LONGER TELOMERES FOR A LONGER HEALTHSPAN ™

TELO-100: SCIENTIFIC SUBSTANTIATION & CLAIMS SUPPORT-- KEY REFERENCES

Overview of the Peer-Reviewed Scientific Research Supporting TELO-100

- **Human Clinical Research** for a Telomerase-activating Compound used in Combination with a Separate "Dietary Supplement Pack" of Multiple Anti-Oxidant, Anti-Inflammatory, and other Telomere-supportive Nutritional Ingredients [References 1, 2]

- The **9 Natural Compounds** in TELO-100 and T-Activator 150™ which are **Documented to Activate the Telomere-Lengthening Enzyme, Telomerase** [References 3,4, 30-67]

- The **Impact of Oxidative Stress on Telomere Length & Telomerase Activity**, and the **17 Ingredients in TELO-100 which help Reduce Oxidative Stress** [References 5-7, 68-121]

- The **Impact of Inflammation on Telomere Length & Telomerase Activity**, and the **13 Ingredients in TELO-100 which help Reduce Inflammation** [References 8,9, 122-161]

- The **Impact of the Inflammatory 'cytokine' TNF-alpha on Telomere Length & Telomerase Activity**, & the **12 Ingredients in TELO-100 which help Maintain Healthy Levels of TNF-alpha** [References 10, 11, 162-184]

- The **Impact of Homocysteine on Telomere Length & Telomerase Activity**, and the **5 Ingredients in TELO-100 which help Maintain Healthy Levels of Homocysteine** [References 12, 13, 185-202]

- The **Impact of Cortisol on Telomere Length & Telomerase Activity**, and the **4 Ingredients in TELO-100 which help Maintain Healthy Levels of Cortisol** [References 14, 203-208]

- **The Major Impact of Telomeres and Telomerase on Adult Stem Cell Health and Function** [References 15-20]

- **The Major Impact of Telomeres and Telomerase on Mitochondrial Health and Function** [References 21-24]

- **The Impact of Telomeres and Telomerase on Skin Health and Skin Aging** [References 25-29]

Telomere Biosciences, LLC.
www.TelomereBiosciences.com

David B. Cross, Founder & President
Cell: 917.370.7456
dcross@TelomereBiosciences.com

I. FROM THE LEADING EXPERTS IN TELOMERE SCIENCE: BACKGROUND

"The Nobel Prize in Physiology or Medicine 2009 is awarded jointly to Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak for the discovery of 'how chromosomes are protected by telomeres and the enzyme telomerase.' If the telomeres are shortened, cells age. Conversely, if telomerase activity is high, telomere length is maintained, and cellular senescence is delayed."

--The Nobel Assembly, 5 October 2009

"Telomere shortness links to common disease states: cancer, pulmonary fibrosis, cardiovascular disease (including plaques, heart attacks), vascular dementia, degenerative conditions (osteoarthritis, osteoporosis), diabetes, general risk factors for chronic disease--obesity and insulin resistance."

- *"Correct telomere maintenance is crucial."*

–Elizabeth Blackburn, Nobel Lecture 2009 & J Imm. Meth., Jan. 31, 2010

"Studies point to a causal relationship between telomere loss, cell aging, reduced tissue regeneration and loss of tissue structure and function. In support of this causal relationship, epidemiological studies show that short telomeres in humans are a risk factor for atherosclerosis, hypertension, cardiovascular disease, Alzheimer's disease, infections, diabetes, fibrosis, metabolic syndrome, cancer, and overall mortality,"

--Calvin Harley, Bill Andrews, Maria Blasco, *et. al*., Rejuvenation Research, September 2010

"The literature is, I would say, 95% certain or better that if we can find a way to lengthen telomeres, we can reverse aging." **–Bill Andrews, Interview on the [U.S.] "Today Show," December 13, 2011**

"Short telomeres are causal of disease, because when they are below a certain length they are damaging for the cells. The stem cells of our tissues do not regenerate and then we have ageing of the tissues." [Very] exciting are the possible future advances to come from telomere research, says Dr. Maria Blasco. *"One is telomerase activation, because of its potential to reverse ageing."*

--Maria Blasco, Head of Spain's National Cancer Institute & a leading Expert in Telomeres and Stem Cells, Interview in the [U.K.] Guardian, October 11, 2011

