Review

Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways

Sonia Ramos

Department of Metabolism and Nutrition, Instituto del Frío, Consejo Superior de Investigaciones Científicas (CSIC), Ciudad Universitaria, Madrid, Spain

Prevention of cancer through dietary intervention recently has received an increasing interest, and dietary polyphenols have become not only important potential chemopreventive, but also therapeutic, natural agents. Polyphenols have been reported to interfere at the initiation, promotion and progression of cancer. They might lead to the modulation of proteins in diverse pathways and require the integration of different signals for the final chemopreventive or therapeutic effect. Polyphenols have been demonstrated to act on multiple key elements in signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis and metastasis; however, these molecular mechanisms of action are not completely characterized and many features remain to be elucidated. The aim of this review is to provide insights into the molecular basis of potential chemopreventive and therapeutic activities of dietary polyphenols with emphasis in their ability to control intracellular signalling cascades considered as relevant targets in a cancer preventive approach.

Keywords: Angiogenesis / Apoptosis / Food-derived polyphenols / Metastasis / Proliferation/survival pathways

Received: August 20, 2007; revised: December 31, 2007; accepted: January 30, 2008

1 Introduction

Cancer is largely environmentally determined, being diet a major variable. Dietary patterns, foods, nutrients and other dietary constituents are closely associated with the risk for several types of cancer, and in this regard, it has been estimated that 35% of cancer deaths may be related to dietary factors [1]. Recently, dietary polyphenols have received much attention for their health benefits, including anticancer properties.

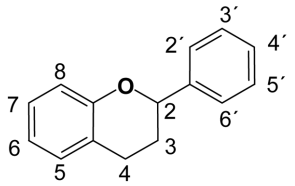
Polyphenols are present in fruits, vegetables, seeds and drinks and it has been described more than 8000 different compounds that can be divided into ten different general classes based on their chemical structure [2, 3]. Phenolic acids, flavonoids, stilbenes and lignans are the most abundantly occurring polyphenols in plants, of which flavonoids and phenolic acids account for 60 and 30%, respectively, of dietary polyphenols. More than 4000 varieties of flavonoids have been identified and classified according to their molecular structure, which consists of two benzene rings joined by a linear three-carbon chain that forms an oxygenated heterocycle ($C_6-C_3-C_6$) (Table 1). Representative groups of flavonoids are listed in Table 1, together with the best-known members of each group and the food sources in which they are present.

Many studies in different cell lines, animal models and human epidemiological trials suggest a protective role of dietary polyphenols against different types of cancers [4–

Correspondence: Dr. Sonia Ramos, Department of Metabolism and Nutrition, Instituto del Frío, Consejo Superior de Investigaciones Científicas (CSIC), José Antonio Novais 10, Ciudad Universitaria, 28040 Madrid, Spain
E-mail: s.ramos@if.csic.es
Fax: +34-91-549-36-27

Abbreviations: AIF, apoptosis-inducing factor; **AKT/PKB,** protein kinase B; **AP-1,** activator protein-1; **bFGF,** basic fibroblast growth factor; **CDK,** cyclins-dependent kinase; **COX-2,** cyclooxygenase-2; **CYP,** cytochrome P450; **DMBA,** dimethylbenz[*a*]anthracene; **ECG,** epicatechin gallate; **EGC,** (−)-epigallocatechin; **EGCG,** epigallocatechin-3-gallate; **EGFR,** epidermal growth factor receptor; **ERK,** extracellular regulated kinase; **FAK,** focal adhesion kinase; **GFR,** growth factor receptors; **GPx,** glutathione peroxidase; **GST,** glutathione-*S*-tranferases; **HIF-1α**, hypoxia-inducible factor 1α; **IAPs,** inhibitor of apoptosis proteins; **IGF,** insulin-like growth factor; **IκB,** inhibitor of κB; **IKK,** IκB kinase; **JNK,** c-Jun N-terminal kinase; **MAPKs,** mitogen-activated protein kinase; **Mcl-1,** myeloid cell leukaemia-1; **MMPs,** matrix metalloproteases; **NF-κB,** nuclear factor-kappa B; **NQO,** NADPH quinone oxidoreductase; **Nrf2,** nuclear-factor-E2-related factor 2; **PCNA,** proliferating cell nuclear antigen; **PDGFR,** PDGF receptor; **PI3K,** phosphatidylinositol-3-kinase; **PKC,** protein kinase C; **PSA,** prostate-specific antigen; **QR,** quinone reductase; **Rb,** retinoblastoma protein; **ROS,** reactive oxygen species; **S6k1,** p70S6 kinase1; **SOD,** superoxide dismutase; **STAT,** signal transducers and activators of transcription; ***t*-BOOH,** *tert*-butylhydroperoxide; **TIMP,** tissue inhibitors of MMP; **TNF**, tumour necrosis factor; **UDPGT,** UDP-glucuronosyl transferase; **uPA,** urokinase-type plasminogen activator; **uPAR,** uPA receptor; **VEGF,** vascular endothelial growth factor; **VEGFR,** VEGF receptor; **XIAP,** X-linked IAP

Table 1. Main groups, individual compounds and dietary sources of commonly occurring flavonoids



Group	Compound	Major food source
Flavones (R5=R7=OH)		
R3′=R4′=OH	Luteolin	Parsley, thyme, celery, oregano, green chilli peppers
R3′= OH; R4′=OCH_3	Diosmetin	
R3′=H; R4′=OH	Apigenin	
R8=OH	Wogonin	
	Chrysin	
Flavanols (R3=R5=R7=OH)		
R3=gallate; R3′=R4′=R5′=OH	Epigallocatechin-3-gallate	Apple, cacao, tea, apricot, peach, red wine, cherry, blackberry, grape, beans
R3′=R4′=R5′=OH	Epigallocatechin	
R3′=R4′=OH	Epicatechin	
R3′=R4′=OH; R5′=H	Catechin	
Flavanones (R5=R7=OH)		
R3′=H; R4′=OH	Naringenin	Orange, grapefruit, lemon
R3′= R4′=OH	Taxifolin	
R3′=OH; R4′=OCH_3	Hesperitin	
R3′=R4′=OH	Eriodictyol	
Flavonols (R3=R5=R7=OH)		
R3′=R4′=OH; R5′=H	Quercetin	Onion, apple, cherry, broccoli, tomato, berries, tea, red wine, leek
R3′=R4′=R5′=OH	Myricetin	
R4′=OH; R3′=R5′=H	Kaempherol	
R3=beta-D-glucopyranosyloxide; R3′=R4′=OH	Rutin	
Isoflavones (R7=R4′=OH)		
R5=OH	Genistein	Soya beans, legumes
R5=H	Daidzein	
Anthocyanidins (R3=R5=R7=R4′=OH)		
R3′=R5′=OH	Delphinidin	Cherry, strawberry, red wine, aubergine, blackberry, black currant, blue berry, black grape, rhubarb
R3′=R5′=H	Pelargonidin	
R3′=R5′=OCH_3	Malvidin	
R3′=OH; R5′=H	Cyanidin	
R3′=OH; R5′=OCH_3	Petunidin	

6]. Clinical trials attempt to correlate polyphenolic intake with prevention of a particular cancer, showing a decreased risk for different types of cancer [7 – 10] or a diminished recurrence of cancer [11, 12] after the consumption of flavonoids or certain foods or drinks (tea) rich in these phenolic compounds. In contrast, certain human studies have also shown no beneficial effects [13, 14] or have failed to find a positive association between intake of flavonoids and reduced risk for different types of cancer [15, 16]. However, it should be highlighted that assessing the real impact of such constituents on human health is difficult, when consider that in many cases the exact composition of foods and the bioavailability of active molecules are not known. Thus, most direct evidence of beneficial effects by a particular food rich in polyphenols, or individual compounds, have come from animal models and *in vitro* experiments. In fact, cell culture studies constitute a valuable tool for identifying the molecular targets modulated by dietary phenolic compounds in cancer cells and for elucidating the molecular pathways involved in the overall disease process.

Cancer chemoprevention attempts to interfere in the progress of the disease by using natural or synthetic substances, and its prevention through dietary intervention has

become an important issue. Many potential chemopreventive polyphenols may interrupt or reverse the carcinogenesis process by acting on intracellular signalling network molecules involved in the initiation and/or promotion, but also phenolic compounds may arrest or reverse the progression stage of cancer [1, 17]. Thus, the anticarcinogenic activity of these dietary components might be attributed to a combination of their cytoprotective effect on normal cells and their cytotoxic effect on pre- and/or neoplastic cells. In this regard, it should be mentioned that a phenolic compound may inhibit the activation of a molecular signal when applied before or during a stimulus, but it may have no effect on the same signal already up-regulated in the absence of external stimuli. Moreover, the effects of the polyphenols seem to be cell type- and dose-dependent; some results obtained *in vitro* point out similar mechanisms of action for the phenolic compounds in cells of different origin, but there are also data showing differences in cells derived from the same tissue, or studies demonstrating opposite effects for the same polyphenol when applied at high or low doses. Thus, how polyphenols do regulate and induce these beneficial processes in cancer remains to be elucidated. In this overview, recent studies on representative dietary polyphenols dealing with their underlying molecular mechanisms associated to cancer are reviewed.

