rate of BC survivors. As the same risk factors are common to cardiovascular diseases, the risk of cardiovascular diseases is also higher among BC survivors. Consequently, the implementation of a healthy diet rich in unrefined cereal, fresh fruit and vegetables could also indirectly improve the outcome of BC survivors by reducing body weight. The nutrients present in a typical Mediterranean diet have shown a positive impact on the biomarkers of inflammation, DNA damage, oxidative

stress and genetic alterations, all factors that can influence BC outcomes. In addition, several studies have reported that a high adherence to MD is associated with a lower risk of the incidence of BC in post-menopausal women (41). A prospective cohort study conducted in the Mediterranean included 10,713 middle-aged, Spanish female university graduates and revealed an inverse association between the total polyphenol intake and the risk of BC for post-menopausal women (42).

The intake of polyphenols from food or as a food supplement for the prevention of BC is actually controversial, as only high concentrations are able to inhibit the proliferation of ER $\alpha$  and ER $\alpha$ <sup>+</sup> BC cells, while lower concentrations can even stimulate the growth of ER $\alpha$ <sup>+</sup> cells (43). One of the polyphenols studied for its inhibitory effects on BC is carnosol. An *in vivo* study demonstrated that this compound can reduce the proliferation of BC cell lines (MDA-MB-231) and can significantly inhibit invasion and metastasis both *in vitro* and *in vivo*; in particular, it has been shown that carnosol exerts its effect against BC through the downregulation of MMP-9 activity and expression, and by the inhibition of the STAT3 signaling pathway through the ROS-dependent proteasome degradation of the STAT3 protein (44).

The antioxidant properties of RES, a natural component of plants such as peanuts, cocoa, grapes, berries and red wine, are attributed to its polyphenolic stilbene structure. RES and its analogues have been classified as phytoestrogens able to bind estrogen receptor, and the results of investigations in ER-positive subtypes strongly suggest their use in hormone anticancer therapy. In fact, the majority of authors agree on the ability of RES to modulate ER $\alpha$  and p53 expression in ER-positive BC: It inhibits the expression of major cell cycle-related genes, through the downregulation of ER $\alpha$  mRNA transcription. Recently, a membrane receptor site for RES on an integrin has been revealed in both ER-positive and ER-negative BC subtypes: Upon binding of RES with this receptor, the p53-dependent induction of apoptosis occurs (45).

Therefore, RES and other stilbene derivatives would elicit significant cytotoxic and pro-apoptotic effects in ER-negative and 'triple-negative' breast cancer (TNBC) cells, lacking receptors for estrogens, progesterone and human epidermal growth factor. While the potential effects against BC of RES and other polyphenols such as curcumin (CUR), genistein, quercetin and silibinin have been widely investigated, interest towards the potential anticancer activity of luteolin is more recent. The mechanisms considered to be responsible for the cancer preventive activity of luteolin are reduced DNA alterations, antioxidant, anti-inflammatory and antiestrogenic action. Moreover, pro-apoptotic (e.g., by inhibiting PI3K/Akt and inducing FOXO3a activation) and chemosensitizing (mainly through JNK activation) effect may confer it a therapeutic potential. Luteolin inhibits BC cell survival, proliferation and migration and reduces angiogenesis, by modulating multiple signaling pathways and miRNAs (46).

EGCG and oleuropein (OLE) have been suggested as potential supplements against BC. Zan *et al* demonstrated that EGCG blocked cell cycle progression at the G2/M phase in MCF-7. EGCG also induced apoptosis by inhibiting miR-25 expression and increasing PARP and pro-caspase expression (47). Oleuropein (OLE), a natural polyphenol, has also shown potential apoptotic and anti-invasive effects on MCF-7 cells. In fact, OLE reduced neoplastic cell invasiveness and viability and at the same time induced apoptosis in MCF-7 cancer cells (48); in particular, OLE acts on cancer control by epigenetic mechanism, such as the inhibition of histone deacetylase (HDAC) (49).

Finally, an *in vitro* study reported the anti-proliferative and cytotoxic effects of a polyphenol complex (catechin and lysine, 1:2) in BC cell lines. In particular, it was shown that this complex acts by interfering with glucose uptake and lactate production by tumor cells. It exerts selective anti-migratory (mediated by JAK2/STAT3 and Wnt pathway inhibition) and pro-apoptotic effects in breast, pancreatic and colorectal cancer cell lines (50). Nonetheless, epidemiological studies on flavonoids and BC have some limitations: Study design, a low sample size, variable doses of flavonoid intake and BC subtype are the most common (51).

