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Telomerase Inhibitors and Activators: Pharmaceutical Importance

Ayşe Gul Mutlu

Additional information is available at the end of the chapter

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Abstract

Telomeres are specialized functional complexes that protect the ends of eukaryotic chromosomes. The telomeric DNA sequences are tandem repeats of a short hexameric sequence unit. The inability to DNA polymerase to replicate the end of the chromosome during lagging strand synthesis results in the loss of telomeric repeats when cell divides. Telomere shortening provides a barrier to cancer progression and the majority of the cancer cells depend on the activation of telomerase to gain proliferative immortality. Thus, telomerase is a molecular target for diseases since its discovery. Telomerase inhibition enables more specific ground for cancer therapy because the telomerase is not detected in most normal tissues. Some of the synthetic and natural telomerase inhibitors were tried on various cancer cells and there was a decrease in the number of cancer cells. But on the other hand, telomere shortening correlates with cellular aging. Some evidence suggests that the progressive loss of telomeric repeats of chromosomes may function as a molecular clock that triggers senescence. Telomerase-related gene mutations also result in some diseases. Because of this, telomerase activators are important for antiaging and telomerase-dependent disease treatments. This chapter summarizes the pharmaceutical importance of telomeres, telomerase structure, telomerase activators, and inhibitors.

Keywords: telomerase, telomerase inhibitors, telomerase activators

1. Introduction

1.1. Importance of telomeres

Telomeres are specialized functional complexes that protect the ends of eukaryotic chromosomes. The telomeric DNA sequences are, in most species, tandem repeats of a short hexameric sequence unit [1]. Overall, telomere sizes range from about 15 to 20 kbp at birth to sometimes less than 5 kbp in chronic disease states. Telomeric repeats help maintain chromosomal integrity [2].

Evolutionary conservation of this repetitive DNA sequence family might indicate that sequence is essential to the cellular function [3]. Telomeric DNA sequences and structure are similar among otherwise widely divergent eukaryotes. The telomeric repeat unit is TTAGGG for humans as well as other vertebrates [4]. The ends of telomeres are protected and regulated by telomere binding proteins and form a t loop structure [2, 5]. Mainly, the inability of DNA polymerase to replicate the end of the chromosome during lagging strand synthesis results in the loss of telomeric repeats when cell divides. This phenomenon eventually results in a growth arrest and telomeres become critically shortened when multiple chromosome end fusions occur, resulting in a loss of cell viability [2]. Telomere shortening provides a barrier to cancer progression by preventing immortalization and the majority of the cancer cells depend on the activation of telomerase to gain proliferative immortality [2, 6]. But on the other hand, telomere shortening correlates with cellular aging. Stem and progenitor cells express low levels of telomerase [6].

1.2. Telomerase structure and function

Greider and Blackburn identified a specialized DNA polymerase in extracts from the *Tetrahymena* that extends the chromosome ends in eukaryotes [7]. Telomerase adds multiple copies of certain DNA unit to the terminal portion of one strand of the repeat tract [1, 4]. This process is required for genomic stability and cell viability. Telomerase is a specialized reverse transcriptase. Telomerase subunit TER identified in the late 1980s and catalytic subunit TERT in 1997. Subsequent studies showed that the TER and TERT together form a tight complex that is sufficient for telomeric DNA repeat synthesis *in vitro* [6]. TER contains RNA template for reverse transcription [8–10]. TERT contains discrete domains that carry out the mechanically complicated reaction of nucleic acid and nucleotide binding and selectivity in a coordinated manner during telomerase replication [8]. Despite only TERT and TER are required for telomerase catalytic activity *in vitro*, the physiologically functional holoenzyme is a multisubunit ribonucleoprotein (RNP). *Tetrahymena* telomerase holoenzyme contains eight subunits, each of which is essential for telomere length maintenance [10].

Telomerase is a very important enzyme for the aging process and carcinogenesis. Primary human cells exhibit limited replicative potential but the cancer cell lines are immortal with passage in culture [11]. In embryonic stem cells telomerase is activated and maintains telomere length but the level of telomerase activity is low or absent in the majority of the stem cells. Thus, even in stem cells, except embryonic stem cells and cancer stem cells, telomere shortening occurs, possibly at a slower rate than that in normal somatic cells [12].

To grow indefinitely, human cancer cells must compensate the progressive loss of telomeric DNA by cell division [13]. This immortality is mainly a result of telomerase activity. Telomerase is expressed in more than 85% of cancer cells [14–17], but in some cells, the telomere length could be maintained in the absence of telomerase. It has been deduced that one or more alternative telomerase-independent mechanisms exist in human cells [13].

