Telomerase and Cancer
The role of polyphenols

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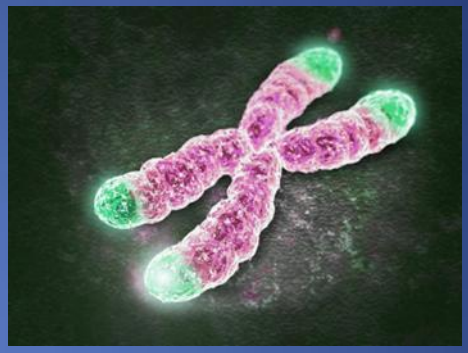
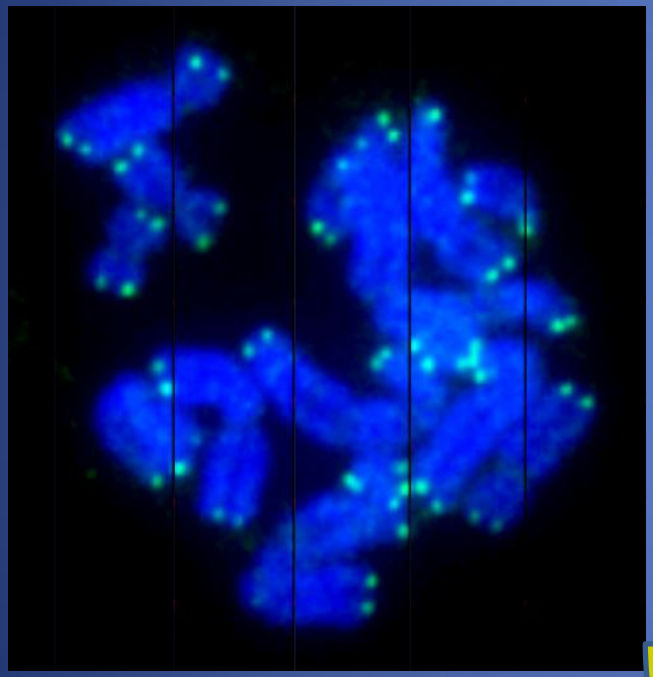
AGENDA



- ✓ What are Telomeres
- ✓ What is Telomerase
- ✓ What role telomerase plays in cancer
- ✓ Attrattive target for anticancer therapeutics
- ✓ Polyphenols
- ✓ The state of the art
- ✓ Possible new horizon

What are telomeres ?

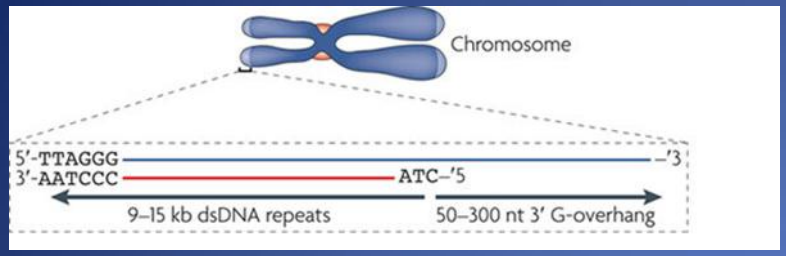


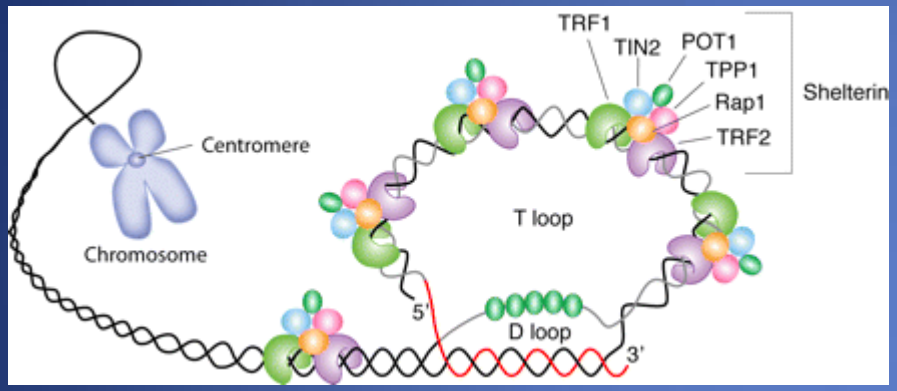
Telomeres 'cap' chromosome ends

Telomeres are the **nucleoprotein** complexes located at the ends of eukaryotic chromosomes.

Telomeres **protect** the ends of chromosomes from degradation and end-to-end fusions, contributing to genomic stability

Telomeres consist of 5 to 20kb of repeating hexanucleotide DNA sequence TTAGGG



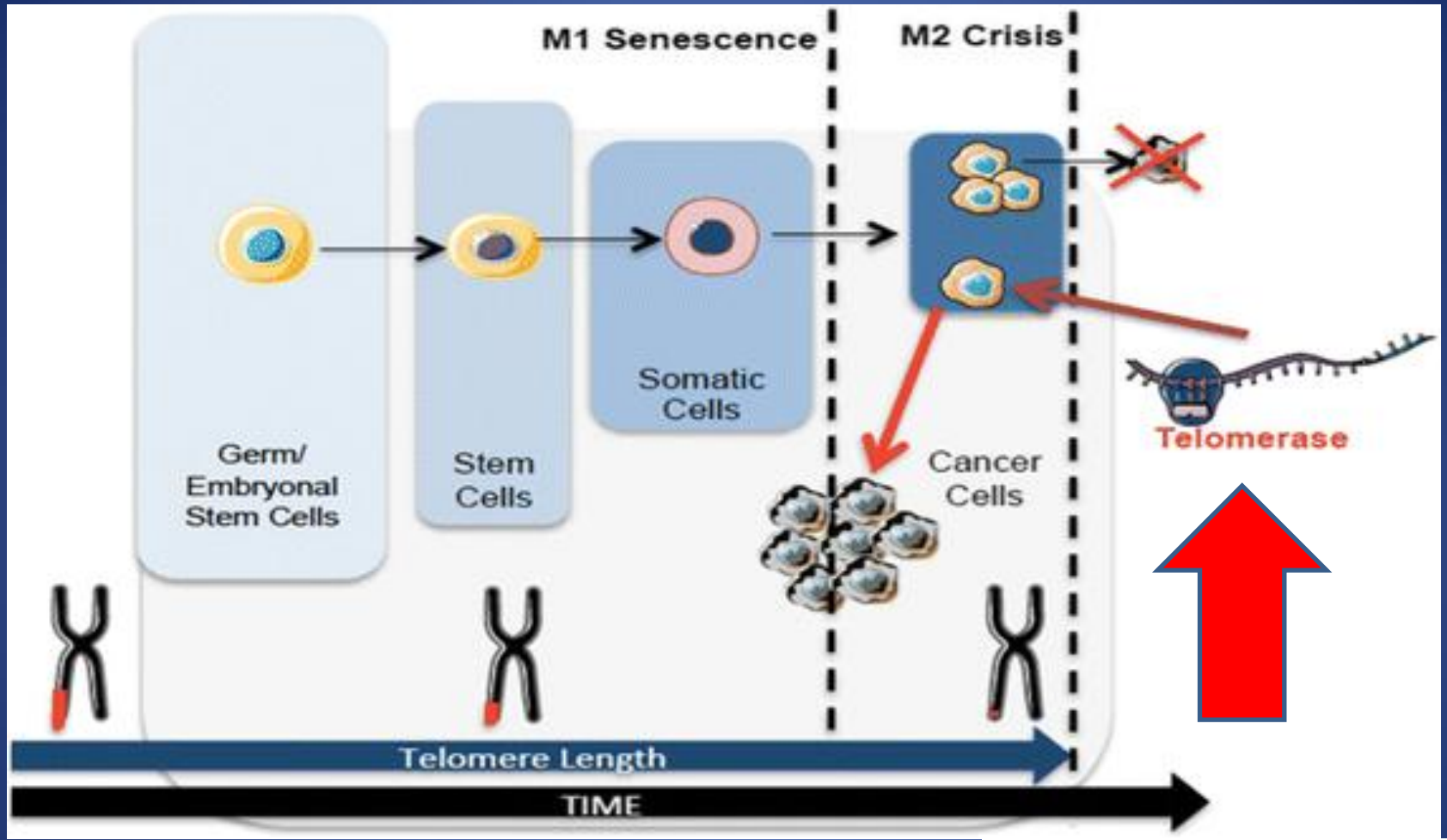


Telomeric DNA has the ability to fold over itself, forming what is called the T-loop.
3’ single-stranded overhang can tuck under itself, forming what is called the D-loop.

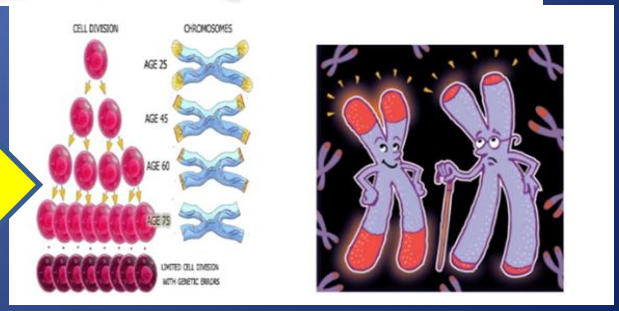
there are a group of regulatory proteins attached to the telomere at several locations,
called the shelterin complex that maintain telomere homeostasis

Shelterin complex

- Mammalian telomeres have a **SIX PROTEIN** complex called “SHELTERIN”.
- TRF1 and TRF2 bind to the TTAGGG sequences in the double strand telomeric DNA.
- POT1 binds to the sequences in single strand form
- TIN2 and TPP1 proteins keep TRF1, TRF2 and POP1 together.
- This six protein complex, SHELTERIN prevents the activation of the DNA damage response.
- SHELTERIN is required for the recruitment of telomerase.