## 7. Lung cancer

Lung cancer (LC) is the second most common type of cancer among both sexes, with a high mortality rate worldwide (52). Small cell (SCLC) and non-small cell LC (NSCLC) represent approximately 15 and 85% of all cases, respectively.

The consumption of fruit, vegetables and natural products is considered useful in the prevention and fight against LC. Some natural polyphenols have potential anticancer activities owing to their anti-proliferative, anti-migratory, anti-metastasis, anti-angiogenic and pro-apoptotic properties. A recent comprehensive review summarized preclinical studies investigating the molecular mechanisms of natural polyphenols or analogs with a potential role in LC. RES, CUR and EGCG emerged as the most studied compounds (53).

Lately, research has made immense progress in the comprehension of the mechanisms through which RES inhibits cell proliferation, induces apoptosis and cell cycle arrest, and suppresses invasion and metastasis. In particular,

RES has been shown to induce apoptosis through multiple signaling pathways, including the kinases, AKT, STAT3, PKC, p38, JNK, ERK, AMPK and PFK; various cyclins (A, D, E and CDK) also act as cell cycle regulators. Multiple growth and transcription factors are also involved, as VEGF, FGF, TGF $\beta$ , EGFR, AhR, Nrf2, NF- $\kappa$ B and p53. The majority of these pathways have been identified to play a role in the pro-apoptotic effects of CUR and EGCG. Moreover, several studies have shown that modulation of miRNAs represent a key mechanism for the antitumor activity of RES in LC: >70 miRNAs related to apoptosis, cell cycle and differentiation have exhibited considerable changes in their expression levels in RES-treated A549 cells (53). CUR also has been shown to exert an anticancer effect in LC through epigenetic alterations and the regulation of miRNA expression (52).

Although the induction of apoptosis appears to be the main mechanism underlying the antitumor activities of polyphenols in LC, there is evidence of other mechanisms being involved in their inhibitory effects on lung tumor survival and progression. RES has been shown to lead to a significant reduction and imbalance in the pools of deoxyribonucleosides triphosphates (dNTP), which suppress subsequent DNA synthesis. Furthermore, the inhibition of DNA synthesis blocks the progression through the S phase in A549 cells, which can partially contribute to the cytotoxic effect of RES (54).

*In vivo* and *in vitro* studies have demonstrated that EGCG, a polyphenol present in green tea, inhibits the proliferation and migration and induces apoptosis in LC A549 and H1299 cells. These effects are partially achieved through inhibition of the NF- $\kappa$ B signaling pathway. Furthermore, the concomitant administration of EGCG and BAY11-7082 has a synergistic effect and may serve as a new therapeutic strategy for LC. The anti-proliferative activity of EGCG seems to be attributable to suppressed phosphorylation of EGFR, ALK, ROS1, and in turn their downstream proteins, Akt and ERK; growth inhibition in xenograft tumors was associated with reduced HIF-1 $\alpha$  expression and tumor angiogenesis, suggesting that tumor response to EGCG is influenced by the tumor microenvironment (53,55).

Dieckol is a polyphenolic substance extracted from brown algae. An *in vitro* study performed by Wang *et al* has shown that this substance has anticancer properties; in particular it acts by inhibiting the invasive and migratory properties of A549 cells and also by inducing apoptosis through inhibition of PI3K/AKT/mTOR signaling, activating the E-cadherin tumor suppressor protein. This suggests that dieckol may be a potent natural anticancer drug for the treatment of NSCLC (56). These data confirm the potential complementary role of RES, CUR and EGCG in cancer treatment to enhance the efficacy of existing therapies, reducing side-effects.

## 8. Bladder cancer

Polyphenols, including EGCG, CUR and RES, are known to exert an antioxidant effect; however, under certain conditions, they can be genotoxic for tumor cells. A study conducted by Almeida *et al* (57) evaluated the antitumor activity of RES and its possible mechanisms of action in bladder cancer cells with a different state of the TP53 gene. This gene responds to stress signals inducing cell cycle arrest, apoptosis, senescence

and DNA repair; its mutations are the most common alterations in bladder cancer cells and are correlated with poor prognosis and recurrence. Its antitumor activity was evaluated in different bladder tumor cells (RT4, grade 1, TP53 wild type; 5637-grade 2; T24-grade 3, TP53 mutated). RES decreased cell proliferation and induced DNA damage in all neoplastic cell lines. However, TP53 wild-type cells were more resistant, while they were more prone to apoptosis, accompanied by AKT, mTOR, and SRC downregulation as well as modulation of the DNMT1 gene. Conversely, the prevalent action in TP53 mutated cells was cell cycle arrest at S phase with PLK1 downregulation, as well as modulation of the HOXB3/RASSF1A pathway and nuclear PCNA reduction in the highest-grade cells.