2 Cellular signalling in cancer

Carcinogenesis is generally recognized as a complex and multistep process in which distinct molecular and cellular alterations occur. In order to simplify the understanding of the different possible options for chemoprevention and chemotherapy in cancer development and progression, three stages have been described: (i) initiation is a rapid phase, comprises the exposure or uptake and interaction of cells, especially DNA, with a carcinogenic agent, (ii) promotion is relatively lengthy when compared to the previous stage, abnormal cells persists, replicates and may originate a focus of preneoplastic cells and (iii) progression stage is the final phase of the tumorigenesis, an uncontrolled growth of the cells (tumour) occurs, involves the gradual conversion of premalignant cells to neoplastic ones with an increase of invasiveness and metastasis potential, and new blood vessel formation (angiogenesis) (Fig. 1).

In the initiation phase, the carcinogenic agent interacts with target cell DNA and causes damage. The blockade of the genotoxic damage at early stages of carcinogenesis constitutes the most effective way for preventing cancer, and it can be achieved by scavenging the reactive oxygen species (ROS) or by inducing the phase-II conjugating enzymes (glutathione-*S*-tranferases (GST), glucuronidases and sulphotransferases) to promote the detoxification of the carcinogenic agent. In the tumour promotion step, mechanisms that stop or slow down cell division could be potentially

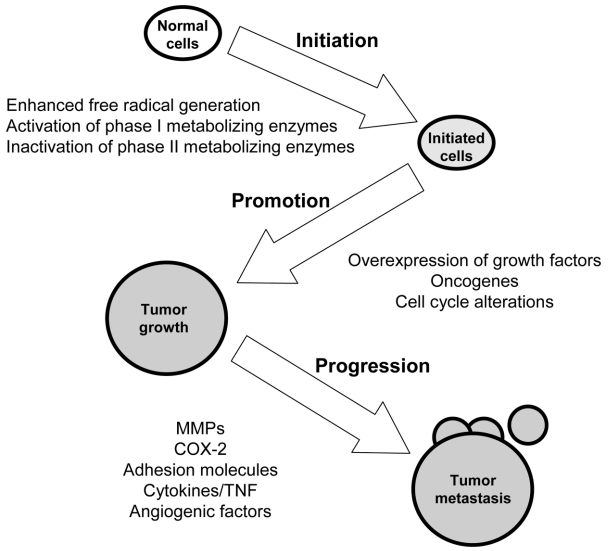


Figure 1. Sequence of multistage carcinogenesis process.

beneficial (induction of cell cycle arrest, apoptosis) in order to restore the lost balance between cell proliferation and apoptosis. At the latest phase of carcinogenesis (progression), the interruption of angiogenesis or the prevention of malignant cells to escape form the original location and invade other tissues could also be potentially useful.

During all the stages of cancer development many key proteins related to cellular antioxidant defences, cellular proliferation and survival transduction pathways are up-regulated (GST, growth factor receptors (GFR), antiapoptotic members of *bcl-2* family genes, AKT, phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPKs), nuclear factor-kappa B (NF-κB), *etc*.) or down-regulated (caspases, proapoptotic members of *bcl-2* family genes, *etc*.) [1, 17] (Figs. 2 and 3). Dietary polyphenols display a vast array of cellular effects, they can affect all stages of carcinogenesis by up- or down-regulating multiple key proteins involved in diverse signal transduction pathways such as regulation of cellular proliferation, differentiation, apoptosis, angiogenesis or metastasis, resulting in a potential beneficial effect [1, 3, 17]. The potential anticarcinogenic effect of polyphenolic compounds seems to be quite specific, and cancer cell lines appear to be more sensitive than normal cells, since polyphenols have shown higher cytotoxicity in cancer cells than in their normal counterparts [18 – 20]. However, it could also be worth mentioning that these anticarcinogenic effects seem to be dependent on the particular dietary polyphenol selected, on the concentration used for the assays, and on the cell type or tissue studied, which points out to an individual analysis for each phenolic compound on a particular cell type or context; consequently, clarifying the molecular mechanisms by which polyphenols might exert a potential anticarcinogenic effect becomes an important challenge.

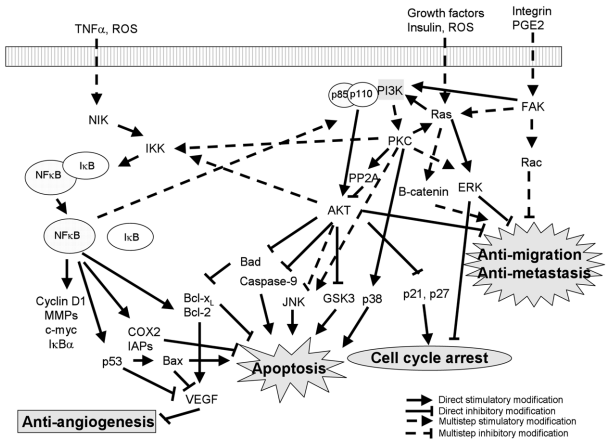


Figure 2. Initiation and regulation of the two principal known apoptotic pathways. Cell-survival and proliferation signalling through PI3K and AKT, ERKs or NF-κB. Signal transduction pathways (key elements) related to cellular inflammation through COX-2, angiogenesis (VEGF) and metastasis.

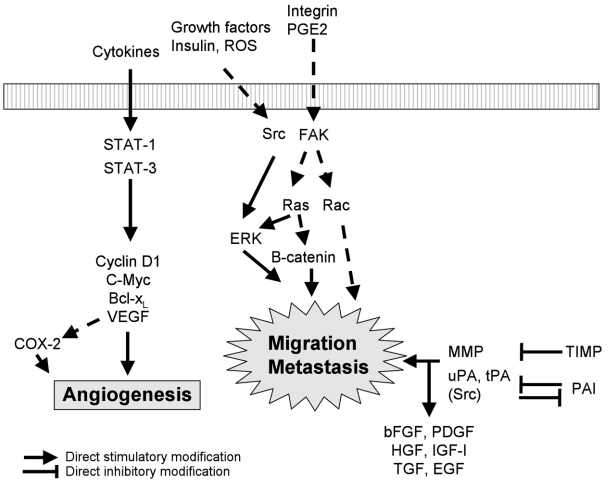


Figure 3. Steps in metastasis: invasive mechanisms of tumours. Regulation in the formation of a vascular network of tumours through STAT.

3 Anticarcinogenic activity of polyphenols in animals

Numerous studies have evaluated the efficacy of polyphenols in various animal models (Table 2). Quercetin, present in apple and onion, apple procyanidins, apple juice and red wine can suppress the tumorigenic activity of different carcinogens in colon cancer [21 – 24]. In studies in mice and rats, resveratrol, which can be found in grapes, was able to inhibit the carcinogenic activity of dimethylbenz[*a*]anthracene (DMBA) and Neuro-2a cells subcutaneously (s.c.) injected to induce breast cancer and neuroblastoma, respectively [25, 26]. In contrast, genistein (abundant in soy) has shown an ability to promote the mammary tumour-initiating activity of DMBA in mice injected with MCF-7 cells s.c. [27].

Green tea polyphenols have shown anticarcinogenic properties during the induction of precancerous gastric lesions and the promotion stage of ileum cancer [28, 29]. Using a slightly different approach, other groups have investigated tea's abilities to prevent tumours by interacting with different signalling pathways in transgenic mice such as Apc^{min} and TRAMP, which develop colon and prostate cancer, respectively [30 – 32]. Moreover, tea also possessed an anticarcinogenic activity against the tumour formation induced by the s.c. injection of HEY cells [33], as well as polyphenon B (present in tea) inhibited the carcinogenic activity of DMBA to produce a buccal cancer [34]. Additionally, one of the most important phenolic compounds in tea, epigallocatechin-3-gallate (EGCG), in a different model of transgenic mice for skin cancer, has exhibited a preventive effect and/or improvement of the situation [35, 36]. EGCG has also shown beneficial effects in lung cancer by decreasing the growth of the primary tumours and metastasis when mice were intraperitoneally (i.p.) injected with B16-F3m cells [37]; however, rats with breast cancer did not improve after receiving EGCG in the drinking water [26].

In others studies, the chemopreventive effects of curcumin, which is present in turmeric powder, were analysed in two rat models of cancer (liver and prostate cancers) [38, 39]. Curcumin showed a preventive effect against hepatocarcinogenesis through the interaction with different signal pathways [38] but not against prostate carcinogenesis [39]. Moreover, the administration of tannic acid (i.p.) induced a significant decrease in the levels of the hepatic CYP2E1, and affected also the phase II enzymes in both hepatic and renal tissues in mice: GST activity was increased in kidneys, but reduced in liver, whereas in both tissues UDP-glucuronosyl transferase (UDPGT) was unchanged and quinone reductase (QR) was unexpectedly diminished [40].