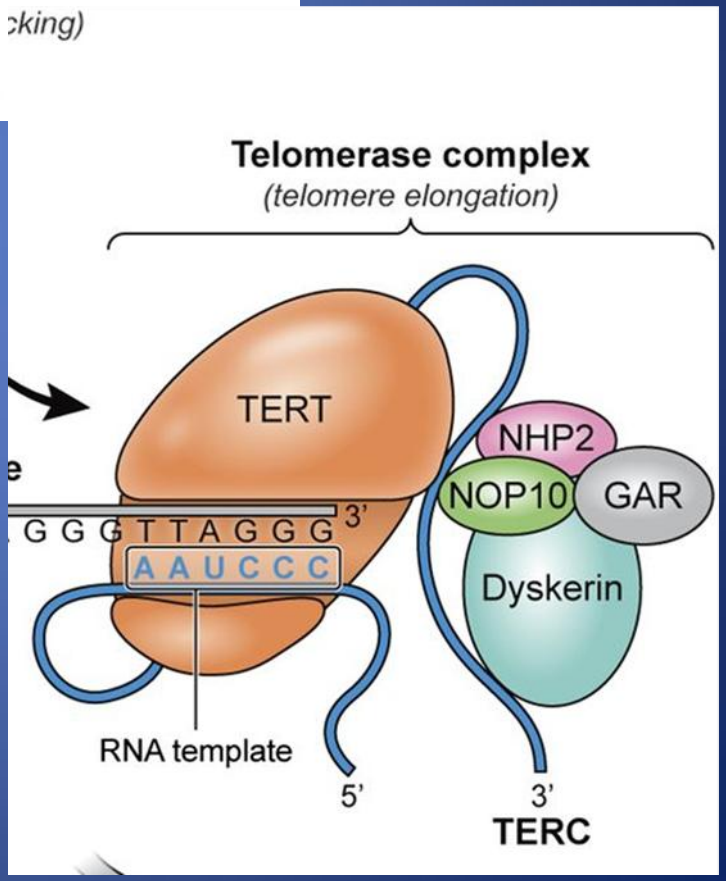
Leão R, Apolónio JD, Lee D, Figueiredo A,Tabori U,, Castelo-Branco P:Mechanisms of human telomerase reverse transcriptase (hTERT) regulation: clinical impacts in cancer. J Biomed Sci. 2018 Mar

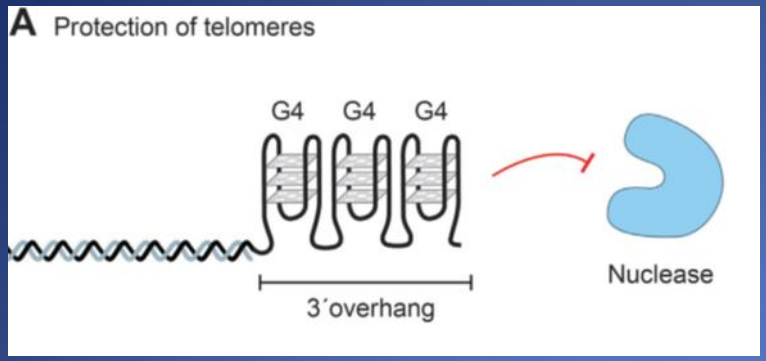


What is Telomerase

- Telomerase is a reverse transcriptase that specifically synthesizes telomeric DNA
- Promotes stability of chromosomes
- Protects linear DNA from degradation at chromosome ends

comprised of two essential core subunits: the telomerase RNA (TERC) and telomerase reverse transcriptase protein (TERT).

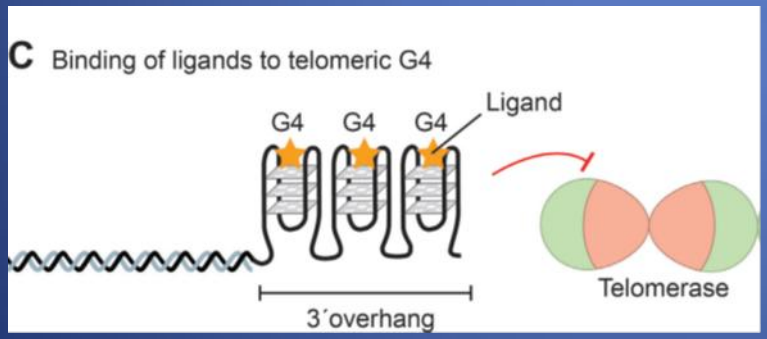




Telomeric DNA can fold into compact G-quadruplex structures involving the interaction of four guanine bases in a **square planar arrangement-** G-quadruplexes can form from one, two or four strands of DNA in a parallel or antiparallel orientation.

Telomerase binds to a parallel G-quadruplex structure.

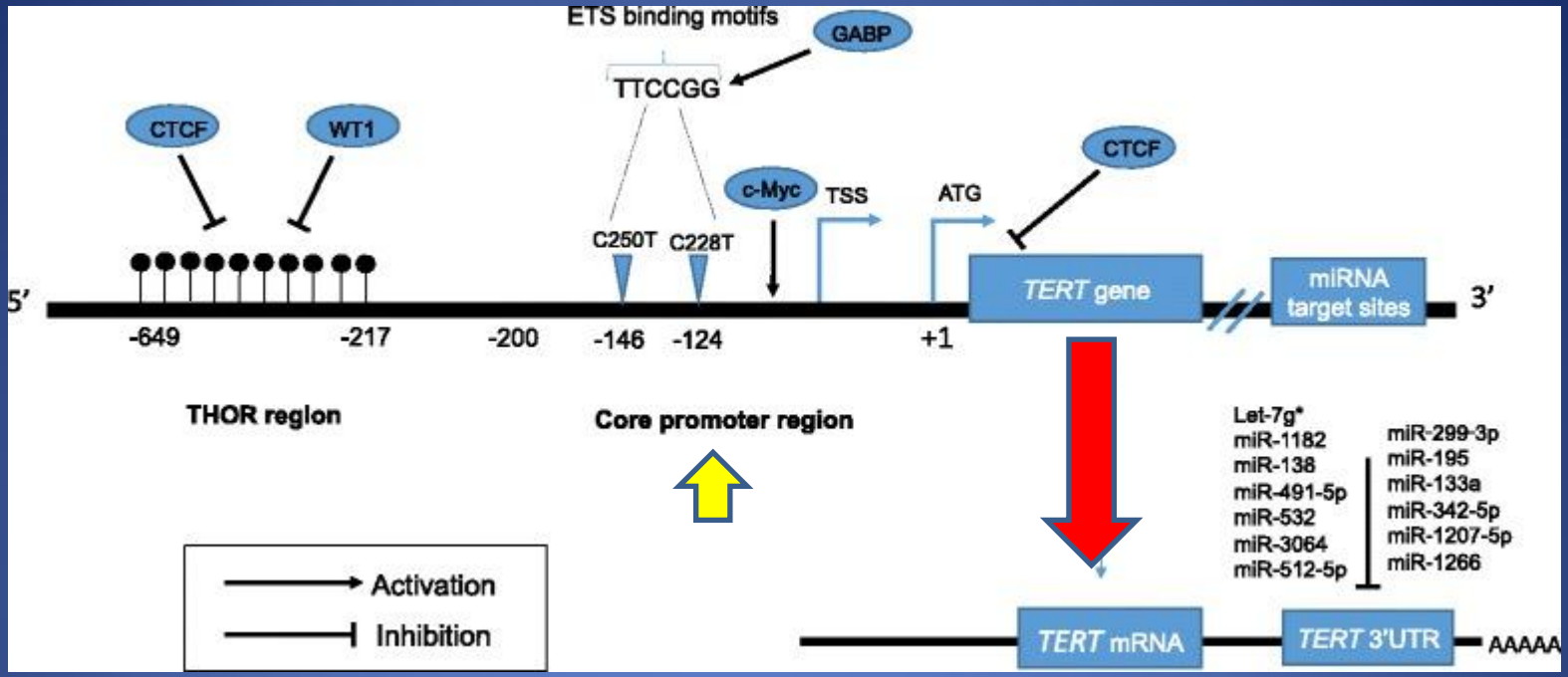
The core telomerase complex is able to partially unwind the G-quadruplex allowing hybridization of the RNA template and DNA extension.



There are a large number of small-molecule ligands that have specificity for G-quadruplexes,
with many of them causing telomere dysfunction in vivo and
inhibiting telomerase activity in vitro

