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TELOMERASE AND NATURAL PRODUCTS: CURRENT STATUS AND NEW THERAPEUTIC APPLICATIONS

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ABSTRACT

Human telomerase fundamentally comprises of two principle segments: a catalytic subunit, hTERT, and a RNA template, hTR whose arrangement is complimentary to the telomeric 5'-dTTAGGG-3' repeat. In individuals, activity of telomerase is ordinarily limited to renewing tissues, for example, germ cells and stem cells, and is commonly missing in ordinary cells. Whereas hTR is constitutively communicated in most tissue types, hTERT expression levels are low enough that telomere length can't be kept up, that sets a proliferative lifetime on ordinary cells. Telomerase is a beneficial and specific target either by inhibition or activation. The development of telomerase inhibitors for cancer treatment is a major field of study. By inhibiting telomerase, it is possible to kill cancerous cells while limiting toxicity to neighbouring normal cells. While telomerase activation is currently being studied for use in immunodeficient patients to stimulate proliferation of T cells as well as in regenerative medicine and a treatment to combat the signs and symptoms of aging.

KEYWORDS

Telomerase, Telomeres, Inhibitors and Activators and Therapeutic applications.

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INTRODUCTION

Telomeres consist of repetitive non-coding DNA sequences (in humans TTAGGG), which are located at the end of the chromosomes. Telomeres, together with the shelterin complex, form a cap to protect the chromosome ends[1–3]. The shelterin complex consists of six telomere-associated proteins[4]. The telomere sequence is recognized by the subunits TRF1, TRF2, and POT1.

These subunits are interconnected by the proteins TIN2, TPP1, and Rap1. The complex allows cells to distinguish telomeres from DNA damage sites.

Without this protection, e.g., when telomeres shorten beyond a critical threshold, unprotected telomeres provoke a DNA damage response[5].

Telomere shortening occurs due to the so-called end replication problem, which means that the 3' end of the DNA strand shortens with each cell division, since the DNA polymerase cannot completely replicate the strand[3,6]. At a certain threshold of telomere attrition the damage-repair system recognizes the unprotected DNA double strand as DNA breaks and activates the p53 or the p16INK4a signaling pathway to initiate a senescence or apoptosis program. Reactive oxygen species (ROS) or other environmental stress factors may also lead to telomere damage and accelerate the telomere attrition. Particularly, the GGG triplet within the human telomere sequence TTAGGG is vulnerable to chemical modifications. From a critical telomere length, onwards, telomeres are unable to claim the shelterin complex resulting in loss of the protective inner nucleotide loop, which ultimately leads to genomic instability[7,8].

In numerous studies, it was observed that a healthy lifestyle is correlated with longer telomeres, likely reflecting protection against age-related diseases[2]. It has been shown in aging mice that cells with short and/or damaged telomeres are accumulating in stress-prone tissues, likely due to replicative exhaustion and/or stress-induced telomere damage. Animal studies suggest that senescence is not only a marker of, but also involved in, the propagation of age-related disorders[3,8].

Telomerase is also permissive for tumorigenesis and 90% of all malignant tumors use telomerase to obtain immortality. Thus, reversal of telomerase upregulation in tumor cells is a potential strategy to treat cancer. Natural telomerase inhibitors are useful treatment strategies. Telomerase is more widely expressed than any other tumor marker. The low expression in normal tissues, together with the longer telomeres in normal stem cells versus cancer cells, provides some degree of specificity with low risk of toxicity[9] (Figure No.1).

TELOMERASE TARGETS

Telomerase inhibitors

Telomerase inhibition is a beneficial and particular target. Since the telomerase isn't distinguished in most normal tissues[11,12], contrasts in telomere length, telomerase expression and cell kinetics among ordinary and cancer tissues recommend that focusing on telomerase for malignant growth treatment might be relatively safe[13]. Besides to various chemical compounds that occur naturally in plants, compounds isolated from marine source have been suggested as telomerase inhibitors. Marine-based organisms are a less common source of telomerase inhibitors. The dictyodendrin family of alkaloids were the first marine derived telomerase inhibitors to be recognized, in 2003. From that point forward, ascididemin and meridine and more newly the sulfated liposaccharide axinelloside A have additionally been distinguished as inhibitors of telomerase[14].

Mechanism of action

Some suggested mechanisms of action and Anticancer potentials of natural products from plants on targeting telomerase are listed in (Table No.1)[10].