4 Chemopreventive effects of polyphenols on cancer cells

Dietary polyphenols can affect the overall process of carcinogenesis by several mechanisms (Fig. 1) and their effects could depend on tissue or cell type and could differ at high and low doses. In addition, most of the anticarcinogenic effects exerted by dietary phenolic compounds have been shown *in vitro* or in animal studies, but these features have not been proved to occur among humans yet. In order to understand the signalling events leading to potential chemopreventive activities by dietary polyphenols, critical insights into the control intracellular signalling cascades activity of these natural compounds in cancer cells are provided.

Table 2. Modulation of dietary polyphenols of induced cancers in animal models

Polyphenol	Dose	Route	Animal	Cancer	Carcinogen	Effect	Reference
Quercetin	1 g/kg	i.p.	Rat	Colon	1,2-Dimethylhydrazine	↓ Crypt cell proliferation	[21]
Apple procyanidins	0.01%	Oral	Rat	Colon	Azoxymethane	↓ Crypt and aberrant cript foci	[22]
Apple juice	667 mg PP/L	Oral	Rat	Colon	1,2-Dimethylhydrazine	↓ Crypt cell proliferation	[23]
Red wine PP	50 mg/kg	Oral	Rat	Colon	Azoxymethane	↓ Cancer	[24]
Resveratrol	40 mg/kg/day	i.p.	Mouse	Neuroblastoma	Neuro-2a cells s.c.	↑ Long-term survival (70%)	[25]
	100 mg/kg	Gavage	Rat	Breast	DMBA	↓ Proliferation; ↑ apoptotic index	[26]
Genistein	750 ppm	Oral	Mouse	Breast	MCF-7 cells s.c.	↑ Proliferation	[27]
Green tea PP	0.5 – 1.5%	Oral	Rat	Gastric	*N*-methyl-*N*-nitrosoguanidine	↓ Proliferation; ↑ apoptotic index	[28]
	1 g/L	Oral	Mouse	Ileum	Irinotecan	↑ GSSG and ↑ MPO prevented	[29]
Tea	1.5%	Oral	Mouse	Colon	Apc^{min}	↓ Crypt, cyclin d, c-jun, β-catenin	[30]
	0.1%	Oral	Mouse	Prostate	TRAMP	↓ PI3K, p-AKT, ERK1/2, COX-2 ↓ VEGF, uPa, MMP-2 and -9 ↓ IGF-I, IGF-IR; ↑ IGFBP-3	[31, 32]
	12.4 g/L	Oral	Mouse	Ovarian	HEY cells s.c.	↓ Tumour growth	[33]
Polyphenon-B	0.05%	Oral	Hamster	Bucal	DMBA	↓ Proliferation; apoptosis induction	[34]
EGCG	0.045%	Oral	Mouse	Skin	ODC/Ras transgenic	↓ Proliferation and survival	[35]
	1 mg/cm^2	Topical	Mouse	Skin	IL-12 KO (UV irradiated)	Formation of cyclobutane pyrimidine dimers and sunburn are resolved more rapidly	[36]
	3 × (2 mg/0.1 mL/wk)	i.p.	Mouse	Lung	B16-F3m cells i.p.	↓ Metastases and primary tumour growth	[37]
	0.065%	Oral	Rat	Breast	DMBA	= Proliferation	
Curcumin	200 – 600 mg/kg	Gavage	Rat	Liver	Diethylnitrosamine	↑ p21, p53; ↓ PCNA, cyclin E, cdc2, NFκB; = c-Jun, c-Fos, Cdk2, cyclin D1	[38]
	15 – 500 ppm	Oral	Rat	Prostate	DMBA	↓ Tumour incidence, PCNA	[39]
Tannic acid	20 – 80 mg/kg	i.p.	Mice			↓ CYP2E1, GST (in kidney), ↑ GST (in liver), = UDPGT, QR	[40]

4.1 Antioxidant

ROS generation is unavoidable in aerobic organisms. Under normal circumstances cells maintain the levels of ROS with antioxidants, for instance glutathione (GSH), and enzymes, such as catalase (CAT) and superoxide dismutase (SOD). When this balance is perturbed, cellular defences can be overwhelmed, and the cell is injured. Additionally to the mentioned natural defence mechanisms of the cell, dietary polyphenols can also act as antioxidants, preventing injury caused by free radicals and blocking the initiation step of cancer [4, 41, 42]. In more detail, polyphenolic compounds can prevent the DNA-damage caused by free radicals or carcinogenic agents through different mechanisms: (i) direct radical scavenging [41, 43], (ii) chelating divalent cations involved in Fenton reaction [44] and (iii) modulation of enzymes related to oxidative stress (glutathione peroxidase (GPx), glutathione reductase (GR), SOD, nitricoxide sinthase, lipooxygenase, xanthine oxidase, *etc*.) [41, 45] (Table 3).

EGCG and genistein are powerful radical scavengers; genistein protected neurons from the oxidative stress induced by a commonly used pro-oxidant such as *tert*-butylhydroperoxide (*t*-BOOH) [43], and EGCG reduced the cytotoxicity evoked by H_2O_2 and increased the levels of the enzymes related to the oxidative stress, resulting in an enhanced cellular GSH content in a human hepatoma cell line (HepG2) [46]. Quercetin and rutin also induced beneficial changes in the antioxidant defence system in HepG2 cells, since both flavonoids prevented or delayed conditions which favoured cellular oxidative stress [41]. Nevertheless, quercetin showed a stronger protector effect of cells against an oxidative insult than its glycoside rutin. Additionally, in HepG2 cells, *t*-BOOH-induced cell death and lipid peroxidation were prevented after the incubation of the cells with a phenolic-rich juice, showing a decrease in the pro-oxidant induced GPx activation, but not that of GST [47]. It is worth mentioning that certain polyphenols, such as luteolin, apigenin, hesperidin and naringin (present in parsley or citrus),

did not protect human vascular endothelial cells (HUVEC) when cells were treated with H_2O_2 in order to induce apoptosis [48]; however, when cells were incubated with EGCG or quercetin in the same pro-oxidant conditions, both polyphenols restored cell viability and inhibited apoptosis, showing that phenolic compounds differ in their antiapoptotic efficacy [48].

Dietary polyphenols can also act as pro-oxidants depending on the cell type, dose and/or time of treatment, as they can enhance ROS production and therefore induce apoptosis [44, 49 – 52]. In this regard, in colon cancer HT-29 cells, flavone increased the mitochondria pyruvate or lactate uptake, which increased the superoxide radical production and led to apoptosis [53]. Moreover, EGCG and (–)-epigallocatechin (EGC) from green tea induced H_2O_2 formation in human lung adenocarcinoma (H661) and in Ha-*ras*-gene-transformed human bronchial (21BES) cells, but exogenous added catalase prevented both EGCG- and EGC-induced cell apoptosis, which suggested that H_2O_2 is involved in the apoptotic process provoked by both flavanols [52, 54].

4.2 Effects on phase-I and -II enzymes

Procarcinogenic metabolism can be altered by dietary polyphenols by inhibiting phase-I drug-metabolizing enzymes (cytochrome P450; CYP), increasing the activity or modulating the gene expression of phase II conjugating-enzymes (glucuronidation, sulphation, acetylation, methylation and conjugation) (Fig. 1) [55, 56] (Table 3).

In vitro studies have demonstrated that polyphenols, *i. e.* myricetin, apigenin, quercetin, kaempferol and EGCG possess a strong inhibitory effect on CYP1A1, whereas flavanones, flavonols and their glycosides (naringenin, hesperetin, naringin, hesperidin, rutin) and resveratrol exhibited a slight inhibitory capacity [55]. Moreover, flavanols (catechins) showed a poor QR induction in comparison to flavonols (myricetin, quercetin, kaempferol, galangin) [57]. A relation among the inhibitory effects of the polyphenols on CYP1A1, their structure and the type of reaction and substrate used in the assay has been suggested [55].

Phenolic compounds can induce phase II conjugating-enzymes, they can be considered as potential candidates for preventing tumour development. Chlorogenic acid, abundant in plum and cherry, increased the activity of the phase II detoxifying enzymes GST and NADPH quinone oxidoreductase (NQO) in mouse epidermal cells [58]. Similarly, drinks rich in phenolic compounds, tea and mate increased QR activity in the Hepa1c1c7 cells [57] and in general, phenolic compounds, such as quercetin, hesperidin, disomin, chlorogenic acid, *etc*., prevented GSH depletion and ROS formation after an oxidative injury caused by different pro-oxidants [45, 59]. Consequently, tea also showed *in vitro* a protective effect on rat hepatic extracts, which was associated with a reduced activity of CYP2E and an increased activity of phase II detoxifying enzyme UDPGT, suggesting that tea can regulate phase I and phase II drug metabolizing enzymes, although GST activity was unaffected [56].

