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Chapter 6

Polyphenolic Compounds Targeting p53-Family Tumor Suppressors: Current Progress and Challenges

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Additional information is available at the end of the chapter

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1. Introduction

The chemotherapeutic properties of polyphenols have recently received an increasing interest since it has been established that these compounds can modulate each step of the cancer progression process (initiation, proliferation, survival, migration, angiogenesis, and metastasis). Polyphenols are believed to be multi-targets drugs and in the present chapter we will give an overview of recent investigations concerning apoptosis induction by three major compounds, resveratrol, curcumin and epigallocatechin-3-gallate (EGCG) mainly through the regulation of the p53 tumor suppressor pathway. The potential regulation by polyphenols of p53 expression at the transcriptional and post-translational levels has been extensively described. Interestingly, polyphenolic compounds are also able to trigger apoptosis of numerous cancer cells, independently of the p53 status (wild-type, mutated or deficient). Moreover alternative mechanisms supported by recent studies highlight the role of p73, a p53 related tumor suppressor, as another key target for polyphenols. Then the molecular mechanisms involved in tumor suppressors (mainly p53 and p73) expression by polyphenols will be discussed with a specific focus on the role of oxidative stress which is believed to be a key element in polyphenols-induced cancer cells death.

2. Anticancer properties of polyphenols: Chemoprevention and chemotherapy

Polyphenols are natural compounds characterized by a structure containing at least one benzene ring substituted by at least one hydroxyl group. Beside this chemical hallmark,

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phenolic products currently constitute a large and still expanding complex and heterogeneous family of molecules (more than 8000 phenolic structures currently known) with a great diversity of structure and size ranging from the low molecular weight simple phenols up to the high molecular weight tannins [1-3]. Polyphenols are also one of the largest and most widespread classes of constituents present in plant kingdom and more particularly in plant-derived foods and beverages giving them their color and taste properties. Polyphenols can be structurally divided into two main families: flavonoids and non-flavonoids. Flavonoids are especially abundant in fruits, vegetables, seeds, spices, herbs, tea, cocoa, and wine. The six major subclasses of flavonoids are anthocyanidins (e.g., cyanidin, delphinidin; primary sources: red berries, red cabbages, cherries, grapes, and onions), flavan-3-ols (e.g., catechin, epicatechin, EGCG; primary sources: tea, grapes, cocoa, apples, and red wine), flavanones (e.g., hesperitin, naringenin; primary sources: oranges, lemons, and grapefruits), flavones (e.g., apigenin, luteolin; primary sources: celery, parsley, and thyme), flavonols (e.g., kaempferol, myricetin, quercetin; primary sources: apples, beans, broccoli, and onions), and isoflavonoids (e.g., daidzein, genistein; primary sources: legumes and soy products). Phenolic acids represent a large subclass of non-flavonoid polyphenolic compounds which can be further divided into two main types: benzoic acids (e.g., gallic acid, ellagic acid, vanillic acid; primary sources: tea, red wine, berries, nuts, and herbs) and cinnamic acids (e.g., caffeic acid, chlorogenic acid; primary sources: coffee, berries, plum, and apple). Other important classes of non flavonoids with healthy properties are stilbenes, such as resveratrol (primary sources: red wine, berries and nuts) and curcuminoids such as curcumin the main component of dried turmeric and curry powder [4]. Polyphenols are considered as secondary plant metabolites and have been associated with several functions in plants such as resistance against microbial pathogens and insects, protection against DNA-damaging UV light, reproduction, nutrition and growth [3]. In parallel to their protective properties in plants, polyphenols have long been regarded as a pool of bioactive natural products with potential benefits for human health. Plant extracts, herbs and spice containing these compounds have been used for thousands of years in traditional medicines. Nowadays, plant polyphenols enjoy an ever-increasing recognition not only by scientific community but also, and most remarkably, by the general public because of their presence and abundance in fruits, seeds, vegetables and derived foodstuffs and beverages, whose regular consumption has been claimed to be beneficial for human health [3, 5]. Indeed, epidemiological and experimental studies have shown the potential of polyphenols or polyphenolic nutritional sources in reducing the risk of chronic diseases such as cardiovascular diseases [6-10] and cancers [10-14], as well as the risk of degenerative diseases [10, 15, 16]. Altogether these observations led to the current nutritional recommendations to eat five servings of fruits and vegetables per days in order to keep healthy.

A wealth of data, including epidemiological and animal studies, has described the chemopreventive and anticancer properties of polyphenolic compounds, such as resveratrol, curcumin or tea catechins, or polyphenol-rich nutritional sources [13, 14, 17-19]. Nonetheless, recent investigations have highlighted additional mechanisms responsible for direct anti-proliferative and chemotherapeutic properties of polyphenols. Indeed, these compounds can interfere with the initiation, as well as the progression of cancer through the modulation of different cellular events, such as cell cycle arrest by decreasing cyclins or apoptosis induction through

cytochrome c release, activation of caspases and down- or up-regulation of Bcl-2 family members, and inhibition of survival/proliferation signals (AKT, MAPK, NF-κB, etc.). Furthermore, they play an important role in inflammation (COX-2, TNF secretion, etc.), as well as in suppression of key proteins involved in angiogenesis and metastasis [13]. Importantly, it has been established that tumor suppressors like p53 and its analogs are key molecular targets of polyphenols responsible for their pro-apoptotic effect in human and animal cancer models. Here we provide an overview of the molecular mechanisms involved in p53 family proteins modulation by three major and well characterized polyphenolic compounds, resveratrol, curcumin and EGCG.

3. p53 family proteins are chemotherapeutic targets of polyphenols

Since the discovery of p53 in 1979 [20-22] numerous studies have been conducted related to its functions in response to stress and its regulatory mechanisms. p53 is a sequence-specific nuclear transcription factor that binds to defined consensus sites within DNA as a tetramer and represses transcription of a set of genes involved in cell growth stimulation, while activating a different set of genes involved in cell cycle control, like p21. It causes growth arrest providing a window for DNA repair or elimination of cells with severely damaged DNA strands. In some conditions, p53 activation triggers the transcription of pro-apoptotic genes such as Bax or PUMA, as well as the repression of anti-apoptotic genes like survivin [23]. Moreover, p53 can induce transcription-independent apoptosis. This mechanism involves early p53 translocation to mitochondria where it binds to Bcl-2 family proteins, such as Bax, Bak and Bcl-XL, activating cytochrome c release and caspases cascade [24]. Undoubtedly p53 exerts major anti-neoplastic effects and is considered actually as the "guardian of the genome" [25]. Tumor suppressive capabilities of p53 are related to a coordinated regulatory circuit that monitors and responds to a variety of stress signals, including DNA damage, abnormal oncogenic events, telomere erosion and hypoxia [26]. Importantly, in unstressed cells, p53 is latent and is maintained at low level by targeted ubiquitin-mediated degradation related to its interaction with ubiquitine ligases, mainly MDM2 [27]. Regarding the "guardian" functions of p53, mutations of p53 gene or disruptions of p53 coordination such as post-translational inactivation, can disturb the normal physiological balance, and lead to cancer if genome disarrangement reachs a critical value [28]. Indeed, low level of functionnal p53 is a common characteristic of cancer from several localizations including lung, colon, rectum, breast, brain, bladder, stomac, prostate, ovary, liver or lymphoid organs [29]. Somatic p53 missense inactivating mutations are found in approximately 50% of human cancers [30] and this inactivating mutations render the mutant p53 protein unable to carry out its normal function, that is, transcriptional transactivation of downstream target genes that regulate cell cycle and apoptosis [31-33]. On the other hand, p53 pathway can be also inactivated in wild-type (WT) p53-carrying tumors via indirect mechanisms such as MDM2 amplification leading to p53 destabilization [34, 35].