Pharmaceutical importance

It would propose that telomerase inhibitors may be best in blends with other ordinary or experimental cancer medicines[112]. Telomerase inhibitors can be helpful for the treatment of some different diseases. Blackburn recommended that telomerase may be focus for medications against eukaryotic pathogenic or parasitic microorganisms, for example, parasitic protozoans or pathogenic yeast[113]. In reality, a few examinations about telomerase activities of eucaryotic pathogenic microorganisms were accomplished. Telomerase activity in extracts of *Trypanosoma brucei*, *Leishmania major*, and *Leishmania tarentolae* were distiguished by Cano and colleagues and they proposed as an objective of the inhibition of telomerase activity[114].

Telomerase activators

Telomeres are repeated deoxyribonucleic acid (DNA) sequences (TTAGGG) which are situated on the 5' ends of chromosomes, and they influence the

life span of eukaryotic cells. Convincing proof has demonstrated that the length of an individual's life is managed by the set number of times that a human cell can divide. The enzyme telomerase has been appeared to bind to and expand the length of telomeres. Consequently, strategies for activating telomerase may help keep up telomere length and, in this manner, may prompt health during aging[115].

A single molecule telomerase activator, TAT2 (cycloastragenol) was developed by Geron Corp. and TA Therapeutics[116]. Cycloastragenol is an aglycone of astragaloside IV (Figure No.2). It was first defined when screening *Astragalus membranaceus* extracts for antiaging properties and a powerful telomerase activator in neuronal cells[117]. 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[118]. Besides, this natural-based product can prolong short telomeres in human leukocytes[119]. Additionally, certain phytochemicals like resveratrol and genistein have been appeared to activate telomerase (Figure No.2). Genistein is a natural isoflavone found in soybean products. Genistein restrains the transcription of hTERT in breast MCF10AT benign cells and MCF7 cancer cells[120]. Genistein also decreases telomerase activity in prostate cancer cells[121,122]. Ouchi *et al.* demonstrated that the expression of hTERT and c-myc mRNA was downregulated by genistein in prostate cancer cells[121]. But, physiologically achievable concentrations of genistein improve telomerase activity in prostate cancer cells[123]. Genistein at low concentrations may activate telomerase activity and inhibit telomerase activity at higher treatment concentrations[116]. There are not many investigations about the effects of *Gingko biloba* on telomerase activity. Dong *et al.* demonstrated that *Gingko biloba* extract increases telomerase activity in endothelial progenitor cell[124].

Mechanism of action

Replicative senescence adds to the decrease in numerous physiological functions and in many tissues and, in this manner, adds to the pathology of chronic diseases[125,126]. As telomerase activity isn't, or just at low levels, detectable in somatic tissues there are numerous circumstances and chronic diseases in which the transient restoration by telomerase immortalization could be a helpful alternative[127-129]. There are several possible strategies to recreate or enhance the enzymatic activity for therapeutic use:

Classical gene therapy with transfection of telomerase sequences

This strategy can be utilized for tissue engineering, for in vitro optimization of stem cell transplantation in donor cells with short telomeres[130] and, on a fundamental level, likewise for the treatment of chronic diseases in the whole organism, gave that induction of telomerase is time-limited.

Re-expression of silenced telomerase

Cell differentiation ordinarily prompts transcriptional down regulation of telomerase induced by signaling and epigenetic alterations[131,132]. Though, telomerase down regulation can, in any event partially, be reversed by several substances and mechanisms. For instances are histone deacetylase inhibitors[133] and estrogen receptor agonists, the last acting by Akt mediated phosphorylation[134]. Numerous medications with primary targets other than telomerase additionally impact hTERT on transcriptional and/or posttranslational level. Included signaling pathways that up regulate hTERT expression and/or activity are PI3/Akt, MAPK/ERK1/2, and the Wnt/ β-catenin pathway.

Activation of residual enzymatic activity

Activation of telomerase activity itself is a possibility for cells with residual telomerase activity, for example, lymphocytes and stem cells of regenerative tissues. In lymphocytes' clonal expansion typically activates telomerase activity by means of enzyme phosphorylation and subsequent nuclear translocation[135]. This function decreases with advanced age and prompts exhaustion of memory cells and could be reestablished by direct interaction with the telomerase holoenzyme or the telomerase activating signaling pathways[136].

Modulation of the intracellular location

The sequestration of telomerase is other viable level of regulation on telomerase activity, implicating telomerase localization as a potential focus for pharmacotherapy[137]. Telomerase can be translocated between the nucleus and the cytosol. In mitochondria, hTERT is as well present with yet unspecified physiological importance[127,138].