An *in vitro* study conducted on BFTC-905 cells, a human urinary bladder transitional cell carcinoma (TCC) cell, treated with EGCG, identified 108 differentially expressed genes and 22 candidate genes with potential miRNA interactions. These genes were mainly involved in the biogenesis of nicotinamide adenine dinucleotide (NAD), in the inflammatory response and in the oxidation-reduction metabolism (58). CUR is capable of suppressing the growth of a variety of cancer cells, including those of bladder cancer. CUR could be considered a promising candidate in bladder cancer therapy as it modulates various signaling pathways such as PI3K, Akt, mTOR and VEGF involved in the progression and malignancy of bladder cancer (59).

## 9. Skin cancer

Skin is considered the protective barrier of the organism, shielding it from harmful substances, mechanical damage, pathological invasion and radiation. Skin cancer (SC) is considered to be the most common type of cancer worldwide; this is the result of several mutations in cancer-related genes, including proto-oncogenes and tumor suppressors in skin cells, which cause an imbalance in cell homeostasis and excessive skin proliferation. The initiation of skin tumors can be attributed to various factors, although excessive exposure to UV radiation is considered the main risk factor for SC. The main classification of SC is between melanoma and non-melanoma. Non-melanoma skin cancer (NMSC) in turn is distinguished into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) originated from epidermal keratinocytes. In a review aimed at elucidating the chemopreventive effects of polyphenols against SC metastasis, 34 *in vivo* mechanistic studies evaluating the efficacy of purified polyphenols were included; the authors of that study concluded that they exerted pro-apoptotic effects via the induction of ASK-1, Caspase-3, JNK-p38 and pRb; suppressed the cell cycle via the upregulation of p21, Bcl2, and Bcl-xL and the downregulation of Bim, Bax, Puma and Noxa; reduced proliferation and angiogenesis through the upregulation of EGFR, MAPK, mTOR, PI3K/Akt, FAK/PTK2, JAK/STAT, VEGF and HIF-1 $\alpha$ . The inhibition of cellular proliferation, invasion and metastasis would occur by modulating the expression of inflammatory and cytokine genes such as IL-6, IL-1, GM-CSF and TNF- $\alpha$ , IL-2, GM-CSF and INF- $\gamma$  and IL-18 in melanoma models (60).

The treatment of melanoma remains a challenging issue, due to its aggressive metastatic ability and resistance to current therapeutic approaches. Though no clinical studies are

yet available assessing the efficacy of the most active polyphenols in SC, epidemiological evidence indicates that the poorly soluble polyphenols, such as CUR, RES, EGCG, coumarin and quercetin, exert anticancer effects. In their review, Heenatigala Palliyage *et al* suggested that poorly soluble polyphenols, such as CUR, RES, quercetin, coumarin and EGCG may have significant benefits in the treatment of melanoma thanks to their antioxidant, anti-inflammatory, antiproliferative and chemoprotective properties. The well-known limitations to their use, i.e., low stability and poor bioavailability, may be overcome by using polyphenol-loaded nanotechnology-based delivery systems for topical and transdermal application, as polymeric nanoparticles, vesicles, lipid nanoparticles, nanofibers and nanohybrids (61).

Rodríguez-Luna *et al* (62) proposed the combination of the carotenoid fucoxanthin and the polyphenol rosmarinic acid (RA) as a natural promising tool in prevention of UVB-induced skin alterations as photo-aging, skin inflammation and its derivation to pre-cancerous lesions and skin carcinomas. RA is a phenolic ester traditionally isolated from some terrestrial plants as *Rosmarinus officinalis L.* or *Melissa officinalis L.* and also abundantly found in *Zostera marina* seagrass beds. RA has been widely studied due to its remarkable biological and pharmacological activities, including anti-microbial, antioxidant and anti-inflammatory properties. The authors of that study demonstrated that the combination of fucoxanthin and RA improved their antioxidant and anti-inflammatory profiles by reducing UVB-induced apoptosis and the consequent ROS production. This association also downregulated inflammatory components, such as NLRP3, ASC and caspase-1 and interleukin (IL)-1 production. Moreover, Nrf2 and HO-1 antioxidant genes expression increased in UVB-exposed pre-treated HaCaT cells.