"*The most exciting possibility suggested by the study is that if we can lengthen people's telomeres, they would live longer and healthier lives."*

–Richard Cawthon, The University of Utah School of Medicine, Institute of Human Genetics

II. SUMMARY OF HUMAN CLINICAL RESEARCH TO-DATE FOR TELOMERE-LENGTHENING SUPPLEMENTS:

Several effective Telomere length and telomerase-activating nutritional compounds have now been discovered, and the first commercial telomerase-activator, a single-compound launched in 2007, while described by the authors as a "*moderate*" telomerase-activator that "*increased telomerase in human cells in culture*," has still shown important benefits in humans when combined with other pro-Telomere nutritional ingredients:

[As reported by Drs. Calvin Harley, Bill Andrews, Maria Blasco, *et.al.,* in Rejuvenation Research September 2010, a Dr. Bill Andrews Presentation to the Age Management Medicine Group on 3 November 2012, and a Calvin Harley, *et.al*. study published in Rejuvenation Research June 2013: based on **the results of the first 12 months in human subjects of:**

> ***"PattonProtocol-1…composed of a natural product-derived telomerase activator (TA-65), a [separate] dietary supplement pack, laboratory testing, and physician counseling."***
> [Source: C. Harley 2013]

It is important to note that the additional 'dietary supplement pack*' was composed of multiple Anti-Oxidant, Anti-Inflammatory, and other Telomere-supportive ingredients, as are combined and integrated into the single-product TELO-100, along with TELO-100's multiple natural product-derived telomerase-activators. [*Supplement Facts Panel Source: C. Harley, B. Andrews 2010]

> ***"As discussed earlier, it is important to note that we cannot determine the contribution of any single component of the PattonProtocol-1 to the observed changes."*** *"These data suggest that PattonProtocol-1 (TA-65* ***in combination with other supplements*** *and physician counseling), improves health and may reduce risk of morbidity and mortality."*
> [Source: C. Harley 2013]

A. Statistically-Significant Improvement in Several Major Age-Related Biomarkers that Normally Decline with Age, including:

1. **Significant reduction in the % of Cells with Short Telomeres, and Lengthening of Critically-Short Telomeres**

2. **Significant improvement in T-cell Count and Immune System Function**
   – "Representing a drop of 20% in [senescent] CD8+/CD28- T-cells, an apparent age reversal of 5-20 years in this biomarker of immune ageing."
   --"In our first analysis of Patton-Protocol-1, a commercial health maintenance program composed of TA-65 (a natural product-derived telomerase activator), other dietary supplements, and physician counseling), we reported positive immune remodeling over a one year period relative to baseline values."

3. **A Significant Increase in Bone Mineral Density of +2%**

4. **Significant decreases in Total and LDL Cholesterol**

5. **Highly-Significant Reductions in Systolic and Diastolic Blood Pressure;** in the case of SBP, an apparent reversal of *">30 years of increase in SBP." "Using the Framingham 10-year CVD event calculator, these reductions [in cholesterol and BP] would cause a 25% reduction in 10 year risk for males."*

   *-- "This **reversal of inflammation along with increased telomerase activation** could rescue presenescent endothelial cells **and increase the production of nitric oxide** which could reduce SBP."*

6. **Significant decreases in both Homocysteine and C-reactive protein (CRP),** which *"**are significant markers of Inflammation** and are associated with arterial dysfunction and cardiovascular disease risk."*

   *--"It is likely that **folate and vitamins B12 and B6 in the supplement packs played a significant role in the decline in homocysteine."***

7. **Significant decrease in Fasting Glucose** *["an apparent reversal of 11 years of mean increase in fasting glucose*"] and also a significant decrease in Insulin, indicating also an improvement in Insulin sensitivity.

   *-- "It is possible that the **combination of antioxidants and increased telomerase activation** improved insulin sensitivity in our subjects."*

   *-- "Insulin resistance is a cardinal element of the metabolic syndrome & thought to be a result of **increased inflammatio**n which the PattonProtocol-1 might have reduced*."