Pharmaceutical importance

Telomerase reconstruction was primary discussed for treatment of diseases with distorted enzymatic activity of telomerase, namely, dyskeratosis congenital and aplastic anaemia[139]. Potential extra applications are production of epithelia for burns or wounds, endothelia for blood vessels, chondrocytes for the treatment of arthritis, osteocytes for bone defects, and hematopoietic cells for bone marrow transplants or for the replacement of immune cells[130,140,141]. By use of this technique human blood vessels have already been engineered *in vitro*[142]. Transient telomerase activation may also be used for the treatment of other chronic diseases such as cardiac muscle disease, atherosclerosis[143], immunodeficiency, and bone marrow failure[144,145], liver disease[144,146], pulmonary fibrosis[144,147], degenerative cartilage defects[148], cataract[149], rheumatoid arthritis[150], organ transplantation[151], or treatments associated with the accelerated formation of senescent cells such as past cancer therapy or HIV[152,153]. Cartilage defects have become the target of cartilage tissue engineering[148]. Thomas and co-workers have demonstrated that bovine TERT-modified bovine adrenocortical cells can be transplanted into severe combined immunodeficient mice, and that these cell clones behave like their normal counterparts and form functional tissue after transplantation. This tissue is histologically similar to tissue formed from normal cells and shows a similar rate of cell division, implying a therapeutic role of telomerase in xenotransplantation[151].

The association between telomere length and aging has also led to the development of telomerase activators which may induce hTERT and/or hTR expression, enhance enzyme activity and/or influence cellular location. The aim behindhand this approach is to reverse normal cellular aging and to treat symptoms of aging[154].

Therapeutic applications

The potential advantages of regulating telomerase activity are clear. Pharmaceutically inhibiting telomerase may demonstrate an imperative choice in cancer therapy in combination with traditional chemotherapeutics. Conversely, the activation of telomerase could be valuable to treat age related diseases and HIV/AIDS patients where lymphocytes have stopped proliferating. Though, the long-term impacts of regulating telomerase either positively or negatively are indistinct. It is possible that inhibition of telomerase could have adverse side effects on normal stem cell function and immune response as stem and immune cells have increased telomerase activity to accommodate frequent proliferation. Understanding of telomerase regulation in normal cells is crucial for the development of telomerase inhibitors and activators. The regulation of telomerase is complex. This complication may make pharmaceutical regulation difficult owing to compensation by further regulatory pathways. Yet, phytochemicals that appear to regulate telomerase afford a starting place. These chemicals can be utilized as lead compounds to create drugs that may be able to be used in the clinic. Some Phytochemicals shown to have telomerase inhibitors/activators properties are listed in (Table No.2)[155].

Table No.1: Some suggested mechanisms of action and Anticancer potentials of natural products from plants on targeting telomerase

Plant source	Compounds	Mechanism of action	Reference
Targeting hTERT—Inhibition of the Catalytic Function			
Brassica oleracea	Indole-3-carbinol	Inhibition of telomerase and down regulated expression of the catalytic subunit of hTERT	[15]
Camellia sinensis	Epigallocatechin gallate	Binding competitively at the active site of hTERT	[16,17,18]
Trigonella foenum-graecum	Diosgenin	Prevention of telomerase activity by down regulation of the hTERT gene expression	[19,20]
Zingiber officinale Roscoe	Gingerol	Reduction of hTERT expression and decrease of c-Myc (myelocytomatosis viral oncogene)	[21]
Suppression of Transcriptional and Post-Transcriptional Regulation			
Angelica sinensis	Butylidenephthalide	Down-regulation of the telomerase activity and hTERT expression	[22, 23, 24, 25-35]
Asian coniferous evergreen trees *Cephalotaxus* sp.	Cephalotaxus alkaloids		
Papaveraceae	Papaverine		
Blueberries	Resveratrol		
Crocus sativus L.	Crocin		
Marine sponge *Petrosia* sp.	Dideoxypetrosynol A		
Marine sponge *Stelletta* sp.	(Z)-Stellettic acid C		
Melissa officinalis	Luteolin-7-O-glucoside		
Secondary plant metabolites	Genistein		
Fruits and vegetables	Quercetin		
Platycodon grandiflorum	Saponins		
Streptomyces sp.	Trichostatin A		
Streptomyces sp.	Vinorelbine		
Salvia miltiorrhiza	Tanshinone I		