An antioxidant response element (ARE) (5′-A/G TGA C/T NNNGC A/G-3′) has been found in the promoters of antioxidant enzymes and several drug-metabolizing enzymes such as GST, QR, *etc*. [60]. Several signalling pathways have been involved in the activation of the ARE that binds transcription factors such as nuclear-factor-E2-related factor 2 (Nrf2) [61], although the detailed molecular mechanism remains unclear. It has been reported that in human hepatoma HepG2 cells, a green tea polyphenol extract stimulated the transcription of phase II detoxifying enzymes through ARE [62, 63] and that a decrease in Nrf-2-ARE binding in lung adenocarcinoma A549 cells was induced by EGCG at high concentration [61]. Chlorogenic acid decreased ROS generation and stimulated the nuclear translocation of Nrf-2 and subsequently induced GSTA1 ARE-mediated GST activity in mice epithelial JB6 cells, providing a protective role against carcinogens [58]. Moreover, quercetin up-regulated mRNA Nrf2 expression and protein by inhibiting the ubiquitination and proteasomal turnover of Nrf2, and also repressed Kelch-like ECH-asso-

Table 3. Dietary polyphenol modulation of cellular antioxidant status and phase I and II enzymes[a)]

Polyphenol	Effects
Genistein	↓ *t*-BOOH-induced death; ↑ QR
EGCG	↓ H_2O_2-induced apoptosis; ↑ H_2O_2 production; ↑ ROS; ↑ GSH; ↓ Nrf-2-mediated HO-1 activation
Green tea extract	↓ CYP2E; ↑ UDPGT; ↑ QR; ↑ GST (ARE)
Quercetin	↓ CYP1A1; ↓ lactate dehydrogenase (LDH), ↑↓ GSH; ↓ malondialdehyde (MDA); ↓ ROS; ↓ GPx; ↓ SOD; ↓ GR; ↓↑ CAT; ↓ H_2O_2-induced apoptosis; ↑ QR; ↑ Nrf-2; ↓ Keap1; ↑ NQO1
Rutin	↓ CYP1A1; ↓ ROS, ↓ MDA
Phenolic juice	↓ GPx
Apigenin	↓ CYP1A1; ↓ H_2O_2-induced apoptosis
Luteolin, naringin, hesperidin	↓ H_2O_2-induced apoptosis
Myricetin, kaempferol	↓ CYP1A1; ↑ QR
Flavone	↑ O_2^- production
Chlorogenic acid	↑ GST (ARE); ↑ NQO1; ↑ Nrf-2

References for: genistein [43, 49]; EGCG [44, 46, 48, 50, 52, 54, 61, 62]; green tea [56, 57, 62, 63]; quercetin [41, 45, 46, 48, 55, 64]; rutin [41]; phenolic juice [47]; apigenin [48, 55]; luteolin, naringin, hesperidin [48]; myricetin, kaempferol [55]; flavone [53]; chlorogenic acid [58].

a) The arrows indicate an increase (↑) or decrease (↓) in the levels or activity of the different analysed parameters. In certain cases, opposing results have been obtained since the studies were carried out in different cell types (nontumorigenic, different cancer cell lines, *etc.*) and/or the final effects may depend on the dose and time of treatment with the phenolic compound.

Table 4. Dietary polyphenol modulation of molecular signals involved in apoptosis, cell proliferation and inflammation[a)]

Polyphenol	Induction of cell cycle arrest	Induction of apoptosis	Inhibition of proliferation and inflammation
EGCG	↓ = cyclin D; ↓ = cyclin E; ↓ CDK1; ↓ = CDK2; ↓ CDK4; ↓ CDK6; ↓ PCNA; ↑ p 16; ↑ p18; ↑ = p21; ↑ = p27; ↑ pRb; ↑ p53; = mdm2	↑ ROS; ↑ caspase-3; ↑ caspase-8; ↑ caspase-9; ↑ cytochrome c; ↑ Smac/DIABLO; ↑↓ = Bax; ↑ Bak; ↑ cleaved PPAR; ↓↑ Bcl-2; ↓ = Bcl-x_L; ↓ Bid; ↓ c-myc; = c-IAP1; ↓ c-IAP2; ↓ Mcl-1; ↓ = survivin; ↓ = XIAP	↓ PI3K; ↓↑ = AKT; ↓↑ ERK; ↓ p90RSK; ↓ FKHR; ↓ PDGF; ↓ PDGFRβ; ↓ EGFR; ↓↑ c-fos; ↓ egr-1; ↓ AP-1; ↓ NFκB; ↓ IKK; ↓ COX-2; ↑ = JNK; ↑ Ras; ↑ MEKK1; ↑ MEK3; ↑↓ p38; ↑ IκB; ↑ AMPK; ↑ PGE2; ↑ TNF-α
ECG		↑ ROS, ↑ caspase-3	
Theaflavin	↑ p53	↑ Caspase-3; ↑ caspase-8; ↑ caspase-9; ↑ cytochrome c; ↑ Bax; ↓ Bcl-2	↓ PI3K; ↓ AKT; ↓ p38; ↓ EGFR; ↓ PDGFR; ↓ NFκB; ↓↑ ERK
Green tea (or extract)	↓ Cyclin D; ↓ cyclin E; ↓ CDK1; ↓ CDK4; ↓ PCNA		
Genistein	↓ Cyclin B1; ↓ Cdc25C; ↓ Cdc2; ↑ p21; ↓ PCNA		↓ AKT; ↓ ERK; ↓ NFκB; ↓ AP-1; ↓ COX-2; ↓ PGE2; ↑ p38; = JNK
Ellagic acid	↓ Cyclin A; ↓ cyclin B1; ↑ cyclin E; ↑ p53	↑ Caspase-3; ↑ caspase-9; ↑ cytochrome c; ↓ = Bcl-x_L	
Punicalagin	↓ Cyclin A; ↓ cyclin B1; ↑ cyclin E		↓ AKT; ↓ NFκB; ↓ COX-2; ↓ PGE2
Curcumin	↓ Cyclin A; ↓ CDK1; ↑ p21; ↑ Cdc2	↑ Caspase-3; ↑ caspase-7; ↑ = caspase-8; ↑ caspase-9; ↑ AIF; ↑ cleaved PPAR; ↓ ψm; ↓ = Bcl-x_L	↓ AKT; ↓ mTOR; ↓ p70S6K1; ↓ 4E-BP-1; ↓ IGF-I; ↓ NFκB; ↓ IKK; ↓ IκB; ↓ COX-2; ↓ PGE2
Anthocyanins	↑ p21	↑ ROS; ↑ Bax/Bcl-2; ↑ Bim	↑ p38;↑ JNK
Quercetin	↑ p53	↑ Caspase-3; ↑ caspase-7; ↑ caspase-8; ↑ caspase-9; ↑ cytochrome c; ↑= Bax; ↑ cleaved PPAR; ↓ ROS, ↓ ψm; ↓ = Bcl-2; ↓ = Bcl-x_L	↓ PI3K; ↓↑ = AKT; ↓↑ ERK; ↓ PKCα; ↓ EGFR; ↓ Erb2R; ↓ Erb3R; ↓↑ JNK; = PKCβ; = PKCδ
Piceatannol	↓ Cyclin A; ↓ cyclin B1; ↓ cyclin E		
Flavone	↓ Cyclin B; ↓ cyclin D; ↓ cyclin E; ↓ Cdc2	↑ Bak; ↓ = Bcl-x_L	↓ NFκB; ↓ COX-2
Sylimarin	↓ Cyclin B; ↓ cyclin D1; ↓ CDK2; ↓ CDK4; ↑ p21; ↑ p27	= ROS; ↑ caspase-3	
Galangin			
Luteolin		↑ Caspase-3; ↑ caspase-8; ↑ caspase-9; ↑ cytochrome c; ↑ Fas/CD45; ↑ Bax; ↑ Bak; ↓ Bcl-x_L; ↓ survivin; ↓ STAT3	↑ JNK; ↓ EGFR
Apigenin		= Caspase-3	↓ AKT; ↓ p70S6K1; ↓ = PKCδ; ↓ Ras; ↓ MEKK1; ↓ AP-1; = PKCα; = PKCβ
Apple procyanidins		↑ Caspase-3	↓ EGFR; ↑ ERK; ↑ = JNK; ↑ PKC
Mangiferin			↓ ICAM1; ↓ COX-2; ↓ IKK; ↓ NKκB; ↓ IκBα

References for: EGCG [18, 19, 50–52, 63, 65–71, 73, 91–96, 112, 115–118, 123, 127, 130–133, 138–140, 142, 168, 169]; ECG [19]; Theaflavin [97, 98, 117, 128]; Green tea (or extract) [69]; Genistein [74–77, 131, 169]; Ellagic acid [79, 83]; Punicalagin [79, 134]; Curcumin [80, 81, 108–110, 120]; Anthocyanins [82, 89]; Quercetin [83, 100–107]; Piceatannol [84]; Flavone [5, 85]; Sylimarin [86]; Galangin [99]; Luteolin [111, 112]; Apigenin [121, 122]; Apple procyanidins [22, 125]; Mangiferin [141].

a) The arrow indicate an increase (↑) or decrease (↓) in the levels, phosphorylation status or activity of the different signals. In certain cases, opposing results have been obtained since the studies were carried out in different cell types (nontumorigenic, different cancer cell lines, *etc.*) and/or the final effects may depend on the dose and time of treatment with the phenolic compound.

ciating protein-1 (Keap1) which were essential for ARE-mediated NQO1 inhibition [64].

