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# Inhibiting Telomerase Activity and Inducing Apoptosis in Cancer Cells by Several Natural Food Compounds

Didem Turgut Cosan and Ahu Soyocak  
*Eskisehir Osmangazi University, Medical Faculty, Department of Medical Biology  
Turkey*

## 1. Introduction

Today cancer is one of the most important causes of death. Therefore, researches pertinent to diagnosis, prognosis and treatment of cancer increase day by day. A large part of cancer can be treated by surgery, radiotherapy and chemotherapy. Various compounds are used for chemotherapy. Most of these anti-cancer compounds are synthetics that have toxic adverse effects. Therefore, it is crucial to reveal beneficial effects of natural compounds such as milder side effects on normal cells and potential anti-tumour effects. A great number of these compounds also have the potential to be anti-cancerogenic. Thus, importance of natural food-derived anti-cancer compound consumption has recently increased. Researches demonstrate these anti-cancerogenic features through various mechanisms. These mechanisms also include inhibition of telomerase activity and induction of apoptosis. It is presumed that these mechanisms are in interaction with each other. After giving brief information on telomeres, telomerase activity and apoptosis in this chapter, we will address the effects of several compounds on telomerase activity and apoptosis and the possible relationship they have with each other.

Telomeres, which are located at both termini of the chromosomes of eukaryotic organisms, contain DNA and protein. Telomeres are different from other chromosomal DNA sequences in terms of both structural and functional aspects. In vertebrates, telomere is shaped by tandem repetitions of a short pattern which consists of TTAGGG hexanucleotide. The lengths of these repetitions in kilo base vary from one organism to another. The telomeric DNA strand, which is rich in guanine, ends with a single stranded 3' overhang. This single-stranded overhang folds onto the double-stranded telomere and forms the structure called t-loop. Through formation of this t-loop, the capping structure formed at the ends of chromosomes protects the ends from end-to-end fusion, degradation and recombination. Telomere can preserve a certain length or gain or lose length through special proteins and telomerase enzyme. It was demonstrated that these special proteins fulfil certain duties by binding to single and double stranded telomere DNA. Telomeric repeat binding factor 1 (TRF1) and telomeric repeat binding factor 2 (TRF2) are double-strand telomere DNA binding proteins. These proteins and some other proteins related to them are responsible for

formation of the telomere complex and t-loop. The telomere is protected through the complex formed by these proteins (Blackburn, 2000; Blackburn, 2001; Celli et al., 2005; Chan & Blackburn, 2002; De Lange, 2002; Griffith et al., 1999; Moyzis et al., 1988; Sfeir et al., 2009; Smogorzewska et al., 2000; van Steensel et al., 1998; van Steensel & de Lange, 1997). The other telomere proteins which compose this complex and their duties are summarized shortly in **Table 1**.

| Proteins  | Functions   | References  |
|---|---|---|
| Rap 1<br>(Repressor activator protein 1)  | Mammalian Rap1, whose function is still unclear, TRF2-binding protein, negative regulator of telomere length. | Li & de Lange (2003); Li et al. (2000); Bae & Baumann (2007); O'Connor et al. (2004); Sarthy et al. (2009); Sfeir et al. (2010); Martinez et al. (2010); Diotti & Loayza (2011); Palm & de Lange (2008); de Lange (2009); Martínez & Blasco (2010). |
| TIN2<br>(TRF1 Interacting Nuclear protein 2)  | TRF1-TRF2 binding protein, negative regulator of telomere length.   | Kim et al. (2004); Ye et al. (2004a); Diotti & Loayza (2011); Palm & de Lange (2008); de Lange (2009); Martínez & Blasco (2010).  |
| TPP1<br>(previously called TINT1 [Houghtaling et al. 2004], PTOP [Liu et al. 2004], and PIP1 [Ye et al. 2004b]) | Plays a role in telomere capping by interacting with TIN2 and POT1.   | Liu et al. (2004); Ye et al. (2004b); Houghtaling et al. (2004); Diotti & Loayza (2011); Palm & de Lange (2008); de Lange (2009); Martínez & Blasco (2010); Zong et al. (2012); Takai et al. (2011); Wang & Lei (2011).                             |
| POT 1<br>(Protection of telomeres 1)  | Binds single-stranded TTAGGG repeats, necessary for telomere-length maintenance and telomere protection.      | Baumann & Cech (2001); Loayza & de Lange (2003); Diotti & Loayza (2011); Palm & de Lange (2008); de Lange (2009); Martínez & Blasco (2010).   |
| TANK1 and TANK2<br>Tankyrase (TANK) telomere-associated poly (ADP-ribose) polymerase (PARP) 1                   | Positive regulator of telomere length through inhibition of TRF1  | Smith et al. (1998); Kaminker et al. (2001).  |
| PINX1<br>(PIN2-interacting protein X1)  | Potential telomerase inhibitor, negatively regulating telomere length by interacting with TRF1.               | Zhou & Lu (2001).   |
| Ku86  | Negative regulator of telomere length, role in telomere capping, regulation of telomerase recruitment.        | Espejel et al. (2002); Pflingsten et al. (2012).  |
| DNA-PK<br>(DNA-dependent protein kinase)  | Plays a role in telomere capping, putative role in post-replicative processing of telomeres.                  | Bailey et al. (2001).   |

| Proteins  | Functions  | References  |
|---|--|---|
| ERCC1/XPF<br>(excision repair cross-complementing 1/ xeroderma pigmentosum group F) | Negative mediator of telomere length maintenance.                          | Zhu et al. (2003); Wu et al. (2008).                                    |
| Mre11/Rad50/Nbs1  | Binds TRF2, DNA-repair complex, possible role in T-loop formation.         | Zhu et al. (2000).  |
| PARP-2<br>(poly (ADP-ribose) polymerase-2)  | PARP activity negatively regulates TRF2.                                   | Dantzer et al. (2004).  |
| Apollo<br>(also called SNM1B)   | TRF2 interacting, protein absence leads to DNA damage signal at telomeres. | Lenain et al. (2006); van Overbeek & de Lange (2006); Wu et al. (2012). |