B. <u>With an Excellent Safety Profile</u>:

"No new cases of cancer or cardiovascular disease were reported during the overall 260 person-years of dosing, and this is statistically significant." [Calvin B. Harley, *et.al.*, Sept. 2010]

III. <u>THE EXPERTS ON TELOMERE BIOSCIENCES AND TELO-100</u>:

"There are 3 Telomerase inducers [activators] on the market; the first was TA-65, from TA Sciences; and the absolute newest is from Telomere Biosciences."

--World-renowned Telomere & Telomerase Expert **Dr. Bill Andrews** Presentation, February 23, 2012

"Other companies are starting to form that target the science of lengthening telomeres. A company that seems to hold particular promise is Telomere Biosciences. Their first nutritional supplement targets all three major causes of telomere shortening: aging, oxidative stress, and inflammation."

--**Jeffry S. Life, M.D., Ph.D.**, in his ground-breaking book & New York Times Bestseller, <u>The Life Plan</u>

"Telomere Biosciences is breaking exciting new ground in the application of the latest advances in Telomere Biology to Age Management medicine. In my professional opinion as an Age Management researcher and clinician, this is truly 'next generation' Telomere Science and the next generation of scientifically-supported Telomere products."

--**Vincent C. Giampapa, M.D., FACS**, Founding President of the American Board of Anti-Aging Medicine and Internationally-recognized Age Management Medicine Clinician and Researcher, October 24, 2011

IV. SCIENTIFIC SUBSTANTIATION & CLAIMS SUPPORT FOR TELO-100 & ITS INGREDIENTS: KEY REFERENCES:

Background:

TELO-100 is the First & Only Integrated "Complex" of 17 Pro-Telomere Nutritional Ingredients, including Multiple Natural Telomerase-Activators, to Target All Major Causes of Telomere Shortening:

# of Ingredients Targeting:	Telomerase Activators	NO*	TNF-alpha	Homocysteine	Cortisol	Oxidative Stress	Inflammation
Competitive Telomerase Activator:	1	--	--	--	--	--	--
TELO-100:	8	8	12	5	4	17	13

-- All 17 ingredients in TELO-100 have multiple methods of action which positively impact Telomere length

***Nitric Oxide (NO) is a documented Telomerase activator [Geron Corp.]**

Scientific Substantiation & Claims Support for TELO-100 and its Ingredients: Key References:

A. Human Clinical Studies of Telomere-Lengthening Supplements:

1. ***A Natural Product Telomerase Activator As Part of a Health Maintenance Program,*** **Harley C, Blasco M, Andrews B, et.al.,** Rejuvenation Research, **September 2010**

2. ***A Natural Product Telomerase Activator as Part of a Health Maintenance Program: Metabolic & Cardiovascular Response,*** **Harley C, Raffaele J, et.al.,** Rejuvenation Research, **June 29, 2013**

B. Identification of Multiple Natural Product Telomerase Activators:

3. "Shortened telomeres and consequent inability to maintain normal tissue function may underlie most age-related disease. Telomerase has been repeatedly proposed as a uniquely effective intervention. **Several effective telomerase activators have been identified."**

--**Michael Fossel, M.D., PhD, *Telomerase & Human Disease,*** Rejuv. Research**, Nov. 23, 2009**

4. "We decided to start screening [several] natural products for telomerase-inducing activity. TA-65, a transient telomerase inducer from Geron, was already on the market through TA Sciences, and we had tested it and proved that it worked. **We ran the [product] screens and found a lot of hits**."

--Bill Andrews, PhD., and CEO of Sierra Sciences, LLC., "*Interview with Bill Andrews, PhD*."
Rejuvenation Research**, August 2011**

***"T-Activator 150"*™ is a Proprietary Blend of the Following 9 Natural Compounds which are Documented to Activate Telomerase:**

A. Nitric Oxide	[Scientific References 30-33; 47-67]
B. Ginsenosides (Triterpenoid saponins from Panax Ginseng)	[References 34-36]
C. Ginkgo biloba	[Reference 37]
D. Silymarin (from Milk Thistle Extract)	[Reference 38]
E. Resveratrol	[References 39-43]
F. N-Acetyl L-Cysteine	[Reference 44]
G. Vitamin D3	[References 45-46]
H. Horny Goat Weed (with the flavonoid Icariin)	[Proprietary data]
I. Bacopa Monnieri (with Triterpenoid saponins)	[Proprietary data]

C. The Impact of Oxidative Stress on Telomere Length & Telomerase Activity, and Compounds in TELO-100 which Reduce Oxidative Stress:

5. ***Oxidative stress shortens telomeres*****.** von Zglinicki T. **Trends Biochem Sci.** 2002 Jul: Telomeres in most human cells shorten with each round of DNA replication, because they lack the enzyme telomerase. This is not, however, the only determinant of the rate of loss of telomeric DNA. Oxidative damage is repaired less well in telomeric DNA than elsewhere in the chromosome, and oxidative stress accelerates telomere loss, whereas antioxidants decelerate it.