2. Telomerase inhibitors and pharmaceutical importance

Synthesis of DNA at chromosome ends by telomerase may be necessary for indefinite proliferation of human cells. According to results of Kim et al. in cultured cells representing

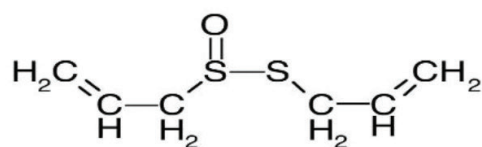
18 different human tissues, 98 of 100 were immortal and none of the 22 mortal populations were positive for telomerase. Similarly, 90 of 101 biopsies representing 12 human tumor types and none of the 50 normal somatic tissues were positive [14]. Tahara et al. observed that the positive telomerase activity in 28 hepatocellular carcinoma (HCC) tissues of 33. Interestingly, hepatitis B virus-positive patients were telomerase positive. Also, in 19 of 38 hepatitis tissues and 6 of 8 cirrhotic liver tissues, weak telomerase activity was detected. These results indicate that the expression of telomerase may play a crucial role in hepatocarcinogenesis [15]. Ferber et al. detected that the integrations of the hepatitis B virus and human papillomavirus into the hTERT gene in liver and cervical cancers [18]. Hiyama et al. showed that the 95% of the advanced stage breast cancer tissues have telomerase activity [16].

Telomerase is a molecular target since its discovery. The most important disadvantage of chemotherapy drugs used today is that they are not selective, they have effect on normal healthy cells together with cancer cells. Telomerase inhibition enables more specific ground because the telomerase is not detected in most normal tissues [2, 17]. Differences in telomerase expression, telomere length, and cell kinetics between normal and cancer tissues suggest that targeting telomerase for cancer therapy may be relatively safe [19]. Telomerase inhibitor effects on stem cells may thus be minor because these telomerase-competent cells only proliferate intermittently and typically have much longer telomeres than cancer cells [2].

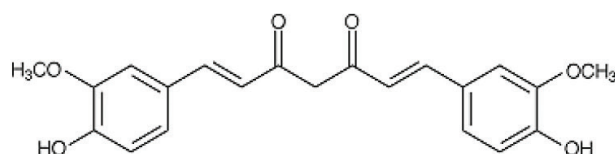
Experimental and clinical studies for telomerase inhibition are currently carried out in many different ways, such as inhibition by nucleotides and nucleoside-type reverse transcriptase inhibitors; direct inhibition by nonnucleoside small molecules; oligonucleotide inhibitors of telomerase activity; gene therapy; telomerase-specific phosphorylation inhibitors; G quadruplex stabilizers; and TER directed hammer head ribozymes [2, 17, 20, 21].

In recent studies, some of the synthetic telomerase inhibitors were tried to bone marrow, prostate, brain, breast cancer, and pancreas cancer cells and there was a decrease in the number of cancer cells [17]. Telomerase inhibitor imetelstat (GRN163L) is the first telomerase inhibitor to advance to the clinical development (www.eron.com/imetelstat). Some isothiazolone derivatives show telomerase inhibition properties [20]. 2-[(E)-3-naphthalen-2-yl-but-2-enoylamino]-benzoic acid was reported as a selective telomerase inhibitor [20, 22]. According to the results of our previous studies (unpublished), some of Imidazo[1, 2-a]pyrazine derivatives can be used for telomerase inhibition. There are some studies which draw attention to various enzyme inhibition and anticancer activities of Imidazo(1,2-a)pyrazine derivatives [23–28].

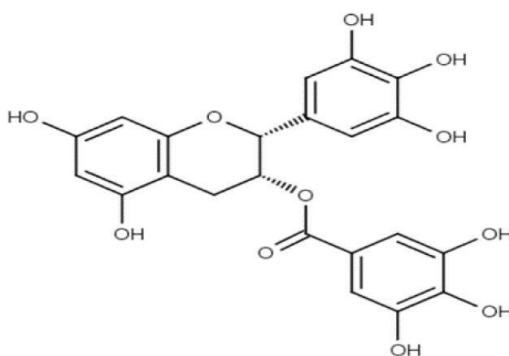
In addition to synthetic compounds, various chemical compounds that occur naturally in plants like allicin, curcumin, and silibinin have been suggested as telomerase inhibitors (**Figures 1 and 2**) [29]. Allicin is organosulfur compound obtained from garlic that can inhibit telomerase activity and induce apoptosis of gastric cancer SGC-7901 cells [30]. Milk thistle's silymarin and silibinin have also been investigated by some researchers in terms of telomerase inhibition and activation. The treatment of the K562 human leukemia cell line with silymarin resulted in a significant inhibition of telomerase activity [31]. In Yurtcu et al.'s study, combination of silymarin and doxorubicin and silymarin alone inhibited telomerase activity in HepG2 hepatocellular carcinoma cell line [32]. But silymarin may activate the telomerase in noncancerous cells according to the results of Parzonko et al. In this study, silymarin increased telomerase activity in endothelial progenitor cells [33]. Thelen et al. showed that inhibition of telomerase