Table No.1

Plant source	Compounds	Mechanism of action	Reference
Arnica montana	Helenalin	Down-regulation of hTERT transcription through inhibition of nuclear factor kappa beta (NF-kB)	[23]
Atractylis lancea (Thunb.) DC.	Atractylenolide	Inhibition of hTERT expression and decreased the expression of both mRNA and protein	[36, 37-45]
Ganoderma tsugae	Fungal immuno-modulatory protein-gts		
Camellia sinensis	Epigallocatechin		

	gallate		
Curcuma longa	Curcumin		
Laminaria japonica	Glycoprotein LJPG (Lamanaria japonica glycoprotein)		
European mistletoe, *Viscum album*	Mistletoe lectin		
Cruciferous vegetables	Indole-3-carbinol		
Common fruits and vegetables	Apigenin	Inhibition of telomerase activity with down-regulation of hTERT expression, attenuating the binding of c-Myc and special protein 1 (Sp1) to the regulatory regions of hTERT	[46-50]
Cordyceps militaris	Phenolic acids		
Dinophysis fortii	Pectenotoxin-2		
Garcinia hurburyi tree	Gambogic acid	Down-regulation of hTERT transcription via inhibition of the transcription activator c-myc, and by the inhibition of the phosphorylation of serine/threonine-protein kinase (Akt); down regulation of the activity of hTERT in a post-translational manner	[51, 52]
Garlic (*Allium sativum*)	Allicin and Ajoene	Reduction of hTERT mRNA levels	[53, 54]
Hellbore (*Veratrum grandiflorum* O. Loes), peanuts (*Arachis hypogea*), legumes (*Cassia* sp.) and grapes (*Vitis vinifera*)	Resveratrol	Down-regulation of the telomerase activity and the nuclear levels of hTERT	[55, 56]
Vitis vinifera	Resveratrol and pterostilbene		
Magnolia sieboldii	Costunolide	Inhibition of telomerase activity, reduction of hTERT mRNA and protein levels, decreasing the bindings of transcription factors in hTERT promoters	[57, 58]
Panax ginseng C. A. MEYER, *Sun Ginseng*	Ginsenoside Rk1	Inhibition telomerase activity with down-regulation of levels of hTERT and c-Myc mRNA	[59, 60, 61]
Scutellaria baicalensis	Baicalin and wogonoside		
Silybum marianum L. Gaertn	Silibinin		
Peumus boldus	Boldine	Inhibition of hTERT expression	[62]

Tripterygium wilfordii	Triptolide	Inhibition of transcription of hTERT through down-regulation of transcription factor specificity protein 1	[63]

Table No.1

Plant source	Compounds	Mechanism of action	Reference
Translocation			
Cottonseed	Gossypol	Inhibition of telomerase activity with reducing the phosphorylation and nuclear translocation of hTERT	[64, 65, 50, 66-68]
Dinophysis fortii	Pectenotoxin-2		
Ganoderma tsugae	Recombinant fungal immunomodulatory protein-gts		
Secondary plant metabolites	Genistein		
Post-Translational Modification			
Broccoli and cauliflower	Sulforaphane	Inhibition of telomerase activity and post-translational modification of hTERT	[66, 69]
Cottonseed	Gossypol		
Inhibition of Telomerase Activity			
Red yeast rice	Rubropunctatin	Inhibition of telomerase activity	[70, 71, 72 73, 74-89]
Mushrooms, onion, and other spices	Crude extract		
Allium sativum L.	Diallyl disulfide		
Berberis vulgaris	Berbarine		
Blueberries	Pterostilbene		
European mistletoe, *Viscum album*	Coloratum agglutinin		
Juglans mandshurica	Polyphenols		
Marine sponge, *Dictyodendrilla verongiformis*	Dictyodendrins		
Phyllanthus urinaria	Gallic acid, ellagic acid, quercetin and cisplatin		
Salvia miltiorrhiza	Tanshinone IIA		
Silybum marianum	Silymarin		
Streptomyces anulatus	Telomestatin		
Trichosanthes cucumerina L.	Cucurbitacins		
Marine sponge, *Axinellan fundibula*	Axinelloside A		