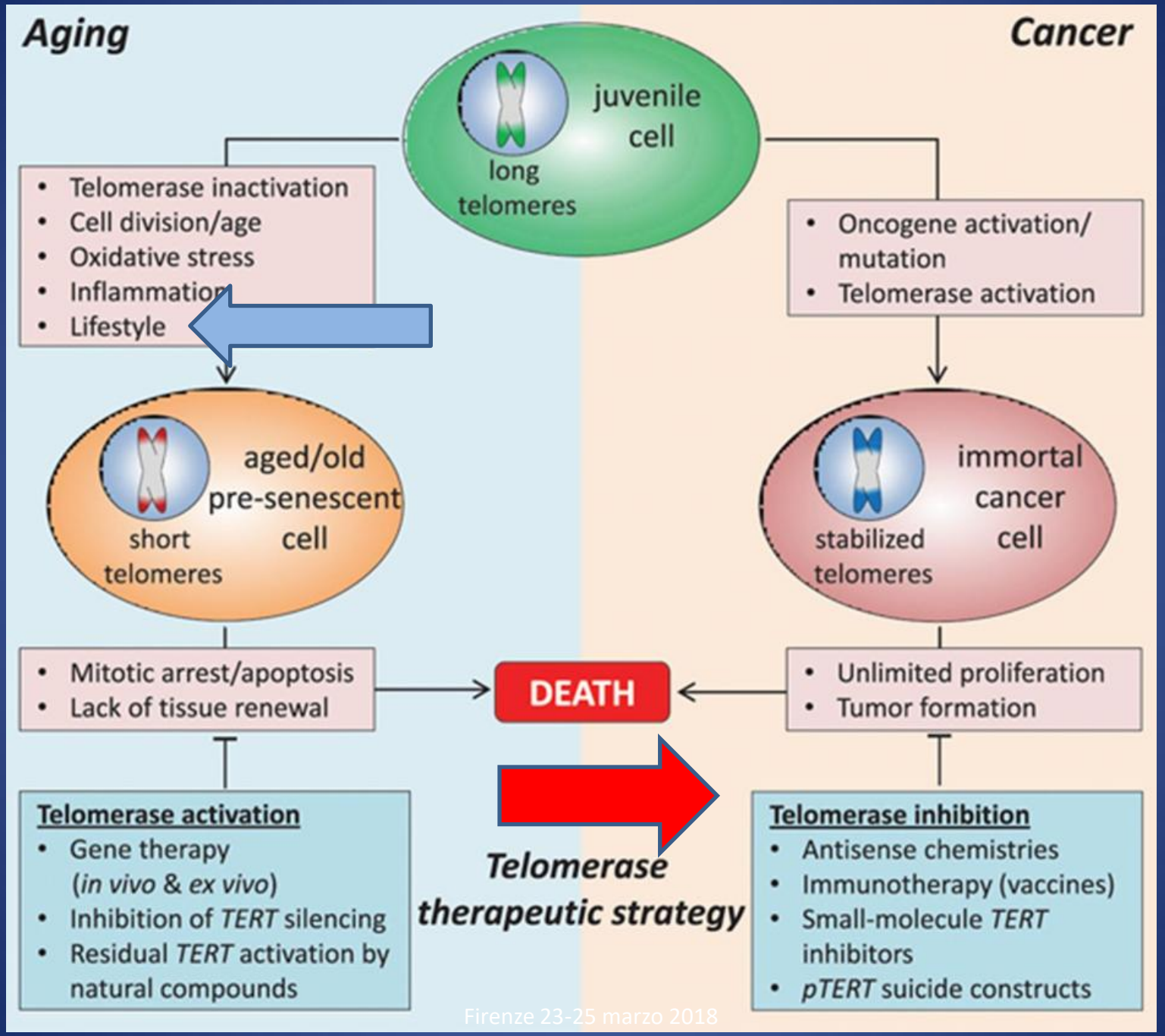
NATURE COMMUNICATIONS 2015

Mechanisms of hTERT regulation in cancer



Telomerase regulation to be controlled uniquely by transcriptional mechanisms

transcriptional activators (c-Myc)
repressors (WT1 and CTCF) to the hTERT promoter may be controlled by DNA methylation, in which methylated CpGs prevent their binding to the target sites, leading to hTERT activation (THOR region). MiRNAs targeting the 3'UTR promotes translation repression of hTERT.


Aging
Cancer
juvenile cell
long telomeres
• Telomerase inactivation
• Cell division/age
• Oxidative stress
• Inflammation
• Lifestyle
• Oncogene activation/ mutation
• Telomerase activation
aged/old pre-senescent cell
short telomeres
immortal cancer cell
stabilized telomeres
• Mitotic arrest/apoptosis
• Lack of tissue renewal
DEATH
• Unlimited proliferation
• Tumor formation
Telomerase activation
• Gene therapy (in vivo & ex vivo)
• Inhibition of TERT silencing
• Residual TERT activation by natural compounds
Telomerase therapeutic strategy
Telomerase inhibition
• Antisense chemistries
• Immunotherapy (vaccines)
• Small-molecule TERT inhibitors
• pTERT suicide constructs

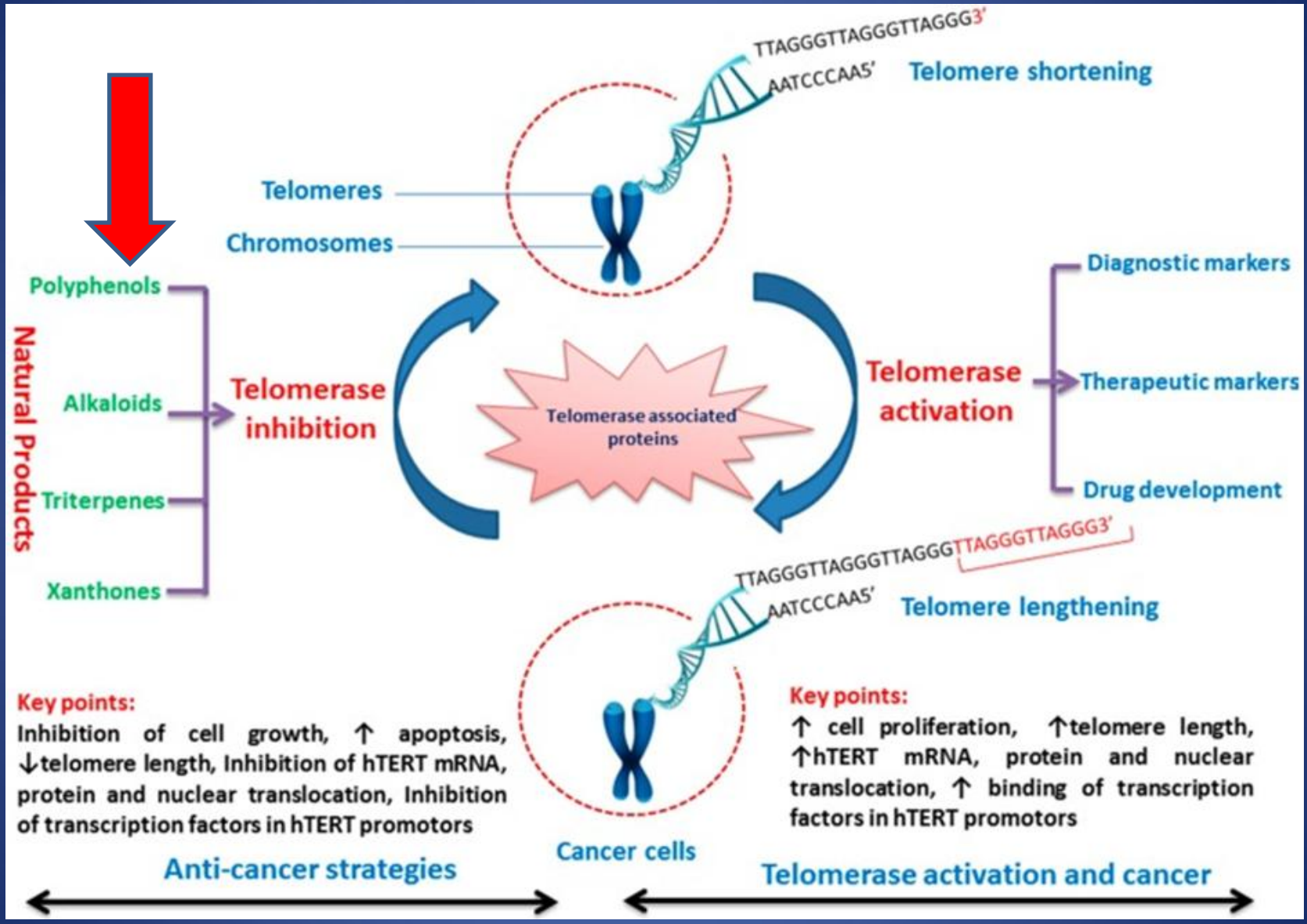

TTAGGGTTAGGGTTAGGG3'
AATCCCAA5'
Telomere shortening
Telomeres
Chromosomes
Polyphenols
Natural Products
Alkaloids
Triterpenes
Xanthones
Telomerase inhibition
Telomerase associated proteins
Telomerase activation
Diagnostic markers
Therapeutic markers
Drug development
TTAGGGTTAGGGTTAGGGTTAGGGTTAGGG3'
AATCCCAA5'
Telomere lengthening
Key points:
Inhibition of cell growth, ↑ apoptosis, ↓telomere length, Inhibition of hTERT mRNA, protein and nuclear translocation, Inhibition of transcription factors in hTERT promotors
Key points:
↑ cell proliferation, ↑telomere length, ↑hTERT mRNA, protein and nuclear translocation, ↑ binding of transcription factors in hTERT promotors
Cancer cells
Anti-cancer strategies
Telomerase activation and cancer

Table 1 Overview of the key telomerase therapeutic strategies directed against telomerase and telomeres [30], modified

Strategy	Factor	Target	Mechanism	References
ASO	GRN163L	hTR	Expression inhibition	[11]
RT inhibition	AZT azidothymidine	DNA elongation	Replication termination	[12]
	BIBR 1532	RT	Non-competitive inhibition	[13]
Immunotherapy	GV1001	HLA	CD4+ stimulation	[14]
	Vx-001	HLA-A		[15]
	GRNVAC1/2 (AST-VAC1/2)	Dendritic cells	Antigen presentation	[16, 17]
G-quadruplex stabilization	BRACO-1910	Telomeric DNA	Access blocking	[13]
	RHPS4			[18]
	TMPyP4			[19]
	Telomestatin			[20]
	Quarfloxin/CX-3543[a]	Telomeric DNA	rRNA biogenesis inhibition[a]	[21]
Uncapping mimicking	T-oligo	Telomeric overhang	Apoptosis, and autophagy induction	[22]
RNAi	hTERT-siRNA	hTERT	Expression repression	[23, 24]
	hTERC-siRNA	hTERC		
Preventing binding of telomerase to telomere	IWR1, IWR2, JW55, flavone, XAV939	Tankyrase inhibition	TRF1 dissociation from telomeres	[25]
Nitroreductase-based gene therapy	CB1954	DNA crosslinks	Suicide gene therapy	[26]
Carboxypeptidase-based gene therapy	ZD2767P	DNA-damaging alkylation		[27]
Oncolytic viruses	Telomelysin (OBP-301)	hTERT positive cells	Cancer cell lysis	[28]
Gene therapy	CRISPR/CAS9	hTERT	Expression repression	[29]
		hTERC		

All strategies aim to stop the main telomerase subunit expression, complex activity, or prevent substrate access to provoke cancer cell senescence, death, or proliferation of target cells