Recently, cDNAs with strong homologies to p53 have been identified and their products were termed p63 and p73 [36-38]. Both proteins are structurally similar and functionally related to

p53, and consequently the entire p53 family may be regarded as a unique signalling network controlling cell proliferation, differentiation and death. Interestingly, in contrary to p53, the role of the other two p53-related proteins in tumor suppression is less obvious, since they are rarely deleted or mutated in cancer, and the respective knockout mice die tumor-free from developmental defects [39-41]. However, increasing number of evidences suggest that both p63 and p73 have a role in tumor suppression. Indeed, different studies indicated that TAp73 and TAp63, the transcriptionally active isoforms, can induce cell cycle arrest, senescence, DNA repair, and apoptosis in response to chemotherapeutic drugs, independently of p53 [42-45]. In addition, even if not mutated, p63 and p73 can be aberrantly expressed in cancer. More particularly, the dominant negative and transcriptionally inactive isoforms ΔNp63 and ΔNp73 are frequently overexpressed in a wide range of tumors, in which they are associated with poor prognosis [46]. Actually, the imbalance in the TAp73/ΔNp73 may be more critical for tumorigenesis and response to chemotherapy than mutations [47]. In summary, despite their differences, the three members of the p53 family may be considered as therapeutic targets for cancer management.

Many *in vitro* studies as well as few *in vivo* studies have shown that resveratrol, curcumin and EGCG, as well as nutritional sources of polyphenols induce overexpression of wild-type p53 (Table 1-4). The p53-related anticancer properties of these three isolated molecules have been extensively evaluated but other polyphenolic compounds such as genistein, luteolin, quercetin, and wogonin have been shown also to upregulate wild-type p53 protein in several cancer cell lines [48-51]. The polyphenol-induced stabilization and expression of wild-type p53 is often associated with a G1 or G2/M phase cell cycle arrest together with transcriptional regulation of target genes such as p21, Bax, PUMA and apoptosis induction [52-56]. The key role of p53 in polyphenol-induced anticancer properties is supported by studies indicating that p53 downregulation counteracts apoptosis triggered by natural products. Indeed, p53 silencing by siRNA abrogate the cytotoxic effect of curcumin in chondrosarcoma cells [57] and genetic invalidation of p53 by shRNA leads to inhibition of EGCG plus luteonin-induced apoptosis of lung cancer cells [58]. In addition, EGCG fails to induce significant cytotoxic effect in p53-null PC-3 prostate cancer cells, but forced expression of p53 in such cell line leads to sensitization to the polyphenolic compound [53]. Indeed, in the later study EGCG induces p53 phosphorylation on Serine 15 and upregulation of p53 and p21 expression together with cell cycle arrest and apoptosis. However the key role of p53 in the anticancer properties of polyphenols is still controversial, especially for curcumin, since many studies have shown its anti-proliferative properties in several p53-mutated or p53-null cancer cell lines (Table 2). For instance, curcumin has significant anti-proliferative effects in two p53-mutated human glioblastoma cell lines, indicating alternative and p53-independent pathway involved in such anticancer properties [59]. Similarly, curcumin reduces glioblastoma cells viability irrespective of p53 mutational status [60]. In this study, curcumin-induced cancer cell death was associated with caspase-3 activity in p53-wild-type cells, but not in p53-mutated cells, indicating that polyphenols can trigger p53- and caspases-independent cell death. p53-independent anticancer properties of polyphenols have been also described in many other cancer cells [61-67]. Interestingly, curcumin reduces the expression of the mutated form of p53 in MDA-MB-231 breast cancer cells together with cell cycle arrest [68], suggesting that a polyphenol-dependent

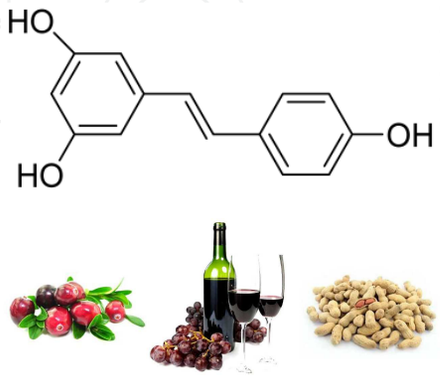
regulatory process can also modulate the expression of a non-functional tumor suppressor. However, despite potential apoptosis induction by polyphenols in absence of functional p53 protein, its wild-type expression makes cancer cells more sensitive to pro-apoptotic effects of polyphenols. Recently, Ferraz da Costa et al. have demonstrated that transient transfection of wild-type p53 in human non-small lung carcinoma cell line H1299 (p53 negative) dramatically increased susceptibility to resveratrol-induced apoptosis [69]. Altogether these data indicate that p53 participates to the cytotoxic effect of polyphenols but also that alternative pathways might be involve in their anticancer properties.

One of this alternative pathway might involve Egr-1, an immediate early-response gene induced by stress, injury, mitogens, and differentiation [70]. Egr-1 regulates the expression of genes involved in the control of growth and apoptosis by transactivating many proteins including p21. One study has shown that transcription of the p21 gene is activated by Egr-1 independently of p53 but under the control of MAPKs in response to curcumin treatment in U-87MG human glioblastoma cells [71]. In addition, the apoptotic effect of resveratrol in colorectal cancer cells as well as EGCG-mediated cytotoxicity in pulmonary cancer cells are also associated with Egr-1 upregulation [72, 73].