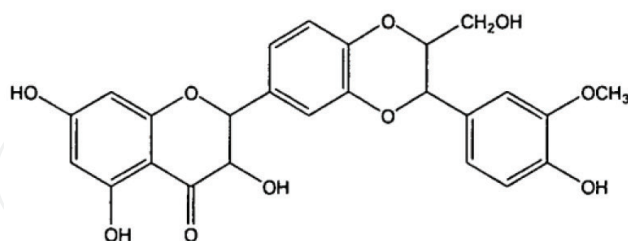
Allicin



Curcumin



Epigallocatechin gallate



Silibinin

Figure 1. Chemical formula of some natural telomerase inhibitors.

activity by silibinin in prostate cancer cells [34]. Silibinin can also inhibit hTERT gene expression in T47D breast cancer cells. Silibinin and curcumin combination could be more effective in the way of inhibition of telomerase [35]. Curcumin is a phenolic compound isolated from the rhizome of the *Curcuma longa* L. Curcumin has antitumor, antiangiogenic, and apoptotic



Figure 2. Various chemical compounds that occur naturally in garlic, turmeric, grape, and milk thistle are telomerase activity modifiers.

properties. Chakraborty et al. suggested that telomerase inhibition is a main mechanism of curcumin-induced apoptosis in human leukemia cell line K-562 [36]. In Ramachandran et al.'s study, increasing concentrations of curcumin caused a steady decrease in the level of hTERT mRNA and inhibited telomerase activity in MCF-7 breast cancer cells [37].

Antibiotics ofloxacin and levofloxacin inhibit the telomerase in cell extracts. Helenalin (a natural sesquiterpene lactone), polyunsaturated fatty acids with cis-double bond, also inhibit the telomerase [20]. However, some dietary polyphenols have been suggested as telomerase inhibitors [38]. Major tea catechin epigallocatechin gallate strongly and directly inhibits telomerase. It is suggested that telomerase inhibition could be one of the major mechanisms underlying the anticancer effects of tea [39]. Naasani et al. proposed that the inhibition of telomerase is a key mechanism in cancer inhibition by epigallocatechin gallate [40]. Besides, epigallocatechin gallate inhibits telomerase and induces apoptosis in drug resistant lung cancer and cervical cancer cells [41, 42]. Epigallocatechin gallate and sulforaphane combination treatment induce apoptosis in paclitaxel-resistant ovarian cancer cells through hTERT and Bcl-2 downregulation [43]. Sulforaphane (SFN) is a dietary isothiocyanate. SFN decreases viability and telomerase activity in hepatocellular carcinoma Hep3B cells. Moon et al. suggested that the reactive oxygen species (ROS) are essential for the suppression of SFN-mediated telomerase regulation [44]. According to Meeran et al.'s results, SFN causes epigenetic downregulation of hTERT expression in human breast cancer cell lines [45].

It would suggest that telomerase inhibitors might be most effective in combinations with other conventional or experimental cancer treatments [2].

There are alternative mechanisms for telomerase maintenance (ALT) and some rare telomerase negative human cancers. Unfortunately, telomerase inhibitors might result in the emergence of drug resistant telomerase-independent cancer cells [2].

Telomerase inhibitors can be useful for the treatment of some other diseases. Blackburn proposed that telomerase might be target for drugs against eukaryotic pathogenic or parasitic microorganisms, such as parasitic protozoans or pathogenic yeast [4]. Actually, some studies about telomerase activities of eucaryotic pathogenic microorganisms were achieved. Cano and colleagues identified telomerase activity in extracts of *Trypanosoma brucei*, *Leishmania major*, and *Leishmania tarentolae* and they proposed as a target the inhibition of telomerase activity [46].

The catalytic subunit of telomerase (TERT) shows a striking similarity to retroviral reverse transcriptases (retroviral RTs) and viral RNA polymerase [8]. Rubomycin and some of its analogs were demonstrated to be potent inhibitors of retroviral RTs and also inhibitors of telomerase [20].

Telomerase inhibition is a good and specific target. Because the telomerase is not detected in most normal tissues [2, 17], differences in telomerase expression, telomere length, and cell kinetics between normal and cancer tissues suggest that targeting telomerase for cancer therapy may be relatively safe [19].