4.3 Cell cycle arrest

In cancer, normal cell growth and behaviour is lost and alterations in the regulation of cell cycle have been described [65–68]. Thus, any perturbation of cell cycle-specific proteins by dietary polyphenols can potentially affect and/or block the continuous proliferation of tumorigenic cells (Figs. 1 and 2 and Table 4).

G1 phase cell cycle arrest was induced after EGCG or green tea polyphenol treatments through down-regulation of cyclin D, cyclin E, cyclins-dependent kinase (CDK)1,

CDK2, CDK4 and proliferating cell nuclear antigen (PCNA) over time in breast and cervical cancer cells [69, 70], and EGCG also inhibited proteins of the ubiquitin-proteasome-mediation degradation pathway such as pRb, p21, p27 and p53 in breast, bladder and prostate cancer cell lines [66–68, 70, 71]. Similarly, down-regulation of cyclin D1, CDK4 and CDK6, but not of cyclin E and CDK2, by EGCG induced G0–G1 cell cycle arrest in human epidermal cancer cells [65], which led to retinoblastoma protein (Rb) hypophosphorylation and prevention of the transcription of crucial genes for S-phase transition such as activation of the E2F/DP heterodimers [72]. Up-regulation of the CDK inhibitors p21, p27, p16 and p18 has also been reported [65]. EGCG inhibited cell proliferation induced by the oncogenic *Ras* and blocked cell cycle transition at G1 phase via inhibition of cyclin D1 [73]. Thearubigin, a black tea polyphenol, led to G2/M phase cell cycle arrest in a dose dependent manner alone or combined with the isoflavone genistein on human prostate PC-3 carcinoma cells [74]. G2/M arrest also resulted after genistein treatment, which in breast and tongue squamous cancer cells increased p21 expression and decreased cyclin B1 and PCNA expressions without changing the number of apoptotic cells [75, 76], whereas in mammary cells, genistein decreased levels of Cdc25C and activity of Cdc2, in concert with an increased expression of p21 [77].

Gallic acid, present in tea and black currant, attenuated progression from G0–G1 to the S-phase cell cycle of HL-60 promyelocytic leukaemia cells [78]. In this regard, treatment of Caco-2 cells (human colon adenocarcinoma cells) with a phenolic acid such as ellagic acid, or punicalagin, hydrolysable tannin which rendered ellagic acid in the culture medium to enter into the cell and that can be found in strawberries, walnuts and pomegranate, provoked S cell cycle arrest, preceded by increased expression of cyclin E and decreased expression of cyclins A and B1 [79]. G2/M cell cycle arrest, down-regulation of the cyclin A and up-regulation of the CDK inhibitor p21 and Cdc2 have also been observed by curcumin in human colon and bladder cancer cells [80, 81] and, interestingly, anthocyanins, predominant phenolic compounds in berry extracts, disrupted the cell cycle by increasing p21 expression [82] similar to ellagic acid and quercetin which also increased p53 levels [83]. Additionally, piceatannol, a grape and wine polyphenol, prevented human melanoma cell proliferation by arresting the cell cycle at G2 phase and down-regulating cyclins A, E and B1 [84], and 2′-OH flavanone, which also led to G2/M phase accumulation, reduced cyclin B, cyclin D and Cdc2 in human lung A459 cancer cells [85]. Moreover, cell-cycle arrest through the induction of cyclin-dependent kinase inhibitor (CDIs; p21 and p27) and the inhibition of CDK4, CDK2, cyclin D1 and cyclin E by silymarin has been reported [86].

Tumour cells seem to be more sensitive to all these influences than normal cells, as green tea polyphenols induced a dose-dependent inhibition of cell growth, morphological alterations, G0–G1-phase arrest of the cell cycle and induction of apoptosis in human osteosarcoma cells (MG-63 and Saos-2), but not in normal rat osteoblasts [20].

4.4 Apoptosis

Apoptosis induction may be considered one of the important targets in a preventive approach against cancer at the moment, by reverting the conversion of a normal cell to a malignant one. This programmed-cell death is a complex process that involves the active participation of affected cells in a self-destruction cascade (Fig. 2 and Table 4).

Many dietary chemopreventive polyphenols, including quercetin, EGCG, apigenin, chrysin, silymarin, curcumin, ellagic acid and resveratrol, evoke their inhibitory effect on carcinogenesis through the induction of apoptosis [1, 17]. Moreover, tumour cells seem to be more sensitive to these influences than normal cells [20, 82, 87–89]. For instance, quercetin exerted the apoptotic effect in a selective manner: it significantly inhibited the growth of highly aggressive PC-3 and moderately aggressive DU-145 prostate cancer cell lines, but it did not affect to poorly aggressive LNCaP prostate cancer cells or normal fibroblasts [90]. Accordingly, cell growth and cell cycle arrest at G0–G1 phase and apoptosis induction were demonstrated in A431 cells but not in normal (NHEK) cells [65]. Moreover, polyphenols exert a differential effect on the oxidative environment of cancer and normal cells, as they might modify the redox system of carcinogenic cells, being more pronounced the cytotoxic effects in carcinogenic than in normal cells [19, 52]. EGCG and epicatechin gallate (ECG) induced ROS generation which may mediate apoptosis by inducing DNA fragmentation, activation of caspases-3 and -9, release of the apoptogenic cytochrome *c*, Smac/DIABLO and apoptosis-inducing factor (AIF), in concert with diminished levels of antiapoptotic proteins such as Bcl-2 and myeloid cell leukaemia-1 (Mcl-1) [19, 50–52]; moreover, catechins contributed to the growth inhibitory effect by inducing cell cycle arrest in cancer cells but not in their normal counterparts [19, 50–52].

EGCG treatment of several cancer cell lines induced apoptosis through the activation of proteins related to the programmed-cell death pathways such as caspases-3, -9 and -8 [91–94], as well as through the inhibition of other proteins such as the inhibitor of apoptosis protein-2 (c-IAP2), X-linked IAP (XIAP), Bcl-2, Bcl-x_L and Bid [93, 95]; moreover, in certain circumstances, apoptotic death occurred in concert with an inhibited telomerase activity [94] and/or with the activation of both apoptotic pathways (extrinsic and intrinsic routes) [91, 92]. Promotion of apoptotic cell death by EGCG in sarcoma 180 cells was induced through G2/M cell cycle arrest, down-regulation of Bcl-2 and *c-myc*, up-regulation of p53 and Bax and without changes in the expression of p21, p27, Bcl-x_L, mdm2 and

cyclin D1 [96]. Up-regulation of p21, p53 and Bax have also been reported in prostate cancer PC-3 cells together with increased levels of caspases-3, -9 and proteolytic cleavage of poly ADP-ribose polymerase (PPARγ) [68]. However, inactivation of p53 by using small interfering RNA (siRNA) generated resistance against EGCG-induced apoptosis, suggesting that EGCG activated growth arrest and apoptosis primarily via a p53-dependent pathway which involved the function of both p21 and Bax [68]. In addition, theaflavin, a black tea phenolic compound, induced DNA fragmentation, activation of caspases-3 and -8, up-regulation of Bax and down-regulation of Bcl-2 [97]. Interestingly, theaflavin also induced apoptosis by up-regulating p53, shifting Bax/Bcl-2 ratio, increasing the release of cytochrome *c* and activating caspases-9 and -3 in human prostate LNCaP carcinoma cells [98].

Anthocyanins decreased cell proliferation of colon cancer HT-29 cells in a concentration-dependent manner, whereas rutin, epicatechin, chlorogenic acid or *p*-hydroxybenzoic acid did not show any significant growth inhibitory effect [82]. Anthocyanins induced apoptosis in colon cancer cells, since DNA fragmentation and unbalance between Bax and Bcl-2 mRNA expressions were observed [82]. Moreover, anthocyanins activated the mitochondrial pathway through Bim, by increasing ROS generation in leukaemia cells, but not in normal human peripheral blood mononuclear cells [89]. Similarly, galangin, a flavonol present in India root spice and propolis, exerted an antiproliferative effect on leukaemia, which was associated to apoptosis induction as it was demonstrated by detected DNA fragmentation, increased hypodiploid peak of DNA content and enhanced expression of active caspase-3, although increased ROS generation was not reported [99].

Quercetin has also been shown to induce apoptosis in several cancer cell types, demonstrated by morphological alterations and DNA fragmentation [100 – 103], activation of caspases-3, -7 and -9, cleavage of PARP [101, 104], release of cytochrome *c* [100], or activation of the mitochondrial pathway [104, 105] with loss of the mitochondrial membrane potential [102]. Down-regulation of antiapoptotic Bcl-2 proteins, Bcl-x_L and Bcl-2, and up-regulation of proapoptotic Bcl-2 proteins such as Bax have also been reported [101]. Interestingly, an apoptotic effect with unchanged levels of Bax or Bcl-x_L, but decreased Bcl-2 expression has been observed [106, 107]. Similarly, ellagic acid induced apoptosis via intrinsic pathway (activation of caspases-3 and -9) through Bcl-x_L down-regulation and release of cytochrome *c* to the cytosol in colon cancer Caco-2 cells [79]. Furthermore, ellagic acid and quercetin induced synergistically apoptosis in diverse cancer cell lines [83].