The study conducted by Shin *et al* analyzed the effects of quercetin on skin aging. In particular, quercetin has been shown to suppress UV-induced matrix metalloproteinase-1 (MMP-1) and cyclooxygenase-2 (COX-2) expression by preventing UV-mediated collagen degradation in human skin tissues; inhibit the activator of protein-1 (AP-1) induced by UV rays and on NF- $\kappa$ B; attenuate UV-ray phosphorylation of extracellular signal-regulated kinase (ERK), terminal kinases C-Jun N (JNK), protein kinase B (Akt) and signal transducer and activator of transcription 3 (STAT3); and to directly inhibit the kinase activity of the protein kinase C $\delta$  (PKC $\delta$ ) and JAK2 (63).

## 10. Pancreatic cancer

Pancreatic cancer is one of the most severe neoplasms due to a very poor prognosis, as in the majority of patients it is usually diagnosed at an advanced stage. Current chemotherapeutic agents administered to patients with metastasis pancreatic cancer are not able to significantly improve life expectancy. For this reason, novel therapeutic strategies are required to prevent or target metastatic disease aiming to improve the patient's outcome. Wei *et al* studied EGCG as a potentially safe and effective agent for use with gemcitabine in blocking the migration and invasion of pancreatic cancer, in part by inhibiting the Akt and EMT pathways. Since Akt signaling plays an important role in pancreatic cancer cell growth,

Table II. Effects of polyphenols on cancer: Antitumor activity and signaling pathways.

Cancer site	Polyphenols	Signaling pathways	Effects
Prostate	EGCG lycopene resveratrol curcumin	Matrix metalloproteinases (MMP) And Their MMP Tissue Inhibitor (TIMP)	<ul style="list-style-type: none"> <li>• Modulation of inflammatory pathways</li> <li>• Induction of apoptosis and cycle arrest</li> <li>• Influences epigenetic changes such as DNA methylation and expression patterns of microRNAs</li> </ul>
Breast	EGCG lycopene resveratrol curcumin oleuropein	ER $\alpha$ ER $\alpha$ <sup>+</sup> STAT3 HER2 MCF-7	<ul style="list-style-type: none"> <li>• Inducing apoptosis and cycle arrest</li> <li>• Modulation of inflammatory pathways</li> <li>• Inhibition of STAT3</li> <li>• Inhibition of histone deacetylase</li> </ul>
Colon	Resveratrol EGCG ginkgetin	AKT/GSK-3 $\beta$ /Snail signaling pathway NF- $\kappa$ B VEGF	<ul style="list-style-type: none"> <li>• AKT1 modulation epithelial mesenchymal transition</li> <li>• Inhibition of NF-<math>\kappa</math>B</li> <li>• Reduction of genomic instability</li> <li>• Inhibition of angiogenesis</li> </ul>
Lung	RESVERATROL CURCUMIN EGCG	NF- $\kappa$ B PI3K/AKT/mTOR	<ul style="list-style-type: none"> <li>• Modulation of inflammatory pathways</li> <li>• Induction of apoptosis and cycle arrest</li> <li>• Influences expression patterns of microRNAs</li> <li>• Inhibition of the NF-<math>\kappa</math>B signaling pathway</li> </ul>
Other types of cancer: Bladder skin pancreatic leukemia	Resveratrol curcumin EGCG quercetin	COX-2 MMP1 DNTM1 gene ERK PFK PI3K AKT mTOR VEGF	<ul style="list-style-type: none"> <li>• Modulation of inflammatory pathways</li> <li>• Induction of apoptosis and cycle arrest</li> <li>• Influence expression patterns of microRNAs</li> <li>• Inhibition of angiogenesis</li> </ul>

downregulation of this kinase may partly explain the reduction in cell growth observed in EGCG-treated tumors. EGCG has effectively reduced pancreatic cancer cell growth *in vitro* and *in vivo*, otherwise there is little evidence of a beneficial effect of EGCG on cancer metastases (64).