ASO antisense oligonucleotides, *RT* reverse transcriptase

[a] Requires verification in further studies

Cell. Mol. Life Sci. (2017) 74:4121–4132

Polyphenols

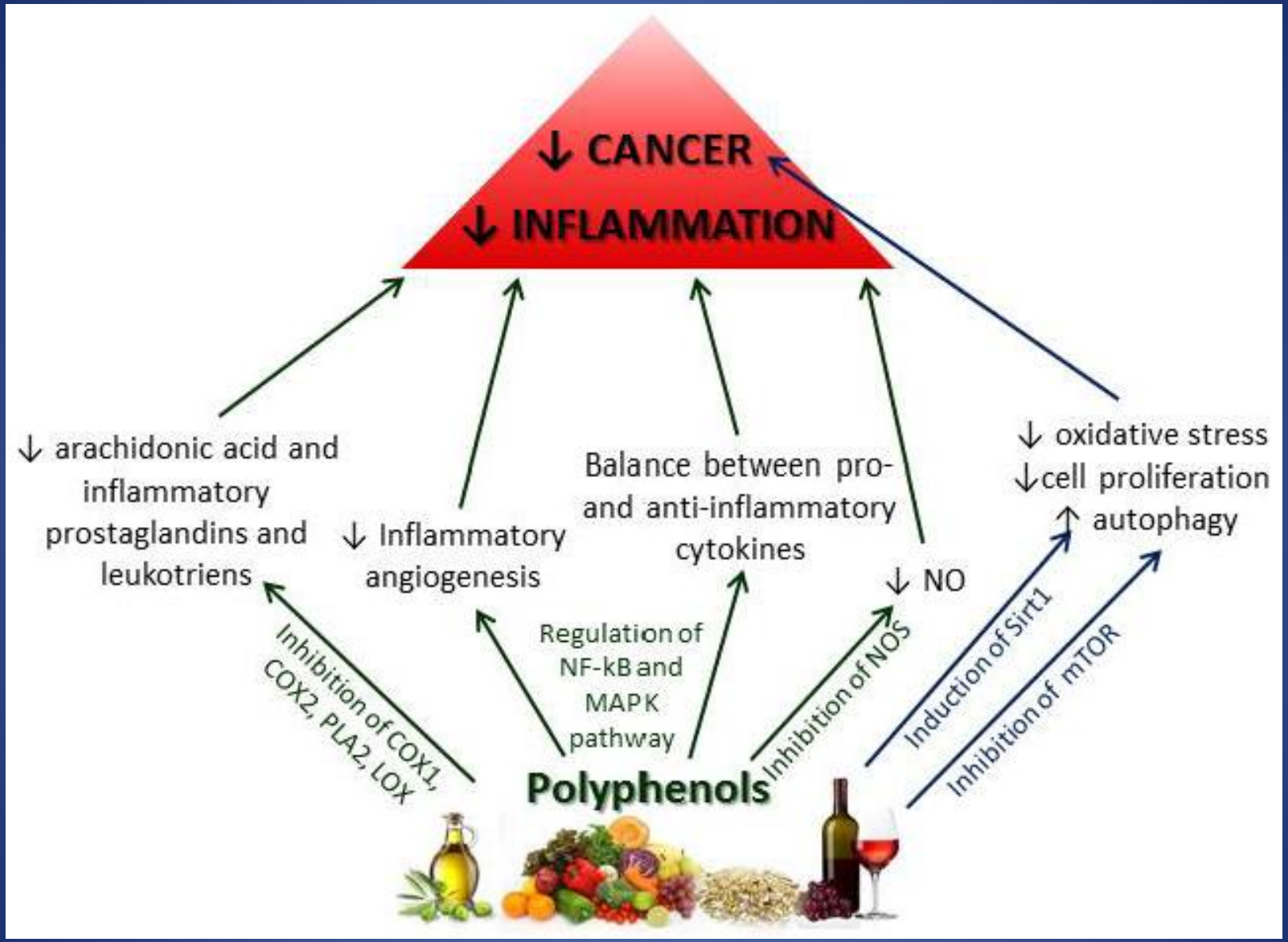
consuming food and beverages rich in polyphenols (e.g., catechins, flavones, and antocyanines) is associated with a lower incidence of cardiovascular disease, diabetes mellitus, cancer

Table 1. The classification of natural polyphenols.

Classification		Representative Members	Major Dietary Sources
flavonoids	anthocyanins	delphinidin, pelargonidin, cyanidin, malvidin	berries, grapes, cherries, plums, pomegranates
	flavanols	epicatechin, epigallocatechin, EGCG, procyanidins	apples, pears, legumes, tea, cocoa, wine
	flavanones	hesperidin, naringenin	citrus fruits
	flavones	apigenin, chrysin, luteolin,	parsley, celery, orange, onions, tea, honey, spices
	flavonols	quercetin, kaempferol, myricetin, isorhamnetin, galangin	berries, apples, broccoli, beans, tea
	isoflavonoids	genistein, daidzein	soy
phenolic acids	hydroxybenoic acid	ellagic acid, gallic acid	pomegranate, grapes, berries, walnuts, chocolate, wine, green tea
	hydroxycinnamic acid	ferulic acid, chlorogenic acid	coffee, cereal grains
lignans		sesamin, secoisolariciresinol diglucoside	flaxseeds, sesame
stilbenes		resveratrol, pterostilbene, piceatannol	grapes, berries, red wine

They are divided into flavonoid and non-flavonoid compounds and exist in two forms as aglycones and sugar conjugates.

Polyphenols exhibit many biologically important activities such as antioxidant and free radical scavenging activity,anti-carcinogenic, anti-inflammatory, anti-allergic,anti-thrombotic and anti-microbial activity.


↓ CANCER
↓ INFLAMMATION
↓ arachidonic acid and inflammatory prostaglandins and leukotriens
↓ Inflammatory angiogenesis
Balance between pro- and anti-inflammatory cytokines
↓ NO
↓ oxidative stress
↓cell proliferation
↑ autophagy
Inhibition of COX1, COX2, PLA2, LOX
Regulation of NF-kB and MAPK pathway
Inhibition of NOS
Induction of Sirt1
Inhibition of mTOR
Polyphenols

[CANCER RESEARCH 63, 824–830, February 15, 2003]

Blocking Telomerase by Dietary Polyphenols Is a Major Mechanism for Limiting the Growth of Human Cancer Cells *in Vitro* and *in Vivo*[1]

Imad Naasani,[2] Fujiko Oh-hashi, Tomoko Oh-hara, Wan Yong Feng, Jeffrey Johnston, Kenneth Chan, and Takashi Tsuruo

Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Kami-Ikebukuro, Toshima-ku, Tokyo 170-8455, Japan [I. N., F. O-h., T. O-h., T. T.]; Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan [I. N., T. T.]; and College of Pharmacy, The Ohio State University, Columbus, Ohio 43210 [I. N., W. Y. F., J. J., K. C.]

ABSTRACT

Animal and epidemiological studies reveal that consuming food and beverages rich in polyphenols (*e.g.*, catechins, flavones, and antocyanines) is associated with a lower incidence of cancer, and several molecular mechanisms have been proposed for explaining this effect. However, because most of these mechanisms were observed only under specific and

colon, liver, pancreas, lung, breast and skin (reviewed in Ref. 12). Various mechanisms were suggested to explain the chemopreventive and anticancer effects of polyphenols. Antioxidant activities, and interaction with certain enzymes or proteins implicated in cancer (*e.g.*, urokinase, ornithine decarboxylase, NADPH-cytochrome P450 reductase, protein kinase C, steroid 5 α reductase, tumor necrosis factor and

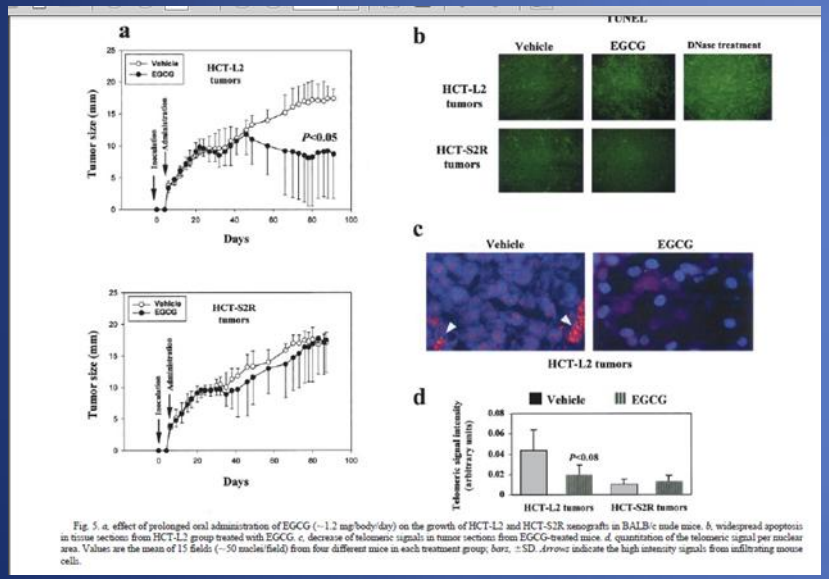
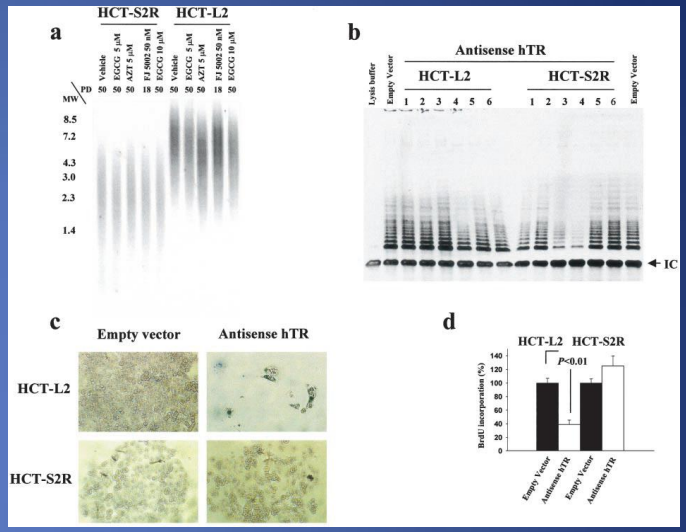


Fig. 5. *a*, effect of prolonged oral administration of EGCG (~1.2 mg/body/day) on the growth of HCT-L2 and HCT-S2R xenografts in BALB/c nude mice. *b*, widespread apoptosis in tissue sections from HCT-L2 group treated with EGCG. *c*, decrease of telomeric signals in tumor sections from EGCG-treated mice. *d*, quantitation of the telomeric signal per nuclear area. Values are the mean of 15 fields (~50 nuclei/field) from four different mice in each treatment group; *bars*, ±SD. *Arrows* indicate the high intensity signals from infiltrating mouse cells.

Epigallocatechin gallate (EGCG)



In nude mice models bearing both telomerase-dependent and -independent xenograft tumors cloned from a single human cancer progeny, only the telomerase-dependent tumors responded to prolonged oral administration of EGCG.

Nutr Cancer. 2008;60(1):109-19. doi: 10.1080/01635580701525869.

Telomerase-associated apoptotic events by mushroom ganoderma lucidum on premalignant human urothelial cells.