Curcumin activated caspases-3, -7, -8 and -9 in several colon cancer cell lines, but a reduced activation of caspases related to the mitochondrial pathway together with a partial blocking of AIF were observed in the presence heat shock proteins, whereas caspase-8 activation was not affected [108, 109]. Moreover, curcumin treatment reduced cell number, since decreased cyclin and CDK1 levels and suppressed Bclx_L levels, resulting in a reduced mitochondrial membrane potential and increased cleavage of PARP [109, 110]. Similarly, treatment of human colon carcinoma HT-29 cells with dietary flavone led to post-G1 arrest and apoptosis, preceded by changes in membrane permeability, DNA fragmentation and increased expression of p21, Bak and decreased expression of cyclin B, cyclin E and Bcl-x_L [5]. Additionally, luteolin, present in capsicum pepper, caused an increase in the apoptotic hepatoma cell death, which was consistent with a caspase-8 activation, enhanced expression of Fas/CD45 and decreased signal transducers and activators of transcription (STAT)3, survivin and Bcl-x_L expression levels [111], whereas this flavonoid triggered the mitochondrial pathway of apoptosis in different hepatoma cells as shown by the activation of caspases-3 and -9, release of cytochrome *c* and increased translocation of Bax/Bak to the mitochondria [112].

4.5 Antiproliferation and antisurvival effects

Signalling pathways through PI3K/protein kinase B (AKT), GFR/Ras/MAPKs and nuclear factor κ B (NF-κB) regulate cell proliferation and survival [113, 114], and thus, they are indirectly involved in the regulation of apoptotic cell death (Fig. 2).

Many dietary phenolic compounds can effectively suppress tumorigenic signalling *in vitro* (Table 4).

4.5.1 Inhibition of signalling through GFR/Ras/MAPK and PI3K/AKT

EGCG, one of the most studied dietary polyphenols, decreased proliferation in diverse cell types, and its anticarcinogenic effect has been attributed to a complete inhibition of platelet-derived growth factor (PDGF-BB), PDGF receptor β (PDGF-Rβ), c-fos, egr-1, PI3K and phosphorylation of extracellular regulated kinase (ERK)1/2, whereas EGF was not affected in vascular smooth muscle cells [115]; moreover, EGCG and theaflavins inhibited the PI3K/AKT signalling pathway by decreasing the levels of both PI3K subunits (p85 and p110) and phosphorylated levels of AKT and ERK-1/2 [116, 117]. On the other hand, opposing effects were observed in no carcinogenic cells: EGCG stimulated *Ras*, MEKK1, MEK3, p38 kinase and activator protein-1 (AP-1) factor activity and gene expression in normal keratinocytes in marked contrast to the EGCG-dependent decrease in AP-1 factor function that was observed in cancer cells, suggesting that the mechanism of EGCG action was markedly different in normal and transformed cells [118]. Moreover, the EGCG-induced effects were suppressed by curcumin [119], indicating the specific and differential regulation of gene expression by dietary polyphenols and that two polyphenols can produce opposite effects.

Curcumin treatment inhibited the phosphorylation of AKT, mammalian target of rapamycin (mTOR) and downstream effector molecules, p70 S6 kinase1 (S6k1), eukaryotic initiation factor 4E (eIF4E) binding protein (4E-BP1), as well as the basal insulin-like growth factor (IGF) I-induced motility in various types of cancer cells, which resulted in cell cycle G1 arrest and apoptosis [120]. Similarly, apple procyanidins inhibited cell growth, activated caspase-3 and increased MAPK (ERK1/2 and c-Jun N-terminal kinase (JNK)) levels and protein kinase C (PKC) activity in colon cancer-derived metastatic cells SW620 [22]. Suppression of PKCδ activity and AP-1 levels together with inhibition of *Ras* and MEKK1 were induced by apigenin (present in parsley, onion, tea, orange) in keratinocytes, showing opposite effects to the green tea polyphenol EGCG [121]; apigenin also caused the suppression of cell proliferation, but not apoptosis [121, 122] and inhibited AKT and p70S6K1 phosphorylation [122]. Quercetin dose-dependently inhibited the expression of PKCα but not that of PKCβ and PKCδ, although induced the translocation from cytosol to the nucleus of PKCδ [107].

Genistein treatment resulted in p38 activation, ERK1/2 inactivation and unchanged JNK activity [77], whereas luteolin activated JNK in HepG2 cells [112]. Similarly, anthocyanins also induced ROS-dependent activation of p38 and JNK, which contributed to the apoptotic effect in leukaemia cells [89].

In contrast, in certain circumstances, low concentrations of dietary polyphenols, such as quercetin, green tea polyphenols and EGCG, may activate MAPK pathways (ERK, JNK) leading to expression of survival genes (*c-fos*, *c-jun*) and eliciting survival and protective mechanisms [63], whereas higher concentrations of quercetin or EGCG were needed to activate the caspase pathway and led to apoptosis [62, 105, 123]. In this context, low concentrations of quercetin increased both AKT and ERK phosphorylation, demonstrating a prosurvival effect, whereas increased caspase-3 activity and inhibition of AKT and ERKs rather than activation of JNK (apoptotic effect) were observed with higher flavonoid concentrations [101, 103 – 105]. Accordingly, quercetin also provoked apoptotic cell death and decreased AKT and ERKs phosphorylated levels without affecting the expression levels of both p85- and p110-PI3K subunits [104] and decreased in a dose-dependent manner Erb2 and Erb3 receptor tyrosine kinase [106].

Inhibition of GFR (epidermal growth factor receptor (EGFR), PDGF-R or HER-2/*neu*) phosphorylation leads to the suppression of downstream events, resulting in the inhibition of cell growth. Luteolin, quercetin, polyphenol-rich apple juice extract and red wine polyphenols inhibited EGFR and induced antiproliferative effects [6, 124 – 126]. Phenolic compounds in red wine showed an antiproliferative effect through the inhibition of ERK1/2 and the activation of p38 and JNK1/2 [126]. Similarly, reduced EGFR protein and phosphorylation levels and decreased PDGF-R phosphorylation after EGCG and theaflavin treatment have also been reported [127, 128]. Moreover, the inhibition of EGFR induced by EGCG depended on ERK1/2 and AKT activation, but not on JNK activation, which was associated to a reduced phosphorylation of downstream substrates (90 kDa ribosome S6 protein kinase (p90RSK), forkhead-relate transcription factor (FKHR) and Bad) and cell cycle arrest [70].

4.5.2 Inhibition of signalling through NF-κB

NF-κB is also indirectly implicated in the regulation of apoptotic cell death since it inhibits apoptosis through the induction of cell-survival genes and down-regulation of mediated cell-death events [129].

ECGC treatment decreased NF-κB levels and activity in a dose dependent manner in cancer (A431) and normal human NHEK epidermal keratinocytes, although these effects occurred at higher doses of the dietary polyphenol in NHEK cells compared to A431 cell line [18]. EGCG also inhibited growth and induced apoptosis through a reduction of the NF-κB p65 and/or p50 subunit levels [5, 93, 116], activation of inhibitor of κB (IκB) protein [71] or inhibition of IκB kinase (IKK) in different cancer cells [130]. Interestingly, theaflavins also induced apoptosis by the down-regulation of NF-κB activity, ERK and p38 phosphorylated expressions [98].

Curcumin inhibited NF-κB, phosphorylation of IκB and IKK, leading to the suppression of AKT activation, induction of apoptosis and G1-S cell cycle arrest [109]. Similarly, genistein inhibited cell growth and induced apoptosis of breast cancer cells through the down-regulation of AKT, ERK, NF-κB and AP-1 [131], which suggested that the inactivation of NF-κB is partly mediated by AKT and demonstrated the crosstalk between AKT and NF-κB pathways [131].

Furthermore, in response to various stimuli, such as repetitive low-grade stress caused by H_2O_2, exposure to UV radiation or tumour necrosis factor (TNF)-α, EGCG and punicalagin (a phenolic compound of pomegranate) impeded the activation of both AKT and NF-κB, as well as its later nuclear translocation, which resulted in an inhibition of the apoptotic cell death, recovering *bcl-2* expression and inhibiting Fas ligand levels [132 – 134]. In this regard, pretreatment of mice epithelial JB6 cells with chlorogenic acid blocked UVB- and 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced transactivation of AP-1 and NF-κB, showing a protection against environmental carcinogen-induced carcinogenesis [58]; at low concentrations, chlorogenic acid decreased the phosphorylation of JNK, p38 and MAPK kinase 4, and higher doses were required to inhibit ERK induced by the carcinogenic agents [58].

4.6 Anti-inflammation

The association between inflammation and cancer has been reported by epidemiological and clinical studies [135], and

among all key molecular players it could be mentioned that NF-κB, TNF and cyclooxygenase-2 (COX-2) are involved in this process, since they promote the inflammation but also cell proliferation, antiapoptotic activity, angiogenesis and metastasis [136] (Figs. 1 – 3).