6. ***Chronic Oxidative Stress Compromises Telomere Integrity and Accelerates the Onset of Senescence in Human Endothelial Cells,*** **Kurz DJ, et.al. , J Cell Sci.,** 2004 May: Intracellular oxidative stress rapidly down-regulates telomerase activity. Fig. 7**:** Rapid decrease in telomerase activity following exposure to oxidative stress.

-a.) A 51-68% Reduction in Telomerase Activity: 'As shown in Fig. 6C, even the first oxidant treatment of HUVEC caused a very rapid (49% of control at 3 hours) and sustained (32% of control at 72 hours) decrease in telomerase activity.'

-b.) Approximately Double the Rate of Telomere Shortening: 'In cultures subjected to oxidative stress, terminal restriction fragment (TRF) analysis demonstrated faster telomere shortening (110 base pair versus 55 base pair).'

7. ***Telomere Length Trajectory and Its Determinants in Persons with Coronary Artery Disease*****, Elizabeth Blackburn, *et. al.*, PLoS One, 2010 January 8:** Oxidative stress directly exerts a negative effect on telomere length maintenance, both through inhibition of telomerase activity and direct erosion of GGG triplets in telomeric DNA.

Compounds in TELO-100 which are Documented to Reduce Oxidative Stress:

A. *Panax ginseng* and its Ginsenosides	[Scientific References 68-71]
B. *Ginkgo biloba* Extract	[References 72-75]
C. Resveratrol	[References 76-80]
D. Green Tea Extract [with EGCG]	[References 81-82]
E. *Pycnogenol* (French Maritime Pine Bark Extract)	[References 83-86]
F. N-Acetyl L-Cysteine	[References 87-89]
G. Vitamin E	[References 90-91]
H. Folate	[References 92-94]
I. L-Arginine	[Reference 95]

J.	**Silymarin (Milk Thistle Extract)**	[References 96-100]
K.	**Bacopa Monnieri**	[References 101-105]
L.	**Horny Goat Weed (Icariin)**	[Reference 106]
M.	**Vitamin D3**	[References 107-109]
N.	**Hydroxytyrosol**	[References 110-114]
O.	**Astaxanthin**	[References 115-117]
P.	**Vitamin B6**	[References 118-120]
Q.	**Vitamin B12**	[Reference 121]

D. The Impact of Inflammation on Telomere Length & Telomerase Activity, & Compounds in TELO-100 which Help Reduce Inflammation:

8. ***Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study*****, EH Blackburn, ES Epel, et.al, PLoS One.** May 2011**:** Inflammatory activity is commonly proposed as a promoter of biological aging in general, and of leukocyte telomere shortening in particular. In addition, senescent cells with critically short telomeres produce pro-inflammatory factors. These data provide preliminary evidence that adjunct anti-inflammatory therapies could potentially prevent accelerated leukocyte telomere shortening.

9. ***Leukocyte Telomere Dynamics: Longitudinal Findings in the Bogalusa Heart Study*****, Abraham Aviv**, *et. al*., **Am J Epidemiol.,** 2009 February 1: Leukocyte telomere dynamics register the accruing burden of oxidative stress and inflammation over the life...This presumption is based on findings that oxidative stress augments telomere attrition per replication, and inflammation heightens the turnover of leukocytes, which would further increase LTL shortening with age.