Table 1. Telomere-binding proteins and their functions

Telomerase, which is a DNA polymerase with special ribonucleoprotein structure, is responsible for synthesis of DNA tandem repeats at chromosomal termini. This enzyme is active in embryonic cells and adult stem cells while inactive or at low level in normal somatic cells. Telomerase, which is a reverse transcriptase, consists of a catalytic subunit (hTERT=Human Telomerase Reverse Transcriptase) and an RNA component (hTR=hTERC=Human Telomerase RNA Complex). Human telomerase enzyme uses a short segment (8-30 bases) of hTR that is complementary to telomeric DNA sequence as the template for extension of 3' strand of DNA sequence. In this way, telomerase enzyme increases the telomere length and prevents DNA loss known as the end replication problem that occurs at each cell division. When telomere length reaches the critical shortness, the cell cannot divide further and go into senescence. Chromosomal instability, cell senescence and apoptosis can not only be induced by critically short telomeres but also by disruption in telomeric protein complex which is responsible for the loop structure at the chromosome ends (Blackburn, 2000; Bryan & Cech, 1999; Collins, 2006; Cong et al., 2002; Feng et al., 1995; Greider & Blackburn, 1989; Morin, 1997; Shay & Wright, 2005; Wong et al., 2010; Zakian, 1995).

Researches have shown that telomerase is reactivated in most tumour cells. These cells, which have been immortalized, need telomerase activity for ensuring the telomere length required for genetic stability and unlimited proliferative ability. Telomerase reactivation is not sufficient in order to transform a normal cell into a carcinogenic cell, but it is necessary for the cells to preserve effective telomere lengths for providing the cells with unlimited growth capacity and being immortal. Studies show that there is no telomerase activity in benign tumours and that these tumour cells return to early stages as their telomeres get shorter. High telomerase activity is observed in more invasive metastatic tumours. For this reason, the studies conducted recently bring telomerase to the forefront as a target for development of diagnostic, prognostic and therapeutic mechanisms of cancer or even as a potential biomarker (Chatziantoniou, 2001; Hiyama & Hiyama, 2002; Kim, 1997; Lichtsteiner et al. 1999; Shay & Bacchetti, 1997; Shay & Wright, 2011).

Another important cellular event associated with telomere and telomerase is apoptosis. Cells, which lose their functions in the organism or have some disorders, are destroyed through a programmed cell death called apoptosis. Therefore, apoptosis plays an important

role in control of normal development in multicellular organisms and regulation of tissue homeostasis. Through apoptosis, which is a physiological mechanism used for elimination of immortalized cells, in-vitro development of carcinogenesis may be prevented.

Apoptosis is characterized by typical morphological changes that cover many factors which are responsible for DNA fragmentation and protein cleavage. It occurs mainly through pathways activated by extrinsic and intrinsic factors. Extrinsic pathway is induced by activation of Tumour Necrosis Factor (TNF) or Fas receptor in target cell membrane. TNF is released from macrophage and initiates cell death. Fas ligand is cell surface protein and causes death of cells such as infected cells and tumor cells. Activated TNF and Fas receptors compose complex (DISC) with adapter proteins such as TNF receptor associated death domain (TRADD) and Fas associated death domain (FADD). DISC activates caspases (cysteine-aspartic-acid-proteases). Caspases are members of cysteine protease family and they are synthesized as an inactive zymogen. Caspases are activated via proteolytic cleavage. In this pathway, caspase-8 is activated. While caspase-8 activates caspase-3, it also directly affects some proapoptotic proteins such as BID. Caspases generally serve as initiator (caspase 2, 8, 9, 10) and effector (caspase 3, 6, 7) in the apoptotic process. Intrinsic pathway is activated by growth factor deprivation, DNA damage, and other stress stimuli. Activated intrinsic pathway is interacted with apoptotic proteins. Bcl-2 family members consist of proapoptotic or antiapoptotic bcl-2 proteins. Among the members of this family, proteins such as Bcl-2, Bcl-X<sub>L</sub> and Mcl-1 inhibit apoptosis, while proteins such as Bax, Bad, Bid, Bak, Bim, PUMA, NOXA stimulate apoptosis. These molecules cause to releasing cytochrom c by creating pores. Cytochrom c is localized in intermembrane space of mitochondria. Disruption of the outer mitochondrial membrane leads to releasing of endonuclease G, Smac/DIABLO, Omi/HtrA2, Apoptosis Inducing Factor (AIF) and cytochrom c into cytoplasm. Additionally, proapoptotic proteins such as Bid, Bim, Bad, inhibit Bcl-2 and activate Bax/Bak heterodimer. Together with cytochrom c, Apaf-1 and dATP compose the apoptosome. The apoptosome cleaves procaspase-9 into caspase-9. Similarly caspase-8 and caspase-9 activate caspase-3. Activated caspase-3 causes DNA fragmentation and apoptosis by death substrates such as poly (ADP-ribose) polymerase (PARP), Caspase Activated DNase (CAD)/Inhibitor of Caspase Activated DNase (ICAD) (Bradshaw et al., 2003; Cain et al., 2002; Cory & Adams, 2002; Debatin et al., 2004; Green & Kroemer, 1998; Holdenrieder et al., 2004; Kaufmann & Earnshaw, 2000; Kerr, et al., 1972; Letai, 2008; Nuñez et al., 1998; Parone et al., 2002; Turgut Cosan & Soyocak, 2012; Wyllie, 1992; Wong, 2011). Proteins related with apoptosis in signal pathways and their functions are summarized in **Figure 1** and **Table 2**.