Phyllanthus urinaria	7ˈ-Hydroxy-3ˈ,4ˈ,5,9,9ˈ-pentamethoxy-3,4-methylene dioxylignan		
Metabolites of sulforaphane from *broccoli*	MTBITC(erucin)		
Brassica oleracea	Indole-3-carbinol and 3,3ˈ-diindolylmethane		
Cladonia furcate	Lichenin CFP-2		
Diterpenoid quinone	Salvicine	Induce apoptosis and Inhibition of telomerase activity	[53, 90, 91]
Garlic (*Allium sativum*)	Allicin and Ajoene		
ent-kaurene Diterpenoids	Xerophilusin B, Macrocalin B, and Eeriocalyxin B		
Glycine max	Daidzein	Inhibition of cell growth and cell cycle in G2/Mm phase. Induce apoptosis and Inhibition of telomerase activity and reduced telomere length	[92, 93, 94, 95]
Panax ginseng C.A. Meyer Radix rubra	Korean red ginseng		
Platycodon grandiflorum	Platycodin		
Pedicularis striata Pall	Verbascoside		

Table No.1

Plant source	Compounds	Mechanism of action	Reference
Targeting hTR (human telomerase RNA component)—Transcriptional Level			
Tabebuia avellanedae (Lapacho tree)	Beta-Lapachone	Inhibition of telomerase activity, down-regulation of the levels of hTR and c-myc expression	[96]
Targeting the Telomerase Substrate and Associated Protein-Competitor for Substrate			
Camellia sinensis	Epigallocatechin gallate	Binding competitively with respect to the RNA substrate primer	[97, 98, 99]
G4 DNA-Interactive Compounds			
Ascidian *Amphicarpa meridian*	Meridine	Inhibition of telomerase activity and stabilization of G4	[100, 101, 102, 103-110]
Berberis vulgaris chinensis (Coptis or goldenthread)	Berberine		
Cryptolepis triangularis	Cryptolepine		
Glycine max	Daidzein, daidzin, genistein and genistin		
Menispermum dauricum and *Rhizoma Menispermi*	Daurisoline, dauricinoline and daurinoline		

Okinawan tunicate Didenum sp.	Ascididemin		
Boraginaceae family (mainly in the genus of *Alkanna Lithospermum*)	Shikonin and its derivatives		
Coptidis rhizoma	Palmatine	Formation of C-myc22 G4 and Hum24 G4	[102, 111]
North American herb bloodroot (*Sanguinaria canadensis*)	Sanguinarine		

Table No.2: Some Phytochemicals shown to have telomerase inhibitors/activators properties

Phytochemical	Cancer type	Cell lines	Mechanism of regulation
Telomerase Inhibitors			
Allicin (Garlic)	Gastric	SGC-7901 [156]	not determined
Curcumin (Turmeric)	Breast	MCF-7 [157]	•Transcriptional [163] •Translational [161] •Post translational– Nuclear Localization [162]
	Cervical	HeLa, SiHa, Ca Ski [158]	
	Gastric	SGC-7901 [159]	
	Leukaemia	HL60 [159, 160], K-562 [161]	
	Liver	Bel7402 [159]	
	Lung	H1299 [162], A549 [163]	
Epigallocatechin Gallate (Green Tea)	Brain	U87-MG, 1321N1 [164]	•Transcriptional– Epigenetics [167] • Translational [166]
	Breast	MCF-7 [165-167], MDA-MB-231 [165]	
	Cervical	OMC-4, TMCC-1 [168]	
	Head and Neck	Hep-2 [169]	
	Leukaemia	HL60 [167]	
	Lung	H69, H69VP [170]	
Genistein (Soybean)	Breast	MCF-7 [171]	•Transcriptional [173, 174] •Post-translational –Nuclear Localization [174]
	Ovarian	SKOV-3 [172]	
	Prostate	LNCaP [173], PC-3 [168], DU-145 [174]	
Resveratrol (Red Grape)	Breast	MCF-7 [175]	•Post-translational –Nuclear Localization [175]
	Colon	HT-29, WiDr [176]	
Silibinin (Milk Thistle)	Prostate	LNCaP [177]	not determined
Sulforaphane (Cruciferous Vegetables)	Breast	MCF-7, MDA-MB-231 [178]	•Transcriptional [179]– Epigenetics [178] •Post-translational [179]
	Liver	Hep3B [179]	
Telomerase Activators			
Resveratrol (Red Grapes)	----------	Epithelial cells [180], Endothelial progenitor cells [181]	•Post-translational [180]
Genistein (Soybean)	Breast	MCF-7 [182]	•Transcriptional [182]
	Ovarian	SKOV-3 [182]	
	Prostate	DU-145, LNCaP [182]	