Yuen JW[1], Gohel MD, Au DW.

Author information

Abstract

The chemopreventive effects of Ganoderma lucidum was tested, using a tumorigenic transformable human urothelial cell (HUC-PC) model. These in vitro data show that G. lucidum can inhibit the viability and growth of HUC-PC. This could be explained by a concomitant induction of apoptosis and inhibition of telomerase activity. Significant exteriorization of phosphatidylserine was detected by Annexin-V on cell surface, and the cells subsequently lost membrane integrity for uptake of 7-amino-actinomycin D dye. Additionally, the levels of hydrogen peroxide and 8-hydroxy-2'-deoxyguanosine (8-OHdG) production of the apoptotic cells were significantly increased. The induction of apoptosis and suppression of telomerase activity help to explain the anti-HUC-PC growth properties; however, the induction of oxidative stress requires further study. This study strongly suggests that G. lucidum is a potential source of chemopreventive agents for bladder cancer based on its effectiveness in controlling the premalignant urothelial cell growth and carcinogen-induced transformation.

Br J Nutr. 2013 Jun 28;109(12):2117-25. doi: 10.1017/S0007114512004333. Epub 2012 Oct 15.

The Australian fruit Illawarra plum (Podocarpus elatus Endl., Podocarpaceae) inhibits telomerase, increases histone deacetylase activity and decreases proliferation of colon cancer cells.

Symonds EL[1], Konczak I, Fenech M.

Author information

Abstract

Fruit antioxidants have many health benefits including prevention of cancer development. The native Australian bush fruit Illawarra plum (Podocarpus elatus Endl., Podocarpaceae) has a high content of anthocyanin-rich phenolics, with an antioxidant capacity at levels higher than most fruits. In the present study the molecular mechanisms of the anti-proliferative activity of Illawarra plum on colorectal cancer cells were investigated. Non-tumorigenic young adult mouse colonic (YAMC) cells and tumorigenic human colonic (HT-29) cells were treated with a polyphenolic-rich Illawarra plum extract (0-1000 microg/ml). Illawarra plum had anti-proliferative properties in only the cancer cells, with growth suppressed in a dose- and time-dependent manner. Treatment of HT-29 cells with Illawarra plum extract (500 mg/ml; 24 h) was also associated with a 2-fold increase in apoptosis, and a cell cycle delay in the S phase ($P < 0.01$). Assessment of biomarkers for DNA damage revealed that plum treatment caused a 93% down-regulation of telomerase activity ($P < 0.001$) and a decrease in telomere length (up to 75%; $P < 0.01$). Treatment with Illawarra plum extract also induced morphological alterations to HT-29 cells that were suggestive of induction of autophagy, as the formation of cytoplasmic vacuoles was observed in many cells. This could be induced by the increased (6-fold) histone deacetylase (HDAC) activity ($P < 0.001$) and the trend for increased expression of the class III HDAC sirtuin 1. The present study has shown that Illawarra plum extract is able to reduce the proliferation of colon cancer cells by altering the cell cycle, increasing apoptosis and possibly inducing autophagy. The active ingredients in Illawarra plum may provide an alternative chemoprevention strategy to conventional chemotherapy.

NIH Public Access
Author Manuscript
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Published in final edited form as:
Cancer Prev Res (Phila). 2011 August ; 4(8): 1243–1254. doi:10.1158/1940-6207.CAPR-11-0009.

A Novel Prodrug of Epigallocatechin-3-gallate: Differential Epigenetic *hTERT* Repression in Human Breast Cancer Cells

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[1]Department of Biology, University of Alabama at Birmingham, Birmingham, AL, USA
[2]Department of Chemistry, McGill University, Montreal, Quebec, Canada

Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 360 (2007) 233–237
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www.elsevier.com/locate/ybbrc

The green tea polyphenol, epigallocatechin-3-gallate inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells

David Sadava [a,b,*], Elizabeth Whitlock [a,1], Susan E. Kane [b]

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[b] *Division of Molecular Medicine, Beckman Research Institute, City of Hope, 1500 E. Duarte Road, Duarte, CA 91010, USA*

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Available online 14 June 2007

Curr Med Chem. 2016;23(22):2380-93.

An Update on Phytochemicals in Molecular Target Therapy of Cancer: Potential Inhibitory Effect on Telomerase Activity.

Alibakhshi A, Ranjbari J, Pilehvar-Soltanahmadi Y, Nasiri M, Mollazade M, Zarghami N[1].

Author information

Abstract

Telomerase is a ribonucleoprotein enzyme, which has a significant role in synthesizing DNA telomeric in eukaryotes. Telomere maintenance can cause to immortalization and malignant transformation of human cells and thereby telomerase activity must be scrutinized as an important factor in most tumor cells. The proliferation of cancer cells or apoptosis induction can be suppressed by telomerase inhibition using different therapeutic agents without any side effects upon normal cells. Natural substances, with anti-tumor effects, such as those derived from plants can be suitable candidates due to their capabilities in preventing some side effects and resistance of tumors with respect to most chemotherapeutic drugs. In this regards, many studies have shown that natural phytochemicals have inhibitory effects on telomerase activity through affecting its subunits and components. Therefore, the aim of this paper is to review the recent studies on these kinds of phytochemicals in terms of property and mechanism. Moreover, strategies for improving the therapeutic efficacy of plant-derived substances such as combination therapy and nanoformulation based approaches are included.

Curr Drug Targets. 2017;18(2):147-159. doi: 10.2174/1389450117666160112113930.

Natural Polyphenols and their Synthetic Analogs as Emerging Anticancer Agents.

Colomer R, Sarrats A, Lupu R, Puig T[1].

Author information

Abstract

Polyphenols are a structural class of natural and synthetic organic chemicals which contain phenol units. Numerous epidemiological, preclinical and clinical studies have strongly supported their benefical effects for human health. Polyphenols group include molecules of utterly different complexity grades, ranging from simple molecules to highly polymerized structures. They are classified into: Phenolic acids, Flavonoids, Lignans and the less common Stilbenes. This work first intends to review the current studies on classification, chemical composition and metabolism of polyphenols. Then, we have reported cancer preventive and treatment effects of polyphenols, especially focused in the green tea polyphenol (GTP) (-)-Epigallocatechin-3-gallate (EGCG). Polyphenols such as EGCG and their synthetic analogs interfere in carcinogenesis by modulating and regulating multiple signaling pathways and transcription factors, membrane-associated receptor tyrosine kinases (RTKs), fatty acid metabolism and lipid rafts or methylation together with other emerging targets such as proteasome, telomerase and cancer stem cells. Here, we have reviewed several potential molecular targets of polyphenols (mainly EGCG and EGCG analogs) and their anticancer effects in cellular and animal models of different human carcinomas and we have also listed Phases I and II clinical trials conducted to study the antitumor properties of GTPs.

Urinary bladder	Telomerase activity is expressed i… abscess of patients (80%) with bladder carcinoma.	Telomerase assays might pl… useful adjunct role in nonin… …ng and …agnosis of bladder ca…	[67,68]
Uterine	Telomerase activity is expressed i… abscess of patients (90%) with liver a… biliary carcinoma.	Telomerase assay gives a prom… …gnostic biomarker for early uterine cancer …detection.	[69]
Therapeutic Implications of Telomerase Inhibition in Human Cancers by Natural Products			
Breast	Treatment with *Melissa officinalis* extract can inhibit telomerase activity in human breast cancer cell line.	Telomerase inhibition might be useful in the treatment of various cancers with telomerase-positive cells.	[70]
Cervical	Treatment with (−)-epigallocatechin gallate can inhibit telomerase activity in human cervical cancer cell line.		[71]
Colon	Treatment with *Morus Rubra* extract can inhibit telomerase activity in human colon cancer cell line.		[72]
Liver	Treatment with *Atractylis lancea (Thunb.) DC* extract can inhibit telomerase activity in human liver cancer cell line.		[73]
Lung	Treatment with *Melissa officinalis* extract can inhibit telomerase activity in human lung adenocarcinoma cell line.		[70]
Prostate	Treatment with *Melissa officinalis* extract can inhibit telomerase activity in human prostate cancer cell line.		[70]
Uterine	Treatment with phenolic-rich extracts from *Satda Munziq* can inhibit telomerase activity in human uterine cancer cell line.		[74]

Int. J. Mol. Sci. 2018, 19, 13

Mol Cell Biochem. 2007 Mar;297(1-2):31-9. Epub 2006 Nov 10.

Curcumin-induced apoptosis in human leukemia cell HL-60 is associated with inhibition of telomerase activity.

Mukherjee Nee Chakraborty S[1], Ghosh U, Bhattacharyya NP, Bhattacharya RK, Dey S, Roy M.

⊕ Author information

Abstract

Curcumin (diferuloylmethane), a natural cancer chemopreventive compound, has been tested for its action in acute myeloblastic leukemia cell line HL-60. The results clearly show that curcumin induces apoptosis in these cells as evidenced by the release of cytochrome c from mitochondria to the cytosol and increase in the DNA content in sub G1 region as observed in FACS analysis. Apoptosis is apparently mediated by up-regulation of apoptotic gene bax and simultaneous down-regulation of anti-apoptotic gene bcl-2 followed by activation of caspases 3 and 8 and degradation of PARP. Telomerase, a reverse transcriptase, has been found to be activated in more than 80% of human cancers and, therefore, can be considered as a potential marker for tumorigenesis. Certain natural compounds have the potential of inhibiting telomerase activity leading to suppression of cell viability and induction of apoptosis. The present study shows that curcumin-induced apoptosis coincides with the inhibition of telomerase activity in a dose dependent manner.

J Complement Integr Med. 2017 May 12;14(3). pii: /j/jcim.2017.14.issue-3/jcim-2015-0107/jcim-2015-0107.xml. doi: 10.1515/jcim-2015-0107.