Telomere dysfunction induces two types of cellular response. These cellular responses are cellular senescence and apoptosis. The researches carried out with regard to the relationship among telomere, telomerase and apoptosis report that apoptosis may be induced through different mechanisms by weakening telomere/telomerase activity in cancer cells. In one of these mechanisms, inhibition of telomerase in cancer cells can result in shortening of telomere length and subsequently induce apoptosis. In another telomere/telomerase and apoptosis relationship, inhibition of telomerase can result in apoptosis by causing telomere uncapping. If telomerase is positive, the tumor grows due to survival signals and long telomeres. If telomerase is negative, telomeres are short due to progressive telomere loss. In the telomerase negativity stage, if telomerase becomes positive then tumor regrowth is initiated. If telomerase is still negative then subsequently telomere fusions, p53 activation,

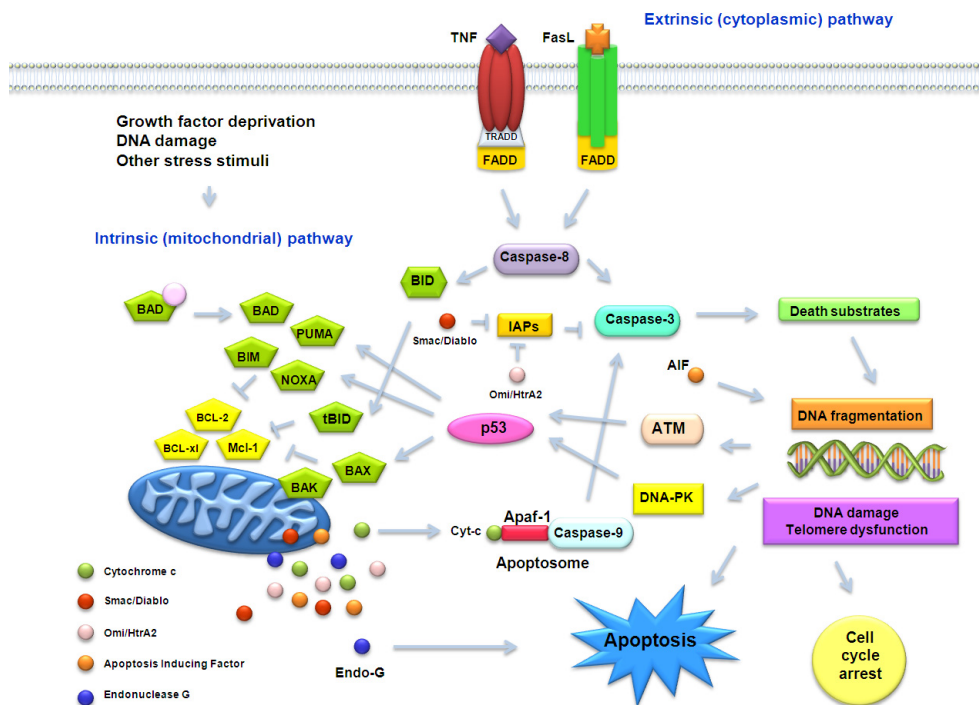


Fig. 1. Proteins related to apoptosis in signal pathways and their functions.

| Apoptotic Proteins  | Functions  | References  |
|---|--|---|
| Caspase Family<br>(e.g. Caspase 3,6,7,2,8,9,10)   | Caspases are members of a cystein protease family and are synthesized in the form of inactive zymogens activated by proteolytic cleavage. The intracellular transmission of the apoptotic signal is regulated by caspase family.     | Bradshaw et al. (2003)<br>Holdenrieder et al. (2004)<br>Wong (2011)                     |
| Bcl-2 Family<br>(e.g. Bcl-2, Bcl-X <sub>L</sub> , Mcl-1, Bax, Bad, Bid, Bak, Bcl-X <sub>S</sub> , NOXA, PUMA) | Bcl-2 family proteins can target the mitochondria and regulated membrane permeabilization.   | Bradshaw et al. (2003)<br>Debatin et al. (2004)<br>Wong (2011)                          |
| p53   | P53 is a tumor-suppressor and transcription factor. It is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA-damage, genomic stability, cell cycle control, and apoptosis. | Aggarwal & Shishodia (2006)   |
| IAPs<br>(Inhibitor of Apoptosis Proteins)<br>(e.g. Survivin, IXAP)  | IAPs block activity of caspases and may target active caspases for degradation.  | Bradshaw et al. (2003)<br>Debatin et al. (2004)<br>Kroemer et al. (2007)<br>Wong (2011) |

| Apoptotic Proteins   | Functions  | References                           |
|--|--|--------------------------------------|
| AIF<br>(Apoptosis Inducing Factor)   | AIF induce apoptosis by causing DNA fragmentation and chromatin condensation.  | Kroemer et al. (2007)<br>Wong (2011) |
| Endonuclease G<br>(Endo G)   | Endo G is a mitochondrion-specific enzyme and it cleaves chromatin DNA into nucleosomal fragments.   | Kroemer et al. (2007)                |
| Smac/DIABLO<br>(second mitochondria-derived activator of caspase/<br>direct IAP binding protein with low pI) | Smac/DIABLO is proapoptotic mitochondrial protein. It promotes caspase activation by binding to IAPs that subsequently leads to disruption in the interaction of IAPs with caspases. | Kroemer et al. (2007)<br>Wong (2011) |
| Omi/HtrA2<br><br>(Omi stress-regulated endoprotease/<br>high temperature requirement protein A2)             | Omi/HtrA2 is proapoptotic mitochondrial protein. It promotes caspase activation by binding to IAPs that subsequently leads to disruption in the interaction of IAPs with caspases.   | Kroemer et al. (2007)<br>Wong (2011) |
| CAD / ICAD<br><br>(Caspase Activated DNase/<br>Inhibitor of Caspase Activated DNase)                         | CAD cleaves chromosomal DNA in a caspase-dependent manner during apoptosis. When apoptosis is activated ICAD is cleaved by executor caspases.  | Nagata (2000)<br>Omata et al. (2008) |

Table 2. Some proteins involved in apoptosis.

cell arrest or/and apoptosis occur (Akiyama et al., 2002; Cong & Shay, 2008; Gao & Chen, 2007; Herbert et al., 1999; Lechel et al., 2005; Mattson et al., 2001; Mondello & Scovassi, 2004; Multani et al., 2000; Shay & Wright, 2006; Yuan & Mei, 2002; Zhang et al., 1999).