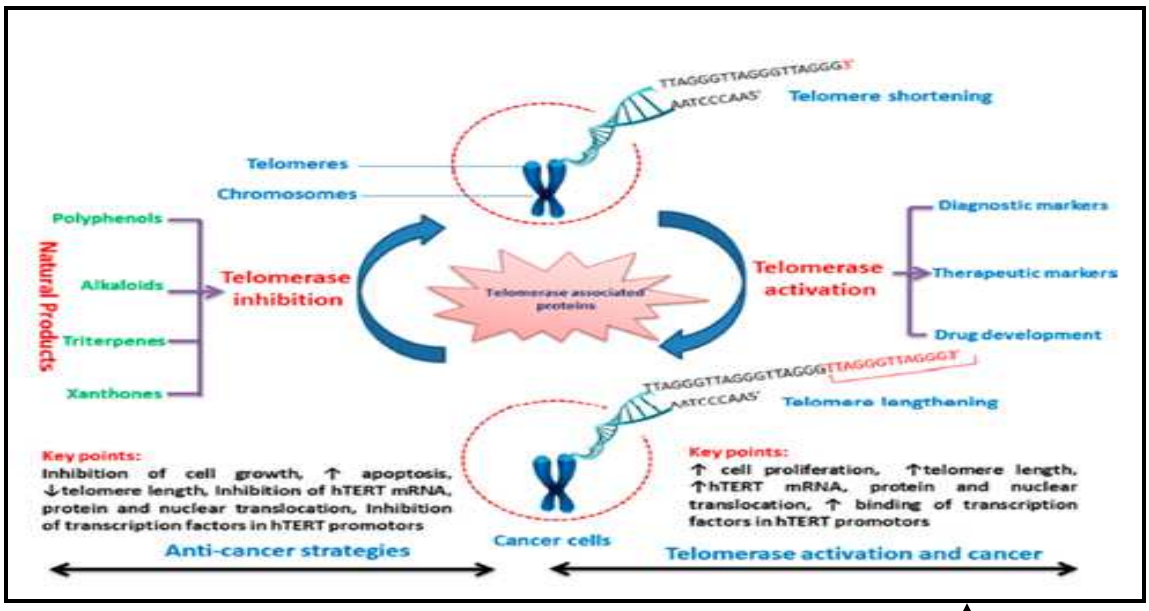

Figure No.1: Telomerase-related anticancer approaches by natural products. : Increment: : decline: ↓ hTERT: human telomerase reverse transcriptase[10]

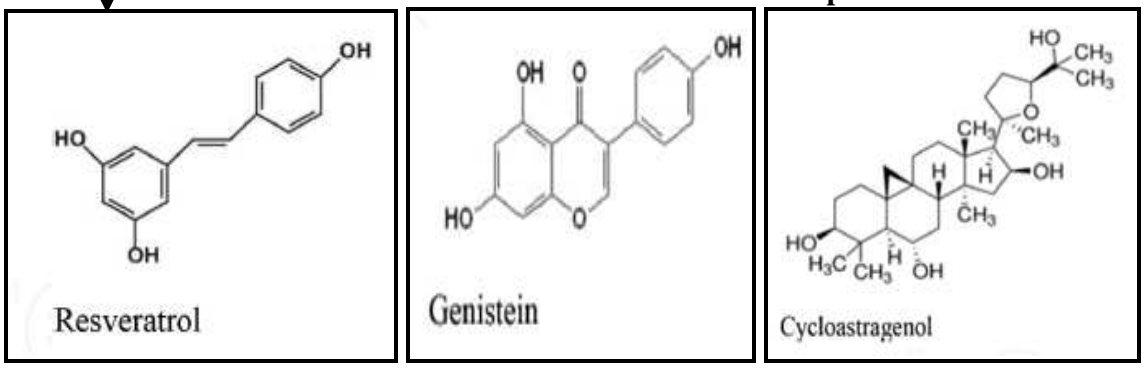

Figure No.2: Chemical formula of some natural telomerase activators

CONCLUSION

Telomerase inhibition empowers more specific ground for cancer therapy in light of the fact that the telomerase isn't distinguished in most normal tissues. . A portion of the synthetic and natural telomerase inhibitors were attempted on different cancer cells and there was a decrease in the number of cancer cells. But on the other hand, telomere shortening relates with cellular aging. Some proof recommends that the progressive loss of telomeric repeats of chromosomes may function as a molecular clock that triggers senescence. Telomere shortening corresponds with cellular aging. Telomerase-related gene mutations also result in some diseases. Therefore, telomerase activators are important for antiaging and telomerase-dependent disease treatments. Based on the investigation, this review concludes that natural products are potential as both telomerase inhibitors and activators.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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