## 11. Leukemia

Leukemia includes a group of hematological malignancies responsible for 8% of all cancers. the effectiveness of chemotherapy agents is low and the disease has an unfavorable prognosis with frequent recurrences and high mortality. Though the *in vitro* anti-leukemic effect of polyphenols has been studied for decades, there are only few *in vivo* studies.

RES has pleiotropic benefits due to its antioxidant and anti-inflammatory properties; recent findings suggest that it may have great potential in adjuvant therapy for leukemia. RES can act as an autophagy modulator and apoptosis inducer in MOLT-4 and HL-60 human leukemia cells (65). It has also been shown to reduce the therapeutic doses of drugs, such as barasertib and everolimus, minimizing their side-effects on both leukemic and normal lymphocytes (66).

RES has also been shown to be effective in reducing drug resistance: In HL-60/ADR cells, this occurs through

the regulation of the PI3K/Akt/Nrf2 signaling pathway and MRP1 expression (67); in combination with prednisolone, in a dose-dependent manner, it reduces the expression of the MDR1 protein (68).

Recent findings suggest that CUR, in addition to its antioxidant and anti-inflammatory effects, may be a promising candidate for acute myeloid leukemia therapy (69). A recent study provided *in vivo* evidence confirming its effect on the apoptosis and invasion of human acute leukemia SHI-1 cells, through activation of JNK and p38 and inhibition of ERK and NF- $\kappa$ B signals. Furthermore, CUR may also downregulate the expression of MMP9 and MMP2 as well as vimentin, leading to suppression of the metastatic potency of SHI-1 (70).

EGCG exerts potent antitumor activity in hematological malignancies, including several types of leukemia. It induces apoptosis in chronic myeloid leukemia cells by regulating Bcr/Abl-mediated p38-MAPK/JNK and JAK2/STAT3/AKT signaling pathways (71).

## 12. Conclusion

There is a rich body of evidence suggesting that a diet rich in fruits and vegetables, mostly owing to the contribution of natural polyphenols, can reduce the incidence of specific



cancers. Among the most extensively studied polyphenols are RES, EGCG and CUR. Many of the effects attributed to these compounds are linked to their antioxidant and anti-inflammatory properties; however, the multiple mechanisms involved include the modulation of molecular events and signaling pathways associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormonal activities, detoxification enzymes and immune responses (Table II) (72-75).

Future research directions can potentially expand upon the use of dietary-based polyphenols as whole foods, whole-food extracts or purified compounds, especially in combinations, as a potent and effective method in cancer prevention and adjuvant therapy.

Notwithstanding their promising role in cancer prevention and treatment, polyphenols often have a poor bioavailability when administered as pure active principles, representing an important limit to their use. Possible interactions with other natural compounds present in the diet can also influence their efficacy. However, the bioavailability and thus efficacy of these compounds can be improved by the administration in combination with other phytochemicals, with anti-cancer drugs or in polyphenol-loaded nanotechnology-based delivery systems (50).

Particular attention should be paid to the safety of polyphenols. It should be noted that some isoflavones, such as genistein and daidzein, seem to have hormone-related adverse effects on cancer. Therefore, the use of these polyphenols in the treatment of cancer should be prudent.

Research interest on the effects of dietary polyphenols on the intestinal microbiota and the relative mechanisms of action has only recently spread. Dietary polyphenols seem to affect gut microbiota thanks to a bi-directional relation. On the one hand polyphenols can modulate the composition of microbiota; on the other hand, the microbiota is able to metabolize them into bioactive compounds. However, it seems clear that correct eating habits, typical of the Mediterranean diet, characterized by a high intake of polyphenols, play an important role in the maintenance of intestinal functions (76).

Recently, significant steps forward have been made in the understanding of the alterations driving to cancer development and progression at a cellular, molecular and genetic level. Relevant advances have been achieved also in the comprehension of the molecular mechanisms explaining the chemopreventive properties of specific polyphenols (45,53).

Nonetheless, evidence from human studies is still inadequate and trials often resulted inconclusive or discordant. The main weaknesses of the studies conducted so far are the imprecise concentration of polyphenols in the tested foods or drinks, poor awareness of their kinetics and of the actual contribution of single compounds to their effect. Therefore, further clinical studies are warranted to support the use of polyphenols in the prevention and treatment of cancer.

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#### Authors' contributions

GB, CC and CF substantially contributed to the conception and design of the study, revising it critically and providing final approval. MP, FG and SC were involved in the drafting, correction and revising the manuscript. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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