Alternatively to p53, its functionally related proteins p63 and p73 might represent targets for polyphenols. Nevertheless only few data are available concerning a potential regulatory effect of polyphenolic compounds on p63 and p73 (Table1-4). Different flavones (luteolin, apigenin, chrysin) and flavonols (quercetin, kaempferol, myricetin) are able to induce cytotoxicity in p53-mutated oesophageal squamous carcinoma cells together with upregulation of p63 and p73 [74]. Similarly, EGCG induces selective apoptosis in multiple myeloma cells with overexpression of p63 and p73 without any change in the p53 expression level [75], as well as overexpression of p73 in p53-mutated T-lymphocyte leukemic cells [76]. As previously mentioned, different isoforms of p73 have been described and quercetin has been shown to control the subcellular localization of the dominant negative isoform ΔNp73 in melanoma cells expressing wild-type p53. In this model, quercetin caused redistribution of ΔNp73 into the cytoplasm and nucleus, which has been associated with increased p53 transcriptional activity and apoptosis [47, 77]. Beside isolated compounds, more complex sources of polyphenol such as red wine polyphenolic extract or berries-derived product can also modulate p53 and/or p73 expression level, *in vitro* and *in vivo* (Table 4) [78-81]. Interestingly, a synthetic analogue of curcumin increases p73 expression level in two distinct p53-wild-type pancreatic cancer cell lines, BxPC-3 and Colo-357 together with upregulation of pro-apoptotic effector Bax and simultaneous downregulation of the anti-apoptotic protein Bcl-2 [82]. Curcumin itself has been shown to stimulate p53 and also p73 expression in p53-mutated C33A cervical cancer cells [83]. Moreover, EGCG upregulates transcriptional target of p53, in a p53-independent but p73-dependent manner in mouse embryonic fibroblasts [84]. These data suggest that independently of the p53 status (wild-type, mutated or deleted), p73 seems to be involde in the anticancer effect of polyphenolic compounds. Many others studies have shown the potential of polyphenols to induce apoptosis of cancer cells in a p53-dependent but also a p53-independent manner (Table 1-4). In summary data concerning the role of tumor suppressors in the polyphenol-induced anticancer effects are inconsistent, probably dependent on the cell type, and conse-

quently remain controversial. Moreover, the molecular mecanisms responsible for p53-family tumor suppressors regulation by polyphenols are only partially elucidated. However some evidences indicate that polyphenols might modulate p53 or p73 expression as well as their stabilization which are under the control of phosphorylation and acetylation levels.

Resveratrol



Cancer model	Described effects on TSG (p53/p73)	References
Prostate cancer cells (LNCaP, DU145, p53-mutated CWR22Rv1, p53-null PC-3)	- No change in p53 mRNA, increased expression of p53-p(ser15) and/or p53-ac(lys382) and total p53 protein - p53 translocation to mitochondria - cell cycle alteration and apoptosis induction maintained in p53-mutated cancer cells - potentiation of radiation–induced p53 expression in p53-mutated cancer cells	[135, 158, 164, 165, 175, 176]
Ovarian carcinoma cells (OVCAR-3)	- nuclear accumulation of p53-p(Ser15)	[110]
Breast cancer cells (MCF-7, p53-mutated MDA-MB-231, p53-mutated MDA-MB-435)	- increased expression of p53-p(ser15), p53-p(ser20), p53-p(ser392) and p53-ac(lys382/lys373)	[177-180]
	- no change in total p53 protein expression, p53-independent apoptosis	[178, 181]
	- increased expression of p53 mRNA and total protein	[182-184]
	- no change in p53 mRNA	[185]
	- p53-independent cytochrome c release	[181]
	- increased p53-dependent transcriptional activity	[50]
Colon cancer cells (HCT116, p53-null HCT116)	- increased p53-p(ser15) expression - resveratrol-induced senescence is p53 dependent	[103]
Pancreatic cancer cells (capan-2, colo357)	- upregulation and nuclear accumulation of p53 in both cell line (restoration of wild-type expression)	[186]

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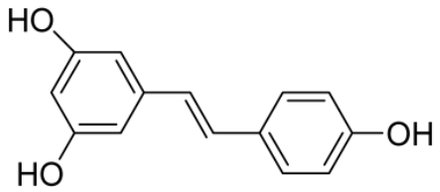
Resveratrol

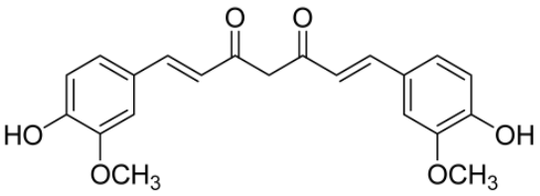


Cancer model	Described effects on TSG (p53/p73)	References
Glioblastoma cells (A172, p53-mutated T98G)	- no change in p53 mRNA	[187]
Hepatocellular carcinoma cells (HepG2)	- no change in p53 mRNA	[185]
Osteosarcoma cells (U-2 OS)	- increased p53-p(ser15) and p53-p(Ser37) expression	[188]
Lung adenocarcinoma cells (A549)	- increased p53-p(ser15) and p53-p(Ser37) expression	[188]
Head and neck squamous cancer cells (UMSCC-22B)	- increased p53-p(ser15) and total p53 expression	[109]
Cervical cancer cells (HeLa)	- increased p53-ac(lys373) and total p53 expression	[185]
Hodgkin lymphoma cells (L-428)	- increased p53-p(ser15) expression	[129]
Follicular lymphoma cells (LY8)	- increased p53-p(ser15) and total p53 expression	[190]
Acute lymphoblastic leukemia cells (MOLT-4)	- increased p53-p(ser15) expression	[189]
Neuroblastoma cells (B65, NUB-7)	- increased p53-p(ser15) and total p53 expression - nuclear translocation of p53	[94, 132]
DMBA-TPA-induced mouse skin tumor ; DEN-induced rat hepatocellular carcinoma	- increased p53-p(ser15) and total p53 expression	[18, 191, 192]
	- increased wild-type p53 and decreased mutated-p53 expression	[193]

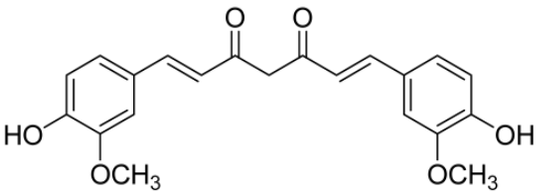
Cancer cell lines express wild-type p53 except where otherwise stated; ac(lys.)=acetylated lysine, p(ser.)=phosphorylated serine

Table 1. p53 family-related anticancer properties of resveratrol

Curcumin



Cancer model	Described effects on TSG (p53/p73)	References
Breast cancer cells (MCF-7, p53-mutated MDA-MB-231, p53-mutated SkBr3)	- increased expression of p53-p(ser15), no change or increased expression of total p53 -decreased expression of mutated p53	[68, 178, 194-197]
Cervical cancer cells (p53-mutated C33A, Caski)	-increased expression of p53 and p73	[83, 198]
Ovarian cancer cells (HEY, OVCA429, p53-mutated OCC1, p53-null SKOV3, CaOV3, Ho-8910)	-p53-independent cell death	[106]
	-increased expression of p53-p(ser15) -increased expression of p53	[107, 199, 200]
Prostate cancer cells (LNCaP, p53-null PC3)	-increased expression of p53-p(ser15),p53-ac(lys) and total p53 protein -p53-independent cell death -p53 translocation to mitochondria	[95, 100, 201]
Bladder cancer cells (p53 mutated-T-24 and AY-27)	-no change or increased expression of p53	[202, 203]
Erhlich Ascite carcinoma cells	-increased expression of p53-ac(lys373) and total p53	[120]
Colorectal cancer cells (LoVo, HCT116, p53-null HCT116, p53-mutated HT29, p53-mutated Colo205)	-increased expression of total p53	[52, 204]
	-increased expression of p53-p(ser15), p53-p(ser33) and total p53	[64]
	-no change in p53 expression	[173]
	-increased expression of p53-p(ser15) -decreased or unchanged expression of mutated p53	[156, 205]