3. Telomerase activators and pharmaceutical importance

Proliferation of telomerase negative cells results in progressive telomere shortening. Cellular senescence is thought to serve as a protecting mechanism against cancer, but subsequent telomere dysfunction will be involved in tumorigenesis late in life [20]. Telomere shortening may cause aging and death. Some evidence suggests that the progressive loss of telomeric repeats of chromosomes may function as a molecular clock that triggers senescence [47–49]. Bodnar et al. analyzed two telomerase-negative normal human cell types. The cells were transfected with vectors encoding to human telomerase catalytic subunit. Telomerase expressing clones had elongated telomeres and showed reduced senescence signs [47]. Numerous epidemiological studies show that shorter telomeres in humans are associated with many age-related diseases [49, 50]. Humans with shorter than average telomere length are at risk of dying from heart disease, stroke, or infection. Individuals with chronic stress or infections have accelerated telomere shortening compared to age-matched counterparts [51].

Telomerase-related gene mutations result in some diseases. The first disease-associated with mutations in human telomerase is dyskeratosis congenita (DKC) [20]. The X-linked form of the DKC is caused by mutations in the gene encoding dyskerin (DKC1). It has been suggested that DKC may be caused by a defect in rRNA processing. Dyskerin is associated also with human telomerase RNA [52]. Autosomal dominant form of DKC is closely associated with the

mutations in the TER and defective telomere maintenance [53]. Mitchell et al. find that primary fibroblasts and lymphoblasts from DKC affected males have a lower level of telomerase RNA, produce lower levels of telomerase activity, and have shorter telomeres [52].

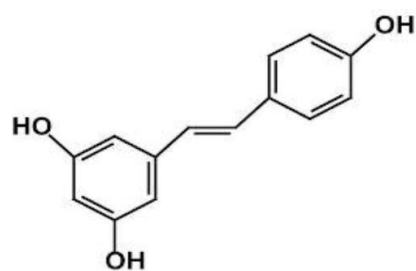
More recently, telomerase mutations have been detected in the context of aplastic anemia, Hoyeraal-Hreidarsson syndrome, idiopathy pulmonary fibrosis, ataxia telangiectasia, Werner syndrome, Bloom syndrome, Nijmegen breakage syndrome, and ataxia telangiectasia-like disorder [20, 54]. The unifying molecular characteristics of these diseases are that patients harbor telomeres that are significantly shorter than the age-matched control subjects [54]. Not only the genetic modulation but also the epigenetic mechanisms may be responsible for the diverse expression status of telomerase in a tissue and cell-type dependent manner [55].

Also, telomere erosion occurred by excessive T-cell proliferation in AIDS or X-linked Lymphoproliferative syndrome. However, cardiovascular diseases have been recently linked with telomere-dependent senescence [20].

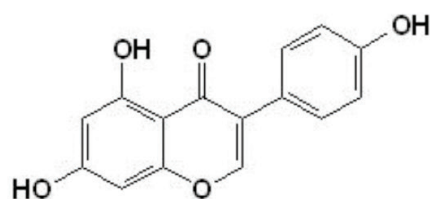
Because of that, telomerase activators are important for antiaging and telomerase-dependent disease treatments. Telomerase gene therapy in adult and old mice delays aging and increases longevity [56, 57]. TERT exhibits neuroprotective effects in experimental models of neurodegenerative disorders suggesting that inducing the telomerase activity in neurons may protect against age-related neurodegeneration and Alzheimer's disease [58]. Geron Corp. and TA Therapeutics developed a single molecule telomerase activator, TAT2 (cycloastragenol) [29]. Cycloastragenol is an aglycone of astragaloside IV (**Figure 3**). It was first defined when screening *Astragalus membranaceus* extracts for antiaging properties and a potent telomerase activator in neuronal cells [59]. The extract of *Astragalus membranaceus* was licensed as a nutritional supplement called TA 65 (TA sciences, Geron Corp.). This extract could elongate short telomeres and increase health span of adult mice without increasing cancer incidence [60]. Also, this natural-based product can elongate short telomeres in human leukocytes [61].

Furthermore, certain phytochemicals like resveratrol and genistein have been shown to activate telomerase (Figure 3). Genistein is a natural isoflavone found in soybean products. Genistein inhibits the transcription of hTERT in breast MCF10AT benign cells and MCF7 cancer cells [62]. Genistein also decreases telomerase activity in prostate cancer cells [63, 64]. Ouchi et al. showed that the expression of hTERT and c-myc mRNA was downregulated by genistein in prostate cancer cells [63]. But, physiologically achievable concentrations of genistein enhance telomerase activity in prostate cancer cells [65]. Genistein may activate telomerase activity at low concentrations and inhibit telomerase activity at higher treatment concentrations [29].