Compounds in TELO-100 which are Documented to Help Reduce Inflammation:

A.	***Panax ginseng* and its Ginsenosides**	[Scientific Reference 122-126]
B.	***Ginkgo biloba* Extract**	[References 127-129]
C.	**Silymarin (Milk Thistle Extract)**	[References 130-131]
D.	**Resveratrol**	[References 132-136]
E.	**Green Tea Extract [with EGCG]**	[References 137-138]
F.	***Pycnogenol* (French Maritime Pine Bark Extract)**	[References 139-143]
G.	**L-Arginine**	[Reference 144]
H.	**N-Acetyl L-Cysteine**	[References 145-146]
I.	**Hydroxytyrosol**	[References 147-149]
J.	**Astaxanthin**	[References 150-151]
K.	**Bacopa Monnieri**	[References 152-153]
L.	**Vitamin D3**	[References 154-158]
M.	**Vitamin B6**	[References 159-161]

E. The Impact of TNF-alpha on Telomerase Activity, and Compounds in TELO-100 which Help Inhibit TNF-alpha:

10. ***Telomere/telomerase dynamics within the human immune system,*** **Effros RB, Exp Gerontol. 2011 Feb-Mar**: "We recently showed that inhibition of TNFα...with a receptor inhibitor significantly increases proliferative potential as well as telomerase activity."

11. ***Modulation of T lymphocyte replicative senescence via TNF-{alpha} inhibition;*** **Parish ST, Effros RB, J Immunol**., 2009 Apr 1:"Here, we show that modulation of TNF-alpha levels in long-term cultures of human CD8 T lymphocytes, by chronic exposure...to an inhibitor of the TNF- alpha receptor-1, increases proliferative potential, delays loss of CD28 expression, retards cytokine profile changes, and enhances telomerase activity"

-- Key Results: **By Inhibiting TNF-alpha, a 1.25 to 1.78-Fold INCREASE in Telomerase Activity vs. Control**

Compounds in TELO-100 which are Documented to Help Inhibit TNF-alpha:

A.	***Panax ginseng* and its Ginsenosides**	[Scientific References 162-163]
B.	***Ginkgo biloba* Extract**	[Reference 164]
C.	**Silymarin (Milk Thistle Extract)**	[References 165-167]
D.	**Resveratrol**	[References 168-169]
E.	**Green Tea Extract [with EGCG]**	[Reference 170]
F.	***Pycnogenol* (French Maritime Pine Bark Extract)**	[References 171-172]
G.	**N-Acetyl L-Cysteine**	[References 173-175]
H.	**Bacopa Monnieri**	[Reference 176]
I.	**Hydroxytyrosol**	[References 177-178]
J.	**Vitamin D3**	[Reference 179]
K.	**Vitamin B6**	[References 180-181]
L.	**Vitamin B12**	[References 182-184]

F. The Impact of Homocysteine on Telomere Length & Telomerase Activity & Compounds in TELO-100 which Help Reduce Homocysteine:

12. ***Homocysteine accelerates senescence and reduces proliferation of endothelial progenitor cells*****,** Zhu JH, et.al. **J Mol Cell Cardiol. 2006 May:** Our previous studies showed that homocysteine (Hcy) reduces endothelial progenitor cell (EPC) numbers and impairs functional activity. [In the present study] Hcy significantly diminished telomerase activity.

13. ***Homocysteine levels and leukocyte telomere length,*** **Aviv A., et.al.,** Atherosclerosis (2008): Increasing tertiles of homocysteine were associated with progressively shorter multiply-adjusted LTL (*p*-value for trend = 0.007). The multiply-adjusted difference in LTL between the highest and lowest tertile of plasma homocysteine was 111 base pairs (95% CI: 35, 189, *p* = 0.004), which is equivalent to 6 years of average telomeric attrition."

Compounds in TELO-100 which are Documented to Help Reduce Homocysteine Levels:

A.	**Vitamin B12**	[Scientific References 185-191]
B.	**Vitamin B6**	[References 185, 192-194]
C.	**Folate**	[References 185, 195-198]
D.	**N-Acetyl L-Cysteine**	[References 199-200]
E.	**Resveratrol**	[References 201-202]

G. The Impact of Cortisol on Telomerase Activity and Compounds in TELO-100 which Help Reduce Cortisol:

14. *Reduced telomerase activity in human T lymphocytes exposed to cortisol,* Effros, RB, *et.al.* **Brain Behav Immun.** 2008 May: Here, we demonstrate that exposure of human T lymphocytes to cortisol is associated with a significant reduction in telomerase activity both during primary stimulation of resting cells & secondary stimulation of previously activated cells.