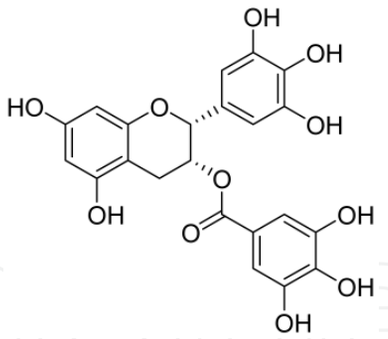
Curcumin

Cancer model	Described effects on TSG (p53/p73)	References
	-cell cycle arrest, senescence and autophagy independent of p53 expression -cytochrome c release independent of p53 expression -increased expression of total p53	[206, 207]
Colitis-associated colorectal cancer in mice	-no change in p53 expression	[17]
Acute lymphoblastic leukemia cells (B6p210, T315I)	-increased expression of total p53	[208]
Chondrosarcoma cells and xenograft in nude mice (JJ012)	-increased expression of total p53 in vitro and in vivo -p53-dependent apoptosis	[57]
Melanoma cells (MMRU, p53-mutated PMWK, B16BL6)	-no change in p53 expression	[209, 210]
Glioblastoma cells (C6, U-87MG, p53-mutated U138MG and U251, DBTRG, T98G, T67)	-p53-independent cell death -unchanged or increased expression of p53	[60, 71, 163, 211, 212]
Neuroblastoma cells (SK-N-AS, NUB-7, p53-mutated SK-N-BE(2))	-p53-independent cell death -nuclear translocation of p53	[65, 94]

Cancer cell lines express wild-type p53 except where otherwise stated; ac(lys.)=acetylated lysine, p(ser.)=phosphorylated serine

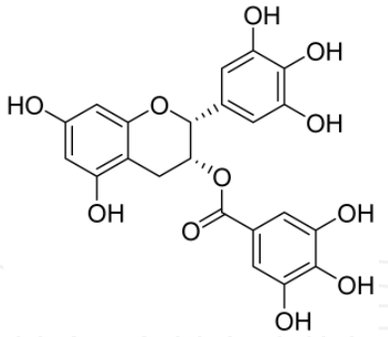
Table 2. p53 family-related anticancer properties of curcumin

Epigallocatechin-3-gallate (EGCG)



Cancer model	Described effects on TSG (p53/p73)	References
Breast Cancer cells (MCF7, p53-mutated MDA-MB-468)	-increased expression of p53-p(ser15) and total p53 -p53-independent cell death	[213, 214]
Prostate cancer cells (LNCaP, p53-null PC-3, p53-expressing PC-3, PC3-ML, p53-mutated DU-145)	-increased expression of p53-p(ser6), p53-p(ser15), p53-p(ser20), p53-p(ser37), p53-p(ser392) , p53-ac(lys373), p53-ac(lys382) and total p53 -p53-dependent and independent cell death -increased expression of p73	[53, 66, 89, 139, 140, 170, 215]
PC3-ML cells (prostate cancer) xenograft in mice	-increased expression of p53 and p73 (synergistic effect with paclitaxel and docetaxel)	[170]
Cervical cancer cells (Hela)	-increased expression of p53	[216]
Ovarian cancer cells (PA-1, p53-null SKOV3, p53-mutated OVCAR-3)	-p53-independent cell death	[217]
Hepatocellular carcinoma cells (HepG2, p53-null Hep3B)	-increased expression of p53 -p53-independent cytotoxicity	[218, 219]
Colorectal cancer cells (HCT116, p53-mutated HT-29)	-increased expression of p53	[55, 155, 157]
Head and neck squamous carcinoma cells (KB, Hep2, Tu686,	-increased expression of p53-p(ser15) and p53-p(ser37), -decreased expression of p53-p(ser6), p53-p(ser392) -unchanged or increased expression of p53	[101, 172, 220]

Epigallocatechin-3-gallate (EGCG)



Cancer model	Described effects on TSG (p53/p73)	References
686NL, Tu212, Tu177, p53-null M4e)	-p53-dependent cytotoxicity	
Head and neck squamous cell carcinoma syngenic mouse model (SCC VII/SF cells xenograft)	-increased *in vivo* expression of p53-p(ser15)	[101]
Lung cancer cells (A549)	-increased expression of p53-p(ser15) and total p53 -absence of p73 expression -p53-dependent activation of caspases 3/7	[221]
Fibrosarcoma cells (HT-1080)	-increased expression of p53	[222]
Sarcoma xenograft (S180)	-increased *in vivo* expression of p53	[90]
Multiple myeloma cells (INA6)	-increased expression of p63 and 73, unchanged expression of p73	[75]
T lymphocyte leukemic cells (p53-mutated Jurkat, HuT-102, C91-PL, p53-mutated CEM)	-increased expression of p73 -increased expression of p53	[76, 223]

Cancer cell lines express wild-type p53 except where otherwise stated; ac(lys.)=acetylated lysine, p(ser.)=phosphorylated serine

Table 3. p53 family-related anticancer properties of EGCG

Polyphenolic source	Cancer model	p53- and p73-related effects	References
Grape-derived products (red wine, grape seed extract)	C26 colorectal cancer cells xenograft in mice	-increased expression of p53 and p73	[78]
	Human colorectal cancer cells (LoVo, p53-mutated HT29, P53-mutated SW480)	-p53-independent apoptosis	[224]
	Oral squamous carcinoma cells (SCC-25, p53-mutated OEC-MI)	-p53-independent cytotoxicity	[225]
	Leukemia cells (p53-mutated Jurkat)	-increased expression of p73	[80]
	Teratocarcinoma cells (P19)	-increased expression of p53	[174]
	Prostate cancer cells (LNCaP, p53-mutated DU145)	-increased expression of p53-p(ser15) and total p53	[226]
Black and green tea	DMBA-induced mammary tumor in rat	-increased expression of wild-type p53 and decreased expression of mutated-p53	[227]
	3,4-benzopyrene-induced lung carcinoma in rat	-increased expression of p53	[228]
	Ehrlich's ascites carcinoma cell xenograft in mice	-increased expression of p53	[229]
	Oral cells from smoker and non-smoker subjects	-increased expression of p53	[230]
	Patients with high-risk oral premalignant lesions	-no association between p53 expression and clinical response	[231]
	Prostate cancer cells (LNCaP, p53-null PC3)	-increased expression of p53-ac(lys373), p53-ac(lys382) and total p53 -p53-independent apoptosis	[139, 140]
	Colorectal cancer cells (LoVo, p53-mutated HT29)	-p53-independent cytotoxicity	[232]
Berry-derived products (aronia juice, strawberry extract)	Leukemia cells (p53-mutated Jurkat)	-increased expression of p73	[79]
	Breast cancer cells (p53-mutated T47D)	-increased expression of p73	[81]