Signals leading to apoptosis in telomerase inhibited cells are still not fully understood. Upon loss of chromosome end protection function, uncapped telomeres are recognized by specialized DNA damage sensors. Uncapped telomeres activate signaling cascades involving the protein kinases member of PI3-kinase like (PIKK) family include Ataxia Telangiectasia Mutated (ATM), Ataxia Telangiectasia and Rad3 related protein (ATR), and DNA-PK. ATM and ATR are protein kinases which regulates cellular response to DNA breaks. ATM and ATR phosphorylate several proteins in response to DNA damage. These responses include the activation of cell cycle checkpoints, DNA repair and apoptosis. Two important phosphorylation substrates of ATM and ATR are cell cycle checkpoint kinase 1 (Chk1) and cell cycle checkpoint kinase 2 (Chk2). These proteins act by regulating cyclin dependent kinases (CDK) inhibitory effectors such as Cdc25a, Wee1 or p53. Chk1 and Chk2 are the central activators of p53 in response to DNA damage. The p53 transcription factor stops the cell cycle in case of an abnormal situation in the cell. PARP is connected to the broken DNA chain and adds poly (ADP-ribose) to nuclear proteins such as histone. Caspase 3 is connected to PARP in apoptosis and prevents repair of damaged DNA. Apoptosis, which is a highly-organized physiological mechanism, plays an essential role as a

mechanism that is protective against carcinogenesis through elimination of genetically-damaged cells (Aggarwal & Shishodia, 2006; Ben-Porath & Weinberg, 2005; d'Adda di Fagagna, 2003; Ljungman, 2009; Lopez-Contreras & Fernandez-Capetillo, 2012; Mondello & Scovassi, 2004; Smith et al., 2003; Takai et al., 2003; Karlseder et al., 1999; Kurz & Lees-Miller, 2004; Roos & Kaina, 2006; von Zglinicki et al. 2005).

Various studies report that some compounds, in particular, natural compounds, inhibit telomerase activity and induce apoptosis. For this reason, it is of great importance for studies to focus on potentials of natural compounds to inhibit telomerase activation and induce apoptosis of tumour cells without giving harm to normal cells. The researches conducted generally emphasize on two beneficial effects of natural compounds. These beneficial effects of natural compounds are potential anti-carcinogenic effects and few or milder side effects in normal cells. Some researches showed that resveratrol, which is the most investigated among the compounds we will discuss in this chapter, does not induce apoptosis in normal cells. *In vivo* studies carried out with resveratrol clearly demonstrate that it is safe in pharmacological terms and it can be used in treatment of cancer. It was also revealed that similar to resveratrol, quercetin has minimized side effects on normal cells and therefore it is safe to be used in certain doses. On the other hand, the number of studies conducted with tannic acid is very limited. Through further studies to be conducted in the following years, behaviours of tannic acid on normal cells can be identified (Aalinkeel et al., 2008; Aggarwal et al., 2004; Fulda & Debatin, 2006; Granado-Serrano et al., 2006; Psahoulia et al., 2007; She et al., 2003; Shu et al., 2011).

Determination of a relation between telomerase enzyme/apoptosis and natural compounds is important as it suggests that undesired effects of the compounds used in the current treatment methods can be eliminated. In this review, an emphasis will be placed on telomerase regulation - which is quite important for formation of human cancers -and on mechanisms that result in apoptosis and impacts and inter-relations of resveratrol, quercetin and tannic acid. The molecular structure of these compounds is shown in **Figure 2**.

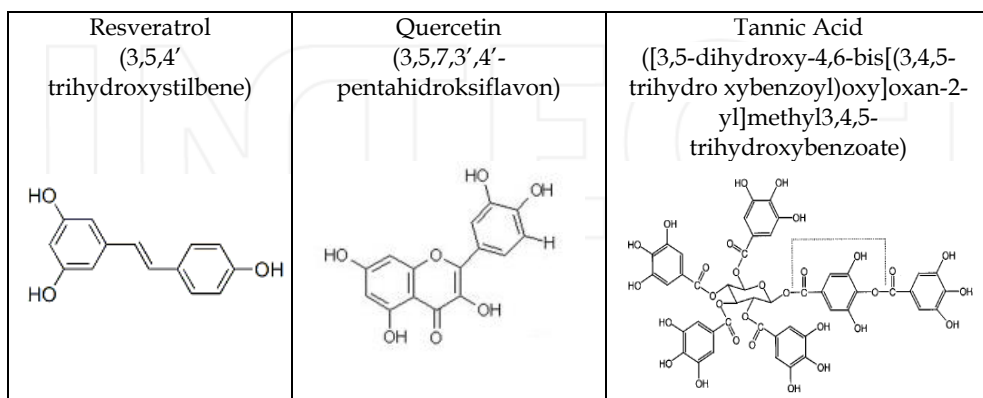


Fig. 2. Name of phenolic compounds and chemical formulas.



## 2. Effects of polyphenols on telomerase activity and apoptosis in cancer cells

It is a known fact that cancer cells, which have the ability to reproduce infinitely, cannot resist some of the compounds in the food we consume daily. One of these compounds, polyphenols, bears anti-carcinogenic properties. These polyphenols are contained in fruits, vegetables, seeds and drinks and are classified as stilbenes, flavonoids, tannins, phenolic acids and their analogues, lignans and others depending on their chemical structures (Huang et al., 2010a; Ramos, 2008).

These polyphenolic compounds that taken by diet show their effects through similar or different molecules in the cells. As a result of these effects, they may lead to inhibition of telomerase activity while inducing apoptosis in cancer cells (Avci et al., 2011; Fuggetta et al., 2006; Lanzilli et al., 2006; Sadava et al., 2007; Turgut Cosan et al., 2011; Wang et al., 2007). The studies that underline the relationship between these two incidents are limited. In this chapter, we aim to draw attention to the effects of resveratrol, tannic acid and quercetin, which are among important polyphenols, on telomerase activity and apoptosis in multiple breast and colon cancer cases and their probable relationships. The effects on telomerase activity and apoptosis of these compounds are summarized in **Figure 3**.