--Higher concentrations of hydrocortisone, comparable to those that might be reached *in vivo* during stress, reduced telomerase activity by as much as 50%."

Compounds in TELO-100 which are Documented to Help Reduce Cortisol Levels:

A. *Ginkgo biloba* Extract	[Scientific Reference 203]
B. Green Tea Extract [with EGCG]	[References 204-205]
C. Vitamin D3	[Reference 206]
D. Vitamin B6	[References 207-208]

H. The Major Impact of Telomeres and Telomerase on Adult Stem Cell Health and Function:

15. *Telomerase at the intersection of cancer and aging*, Blasco MA, et.al., **Trends Genet. 19 July 2013**: In particular, telomere shortening in the context of adult stem cell compartments has been previously demonstrated to cause severe impairment of stem cell mobilization and a subsequent defect in the ability to regenerate tissues. Indeed, cells with the longest telomeres are enriched at adult stem cell niches in both mice and humans.

16. *Telomere length, stem cells and aging,* Maria A. Blasco, Nat Chem Biol., October 2007: These findings suggest that telomerase activity and telomere length can directly affect the ability of stem cells to regenerate tissues.

***17*. *Telomeres, senescence, and hematopoietic stem cells* (HSCs), Zimmermann S, Martens UM,. Cell Tissue Res., January 2008:** Although blood cells have to be produced continuously throughout life, the HSC pool seems not to be spared by aging processes. Indeed, limited expression of telomerase is not sufficient to prevent telomere shortening in these cells, which is thought ultimately to limit their proliferative capacity. In this review, we discuss the relevance of telomere maintenance for the hematopoietic stem cell compartment.

***18. Linking functional decline of telomeres, mitochondria and stem cells during ageing*, Sahin E, Depinho RA., Nature,** 2010 Mar 25; In particular, age-associated telomere damage, diminution of telomere 'capping' function and associated p53 activation have emerged as prime instigators of a functional decline of tissue stem cells and of mitochondrial dysfunction that adversely affect renewal and bioenergetic support in diverse tissues.

19. *Telomere Shortening in Neural Stem Cells Disrupts Neuronal Differentiation and Neuritogenesis*, María A. Blasco, et.al., The Journal of Neuroscience, November 18, 2009: Aging in mammals is associated with reduced stem cell activity in different organs, leading to deficiencies in cell turnover and tissue repair. Telomere maintenance appears to be essential for the prolonged persistence of stem cell function in organs with extensive cell turnover.

20. ***Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice*****, Jaskelioff M, DePinho, RA, *et.al.,* Nature, November 2010:** Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure and impaired tissue injury responses. Accumulating evidence implicating telomere damage as a driver of age-associated organ decline and disease risk and the marked reversal of systemic degenerative phenotypes in adult mice observed here support the development of regenerative strategies designed to restore telomere integrity...together demonstrating preservation of neural stem/progenitor reserves & their neurogenic capacity in vivo.

I. The Major Impact of Telomeres and Telomerase on Mitochondrial Health and Function:

21. ***Linking Functional Decline of Telomeres, Mitochondria & Stem Cells during Ageing*****, Sahin E, Depinho RA., Nature, 2010 Mar 25:** Age-associated telomere damage, diminution of telomere 'capping' function and associated p53 activation have emerged as prime instigators of a functional decline of tissue stem cells and of mitochondrial dysfunction that adversely affect renewal and bioenergetic support in diverse tissues.

--- Taken together, evidence from the study of a wide range of human degenerative diseases, both inherited and acquired, points to limiting telomeres as key pathogenetic elements driving degenerative pathologies, increasing cancer risk & shortening lifespan. In this light, the sizes of telomere reserves may offer new opportunities for proactive therapeutic interventions involving transient somatic activation of endogenous telomerase to replenish or repair telomeres.

22.. ***Telomere Dysfunction Induces Metabolic and Mitochondrial Compromise*****. Sahin E., Depinho RA**, *et. al*., Dana-Farber Cancer Institute, **Nature.** 2011 Feb 9: Telomere dysfunction is associated with impaired mitochondrial biogenesis and function. In the setting of telomere dysfunction, enforced Tert [telomerase] substantially restores PGC network expression, mitochondrial respiration, cardiac function and gluconeogenesis.