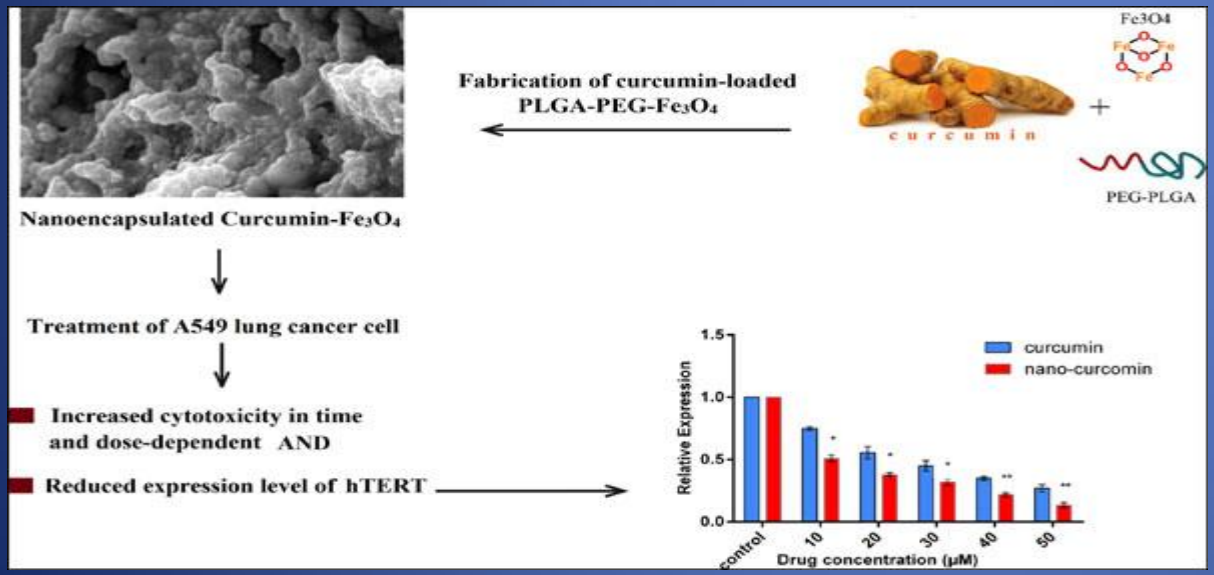
Effects of water extract of Curcuma longa (L.) roots on immunity and telomerase function.

Pan MH[1], Wu JC[1], Ho CT[1], Badmaev V[1].

⊕ Author information

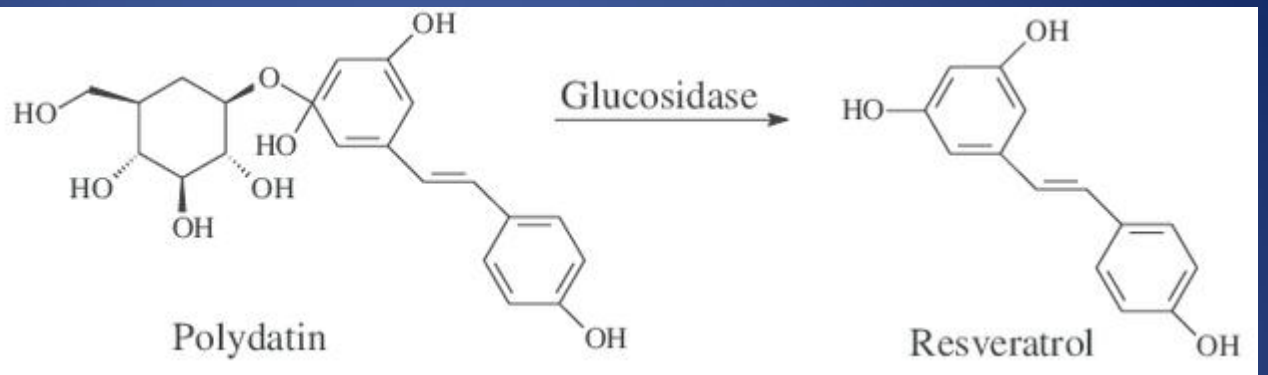
Abstract

Background Immunity and Longevity Methods A water extract of Curcuma longa (L.) [vern. Turmeric] roots (TurmericImmune™) standardized for a minimum 20 % of turmeric polysaccharides ukonan A, B, C and D was evaluated for its biological properties in in vitro tissue culture studies. Results The water extract of turmeric (TurP) exhibited induced-nitric oxide (NO) production in RAW264.7 macrophages. These results suggested the immunomodulatory effects of TurP. In addition, the polysaccharides up-regulated function of telomerase reverse transcriptase (TERT) equally to the phenolic compound from turmeric, curcumin. Conclusions The ukonan family of polysaccharides may assist in promoting cellular immune responses, tissue repair and lifespan by enhancing immune response and telomere function.



Anticancer Agents Med Chem. 2017;17(10):

Firenze 23-25 marzo 2018



Trans-hydroxystilbenes

Trans-resveratrol, which is mainly found in grapes and red wine, is one of the most important in terms of biological activities.

Polydatin originally isolated from the root and rhizome of Polygonum cuspidatum It is a glucoside of resveratrol in which the glucoside group bound to the position C-3 substitutesa hydroxyl group

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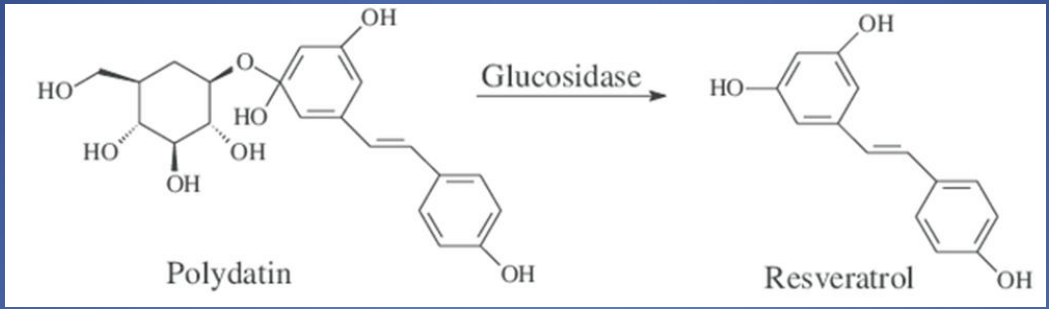
Phytomedicine. 2015 May 15;22(5):553-9. doi: 10.1016/j.phymed.2015.03.014. Epub 2015 Apr 6.

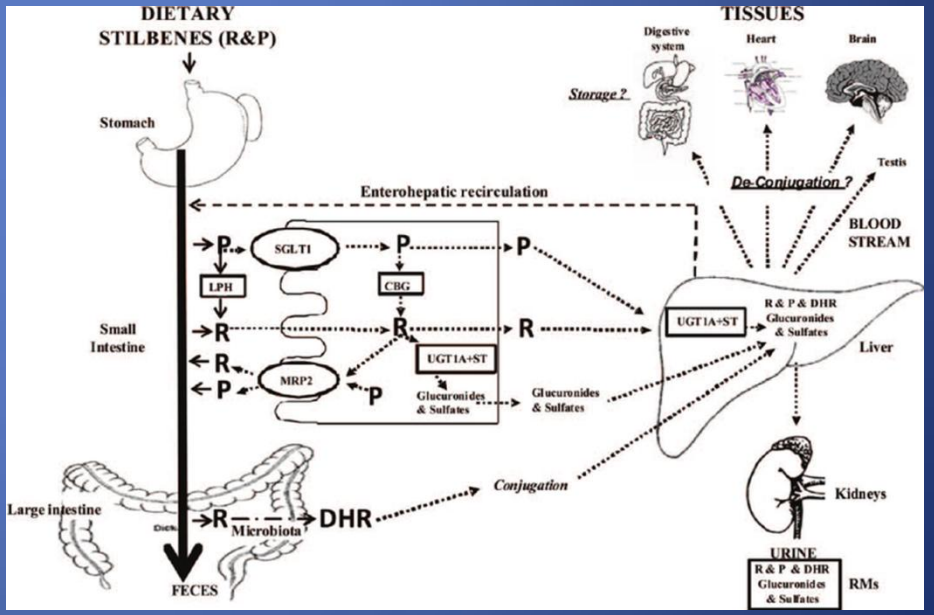
Comparative studies of polydatin and resveratrol on mutual transformation and antioxidative effect in vivo.

Wang HL[1], Gao JP[2], Han YL[3], Xu X[4], Wu R[5], Gao Y[6], Cui XH[7].