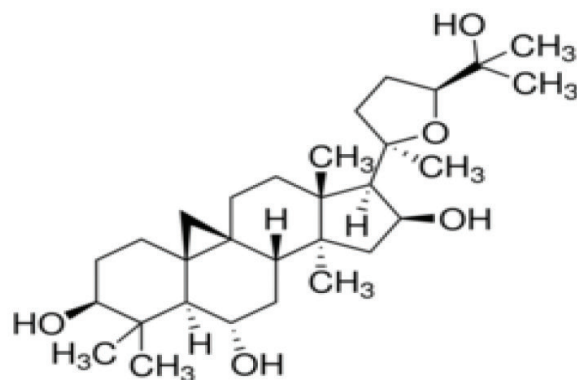
The *trans*-isomer of resveratrol is a natural phytoalexin present in a limited number of Spermatophyta, especially in grapes, fruits, and root extracts. It is synthesized in response to stress conditions. Resveratrol has a direct inhibitory effect on cell proliferation. Studies showed that resveratrol treatment downregulates the telomerase activity and levels of hTERT in MCF7 breast cancer cells [66]. Besides, relatively high concentrations of resveratrol were found to be able to downregulate telomerase activity in human colon cancer cells [67]. Several compounds like resveratrol have been shown to act as both inhibitors and activators



Resveratrol



Genistein



Cycloastragenol

Figure 3. Chemical formula of some natural telomerase activators.

of telomerase though this may be due to treatment concentration or cell type differences. Resveratrol has been shown to inhibit telomerase activity in cancer cells but activate telomerase in epithelial and endothelial progenitor cells [29, 68].

There are few studies about the effects of *Gingko biloba* on telomerase activity. Dong et al. showed that *Gingko biloba* extract increases telomerase activity in endothelial progenitor cell [69].

Also, HMG-CoA reductase inhibitor therapy and statin treatment are associated with delay of senescence and reduced cardiovascular diseases [29]. Moreover, in our study (unpublished) it was observed that dimethylsulfoxide (DMSO), which is used for solving chemical substances increases telomerase activity. In the study of Alfonso-De Matte et al., DMSO increased telomerase activity in some cell lines that is known to have no/low telomerase activity [70].

Also, in a study which was carried out about differentiation of embryonic stem cell on rats, TERT gene upregulated as a result of dimethylsulfoxide (DMSO) application on each individual and telomerase activity increased [71].

Telomere shortening correlates with cellular aging [6]. Telomerase-related gene mutations also result in some diseases [20]. Because of that, telomerase activators are important for anti-aging and telomerase-dependent disease treatments.

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References

- [1] Blackburn EH. Switching and signaling at the telomere. *Cell*. 2001; 106: 661–673.
- [2] Shay JW, Wright WE. Telomerase: a target for cancer therapeutics. *Cancer Cell*. 2002; 2: 257–262.
- [3] Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, Meyne J, Ratliff RL, Wu J. A highly conserved repetitive DNA sequence, (TTAGGG)_n, present at the telomeres of human chromosomes. *Proceeding of the National Academy of Sciences of USA*. 1988; 85: 6622–6626.
- [4] Blackburn EH. Structure and function of telomeres. *Nature*. 1991; 350: 569–573.
- [5] Griffith JD, Comeau L, Rosenfield S, Stansel RM, Bianchi A, Moss H, de Lange T. Mammalian telomeres end in a large duplex loop. *Cell*. 1999; 97: 503–514.
- [6] Sandin S, Rhodes D. Telomerase structure. *Current Opinion in Structural Biology*. 2014; 25: 104–110.
- [7] Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. *Cell*. 1985; 43: 405–413.
- [8] Mitchell M, Gillis A, Futahashi M, Fujiwara H, Skordalakes E. Structural basis for telomerase catalytic subunit TERT binding to RNA template and telomeric DNA. *Nature Structural and Molecular Biology*. 2010; 17: 513–518.