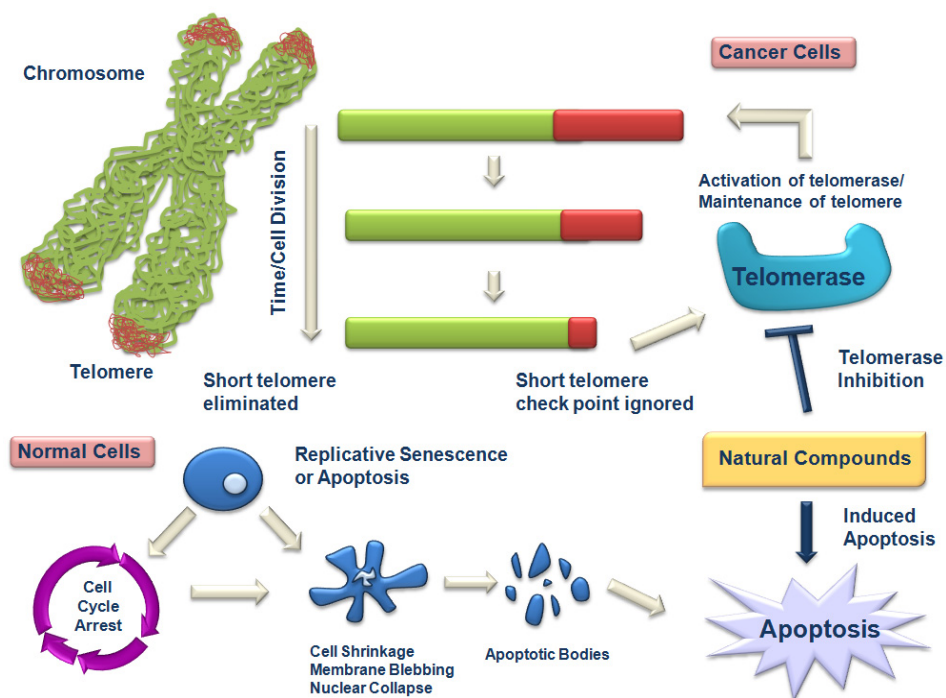


Fig. 3. Interaction of telomerase activity and apoptosis in cancer cells.

### 2.1 Resveratrol

Resveratrol (3,5,4' trihydroxystilbene) is a phytoalexin phenolic compound. Resveratrol is contained in the root of *Polygonumcuspidatum* plant and peanut as well as small soft fruits

such as grape, mulberry, strawberry, blackberry and drinks made of these. Resveratrol chelates copper, is neuroprotective, has oestrogen regulation activity, inhibits lipid peroxidation, causes alteration of eicosanoid, and inhibits platelet aggregation. It has anti-oxidant, anti-carcinogenic, anti-inflammatory, anti-mutagen, anti-proliferative, anti-viral, anti-bacterial activities, and cardioprotective and vasorelaxing activities (Aziz et al., 2003; Corre et al., 2005; Gusman et al., 2001; Ignatowicz & Baer-Dubowska, 2001; Pervaiz, 2003).

### **2.1.1 Resveratrol, telomerase and apoptosis**

Studies have been carried out to investigate the effect of resveratrol on telomerase enzyme and apoptosis in cancer cells. In one of these researches, Del Bufalo et al. (2005) also stated that hTERT plays an important role in direct or indirect control of cell survival upon regulation of genes that function in apoptosis. hTERT appears to affect apoptosis by directly intervening in early phases of upstream of intrinsic apoptotic pathway.

Fuggetta et al. (2006) indicated that tumour growth and progression can be prevented through resveratrol. These authors examined the effect of resveratrol on telomerase activity and growth in human colon cancer cell lines HT-29 and WiDr. Resveratrol showed a dose-dependent inhibiting effect on cell proliferation in both cell lines. In addition, this compound down-regulated telomerase activity in higher concentrations. It was stated in this study that in various epithelial cancers including colon cancer, a close relationship existed between hTERT mRNA expression and high telomerase activity. hTERT inhibition results in telomere loss, which leads to apoptosis and limits tumour cells growth. In this case, telomeres of these cells reached a critically short length.

A study conducted by Lanzilli et al. (2006) investigated the potential role of resveratrol as chemoprevention/chemotherapy for breast cancer. They indicated that resveratrol showed direct inhibitive impact on cell proliferation. They demonstrated that resveratrol induced apoptosis in MCF-7 breast cancer cells depending on time and concentration. Furthermore, they indicated that it reduced telomerase activity, inhibited growth in connection with this and that it did so through induction of apoptosis and S-phase arrest. According to hypothesis of this study, resveratrol directly down-regulates telomerase activity and indirectly affects the signal pathways including apoptosis and cell cycle control.

Various studies demonstrate that the catalytic subunit hTERT can activate telomerase activity as a result of its post translational phosphorylation and nuclear translocation (Liu et al., 2001; Seimiya et al. 2000). In addition, in a research they conducted on colon cancers, Wang et al. (2010) reported that resveratrol reduced promoter activity of hTERT and, in this way, prevented proliferation of cancer cells by inhibiting hTERT expression.

In their studies, Turgut Cosan et al. (2011) examined the impacts of resveratrol on telomerase activity and apoptosis in MCF-7 human breast and CaCo-2 human colon cancer cell lines. They found that resveratrol was more effective in reducing cell viability of MCF-7 cells compared to CaCo-2 cells. Resveratrol also had a negative regulatory effect on telomerase activity. DNA fragmentation, which is seen at all times and concentrations, shows that apoptosis occurs in cells treated with resveratrol. These impacts do not entirely depend on time and concentration. The study supports this impact of resveratrol with the alterations in cell count and cell viability.