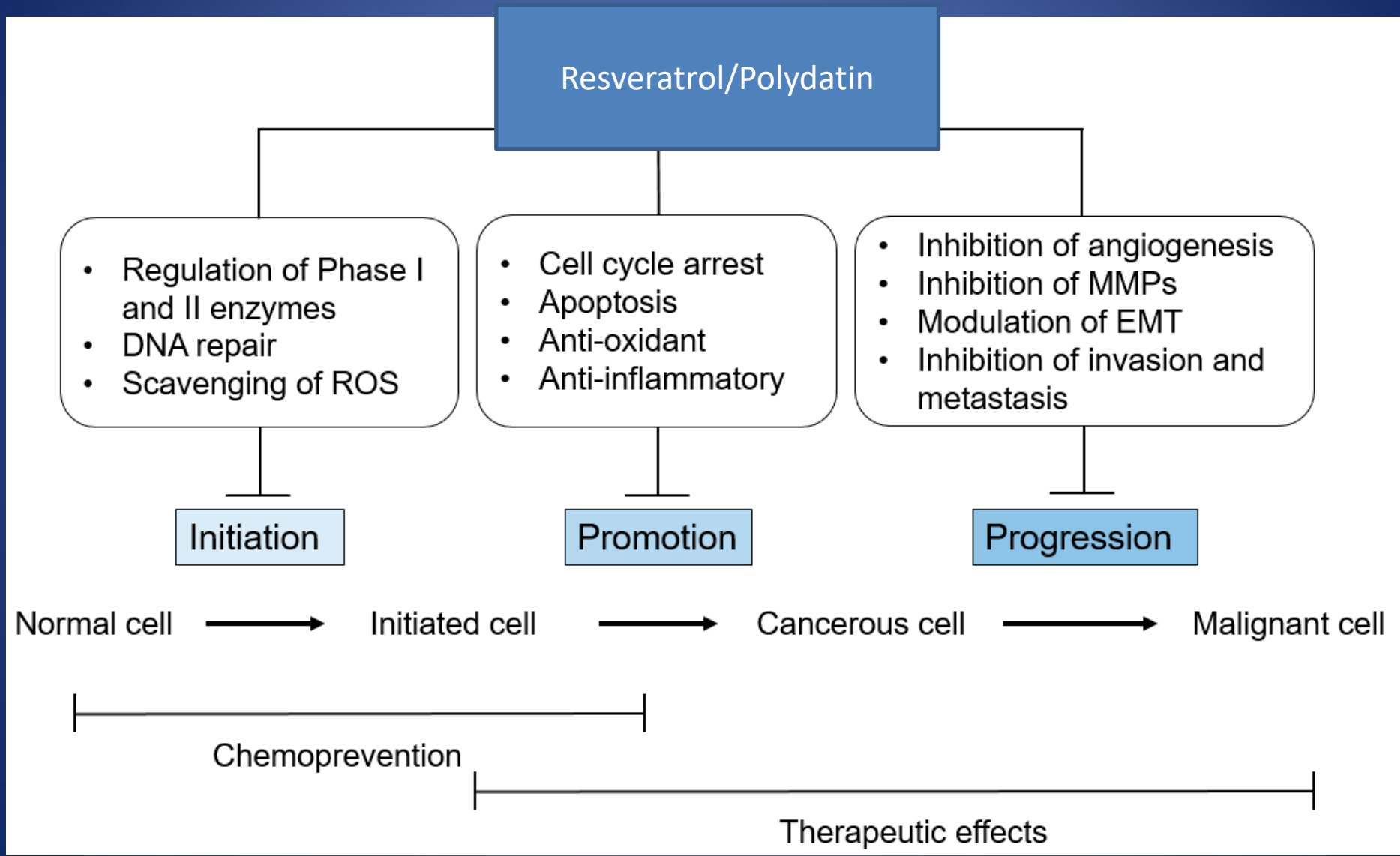
⊕ Author information



Pathways of resveratrol and polydatin absorption, distribution, metabolism, and excretion.



The solution to the poor bioavailability of resveratrol may be found in the resveratrol precursor, Polydatin.



Int. J. Mol. Sci. 2017, MOD.

J. Exp. Clin. Cancer Res., 25, 2, 2006

Effect of Resveratrol on Proliferation and Telomerase Activity of Human Colon Cancer Cells *In Vitro*

M.P.Fuggetta[1], G. Lanzilli[2], M.Tricarico[2], A. Cottarelli[2], R.Falchetti[2], G.Ravagnan[1], E. Bonmassar[1,2]

Institute of Neurobiology and Molecular Medicine[1], National Research Council - CNR - Area Ricerca "Tor Vergata"; Department of Neuroscience[2], University of Tor Vergata; Rome; Department of Environmental Science[3], Cà Foscari, University of Venice, Venice - Italy.

A number of studies performed in c
cinogenesis and to impair tumor g
pleiotropic effects of resveratrol on
of the compound on the growth and
firmed that resveratrol has a direct,
tion, for the first time, relatively hi
down-regulate telomerase activity.
chemoprevention/chemotherapy of

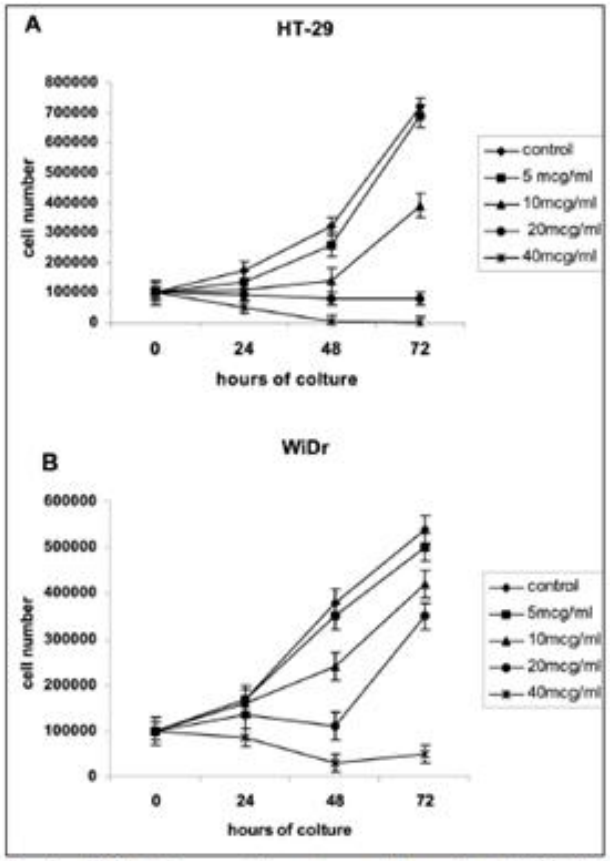


Fig. 1 - Effect of resveratrol on tumor cell growth in HT-29 (A) and WiDr (B) human colon cancer cells. Cells were cultured in CM or CM containing the indicated concentrations of resveratrol for 24, 48 and 72 hrs. Control groups were treated with DMSO alone. Cell proliferation was de-

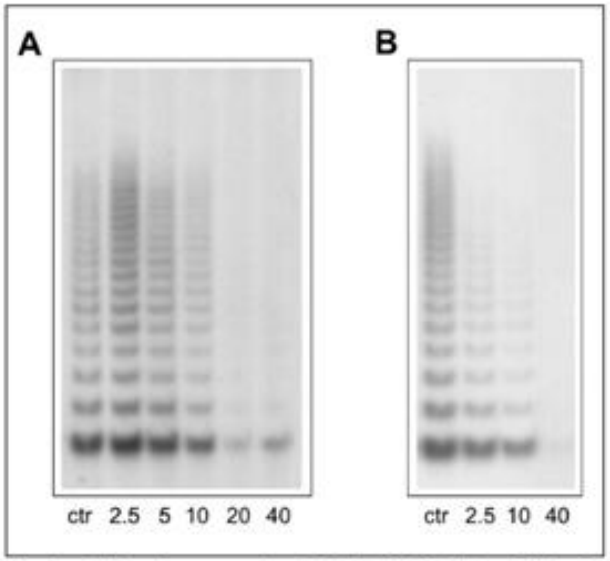


Fig. 2 - Effect of resveratrol on TLMA in HT-29 (A) and WiDr (B) cell lines. Cells were incubated with resveratrol at final concentration of 2.5, 10 and 40 mg/ml (3 wells for each treatment), or DMSO alone as control. Cells plated on day 0 were harvested 48 hrs (A) and 72 hrs (B) after resveratrol treatment and evaluated by TRAP assay as illustrated in Panel A and B. Data are also expressed in terms of percentage of variation with respect to DMSO controls (see table below) calculated by densitometric analysis as described in Materials and Methods.

TREATMENT	HT-29	WiDr
resveratrol 2.5 mg/ml	0 %	15.4 %
resveratrol 10 mg/ml	38.5%	20.3%
resveratrol 40 mg/ml	94%	93.1%

INTERNATIONAL JOURNAL OF ONCOLOGY 28: 641-648, 2006

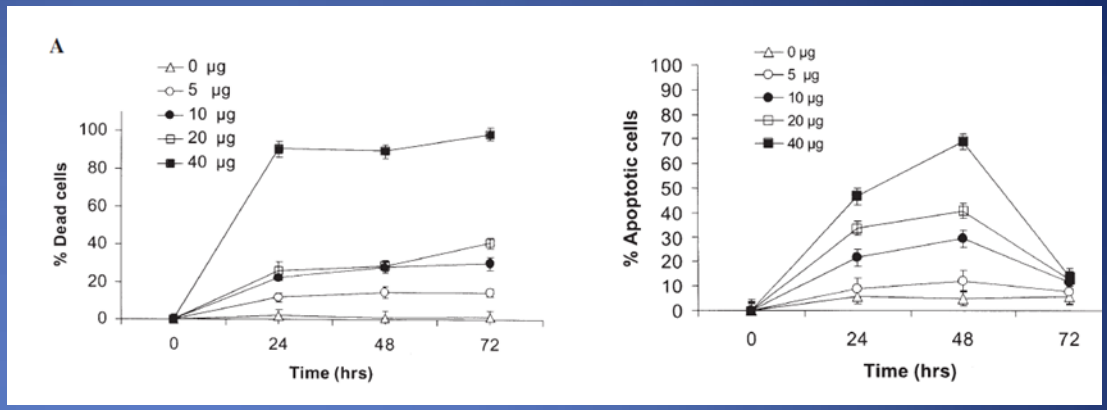
Resveratrol down-regulates the growth and telomerase activity of breast cancer cells *in vitro*

GIULIA LANZILLI[1*], MARIA PIA FUGGETTA[1*], MARIA TRICARICO[1], ANDREA COTTARELLI[1], ANNALUCIA SERAFINO[1], ROBERTO FALCHETTI[1], GIAMPIETRO RAVAGNAN[2], MARIO TURRIZIANI[3], RICCARDO ADAMO[4], ORNELLA FRANZESE[4] and ENZO BONMASSAR[1]

[1]Institute of Neurobiology and Molecular Medicine, National Research Council - CNR, Area Ricerca Roma 'Tor Vergata', Via Fosso del Cavaliere 100, I-00133 Rome; [2]Department of Environmental Science, Cà Foscari, University of Venice, Venice; [3]Department of Internal Medicine, University of Tor Vergata, Via Montpellier 1; [4]Department of Neuroscience, University of Tor Vergata, Via Montpellier 1, I-00133 Rome, Italy

Received September 19, 2005; Accepted November 11, 2005

Abstract. A number of previous studies investigated the *in vitro* effects of resveratrol on malignant human breast epithelial cell transcriptase subunit of the telomerase complex. In our