- [9] Banik SSR, Guo C, Smith AC, Margolis SS, Richardson DA, Tirado CA, Counter CM. C terminal regions of the human telomerase catalytic subunit essential for in vivo enzyme activity. *Molecular and Cellular Biology*. 2002; 22: 6234–6246.
- [10] Jiang J, Miracco EJ, Hong K, Eckert B, Chan H, Cash DD, Min B, Zhou ZH, Collins K, Feigon J. The architecture of tetrahymena telomerase holoenzyme. *Nature*. 2013; 496: 187–192.
- [11] Artandi SE, Depinho RA. Telomeres and telomerase in cancer. *Carcinogenesis*. 2010; 31: 9–18.
- [12] Hiyama E, Hiyama K. Genetic and epigenetic modulation of telomerase activity in development and disease. *British Journal of Cancer*. 2007; 96: 1020–1024.
- [13] Shay JW, Reddel RR, Wright WE. Cancer and telomeres an alternative to telomerase. *Science*. 2012; 336: 1388–1390.
- [14] Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PLC, Coviello GM, Wright WE, Weinrich SL, Shay JW. Specific association of human telomerase activity with immortal cells and cancer. *Science*. 1994; 266: 2011–2015.
- [15] Tahara H, Nakanishi T, Kitamoto M, Nakashio R, Shay JW, Tahara E, Kajiyama G, Ide T. Telomerase activity in human liver tissues: comparison between chronic liver disease and hepatocellular carcinomas. *Cancer Research*. 1995; 55: 2734–2736.
- [16] Hiyama E, Gollahon L, Kataoka T, Kuroi K, Yokoyama T, Gazdar AF, Hiyama K, Piatyszek MA, Shay JW. Telomerase activity in human breast tumors. *Journal of the National Cancer Institute*. 1996; 88: 116–122.
- [17] Buseman CM, Wright WE, Shay JW. Is telomerase viable target in cancer. *Mutation Research*. 2012; 730: 90–97.
- [18] Ferber MJ, Montoya DP, Yu C, Aderca I, McGee A, Thorland EC, Nagorney DM, Gostout BS, Burgart LJ et al. Integrations of the hepatitis B virus (HBV) and human papillomavirus (HPV) into the human telomerase reverse transcriptase (hTERT) gene in liver and cervical cancers. *Oncogene*. 2003; 22: 3813–3820.
- [19] Harley CB. Telomerase and cancer therapeutics. *Nature Reviews Cancer*. 2008; 8: 167–179.
- [20] Tarkanyi I, Aradi J. Pharmacological intervention strategies for affecting telomerase activity: Future prospects to treat cancer and degenerative disease. *Biochimie*. 2008; 90: 156–172.
- [21] Saretzki G. Telomerase inhibition as cancer therapy. *Cancer Letters*. 2003; 194: 209–219.
- [22] Damm K, Hemmann U, Garin-Chesa P, Huel N, Kauffmann I, Priepke H, Niestroj C, Daiber C et al. A highly selective telomerase inhibitor limiting human cancer cell proliferation. *The EMBO Journal*. 2001; 20: 6958–6968.
- [23] Leng Y, Lu T, Yuan HL, Liu HC, Lu S, Zhang WW, Jiang YL, Chen YD. QSAR studies on imidazopyrazine derivatives as Aurora A kinase inhibitors. *SAR and QSAR in Environmental Research*. 2012; 23: 705–730.

- [24] Mitchell SA, Danca MD, Blomgren PA, Darrow JW, Currie KS, Kropf JE, Lee SH, Gallion SL, Xiong JM, Pippin DA, DeSimone RW, Brittelli DR, Eustice DC, Bourret A, Hill-Drzewi M, Maciejewski PM, Elkin LL. Imidazo[1,2-a]pyrazine diaryl ureas: Inhibitors of the receptor tyrosine kinase EphB4. *Bioorganic and Medicinal Chemistry Letters*. 2009; 19: 6991–6995.
- [25] Matthews TP, McHardy T, Klair S, Boxall K, Fisher M, Cherry M, Allen CE, Addison GJ, Ellard J, Aherne GW, Westwood IM, Montfort R, Garrett MD, Reader JC, Collins I. Design and evaluation of 3,6-di(hetero)aryl imidazo[1,2-a]pyrazines as inhibitors of checkpoint and other kinases. *Bioorganic and Medicinal Chemistry Letters*, 2010; 20: 4045–4049.
- [26] Rosse G. Imidazopyrazine derivatives as inhibitors of mTOR. *ACS Medical Chemistry Letters*. 2013; 4: 498–499.
- [27] Chen L, Monti S, Juszczynski P, Ouyang J, Chapuy B, Neuberg D, Doench JG, Bogusz AM, Habermann TM, Dogan A, Witzig TE, Kutok JL, Rodig SJ, Golub T, Shipp MA. SYK inhibition modulates distinct PI3K/AKT dependent survival pathways and cholesterol biosynthesis in diffuse large B cell lymphomas. *Cancer Cell*. 2013; 23: 826–838.
- [28] Baviskar AT, Madaan C, Preet R, Mohapatra P, Jain V, Agarwal A, Guchhait SK, Kundu CN, Banerjee UC, Bharatam PV. N-fused imidazoles as novel anticancer agents that inhibit catalytic activity of topoisomerase II α and induce apoptosis in G1/S phase. *Journal of Medical Chemistry*. 2011; 54: 5013–5030.
- [29] Sprouse AA, Steding CE, Herbert B. Pharmaceutical regulation of telomerase and its clinical potential. *Journal of Cellular and Molecular Medicine*. 2012; 16: 1–7.
- [30] Sun L, Wang X. Effects of allicin on both telomerase activity and apoptosis in gastric cancer SGC-7901 cells. *World Journal of Gastroenterology*. 2003; 9: 1930–1934.
- [31] Faezizadeh Z, Mesbah-Namin SAR, Allameh A. The effect of silymarin on telomerase activity in the human leukemia cell line K562. *Planta Medica*. 2012; 78: 899–902.
- [32] Yurtcu E, Darcansoy Iseri O, Sahin FI. Effects of silymarin-doxorubicin applications on telomerase activity of human hepatocellular carcinoma cell line HepG2. *Journal of Balkan Union Oncology*. 2015; 20: 555–561.
- [33] Parzonko A, Naruszewicz M. Silymarin inhibits endothelial progenitor cells' senescence and protects against the antiproliferative activity of rapamycin: preliminary study. *Journal of Cardiovascular Pharmacology*. 2010; 56: 610–618.
- [34] Thelen P, Wuttke W, Jarry H, Grzmil M, Ringert RH. Inhibition of telomerase activity and secretion of prostate specific antigen by silibinin in prostate cancer cells. *The Journal of Urology*. 2004; 171: 1934–1938.
- [35] Nasiri M, Zarghami N, Koshki KN, Mollazadeh M, Moghaddam MP, Yamchi MR, Esfahlan RJ, Barkhordari A, Alibakhsi A. Curcumin and silibinin inhibit telomerase expression in T47D human breast cancer cells. *Asian Pacific Journal of Cancer Prevention*. 2013; 14: 3449–3453.