Cancer cell lines express wild-type p53 except where otherwise stated; ac(lys.)=acetylated lysine, p(ser.)=phosphorylated serine

Table 4. p53 family-related anticancer properties of polyphenolic sources

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4. Polyphenols as regulator of p53 expression and localization

Under physiological conditions, the transcriptional activity of p53 is downregulated by three different ways: i) ubiquitin-mediated proteasomal degradation mainly through the action of mouse double minute protein (MDM2), ii) nuclear export leading to a decrease in nuclear level, or iii) transcriptional repression of chromatin. MDM2 is an ubiquitin E3 ligase considered as an oncoprotein because of its activity in promoting p53 ubiquitination and proteasomal degradation. Moreover MDM2 binds to the NH2 terminus of p53 and blocks its transactivational activities [27]. Interestingly, MDM2 promotes also cell cycle progression independently of p53 for instance by modulating the activity of p21 [85]. Then MDM2 itself represents a potential target for new drug with chemotherapeutic properties including polyphenolic compounds [86]. Indeed, curcumin has been identified as an inhibitor of MDM2 expression (Figure 1) *in vitro* and *in vivo* in p53-null and p53-wild-type human prostate cancer cells and this inhibitory effect seems to be related to the inhibition of the PI3K/mTOR pathway [87]. In addition, the curcumin analog EF24, which displays higher potency, increases phosphorylation of p53 together with downregulation of MDM2, which likely leads to p53 overexpression and cytotoxicity in hepatocellular carcinoma cells [88]. Similarly, EGCG reduces MDM2 expression in prostate cancer cells [89], but not in sarcoma cells [90]. Data concerning the effect of resveratrol on MDM2 expression are more controversial since upregulation or downregulation have been observed in different cancer models [91, 92].

As mentioned previously, p53 activity depends upon its expression level but also its subcellular localization. Indeed, p53 displays direct pro-apoptotic effects related to mitochondrial translocation and this pathway works in synergy with transcriptional activation function of p53 dependent upon its nuclear translocation [24, 93]. Therefore, the control of p53 subcellular localization might interfere with p53-mediated cell death. For instance, treatment of neuroblasma cells by either curcumin or resveratrol transiently upregulated p53 expression and induced nuclear translocation of p53, followed by induction of p21 and Bax expression associated with apoptosis [94]. In addition curcumin increases p53 and Bax expression in mitochondrial fraction under the control of the PI3K/Akt pathway in prostate cancer cells followed by caspase-dependent apoptosis [95]. Altogether, these data indicate that polyphenols are able to control not only p53 expression, but also its localization and therefore its pro-apoptotic activity in cancer cells. However, other post-translational regulatory effects of polyphenols have been also described and related to phosphorylation and acetylation of the tumor suppressor.

5. Polyphenols as regulator of p53 phosphorylation

Phosphorylation of serine/threonine residues are essential for stabilization and activation of p53, the most extensively studied being serine 15 (Ser 15). These phosphorylation sites are mainly concentrated in the N-terminal transactivation domain and in the C-terminal regulatory domain [96]. Recent data about p53 phosphorylation induced by resveratrol,