23. ***Non-telomeric activities of telomerase*****,** Majerská J, et.al**. Mol Biosyst.** 2011 Feb 1: Recent results suggest that telomerase is involved in many more cellular processes than merely telomere elongation. These include telomere-independent anti-apoptotic, cytoprotective and pro-proliferative effects of telomerase or protection of mitochondrial DNA against oxidative stress.

24. ***Telomerase does not counteract telomere shortening but protects mitochondrial function under oxidative stress*****,** Ahmed S, et. al., **J Cell Sci. 2008 Apr 1**: *TERT protects mitochondria*: While TERT maintains telomere length under standard conditions, telomeres under increased stress shorten as fast as in cells without active telomerase. In TERT-overexpressing cells, mtDNA is protected, mitochondrial membrane potential is increased and mitochondrial superoxide production and cell peroxide levels are decreased, all indicating improved mitochondrial function and diminished retrograde response.

J. The Impact of Telomeres and Telomerase on Skin Health and Skin Aging:

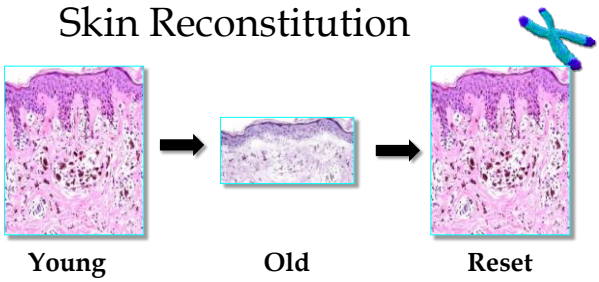
25. ***The Role of Telomeres in the Ageing of Human Skin***, **Buckingham EM, Klingelhutz AJ. Exp Dermatol.** 2011 Apr; Telomerase is also active in certain somatic cells such as those in the epidermis but is almost undetectable in the dermis. Increasing evidence indicates that telomerase plays a significant role in maintenance of skin function and proliferation. Telomeres in skin cells may be particularly susceptible to accelerated shortening because of both proliferation and DNA-damaging agents such as reactive oxygen species. Skin might present an accessible tissue for manipulation of telomerase activity and telomere length with the potential of ameliorating skin diseases associated with ageing.

26. ***Relation Between Maximum Replicative Capacity and Oxidative Stress-Induced Responses in Human Skin Fibroblasts In Vitro*****. Dekker P, Maier AB**, et.al, **Gerontol A Biol Sci Med Sci.**, Oct. 11, 2010: We investigated the relation between maximum replicative capacity, telomere length, stress-induced cellular senescence, and apoptosis/cell death in human primary fibroblast strains obtained from nonagenarians of the Leiden 85-plus Study. Fibroblast strains with a higher replicative capacity had longer telomeres ($p = .054$), [and] are less prone to go into stress-induced cellular senescence.

27. ***Telomerase reverses epidermal hair follicle stem cell defects and loss of long-term survival associated with critically short telomeres*****, Blasco MA,** et.al.; **J Cell Biol.** 2007 Oct 22; We recently found that short telomeres impair the ability of epidermal stem cells to mobilize out of the hair follicle (HF) niche, resulting in impaired skin and hair growth and in the suppression of epidermal stem cell proliferative capacity in vitro. Here, we demonstrate that telomerase reintroduction in mice with critically short telomeres is sufficient to correct epidermal HF stem cell defects. Additionally, telomerase reintroduction into these mice results in a normal life span by preventing degenerative pathologies in the absence of increased tumorigenesis.

28. ***Effects of telomerase & telomere length on epidermal stem cell behavior*****.** Flores I, Blasco MA; **Science.** 2005 Aug 19; A key process in organ homeostasis is the mobilization of stem cells out of their niches. We show through analysis of mouse models that telomere length, as well as the catalytic component of telomerase, Tert, are critical determinants in the mobilization of epidermal stem cells. Telomere shortening inhibited mobilization of stem cells out of their niche, impaired hair growth, and resulted in suppression of stem cell proliferative capacity in vitro. In contrast, Tert overexpression in the absence of changes in telomere length promoted stem cell mobilization, hair growth, and stem cell proliferation in vitro.