More studies are needed to further increase our knowledge of resveratrol induced telomerase-apoptosis interactions. In this way, whether resveratrol induces any link between telomerase and apoptosis and, if it does, which molecular mechanisms are utilized by it can be revealed clearly.

## **2.2 Tannic acid**

Tannins are polyphenolic compounds with molecular weight of 500-3000 Dalton. Tannins are divided into two classes as hydrolyzed and condensed. Tannic acid, which is hydrolyzed tannin, is contained in tea, coffee, grapes, red wine, beans, and nuts such as hazelnut and most fruits and vegetables. Apart from their anti-angiogenic, anti-bacterial, anti-carcinogenic, anti-oxidant, anti-mutagenic, anti-microbial, anti-allergic and anti-proliferative activities, tannic acids have such biological activities as chemopreventive effects (Chen et al., 2003; Chung et al., 1998; Khan & Hadi, 1998; Khan et al., 2000; Naus et al., 2007; Taffetani et al., 2005).

### **2.2.1 Tannic acid, telomerase and apoptosis**

Various studies are available in which cancer chemopreventive activity of tannic acid is presented (Chen et al., 2003; Chung et al., 1998; Gali-Muhtasib et al., 2000; Kazi et al., 2003; Khan & Hadi, 1998; Koide et al., 1999; Marienfeld et al., 2003; Nam et al., 2001a; Nepka et al., 1999a; Nepka et al., 1999b). Gali-Muhtasib et al., 2000, demonstrated that tannic acid can suppress promotion of skin tumour induced by ultraviolet-B radiation in an animal study. Nepka et al., 1999b, reported that dietary consumption of low-dose tannic acid strongly showed dose-dependent chemopreventative activity against spontaneous liver tumour development in C3H male rats. It was revealed by Koide et al., 1999 that tannic acid increased survival rate of Balb/c rats carrying syngeneic tumours. In other researches, it was demonstrated that ester bond-containing tea polyphenols of tannic acid inhibit potently and specifically chymotrypsin-like activity of proteasome in vitro and in vivo (Marienfeld et al., 2003; Nam et al., 2001a; Nam et al., 2001b). Nam et al., 2001a, and Kazi et al., 2003, reported that anti-cancer impact of tannic acid arose from induction of apoptosis as well as inhibition of proteasomal activity. Other researches executed also showed that tannic acid could induce apoptosis (Labieniec et al., 2006; Pan et al., 1999; Romero et al., 2002; Sakagami et al., 2000; Wang et al., 2000; Yang et al., 2000).

However, the impacts of tannic acid on telomerase enzyme activity and apoptosis have not been addressed except in the research we executed (Turgut Cosan et al. 2011). We investigated the impact of tannic acid in breast and colon adenocarcinoma cells and found that cell viability and cell count dropped dramatically when cells were treated with tannic acid. Tannic acid reduced telomerase activity in all concentrations independent of time and dose. On the other hand, DNA fragmentation, which is seen at all times and concentrations, shows that tannic acid induces apoptosis in breast and colon cancer cells. Thus, it can be asserted that tannic acid has a suppression effect on telomerase activity and inducing effect on apoptosis. We also found that telomerase activity is lower in breast cancer cells than in colon cancer cells. In line with this conclusion, it can be mentioned that tannic acid has different effects in different cell lines.

In various studies, the impacts of (-) epigallocatechin-3-gallate (EGCG), a tea polyphenol like tannic acid, on telomerase enzyme activity and apoptosis in cancer cells were examined.

In 2007, Sadava et al. examined DNA fragmentation and telomerase activity in cancer cells treated with EGCG, similarly to studies by Turgut Cosan D et al. 2011. These studies were performed on drug resistant and drug sensitive lung cells (H69VP, H69). They reported that EGCG and green tea inhibit telomerase activity in cancer cells and these cells show molecular characteristics of apoptosis. These results imply that EGCG may have simultaneous impact on both apoptosis and telomerase activity in small cell lung carcinomas. There are some studies reporting that EGCG, abundant in green tea such as tannins, has growth inhibitory effect on cancer cells but not on normal cells (Bode& Dong, 2009; Chung et al., 2003).

Another study demonstrated that, following long term treatment of non-toxic low dose EGCG, carcinoma cells aged, telomere shortening was induced and telomerase inhibition occurred in vitro (Naasani et al., 2003). In another study conducted on lung, oral cavity, thyroid and liver carcinoma cells, it was reported that low cytotoxic dose EGCG and (-) epigallocatechin (EGC) suppressed hTERT expression on reporter system and hTERT mRNA level (Lin et al., 2006). On the other hand, it was demonstrated in this study that tea polyphenols can materialize inhibition of cancer cells in many ways.

Understanding the effect of tea polyphenols like tannic acid on molecular mechanism of malignancies bears importance in order for these polyphenols, which seem to be advantageous for treatment and prevention, to become useable.

## 2.3 Quercetin

Quercetin (3,5,7,3',4'-pentahidroksiflavanon) is a flavonoid which is contained very commonly in fruits and vegetables including onion, tomato, broccoli, red wine, green tea, apples, grapes, berries, cherries, and citrus fruits. Apart from anti-cancer, anti-allergic, anti-inflammatory, anti-oxidant, anti-tumour, anti-viral and anti-microbial properties, quercetin has many beneficial impacts on human health such as inhibition of lipid peroxidation, anti-platelet, anti-hypertensive, anti-cataract and anti-neurodegenerative effects (Aherne & O'Brien, 2002; Bischoff, 2008; Middleton et al., 2000; Perez-Vizcaino, 2009).

### 2.3.1 Quercetin, telomerase and apoptosis

Biologically useful impacts of quercetin are revealed by many studies. One of the objectives of these studies is to be able to understand the molecular mechanisms of these useful impacts in cancer and the interactions among them. Various researches demonstrate that this polyphenol can play a role in cancer treatment and prevention by inhibiting telomerase activity and inducing apoptosis and cell cycle arrest.