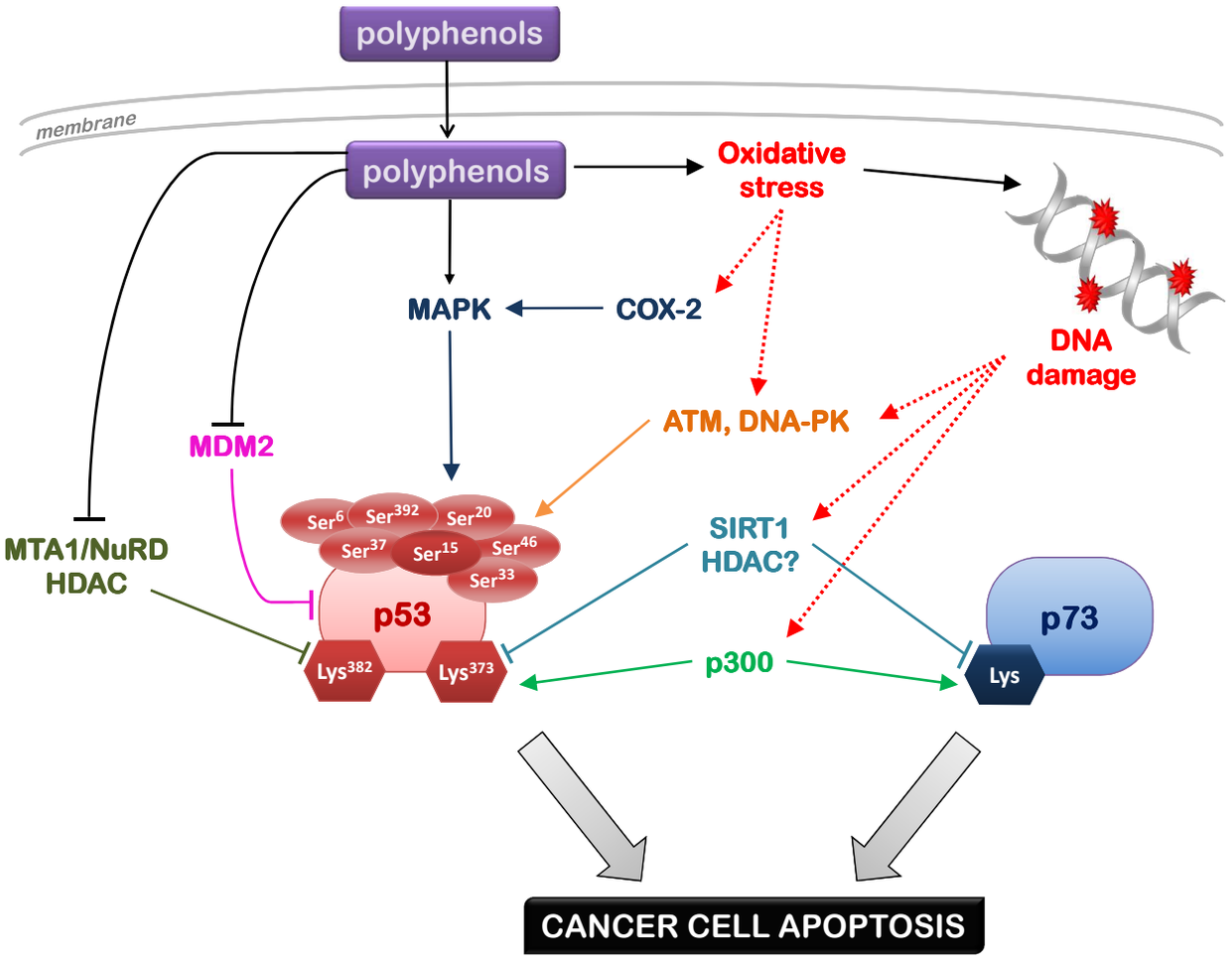

Figure 1. Overview of p53- or p73-mediated pro-apoptotic effects of polyphenols in cancer cells. Polyphenols likely induce intracellular oxidative stress and DNA damage with subsequent activation of kinases (MAPK, ATM, DNA-PK) responsible for p53 phosphorylation. Simultaneously, and also in response to DNA damage, acetylation of p53 or p73 have been described due to enhanced acetylase activity from p300 and/or to reduced deacetylase activity from SIRT1 or HDAC. In addition, p53 expression has been shown to be under the control of MDM2 as well as MTA1/NuRD, both factors being downregulated by polyphenols. Phosphorylation and acetylation, together with MDM2 inhibition result in p53, and to a less extend, p73 stabilization and sustained expression which activate cell death cascade in cancer cells.

curcumin or EGCG, *in vitro* and *in vivo*, are summarized in Tables 1, 2 and 3 as well as in Figure 1. The DNA damage is one of the main signals relayed to p53 subsequently activated by phosphorylation at serine residues that are the target of ataxia-telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR) and DNA-dependent protein kinase (DNA-PK) [97]. The DNA damage response could be activated by chemotherapeutic drugs, UV or oxidative stress [98, 99], but activation of this pathway by polyphenols remains controversial. Watson et al. investigated the pro-apoptotic effect of curcumin which is similar in p53+/+ (wild-type) and p53-/- (knockout) HCT116 colorectal cancer cells. Moreover, they demonstrated the ability of this polyphenol to induce up regulation of p53-p(Ser 15) and total p53 without any change in the expression level of ATM, ATR or DNA-PK. In contrast, curcumin enhances p38, JNK and ERK1/2 phosphorylation in both p53+/+ and p53-/- HCT116 cell lines; this suggests that the cytotoxic effects of curcumin are

independent of the DNA-damage/ATM/ATR/DNA-PK pathway but associated with Mitogen-Activated Protein Kinases (MAPKs) activities [64]. On the other hand, treatment of LNCaP prostate cancer cells or HCT116 colorectal cancer cells with curcumin induces the phosphorylation of ATM, histone H2AX (a marker of DNA damage) and p53 at Ser 15 together with increased expression of p53, suggesting p53 activation through the DNA damage/ATM pathway [52, 100]. The importance of ATM in polyphenols-induced cytotoxicity is also supported by recent data showing that EGCG lose the ability to trigger p53 phosphorylation at Ser 15 in absence of ATM [101]. In addition, genistein induced p53 phosphorylation at Ser 6, 9, 15, 20, 46 and 392 in the ATM-proficient human lymphoblastic cell lines, but not in ATM-deficient cell lines, indicating a key role of ATM kinase activity for polyphenol-induced p53 activation [102]. Moreover, stimulation of the ATM/p53 pathway by polyphenols like resveratrol has been shown to also participate in senescence of cancer cells [103]. On the other hand, quercetin strongly induced DNA-PK expression, p53 phosphorylation and apoptosis in melanoma cells, suggesting that other kinases might be activated by polyphenols [77].

Alternatively, MAPKs such as ERK1/2, p38 or JNK have been involved in p53 activation and phosphorylation [104, 105]. Therefore, the potential MAPKs/p53-dependent activation of apoptosis by polyphenols has been investigated. As previously mentioned, curcumin induces phospho-p38, phospho-ERK1/2 and phospho-JNK in colorectal as well as ovarian cancer cells [64, 106, 107]. In addition, it has been shown that resveratrol- or luteolin-induced apoptosis depends on the activities of ERK1/2, JNK and p38 kinase which target p53 phosphorylation at Ser 15 [49, 108]. An alternative pathway which implicates cyclooxygenase (COX)-2 activity and expression has been decribed by Lin et al. They have shown that resveratrol-induced apoptosis of human head and neck squamous cancer cells or human ovarian carcinoma cells is associated with p53 phosphorylation at Ser 15 and that both processes are downregulated by pERK1/2 and COX-2 specific inhibitors [109, 110]. Recent investigations indicate that ERK and p53 regulate each other and that ATM controls their interaction [104]. Therefore polyphenols might likely trigger p53 activation through ATM and MAPKs complementary pathways.

6. Polyphenols as regulators of p53 and p73 acetylation

Functions of p53 and p73 are also regulated by acetylation on different lysine (Lys) residues. These posttranslational covalent modifications occur in response to DNA damage in the close vicinity of the oligomerization domain. The main Histone Acetyl Transferases (HATs) responsible for these modifications include p300, CREB-Binding Protein (CBP), P300/CBP-Associated Factor (PCAF) and Tat-Interactive Protein of 60 kDa (TIP60) [38]. As a consequence of its acetylation, p53 is stabilized by excluding ubiquitination on the same site and acetylation also promotes p53 transcriptional activity [96]. In comparison to p53, only few data are available concerning p73 interaction with HAT and acetylation. It has been established that p300 can acetylate p73 in response to DNA damage, but p300 can also behave as a co-activator of p73 independently of its HAT activity [111]. Importantly, the level of p53 or p73 acetylation

seems to be a major way of regulation for the tumor suppressors function since deacetylated p53 and p73 are compromised in their ability to induce cell cycle arrest and apoptosis [91, 112].

The transcriptional coactivator p300 is a large multidomain protein that possesses histone acetyl-transferase ability [113]. Together with its homolog CBP, p300 mediate transcription through binding to transcriptional activators such as JUN, E1A, NF-κB, as well as to the p53 family members and they have been involved in human diseases including cancers [114]. Recent studies indicate that the transcriptional activity of p53 and p73 in response to genotoxic stress is regulated by its interaction with p300 [115-117]. Indeed, it has been established that interaction between p73 and p300 acetyl-transferase promotes first p73 stability and then its transcriptional activity.

Narayanan et al., have suggested that resveratrol-induced apoptosis of prostate cancer cells is mediated by transcriptional activation of p300 which subsequently acetylates and stabilizes p53 [118]. Similarly in breast cancer cells, resveratrol enhanced p300 expression and interaction with the phosphorylated form of p53 by a MAPK-dependent mechanism [119]. Interestingly, p53-p300 interaction fails to occur in doxorubicin-resistant cells, but curcumin pre-treatment could restore this interaction. Consistently, curcumin also restored drug-induced p53 acetylation (lysine 373) and p53-dependent transcription of Bax, PUMA, and Noxa in resistant cells leading to their apoptosis [120]. Therefore, polyphenols-induced acetylation of p53 by p300 might represent a key molecular mechanism for the cytotoxic properties of these natural compounds in cancer cells including chemoresistant cells (Figure 1).