- [36] Chakraborty S, Ghosh U, Bhattacharyya NP, Bhattacharyya RK, Roy M. Inhibition of telomerase activity and induction of apoptosis by curcumin in K-562 cells. *Molecular Mechanisms of Mutagenesis*. 2006; 596: 81–90.
- [37] Ramachandran C, Fonseca HB, Jhabvala P, Escalon EA, Melnick SJ. Curcumin inhibits telomerase activity through human telomerase reverse transcriptase in MCF-7 breast cancer cell line. *Cancer Letters*. 2002; 184: 1–6.
- [38] Cosan DT, Soyocak A. Inhibiting telomerase activity and inducing apoptosis in cancer cells by several natural food compounds. In: Bibo Li, editor. *Reviews on Selected Topics of Telomere Biology*. InTech, Rijeka, Croatia; 2012. P. 123-148.
- [39] Naasani I, Seimiya H, Tsuruo T. Telomerase inhibition, telomere shortening and senescence of cancer cells by tea catechines. *Biochemical and Biophysical Research Communications*. 1998; 249: 391–396.
- [40] Naasani I, Oh-Hashi F, Oh-Tara T, Feng WY, Johnston J, Chan K, Tsuruo T. Blocking telomerase by dietary polyphenols is a major mechanism for limiting the growth of human cancer cells in vitro and in vivo. *Cancer Research*. 2003; 63: 824–830.
- [41] Sadava D, Whitlock E, Kane SE. The green tea polyphenol, epigallocatechin-3-gallate inhibits telomerase and induces apoptosis in drug resistant lung cancer. *Biochemical and Biophysical Communications*. 2007; 360: 233–237.
- [42] Yokoyama M, Noguchi M, Nakao Y, Pater A, Iwasaka T. The tea polyphenol, (-)-epigallocatechin gallate effects on growth, apoptosis, and telomerase activity in cervical cell lines. *Gynecologic Oncology*. 2004; 92: 197–204.
- [43] Chen H, Landen CN, Li Y, Alvarez RD, Tollefsbol TO. Epigallocatechin gallate and sulforaphane combination treatment induce apoptosis in paclitaxel-resistant ovarian cancer cells through Htert AND Bcl-2 down-regulation. *Experimental Cell Research*. 2013; 319: 697–706.
- [44] Moon D, Kang S, Kim K, Kim M, Choi YH, Kim G. Sulforaphane decreases viability and telomerase activity in hepatocellular carcinoma Hep3B cells through the reactive oxygen species-dependent pathway. *Cancer Letters*. 2010; 295: 260–266.
- [45] Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of Htert expression in human breast cancer cell lines. *PLoS One*. 2010; 5: e11457.
- [46] Cano MIN, Dungan JM, Agabian N, Blackburn EH. Telomerase in kinetoplastid parasitic protozoa. *Proceeding of the National Academy of Sciences of USA*. 1999; 96: 3616–3621.
- [47] Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu C, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE. Extension of life-span by introduction of telomerase into normal human cells. *Science*. 1998; 279: 349–352.
- [48] Harley CB, Futcher AB, Greider CW. Telomerase shorten during ageing of human fibroblasts. *Nature*. 1991; 345: 458–460.
- [49] Boccardi V, Paolisso G. Telomerase activation: a potential key modulator for human healthspan and longevity. *Ageing Research Review*. 2014; 15: 1–5.