Inhibition of COX, particularly the COX-2 isoenzyme, and blocking the prostaglandin (PG) cascade may have an impact on neoplastic growth and its development by inhibiting proliferation, angiogenesis and metastasis. COX-2 is highly overexpressed in premalignant and malignant conditions in colon, liver, pancreas, breast, lung, bladder, skin, stomach, head, neck and oesophagus cancer cells [137]. Therefore, the potential utility of selective COX-2 inhibitors in the prevention and treatment of cancer is important (Table 4).

Genistein treatment resulted in cell cycle arrest, suppression of PGE2 synthesis and inhibition of COX-2 activity without increasing apoptosis in head and neck cancer cells [76]. On the other hand, flavone induced apoptosis in human colon carcinoma cells through changes in mRNA levels of cell-cycle- and apoptosis-related genes including COX-2 and NF-κB [5]. EGCG treatment led to a down-regulation of ERK1/2 and AKT pathways and inhibition of constitutive COX-2 mRNA and protein overexpression, which resulted in decreased COX-2 promoter activity by inhibiting NF-κB activity [138]). AMP-activated protein kinase (AMPK) has also been demonstrated to be involved in the apoptotic effect of EGCG by promoting apoptotic proteins such as p53 and PARP [139]. Moreover, this green tea flavonoid enhanced ROS generation, an upstream modulator that activated AMPK, which in turn down-regulated COX-2 expression, and reduced the levels of vascular endothelial growth factor (VEGF) and glucose transporter-1 [139]. Curcumin decreased the levels of COX-2 mRNA and protein expression without significant changes in the values of COX-1, which correlated with a diminished synthesis of PEG2 [80].

In contrast, gallic acid inhibited both COX-1 and -2, which was in concert with a dose-dependent induced apoptosis [78]. Punicalagin and EGCG impeded the activation of TNF-α-induced COX-2 protein expression or chemokines and PGE2 production, respectively in colon cancer cells [134, 140]. Similarly, mangiferin blocked TNF-induced NF-κB activation and NF-κB-dependent genes such as *ICAM1* and *COX2* through inhibition of IKK activation and subsequent blocking of phosphorylation and degradation of IκBα [141]. Additionally, mangiferin inhibited TNF-induced NF-κB p65 phosphorylation, its translocation to the nucleus and NF-κB activation induced by other inflammatory agents, together with inhibition of TNF-induced ROS generation and enhanced GSH levels and catalase activity [141]. Other natural phenolic compounds have also shown an activity to inhibit the TNF-α release in cancer, such as geraniin, corilagin and EGCG [142]. EGCG and sulindac co-treatment in human lung cancer PC-9 cells, up-regulated expressions of *GADD153* and *WAF-1* genes, and also induced down-regulation of T-plasminogen activator, tissue inhibitors of MMP (*TIMP3*), IL-1β and integrin β4 gene expressions, which were not observed with EGCG or sulindac alone [142].

5 Potential therapeutic effects of polyphenols on cancer cells

5.1 Antiangiogenesis

Angiogenesis is a key stage in tumour growth, invasion and metastasis (Figs. 1 and 3). Phenolic compounds possess antiangiogenic effects (Table 5), but their molecular mechanisms are not clear yet. It has been reported antiangiogenic effects for ellagic acid, EGCG, genistein and anthocyanin-rich berry extracts through down-regulation of VEGF, VEGF receptor-2 (VEGFR-2), PDGF, PDGF receptor (PDGFR), hypoxia-inducible factor 1α (HIF-1α) and matrix metalloproteases (MMPs), as well as inhibition of phosphorylation of EGFR, VEGFR and PDGFR [143 – 146]. Moreover, polyphenols exert a differential effect on antiangiogenic factors of cancer and normal cells; EGCG induced a dose-dependent increase in HIF-1-mediated transcription and HIF-1α protein levels under normoxia, but both parameters decreased after cotreatment of prostate cancer cells with EGCG and ferrous ions, suggesting that the green tea polyphenol may act as a ferrous ion chelator and as a preventive agent against enhanced HIF-1α in cancer cells [147].

Quercetin, myricetin, kaempferol and galanin were able to suppress the VEGF-stimulated HUVEC tubular structure formation and to inhibit the activated U937 monocytic cell adhesion to HUVEC cells, playing an important role in the prevention of angiogenesis [148]. Schindler and Mentleiny [149] have reported that flavonoids reduced the release of VEGF from human breast cancer cells, being the order of the inhibitory potency as follows: naringin > rutin > apigenin > genistein > kaempferol. Delphinidin also inhibited VEGF-induced migration and proliferation through the blockade of cell cycle in G0/G1 phase (increased expression of p21, p27 and reduced levels of cyclin D1, cyclin A) [150]. Moreover, the delphinidin-induced antiproliferative effect might also be triggered by the additional contribution of an early activation of ERK1/2, overexpression of caveolin-1 and down-regulation of *Ras* [151]. Luteolin inhibited VEGF-induced survival and proliferation of HUVEC cells through the blockage of PI3K/AKT pathway, and the antimitotic effect of the polyphenol was mediated by inhibiting the PI3K/p70S6K pathway [152]. Similarly, apigenin also inhibited VEGF transcriptional activation through the HIF-1 binding site, decreasing HIF-1α but not HIF-1β subunit, and inhibited both AKT and p70S6K1 activation in A459 lung cancer cells [122]. In addition, EGCG induced apoptosis by activating caspase-3 and suppressing Bcl-2, XIAP

Table 5. Dietary polyphenol modulation of molecular signals in angiogenesis and metastasis[a)]

Polyphenol	Inhibition of angiogenesis	Inhibition of metastasis
Ellagic acid	↓PDGFR; ↓VEGFR	
EGCG	↓HIF-1α; ↓VEGF; ↓VEGFR1; ↓VEGFR2	↓MMP-2; ↓MMP-9; ↓FAK; ↓proMMP-2; ↓MRLC; ↓vimentin; ↓laminin; ↓integrinα2β1; ↓uPA; ↓HuR; ↑proMMP-7; = TIMP-2; = MT1-MMP
EGC, EC, baicalein		↓MMP-9; ↓HuR
Genistein	↓VEGF; ↓FGF	↓uPA; ↓uPAR; ↑PAI;
Daidzein		↓uPA; ↓uPAR
Anthocyanins	↓VEGF	↓uPA; ↓MMP-9
Quercetin	↓VEGF; ↓VCAM1; ↓I-CAM1	↓FAK; ↓MMP-2; ↓MMP-9
Myricetin, kaempferol	↓VEGF; ↓VCAM1; ↓I-CAM1	
Apigenin	↓VEGF; ↓= HIF-1α; = HIF-1β	↓MMP-2; ↓MMP-9
Delphinidin, naringin, rutin	↓VEGF	
Luteolin	↓VEGF	↓MMP-2; ↓MMP-9; ↓FAK
Curcumin		↓MMP-1; ↓MMP-2
8-Prenylnaringenin	↓VEGF; ↓FGF	
Pomegranate (extract)	↓VEGF; ↓MIF	
Hydrolysable tannins		↓MMP-2; ↓MMP-9

References for: Ellagic acid [145]; EGCG [95, 106, 139, 143, 144, 147, 158–160, 164, 165, 167, 168]; ECG, EC, baicalein [156, 160]; genistein [149, 153, 169–171]; daidzein [169, 170]; anthocyanins [146, 172]; quercetin [124, 148, 161, 162, 169]; myricetin, kaempferol [148]; apigenin [122, 149]; delphinidin, naringin, rutin [149, 150]; luteolin [124, 152, 161]; curcumin [149, 163]; 8–prenylnaringenin [153]; pomegranate (extract) [154]; hydrolysable tannins [157].

a) The arrows indicate an increase (↑) or decrease (↓) in the levels, phosphorylation status or activity of the different signals. In certain cases, opposing results have been obtained since the studies were carried out in different cell types (nontumorigenic, different cancer cell lines, *etc.*) and/or the final effects may depend on the dose and time of treatment with the phenolic compound.

and Mcl-1 proteins, which subsequently regulated VEGF signalling and led to the inhibition of VEGF and VEGF-R1 and VEGF-R2 phosphorylation [95, 139]. A novel polyphenol, 8 prenylnaringenin, and genistein inhibited angiogenesis induced by basic fibroblast growth factor (bFGF), VEGF or by the synergistic effect of both cytokines combined [153]. Moreover, antiangiogenic potential of polyphenolic pomegranate fractions, through the inhibition of migration inhibitory factor (MIF) and VEGF have been demonstrated [154].

5.2 Inhibition of metastasis

Metastasis involves the interplay among extracellular matrix (ECM) degradation, proteolysis, cell adhesion, cell migration, angiogenesis and invasion [155] (Figs. 1 and 3). Dietary polyphenols possess anti-invasive and antimetastasic properties (Table 5), but the molecular mechanism remains unclear.