In a 2000 study, Nakayama et al. stated that growth and telomerase activity was inhibited as a result of treatment with estrogen receptor beta ligands (such as quercetin and tamoxifen) in colon cancer cells. In another study, Naasani et al. (2003) also reported that quercetin has the ability to inhibit telomerase activity. On the other hand, Hu et al. (2004) indicated that quercetin administered to these cells did not inhibit hTERT mRNA in malignant melanoma cells. In literature, apart from studies reporting that quercetin has an effect on telomerase activity, information on its ineffectiveness is also available.

With respect to the researches on the impact of quercetin on apoptosis, Choi et al. (2001) reported that quercetin induces growth inhibition with at least two different mechanisms in

MCF-7 cell lines. One of these is the inhibition of cell cycle progression through a transient M phase accumulation and subsequent G2 arrest while the other one is induction of apoptosis. Kang & Liang (1997) administered quercetin to human promyelocytic leukemia cells (HL-60) and observed its anti-tumour activity. They emphasize that one of the mechanisms used by quercetin is its inducing of apoptosis. Kuo et al. (2004) showed that quercetin induces apoptosis and cytotoxic effects in human lung cancer cell lines in a dose dependant manner. When quercetin is administered to the cells at higher doses, cell proliferation was almost completely inhibited. Lee et al. (2006) demonstrated that quercetin administered to human leukemic monocyte lymphoma cells increased DNA fragmentation in a dose dependent manner and induced apoptosis by caspase activation and G2/M phase arrest. In a different study, Kou (1996) observed that quercetin can induce apoptosis in colon cancer cells in a dose dependant manner. On the other hand, Gibellini et al. (2011) emphasized that in various types of cancer cells; quercetin can arrest the cells at different cycles and block their growth. Therefore, they exhibit pro-apoptotic feature. Furthermore, this article touches on quercetin showing anti-proliferative and pro-apoptotic effects as well as anti-carcinogenic properties. Therefore, it was pointed out that studies need be conducted on more complex and sophisticated animal models in order to understand mechanisms of chemopreventive and chemotherapeutic effects of quercetin. Tang et al. (2010) stated that quercetin shows many properties in cancer cells such as death receptor 5 (DR5) upregulation, p53 activation, cell cycle arrest and caspase-mediated apoptosis. It was underlined in this study that while quercetin down regulates expression of heat shock protein 90 (Hsp90) in prostate cancer cells and induces growth inhibition and apoptosis; it has no measurable effect on normal prostate epithelial cells. Unlike the unclear statements about the impact of quercetin on telomerase activity, the effect of quercetin on apoptosis is obvious. Almost all studies prove that quercetin induces apoptosis in cancer cells.

Although there are limited number of studies which examine both telomerase activity and apoptosis together, in a recent research conducted by Avci et al. in 2011, the impacts of quercetin on telomerase activity, apoptosis-mediated cell death, and cell reproduction in leukemic cells were addressed. In CCRF-CEM human T-cell acute lymphoblastic leukemia, HL-60 human acute promyelocytic leukemia, and K-562 human chronicmyeloid leukemia cells, quercetin suppresses telomerase activity and induces apoptosis. It was therefore stated that quercetin is a potential therapeutic agent for treatment of leukaemia. In 2007, Wang et al. demonstrated that quercetin inhibited growth in lung cancer cell line, induced apoptosis and down regulated hTERT expression in a dose dependant manner. Wei et al. (2007) reported that quercetin has a suppressing effect on growth in gastric cancer cells SGC-7901. They found that quercetin realized anti-cancer activity by suppressing telomerase activity and inducing apoptosis. Cheng et al. (1998) emphasized that treatment of nasopharyngeal carcinoma cells (NPC) with cisplatin or quercetin ensured activation of mitotic arrest and apoptotic pathways. They indicated that apoptosis of NPC cells can be induced through induction of mitotic arrest. Furthermore, it was emphasized that it has still not been clarified whether there is a correlation between apoptosis and telomerase activity. In another study conducted by Ak et al. (2011), it was reported that quercetin induce apoptosis in breast cancer cells but did not reduce telomerase activity. In a 2011 study, Turgut Cosan et al. stated that quercetin is effective on apoptosis in CaCo-2 human colon cancer cell lines. In this study, it was found that quercetin has no effect on cell viability and cell count, and that it has very little effect on telomerase activity. On the other hand, when the level of DNA

fragmentation was examined, quercetin is reported as effective. In this case, a full correlation is not observed between apoptosis and telomerase activity. When all these studies are taken into consideration, it can be provided that quercetin is more effective on apoptosis and mainly shows its anti-carcinogenic effect via this mechanism.

After giving all the above information, we cannot proceed without mentioning the fact that natural compounds have separate impacts on cancer cells and they can have increased impact when combined. Zamin et al. (2009) found that quercetin and resveratrol combination forms a very strong synergy in inducing senescence-like growth arrest in glioblastoma cells. The same study revealed that apoptosis induction does not occur through combinations made at low concentrations but that higher concentration combinations are effective. Kuhar et al. (2007) administered curcumin and quercetin together with cisplatin to human laryngeal carcinoma (Hep-2) cells. It was concluded that both compounds induce apoptosis through mitochondrial pathway and their adverse effects can be minimized. Identification of therapeutic concentrations in anti-tumoural activity bears great importance in emergence of these effects.

It is beyond doubt that further research is needed where all important molecules in anti-cancer mechanisms are addressed together in order to understand better the mechanism of impacts of quercetin on telomerase enzyme activity and apoptosis.

### 3. Inhibition of telomerase and induction of apoptosis by other polyphenols

Dietary polyphenols are compounds contained in fruits, vegetables and seeds and classified according to their chemical and structural differences. The idea that these polyphenols, which approximately has 8,000 varieties, can play a role in preventing cancer has recently created the necessity to illuminate the mechanisms of their action in cancer cells (Han et al. 2007; Ramos, 2007; Saunders & Wallace, 2010).