- [50] Blasco MA. Telomeres and human disease: ageing, cancer and beyond. *Nature Reviews Genetics*. 2005; 6: 611–622.
- [51] Harley CB. Telomerase therapeutics for degenerative diseases. *Current Molecular Medicine*. 2005; 5: 29–38.
- [52] Mitchell JR, Wood E, Collins K. A telomerase component is defective in the human disease dyskeratosis congenita. *Nature*. 1999; 402: 551–555.
- [53] Marrone A, Walne A, Dokal I. Dyskeratosis congenita: telomerase, telomeres and anticipation. *Current Opinion in Genetics and Development*. 2005; 15: 249–257.
- [54] Gomez DE, Armando RG, Farina HG, Menna PL, Cerrudo CS, Ghiringhelli PD, Alonso DF. Telomere structure and telomerase in health and disease. *International Journal of Oncology*. 2012; 41: 1561–1569.
- [55] Liu L, Lai S, Andrews LG, Tollefsbol TO. Genetic and epigenetic modulation of telomerase activity in development and disease. *Gene*. 2004; 340: 1–10.
- [56] De Jesus BB, Vera E, Schneeberger K, Tejera AM, Ayuso E, Bosch F, Blasco MA. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Molecular Medicine*. 2012; 4: 691–704.
- [57] De Jesus BB, Blasco MA. Telomerase at the intersection of cancer and aging. *Trends Genet*. 2013; 29: 513–520.
- [58] Mattson MP. Emerging neuroprotective strategies for Alzheimer's disease: dietary restriction, telomerase activation, and stem cell therapy. *Experimental Gerontology*. 2000; 35: 489–502.
- [59] Ip FCF, Ng YP, An HJ, Dai Y, Pang HH, Hu YQ, Chin AC, Harley CB, Wong YH, Ip NY. Cycloastragenol is a potent telomerase activator in neuronal cells: implications for depression management. *Neurosignals*. 2014; 22: 52–63.
- [60] de Jesus BB, Schneeberger K, Vera E, Tejera A, Harley CB, Blasco MA. The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging Cell*. 2011; 10: 604–621.
- [61] Harley CB, Liu W, Blasco M, Vera E, Andrews WH, Briggs LA, Raffaele JM. A natural product telomerase activator as part of a health maintenance program. *Rejuvenation Research*. 2011; 14: 45–56.
- [62] Li Y, Liu L, Andrews LG, Tollefsbol TO. Genistein depletes telomerase activity through cross-talk between genetic and epigenetic mechanisms. *International Journal of Cancer*. 2009; 125: 286–296.
- [63] Ouchi H, Ishiguro H, Ikeda N, Hori M, Kubota Y, Uemura H. Genistein induces cell growth inhibition in prostate cancer through the suppression of telomerase activity. *International Journal of Urology*. 2005; 12: 73–80.

- [64] Jagadeesh S, Kyo S, Banarjee PP. Genistein represses telomerase activity via both transcriptional and posttranslational mechanisms in human prostate cancer cells. *Cancer Research*. 2006; 66: 2107.
- [65] Chau MN, El Touny LH, Jagadeesh S, Banerjee PP. Physiologically achievable concentrations of genistein enhance telomerase activity in prostate cancer cells via the activation of STAT3. *Carcinogenesis*. 2007; 28: 2282–2290.
- [66] Lanzilli G, Fuggetta MP, Tricarico M, Cottarelli A, Serafino A, Falchetti R, Ravagnan G, et al. Resveratrol down-regulates the growth and telomerase activity of breast cancer cells in vitro. *International Journal of Oncology*. 2006; 28: 641–648.
- [67] Fuggetta MP, Lanzilli G, Tricarico M, Cottarelli A, Falchetti R, Ravagnan G, Bonmassar E. Effect of resveratrol on proliferation and telomerase activity of human colon cancer cells in vitro. *Journal of Experimental Clinical Cancer Research*. 2006; 25: 189.
- [68] Xia L, Wang XX, Hu XS, Guo XG, Shang YP, Chen HJ, Zeng CL, Zhang FR, Chen JZ. Resveratrol reduces endothelial progenitor cells senescence through augmentation of telomerase activity by Akt-dependent mechanisms. *British Journal of Pharmacology*. 2008; 155: 387–394.
- [69] Dong XX, Hui ZJ, Xiang WX, Rong ZF, Jian S, Zhu CJ. Ginkgo biloba extract reduces endothelial progenitor-cell senescence through augmentation of telomerase activity. *Journal of Cardiovascular Pharmacology*. 2007; 49: 111.
- [70] Alfonso-De Matte AMY, Cheng JQ, Kruk PA. Ultraviolet irradiation- and dimethyl sulfoxide-induced telomerase activity in ovarian epithelial cell lines. *Experimental Cell Research*. 2001; 267: 13–27.
- [71] Armstrong L, Lako M, Lincoln J, Cairns MP, Hole N. mTERT expression correlates with telomerase activity during the differentiation of murine embryonic stem cells. *Mechanisms of Development*, 2000; 97: 109–116.