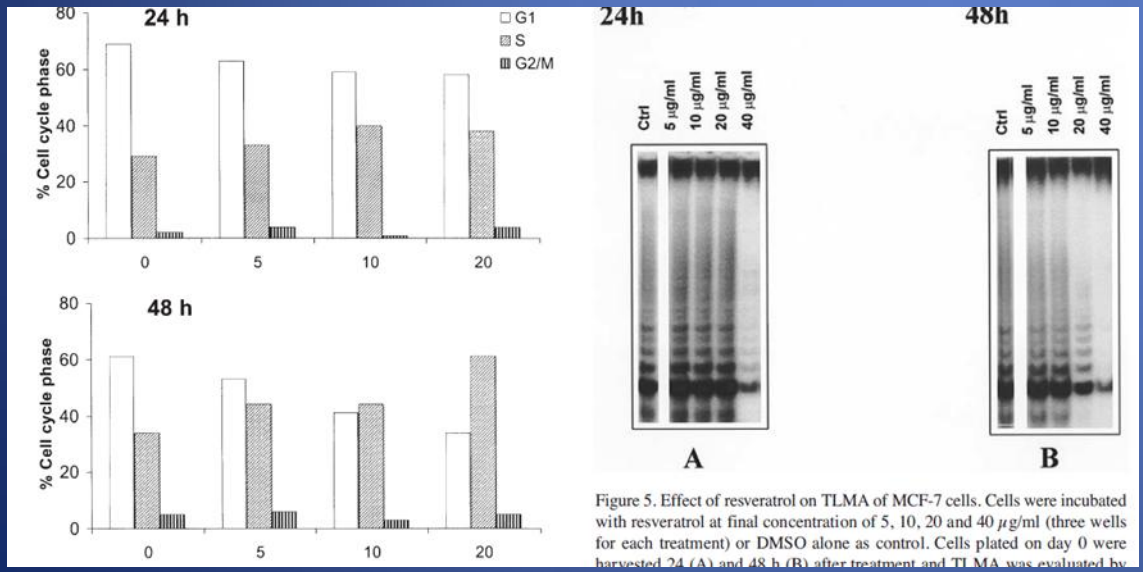
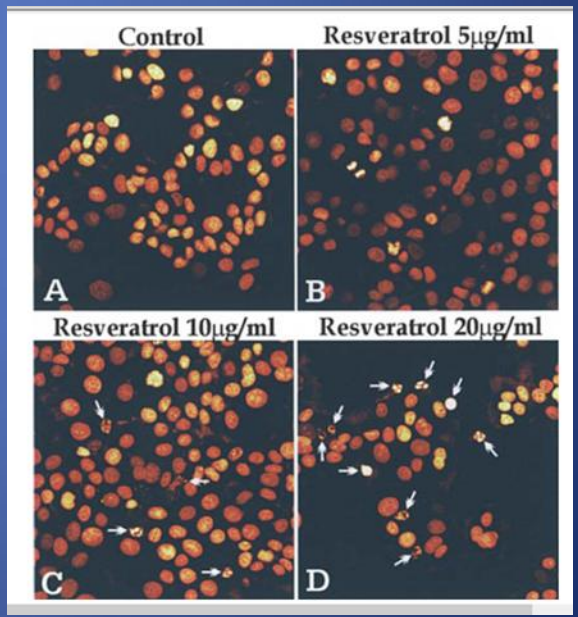


Figure 5. Effect of resveratrol on TLMA of MCF-7 cells. Cells were incubated with resveratrol at final concentration of 5, 10, 20 and 40 μg/ml (three wells for each treatment) or DMSO alone as control. Cells plated on day 0 were harvested 24 (A) and 48 h (B) after treatment and TLMA was evaluated by



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Antitumour activity of resveratrol on human melanoma cells: A possible mechanism related to its interaction with malignant cell telomerase

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[a] Department of Chemical Sciences, University of Naples Federico II, Via Cinzia 21, I-80126 Naples, Italy
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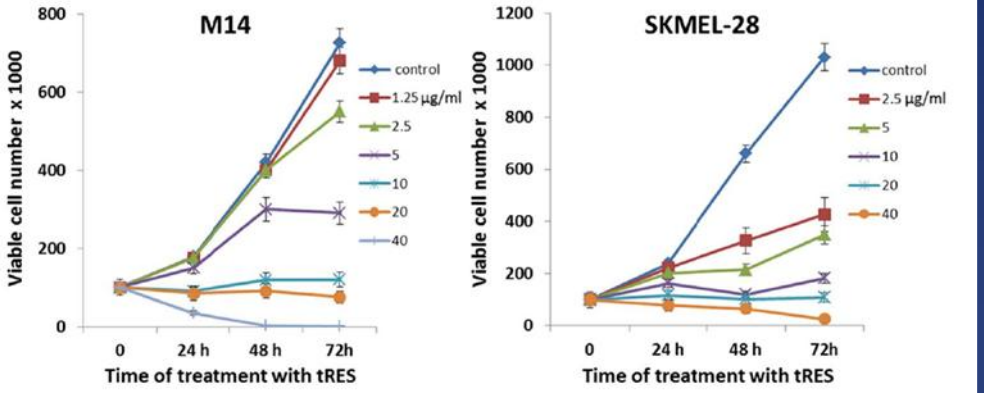
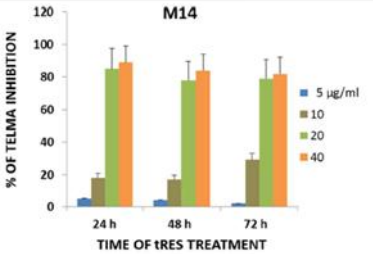
ARTICLE INFO

Keywords:
Resveratrol
Telomerase activity

ABSTRACT

Background: *trans*-Resveratrol (tRES) is a polyphenolic stilbene found in plant products attention because of its antioxidant, anti-inflammatory and anticancer properties.
Methods: The possible correlation between tRES-induced suppression of melanoma ce





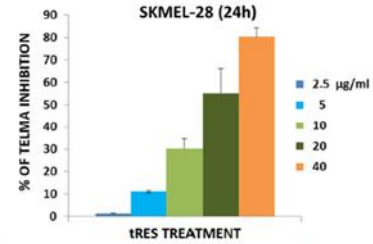


Fig. 4. Effect of tRES on TELMA of M14 melanoma cells (top); TELMA inhibition of SKMEL-28 melanoma cells by tRES after 24 h drug treatment (bottom). All data are expressed as percentage of inhibition with respect to untreated control. Values represent the mean ± SE from at least three independent experiments.

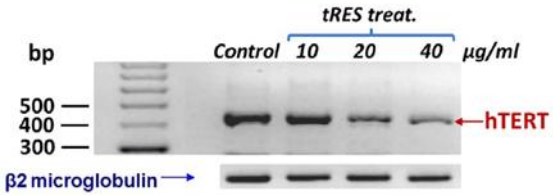


Fig. 5. RT-PCR analysis of hTERT transcript. Agarose gel electroph of graded concentration of tRES on hTERT mRNA in M14 melanom treatment. β_2 microglobulin was used as internal control.

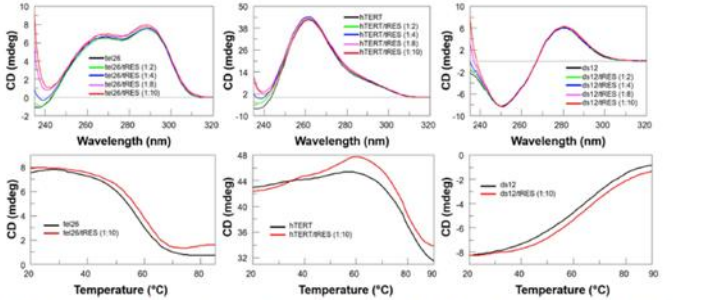
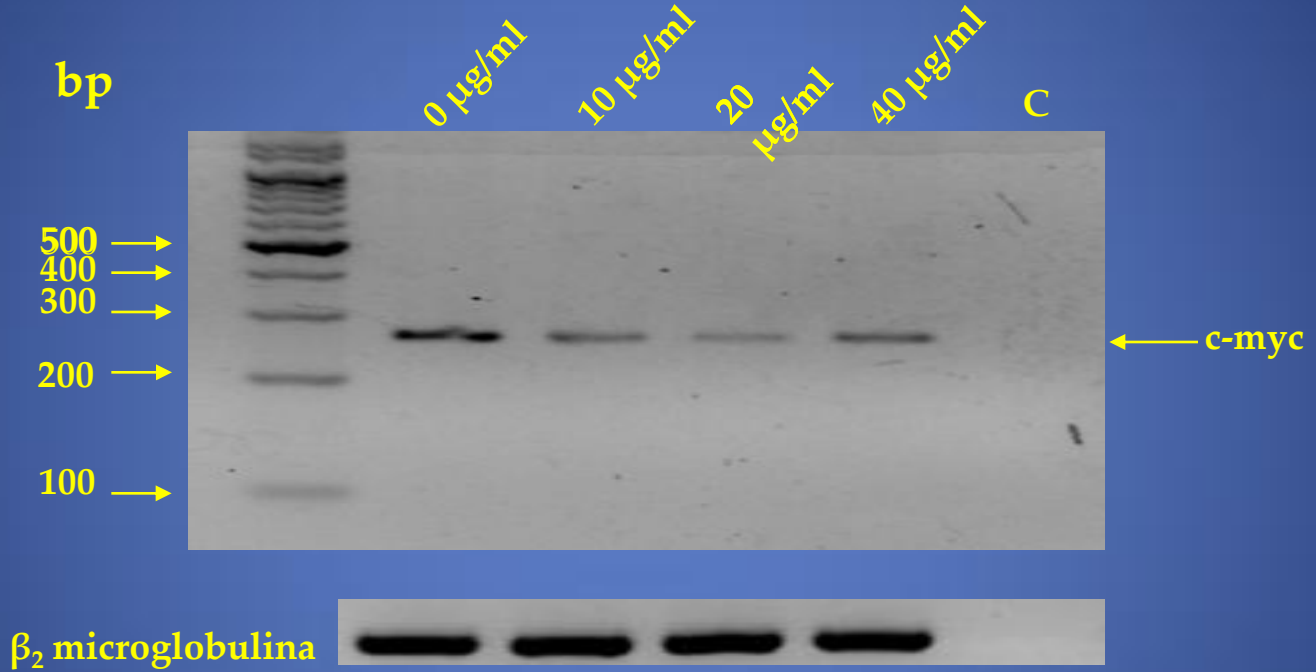


Fig. 7. CD titration curves (top) obtained by adding increasing amounts of tRES to a 2 µM solution of tel$_{26}$, hTERT and ds$_{12}$ (left, middle and right, respectively) and related CD-melting curves (bottom) for the mixtures DNA/tRES (1:10).


bp
0 µg/ml
10 µg/ml
20 µg/ml
40 µg/ml
C
500
400
300
200
100
c-myc
β2 microglobulina

new horizons

- The discovery of the positive interaction use with chemotherapy and radiotherapy of substances such polyphenols as polydatin, has opened a new cancer treatment scenario:
- the Integrative Oncology

Thank you