In addition to some polyphenols focused on here, relationships of telomerase inhibition and apoptosis induction of other polyphenols with cancer are shown in **Table 3**.

| Products        | Cells   | Mechanisms of action   | Reference                  |
|-----------------|---|--|----------------------------|
| Curcumin        | MCF-10A<br>Human mammary epithelial cells<br>MCF-7<br>Human breast cancer cells | Inhibits telomerase activity by down-regulating hTERT expression.                                      | Ramachandran et al. (2002) |
|                 | HL-60<br>Human acute myeloblastic leukemia cells                                | Induced apoptosis.<br>Inhibition of telomerase activity in a dose dependent manner.                    | Mukherjee et al. (2007)    |
|                 | K562<br>Human chronic myelogenous leukaemia cells                               | Induced apoptosis.<br>Inhibits telomerase activity.  | Chakraborty et al. (2006)  |
| Ginsenoside Rk1 | HepG2<br>Human hepatocellular liver carcinoma cells                             | Inhibited cell growth.<br>Induce apoptosis.<br>Inhibit telomerase activity.                            | Kim et al. (2008a)         |
| Verbascoside    | MKN45<br>Human gastric carcinoma cells  | Inhibited telomerase activity.<br>Reduced telomere length.<br>Arrested tumor cell cycle in G2/M phase. | Zhang et al. (2002)        |

| Products  | Cells   | Mechanisms of action  | Reference                |
|---|---|---|--------------------------|
| Allicin   | SGC-7901<br>Human gastric cancer cells  | Induce apoptosis.<br>Inhibit telomerase activity.   | Sun & Wang (2003).       |
| Diterpenoids<br>-Xerophilusin B<br>-Macrocalin B<br>-Eeriocalyxin B | K562<br>Human chronic myelogenous leukaemia cells<br>HL-60<br>Human acute myeloblastic leukemia cells A549<br>Human lung carcinoma cells HCT<br>Human colorectal carcinoma cells MKN<br>Human gastric adenocarcinoma cells CA<br>Human live carcinoma cells | Inhibit the proliferation and the telomerase activity.  | Yang et al. (2009)       |
| Salvicine   | HL-60<br>Human acute myeloblastic leukemia cells  | Induce apoptosis.<br>Inhibit telomerase activity.   | Liu et al. (2002)        |
| (Z)-Stellettic acid   | U937<br>Human leukemic cells  | Dose-dependent growth inhibition.<br>Induce apoptosis was associated with an increase in Bcl-2 family expression, activation of caspases and down regulation of IAPs family members.<br>Down regulation of hTERT expression . | Park et al. (2007)       |
| Methylenedioxy lignan   | Hep-2<br>Human alveolar epithelial carcinoma cells<br>MCF-7<br>Human breast cancer cells<br>HeLa<br>Human cervical cancer cells<br>EL-1<br>Human monocyte cells   | Induces apoptosis by Bcl-2 suppression and activation of caspases.<br>Decrease in the activity of telomerase.   | Giridharan et al. (2002) |
| Mistletoe Lectin (VCA)  | SK-Hep-1<br>Human hepatocarcinoma cells (p53-positive)<br>Hep 3B<br>Human hepatocarcinoma cells (p53-negative)  | Apoptosis by down regulation of Bcl-2 and by up regulation of Bax functioning upstream of caspase-3 in both cell lines.<br>Down regulation of telomerase activity.  | Lyu et al. (2002)        |
|   | A253<br>Human submandibular carcinoma cells   | Induction of apoptotic cell death through activation of caspase.<br>Inhibition of telomerase activity through   | Choi et al. (2004)       |

| Products                   | Cells  | Mechanisms of action  | Reference            |
|----------------------------|--|---|----------------------|
|                            |  | transcriptional down regulation of hTERT. Inhibition of telomerase activity and induction of apoptosis resulted from dephosphorylation of Akt in the survival signaling pathways.   |                      |
| Daidzein                   | HeLa<br>Human cervical cancer cells  | Inhibited the cell growth and cell cycle. Induce apoptosis. Inhibit telomerase activity.  | Guo et al. (2004)    |
| Korean red ginseng         | U937<br>Human leukemic cells   | Induction of apoptosis. Inhibit telomerase activity. Cell growth inhibition.  | Park et al. (2009a)  |
| Cordyceps militaris (WECM) | A549<br>Human lung carcinoma cells<br>NSCLC<br>Human non-small cell lung cancer cells  | Cell growth inhibition. Apoptosis induction (associated with the induction of Fas, catalytic activation of caspase-8, and Bid cleavage). Dose-dependent inhibition of telomerase activity via down regulation of human telomerase reverse transcriptase (hTERT), c-myc and Sp1 expression | Park et al. (2009b)  |
| Wogonin                    | HL-60<br>Human acute myeloblastic leukemia cells   | Growth inhibition. Induction of Bax/Bcl-2 apoptosis. Telomerase inhibition through suppression of c-myc.  | Huang et al. (2010b) |
| Platycodin D               | U937<br>Human leukemic cells<br>THP-1<br>Human acute monocytic leukemia cells<br>K562<br>Human chronic myelogenous leukaemia cells | Induces apoptosis. Represses telomerase activity.   | Kim et al. (2008b)   |

Table 3. Mechanisms of action of natural products.

#### 4. Conclusion

In this chapter, recent research results of the impacts of natural compounds on telomerase inhibition and apoptosis induction in cancer cells are summarized. Researches suggest that polyphenols alter telomerase activity and induce apoptosis by affecting proteins that function in various signal pathways. We showed that the possible relationship between the



impacts of natural compounds on telomerase inhibition and apoptosis induction. Some studies suggest that telomerase activity is connected to regulation of apoptosis in physiological and pathological terms. However, it is also a fact that every compound cannot directly affect both of the mechanisms simultaneously. More detailed knowledge about polyphenols and the mechanism responsible for telomerase inhibition and apoptosis induction and the true effectiveness of polyphenols would help to determine whether polyphenols is a potential chemopreventive and chemotherapeutic reagent for treatment of cancer.

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