Acetylation level of tumor suppressors is dependent upon the balance between acetylation and deacetylation reactions. Indeed, deacetylation of p53 or p73 by SIRT1 (silent information regulator 1), a member of the sirtuin Histone DeACetylase (HDAC) class III family, prevents p53-mediated transactivation of cell cycle inhibitor p21 and pro-apoptotic factor Bax, allowing promotion of cell survival after DNA damage and ultimately tumorigenesis [121]. Members of the Silent Information Regulator family (SIRT or sirtuins) are evolutionary conserved NAD-dependent protein deacetylases and adenosine diphosphate (ADP)-ribosylases. There are seven identified isoforms (SIRT1-7) that differ in their subcellular localization (cytoplasmic, mitochondrial or nuclear), substrate specificities and functions [122]. The founding member of this class of deacetylases, SIRT1 (homolog of yeast silent information regulator, Sir2), is the most widely studied sirtuins. SIRT1 has been associated with aging processes as well as a variety of human diseases such as metabolic syndrome, inflammation, neurodegeneration and more recently cancer [123, 124]. SIRT1 can deacetylate a variety of histones as well as a number of non-histone substrates, the first identified of these non-histone substrates being p53 (Lys 382-p53). The SIRT1 activity on p53 results in repression of p53-dependent apoptosis in response to DNA damage and oxidative stress [125, 126]. SIRT1 deacetylates also other tumor suppressors such as p73 [91]. Then SIRT1 has been considered as an oncogenic protein because of its role in inactivating tumor suppressors such as p53, p73 but also PTEN [127], and/or activating other oncogenic proteins like N-Myc [128]. Nevertheless, the oncogenic potential of SIRT1 has been controversial and, depending on the context, SIRT1 might also act as a tumor suppressor [122]. However, inhibition of the oncogenic potential of SIRT1 is likely able to

induce apoptosis by counteracting the deacetylation of p53 or p73 and other key factors such as FOXO3a [91, 125, 129].

In 2003, resveratrol was the top hit in a screen designed to identify activators of sirtuin enzymes [130] and was subsequently shown to extend lifespan in yeast. However following experiments led to confusing data suggesting that resveratrol might not be a direct activator of SIRT1 [131]. Regardless of the controversy about its mode of action, resveratrol has been confirmed to have numerous health benefits, including anticancer properties. Nevertheless, the role of SIRT1 in the anti-proliferative and pro-apoptotic effects of resveratrol on cancer cells is still unclear. Indeed, in neuroblastoma cells, resveratrol-induced apoptosis was associated with a reduced expression of SIRT1 as well as up-regulation of the acetylated and active form of p53, but the pre-treatment of cancer cells with SIRT1 enzymatic inhibitors such as sirtinol or nicotinamide has no cytotoxic effect suggesting that resveratrol-induced apoptosis is independent of SIRT1 activity [132]. In the opposite, siRNA-mediated downregulation of SIRT1 in lymphoma cells decreased the resveratrol-induced apoptosis, indicating in this case a critical role of SIRT1 in polyphenol-mediated cancer cell death [133]. Interestingly, Frazzi et al., have recently described anti-proliferative effect of resveratrol associated with downregulation of SIRT1 expression and activity together with upregulation of acetylated-Lys 373-p53, the active form of p53, and total p53 overexpression [129]. All together, these data suggest that, in the context of cancer cells, resveratrol might be an inhibitor, instead of an activator, of SIRT1 functions (Figure 1). However, only few data are available concerning potential regulation of SIRT1/p53 pathway by other polyphenolic compounds [134]. Therefore additional investigations are needed to further understand the role of SIRT1 in polyphenols-mediated anticancer effects.

On the other hand, resveratrol has been shown to enhance p53 acetylation and apoptosis in prostate cancer cells through alternative pathways. Indeed, resveratrol caused down-regulation of MTA1 protein, leading to destabilization of MTA1/NuRD complex thus allowing acetylation/activation of p53 [135]. Metastasis-associated protein 1 (MTA1) is part of the nucleosome remodelling deacetylation (NuRD) complex involved in global and gene-specific histone deacetylation, alteration of chromatin structure and transcriptional repression [136, 137]. This complex, which also contains Histone DeACetylase (HDAC)1 and HDAC2, plays an essential role in governing deacetylation of histones but also non histone proteins, such as p53 [138]. In addition, green tea polyphenols have been shown to behave as HDAC class I inhibitors which results in p21 and Bax expression irrespective of p53 status in prostate cancer cells [139, 140]. Moreover HDAC inhibition by EGCG is associated with p53 acetylation in p53-wild-type LNCAP prostate cancer cells suggesting an increase of p53 halftime and binding to p21 and Bax promoters as previously described [141]. The mechanism by which HDAC inhibition could induce apoptosis in absence of functional p53 in p53-null PC3 prostate cancer cells might be related to interaction with p73 pathway as previously suggested [142, 143] or direct regulation of p21 promoter activation [144]. Similar HDAC inhibition by curcumin has been also seen in prostate cancer cells [145]. However the exact role of HDAC inhibition in polyphenol-induced apoptosis of cancer cells remains to be elucidated especially *in vivo*.

7. Role of oxidative stress and DNA damage in p53/p73 regulation by polyphenols

Polyphenolic compounds have been extensively described as anti-oxidant molecules with the capability to scavenge reactive oxygen species (ROS), which include radical oxygen and nitrogen species such as $O2^-$ (superoxide anion), $HO^\cdot$ (hydroxyl radical), $NO^\cdot$ (nitric oxide radical), $ONOO^{-\cdot}$ (peroxinitrite anion) and H_2O_2 (hydrogen peroxide), as well as oxidatively generated free radicals $RO^\cdot$ and $ROO^\cdot$ from biomolecules like lipids, proteins or nucleic acids (DNA and RNA) [3, 146]. Polyphenols are not only able to quench the ROS but also to regulate directly the oxidative stress-mediated enzyme activity, therefore reducing the formation of ROS. These anti-oxidant properties have been linked to the polyphenol-mediated reduction of chronic disease risk including cancer chemoprevention [13, 147]. Indeed, redox changes are often reported as important inducer of neoplastic transformation as well as chemoresistance. Cerutti et al. identified for the first time in 1985 the close relationship between pro-oxidant conditions and cancer development [148]. More than twenty years later, accumulated evidences indicate that the non-physiological alterations of the intracellular redox state could be considered as a hallmark of tumor biology. Indeed, redox changes have been involved in several key events of carcinogenesis such as self-sufficiency in growth signals [149, 150], resistance to apoptosis [151, 152], sustained angiogenesis [153, 154], autophagy and invasiveness. However, recent findings also suggest that this redox changes might be exploited as therapeutic strategy to selectively kill tumor cells.