Baicalein, epicatechin and EGC inhibited cell shedding and invasion by a decreased ROS generation and down-regulated MMP-9 expression [156]. Delphinidin inhibited cell migration [150], as well as hydrolyzable tannins, which also inhibited MMP-2 and -9 activities without suppressing the activation of ERK-MAPK or PI3K/AKT pathways [157]. EGCG prevented metastasis and invasion through its inhibitory effects on expression or activity of MMP [143, 144, 158, 159] and focal adhesion kinase (FAK) and without affecting MT1-MMP and tissue inhibitor of MMP-2 (TIMP-2) [158, 159]. Similarly, green tea catechins such as EGCG, catechin-gallate and ECG inhibited in a time- and dose-dependent manner MMP-9 secretion and mRNA stabilizing factor HuR, which plays a pivotal role in the development of tumours, whereas the 67 kDa laminin remained unaffected [160]. Thus, EGCG seemed to prevent metastasis and invasion, but it is worth mentioning that EGCG unexpectedly induced proMMP-7 induction and production in HT-29 human colorectal cancer cells through ROS formation and activation of JNK1/2, c-JUN, c-FOS and AP-1, but not p38 MAPK or ERK1/2 [106]. On the other hand, quercetin and luteolin were able to inactivate the EGFR tyrosine kinase activity, which has been proposed to stimulate cell migration and downstream signalling pathways and to reduce FAK phosphorylation and MMP secretion (MMP-2 and -9) by unclear mechanisms at present [124, 161, 162]. Down-regulation of MMP-1 and -2 has also been reported by curcumin due to the inhibition of NFκB/AP-1 mediated transcription which can explain the reduced invasion *in vitro* and metastasis *in vivo* [163].

Dietary polyphenols might also interfere with cancer cell adhesion and movement processes through multiple mechanisms [1]. EGCG disrupted the stress fibres and decreased the phosphorylation of the myosin II regulatory light chain (MRLC), which are necessary for both contractile ring formation and cell division, through the binding of the flavanol to the 67 kDa laminin receptor [164]. Moreover, EGCG also inhibited the phosphorylation of the intermediate filament protein vimentin, which is essential to maintain the

Table 6. Clinical trials carried out with phenolic compounds in patients with cancer

Polyphenol	Cancer	Phase	Dose/frequency	No. patients	End point	Reference
Pomegranate juice	Prostate	II	570 mg gallic acid/day	48	↓PSA	[173]
Quercetin	Multi-organ cancer	I	60 – 1400 mg/m^2/wk	51	Antitumour activity. Renal toxicity	[174]
Green tea	Solid tumours	I	0.5 – 5.05 mg/m^2/day 1 – 2.2 mg/m^2/3 days	49	4.2 mg/m^2/day or 1 mg/m^2/3 days are tolerated	[175]
	Lung	I	3 g/m^2/day	17	Limited activity as cytotoxic agent	[176]
	Prostate	II	6 g/ day in 6 doses	42	↓PSA	[177]
	Liver	II	500 – 1000 mg/day	124	↓Urinary 8-OHdG	[178]
Curcuma	Colorectal		2.2 g/day (= 180 mg curcumin)	15	Well tolerated. Dose-limiting toxicity was not observed. Low oral bioavailability and possible intestinal metabolism	[179]

structure and mechanical integration of the cellular space, and this dephosphorylation might also be related to the inhibition of cell proliferation induced with the EGCG incubation [165]. Inhibition of cell adhesion to fibronectin and fibrinogen by EGCG have been demonstrated, but the flavanol also affected to the expression and affinity of integrin α2β1, FAK phosphorylation, actin cytoskeleton, MMPs activities and expressions, migration and tubular network formation on 3-D Matrigel, suggesting a profound effect on tumour cell behaviour [159]. Quercetin also induced cytoskeletal alterations in microtubule polymerization dynamics through the direct binding to tubulin [166].

Urokinase is involved in the degradation of the ECM and tumour invasion. EGCG was able to suppress the urokinase-type plasminogen activator (uPA) expression and its promoter activity [167, 168]. EGCG regulated the uPA expression by at least two different mechanisms: inhibition of ERK and p38, which led to the suppression of the uPA promoter activity, and destabilization of uPA mRNA in a MAPKs (ERK and p38) independent-pathway [168]. Accordingly, genistein and daidzein inhibited cell migration by suppressing the secretion of uPA, reducing uPA receptor (uPAR), NF-κB and AP-1 [169, 170], whereas genistein alone also attenuated uPA activity and stimulated PAI activity in neuroblastoma cells [171]. Black rice anthocyanins (peonidin-3 glucoside and cyanidin-3 glucoside) reduced invasion and motility of diverse types of cancer cells (SSC-4, Huh-7 and HeLa) through an inhibitory effect on DNA binding activity and nuclear translocation of AP-1, which were associated to a decreased expression of MMP-9 and u-plasminogen (u-PA) [172].

6 Polyphenols and clinical trials

The growing mass of *in vitro* and *in vivo* evidences related to the chemopreventive and therapeutic effects of polyphenols in cancer has encouraged the clinical trials in order to address the pharmacokinetics, efficacy and safety of phenolic compounds in humans (Table 6).

Pomegranate juice, containing 570 mg total polyphenol gallic acid equivalent, was well tolerated and no serious events were reported, and when the effect in patients with recurrent prostate cancer was evaluated, an improvement in prostate-specific antigen (PSADT) was reported [173]. An antitumour activity was also shown when quercetin was administrated to patients with confirmed diagnosis of cancer, but dose-limiting nephrotoxicity was described [174].

In another study, it has been reported that the administration of a green tea extract to patients with histological or cytological proofs of incurable malignancies was safe up to 4.2 g/m^2 once daily or 1.0 g/m^2 three times daily, and in patients with advanced lung cancer a dose of 3 g/m^2 *per* day was well tolerated [175, 176]. In both studies no major responses occurred and the reported dose-limiting toxicity was related to caffeine (neurological and gastrointestinal effects) [175, 176]. In subsequent studies, Jatoi *et al*. [177] and Luo *et al*. [178] have described an antineoplastic activity in terms of biomarkers: diminished PSA levels [177] and decreased urinary 8-hydroxydeoxyguanosine [178] in patients with prostate and hepatic cancer, respectively. In these trials, patients with prostate cancer received 6 g of green tea *per* day in six divided doses [177], and four capsules daily containing either 500 or 1000 mg of green tea polyphenols were administrated to the patients with liver cancer [178].

The potential use of curcumin as chemopreventive or therapeutic agent has also raised the questions of toxicity and tolerance. In one study with 15 patients with colorectal cancer, curcumin was given daily (36 – 180 mg) for up to 4 months, being well tolerated and not observing dose-limiting toxicity; however, the oral bioavailability was low and metabolites were detected in faeces, but not in blood or urine, suggesting a possible intestinal metabolism [179].

7 Conclusion

Dietary polyphenols can interfere at the initiation, development and progression of cancer through the modulation of different cellular processes, showing certain common signalling events (Fig. 1), *i. e*. arrest of cell cycle by increasing levels of CDIs and inhibition of cyclins, induction of apoptosis through cytochrome *c* release, activation of caspases and down- or up-regulation of Bcl-2 family members, inhibition of survival/proliferation signals (AKT, MAPK, NF-κB, *etc*.) and inflammation (COX-2, TNF secretion, *etc*.), as well as suppression of key proteins involved in angiogenesis and metastasis. It is worth mentioning that the cancer chemopreventive effect of dietary phenolic compounds seems to be specific, as carcinogenic cells demonstrate higher sensitivity than normal cells when incubated with the phenolic compounds. In addition, differences on protein modulation and regulatory events over time have been observed, which also suggests a specific and differential manner of gene expression regulation by dietary polyphenols. Therefore, more studies are needed to clarify the molecular mechanisms of dietary polyphenols as inductors of anticarcinogenic effects and to evaluate their potential as anticancer agents. Caution is mandatory when attempting to extrapolate these observations to in vivo animal tumour models and, most importantly, to humans, since none of these experimental features (detailed molecular mechanism) have been proved to occur among humans yet; moreover, most of the mechanistic data have been obtained *in vitro* and may not necessarily be physiologically relevant. Altogether indicates that experimental conditions (dose, cell type, culture conditions and treatment length) must be seriously considered because they can determine the biological outcome, which shows the difficulty for predicting the outcome and the need to understand the molecular mechanism of action of these natural compounds in each particular context. Because of the complexity and inter-relationship of signalling pathways, more information on the primary targets within cells for these dietary compounds is required such as nuclear signals, but also related to the potential interaction with receptors to initiate the signalling cascade, the entrance into the cell. In this line, it might be possible to determine whether polyphenols are acting through common mechanisms to achieve the same final effect. Additionally, more extensive, well-controlled clinical trials are needed to fully evaluate the potential of phenolic compounds in terms of optimal dose, route of administration, cancer targets and potential interactions with other drugs.

The author thanks Dr. Luis Goya for critical review of this manuscript. S. Ramos has a Ramón y Cajal contract from the Spanish Ministry of Science and Technology. This work was supported by the grants AGL2004-302 from the Spanish Ministry of Science and Technology (CICYT).

The author has declared no conflict of interest.

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