Recently and unexpectedly, it has been established that various and structurally different (flavonoids or non-flavonoids) polyphenols are able to induce ROS (mainly superoxide anions or hydrogen peroxide) formation in cancer cells and for some of them to activate the DNA-damage response pathway [51, 79, 80, 95, 102, 103, 155-158]. Heiss et al. have also shown that the resveratrol-induced senescence in colon cancer cells is dependent upon an increased formation of ROS and the subsequent phosphorylation of p53 on the Ser15, suggesting a relationship between polyphenol-induced oxidative stress and p53 activation [103]. On the other hand, curcumin and wogonin induce ROS production and cause cytotoxicity in p53+/+ and p53-/- cancer cells [56, 64], indicating that ROS formation is an event independent of p53 and might be an earlier step in the cell death pathway. This hypothesis is supported by the study showing ROS in cancer cells as earlier as 20 minutes after the beginning of wogonin treatment. Moreover, in the same study, the subsequent up-regulation of p53 (maximal activation at 16 hours) is significantly inhibited by anti-oxidants such as N-Acetyl-Cysteine. Importantly, most of the studies did not investigate the possible alternative role of p73 in p53-mutated cells, but we and others have shown that in p53-mutated or p53-deficient cells, a polyphenolic compound (EGCG) or source (red wine polyphenolic extract, polyphenol-rich aronia juice) strongly induced oxidative stress-mediated up-regulation of p73 and apoptosis [79, 80, 84]. Further reports also supported that p53-family tumor suppressors regulation might be related to oxidative stress [159].

Interestingly, the cytotoxic effects induced by curcumin or its analogue HO-3867 were reduced in non-cancerous cells as well as the ROS formation in comparison to human ovarian cancer

cells. This suggests that the specific pro-oxidant activity of polyphenols in cancer cells might explain the selective anticancer properties of these compounds, sparing healthy normal cells [107, 160]. Similarly, EGCG increased preferentially ROS formation, p53 and p21 expression and cytotoxicity in colorectal cancer cells but not in human embryonic kidney cells and normal human lung cell line [157].

Oxidative stress is one of the major conditions that damages DNA, acting as a mediator of environmental stressors such as UV- and X-rays irradiation, drugs, and of metabolic imbalance [161]. Since p53 might be regulated by the redox environment [162], especially by the ROS/DNA damage pathway, it has been proposed that polyphenol-mediated anticancer effects are related to a ROS/DNA damage/p53 pathway (Figure 1). Indeed polyphenol-induced DNA damage and apoptosis have been demonstrated with various compounds such as curcumin in glioblastoma and prostate cancer cells [100, 163], resveratrol in prostate cancer cells [164, 165], EGCG in lung cancer cells and xenograft in mice [166], wogonin in glioblastoma and prostate cancer cells [51, 56], and luteolin in lung and head and neck cancer cells [58]. Therefore the current molecular mechanism of the anticancer properties of polyphenols might involve selective ROS formation together with DNA damage in cancer cells. Thus, this process might lead to the regulation of several pathways (ATM/DNA-PK, MAPKs, p300, SIRT1, HDAC, see Figure 1), and ultimately to the expression and stabilization of p53-family tumor suppressors triggering programmed cell death.

8. Therapeutic perspectives

Recent investigations have demonstrated additional or synergistic effects when polyphenols are combined with chemo- or radiotherapy. Indeed, resveratrol induces synergistic apoptosis with 5-fluorouracile [167]. Similar observations have been made with curcumin associated with doxorubicin, cisplatin, gemcitabine or radiation for cell death induction of glioblastoma cells and prostate cancer cells [60, 87]. More importantly, curcumin and its analogue, HO-3867 sensitized doxorubicin-resistant ascite carcinoma cells and breast cancer cells as well as cisplatin-resistant ovarian carcinoma cells together with enhanced p53 expression [107, 120, 168, 169]. Similarly, EGCG displayed synergistic upregulation of p53 and p73 as well as anticancer properties with taxanes (paclitaxel and docetaxel) *in vitro* but also *in vivo* in prostate cancer models [170, 171]. Because all of the previously mentioned drugs demonstrated the ability to induce DNA damage, it is likely that polyphenols might amplify these damages leading therefore to synergistic effects. Surprisingly, EGCG has also synergistic effects with targeted therapy such as erlotinib (inhibitor of epidermal growth factor receptor) to induce p53 phosphorylation on Ser15 and expression together with apoptosis [172].

Interestingly, curcumin also ameliorated oxaliplatin-induced chemoresistance in colorectal cancer cells without significant effect on p53 expression [173]. Similarly, curcumin and EGCG sensitized glioma cells *in vitro* and *in vivo* to chemotherapeutic drugs and also to radiation in a p53-independent manner [163]. These data suggest that polyphenols can effectively circumvent resistance of cancer cells to chemotherapy, but likely through a p53-independent pathway.

Numerous *in vitro* studies have demonstrated the cytotoxic effects of polyphenols by using micromolar concentrations which are much higher than current chemotherapeutic drugs under development. However, polyphenols still keep their potential as chemotherapeutic drug, firstly because of their activity on chemo- or radioresistant cancer cells and secondly because of their very low toxicity on healthy tissues giving them a large therapeutic index. Indeed, many recent *in vitro* studies have highlighted the selective pro-apoptotic properties of polyphenols or analogues with no or low cytotoxic effect on non-cancer healthy cells, such as endothelial cells, cardiomyocytes, lymphocytes, chondrocytes, ovarian cells, prostate and mammary epithelial cells, astrocytes, or neurons [54, 57, 60, 79, 95, 107, 158, 163, 169, 174]. Interestingly, the selective pro-apoptotic effect of curcumin in breast cancer cells is associated with an increased expression of p53, whereas p53 is only slightly upregulated in normal mammary epithelial cells, suggesting a selective activation of p53 pathway in cancer cells sparing normal cells [54]. Moreover, *in vivo* treatment with polyphenolic compounds or products in tumor model such as cancer cells xenografts induced a significant inhibition of tumor growth together with a very good tolerance for healthy tissues, including heart, liver, kidney, lung and haematopoietic tissue [60, 78]. However, more animal studies and human clinical trials are now necessary to clearly determine whether polyphenols or their natural nutritional sources are safe and efficient to treat cancer.

9. Concluding remarks

The present literature review has summarized the results of recent studies focusing mainly on the p53-related anticancer properties of three major polyphenolic compounds (resveratrol, curcumin and EGCG). Despite highly active research in this area, the data are still controversial concerning the possible key role of the tumor suppressor p53 in the polyphenol-mediated apoptosis of tumor cells. However, according to the emerging evidences suggesting that polyphenols might alternatively regulate also the structurally- and functionally-related tumor suppressors such as p73, these natural compounds might be considered as general executors of the p53 family-mediated programmed cell death in cancer cells. Importantly, the selective anticancer properties of polyphenols are maintained even when p53 is mutated or absent, as well as when cells are resistant to current therapies. However, further investigations are still mandatory to better understand the underlying molecular mechanism *in vitro* as well as *in vivo* before a potential clinical development.

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