29. ***Telomerase expression restores dermal integrity to in vitro-aged fibroblasts in a reconstituted skin model*****. Funk WD, Harley CB**, et.al, **Exp Cell Res.** 2000 Aug 1; The lifespan of human fibroblasts and other primary cell strains can be extended by expression of the telomerase catalytic subunit (hTERT). Thus, telomerase activity not only confers replicative immortality to skin fibroblasts, but can also prevent or reverse the loss of biological function seen in senescent cell populations.



Telomeres determine the age of the skin:
resetting telomere lengths results in young skin.
Funk et al, *Exp Cell Res*, 258:270-278, 2000.

I. Compounds in TELO-100 which are Documented to Activate Telomerase:

A. Nitric Oxide
B. Ginsenosides (Triterpenoid saponins from Panax Ginseng)
C. Ginkgo biloba
D. Silymarin (from Milk Thistle Extract)
E. Resveratrol
F. N-Acetyl L-Cysteine
G. Vitamin D3

A. Nitric Oxide:

30. Geron Cites Nitric Oxide as a Telomerase-Activator in their Patent Support--"*Compositions and Methods for Increasing Telomerase Activity,*" Issued 12-7-10: BACKGROUND OF THE INVENTION AND REFERENCES: "Vasa *et. al.* described activation of telomerase, and a resulting delay in endothelial senescence, by administration of a nitric oxide (NO) precursor." Vasa, M. et al., "***Nitric oxide activates telomerase and delays endothelial cell senescence*****,"** Circ. Res. (2000).

31. *Nitric Oxide Activates Telomerase and Delays Endothelial Cell Senescence*, M. Vasa, et.al. **Circulation Research**. 2000. We investigated the role of telomerase activity for EC senescence and the potential effects of NO on the age-related changes in telomerase activity**... In both HUVECs** starved for 12 hours in 1% BSA and ECs at passage 11 or 13 in complete medium, incubation with the NO donors was associated with a significant increase in telomerase activity. The demonstration that NO affects telomerase activity and delays EC senescence establishes a novel endothelial protective function of NO.

32. *Endothelial Cellular Senescence is Inhibited by Nitric Oxide*, [Nobel Laureate] Louis J. Ignarro, et.al., Proc Natl Acad Sci U S A. 2006 Nov. Treatment with NO donor and transfection with endothelial NO synthase (eNOS) into HUVECs ...increased telomerase activity. The ingestion of NO-boosting substances, including l-arginine, l-citrulline & antioxidants, can delay endothelial senescence under high glucose. When l-arginine, l-citrulline and antioxidants were given together, the recovery of nitrite production was more marked.

33. *The telomerase tale in vascular aging: regulation by estrogens and nitric oxide signaling*, Antonella Farsetti, et.al., **J Appl Physiol. 2009 Jan**: Of interest, both estrogen and NO signaling, specifically through the estrogen receptor-α (ERα) and the endothelial isoform of the nitric oxide synthase (eNOS), have been shown to counteract endothelial senescence through a shared downstream effector, the catalytic subunit of human telomerase (hTERT), a key molecule in the aging process; and several therapeutic approaches targeting this enzyme have been pursued with the goal of delaying senescence in a variety of experimental systems, including endothelial cells.

From the Geron Corp. Patent Application June 23, 2004: "*Compositions and Methods for Increasing Telomerase Activity*":

-- "**Preferred compounds** of formulas I, II or III are **able to produce**, at a concentration of 1 .mu.g/ml or less, **a level of telomerase activity in fibroblasts or keratinocytes at least 25% greater than** the level of such activity seen in a solvent **control**."
-- "**More preferably**, the compound is able to produce, at a concentration of 1 .mu.g/ml or less, a telomerase activity **at least 50% greater than** seen in a solvent **control**.

-- "**Exemplar TRAP Assay Results**: a compound that produced a level of telomerase activity **twice** that seen in a control (**+100%)"**

B. Ginsenosides (from *Panax ginseng*):

34. Geron Cites Ginsenoside RH1 as an "Exemplary compound" for Telomerase Activation in their Patent Application June 23, 2004 --"***Compositions and Methods for Increasing Telomerase Activity***": "The invention described herein is related to methods for increasing telomerase activity in cells, and compositions for use in such methods. In particular embodiments, the compositions comprise a compound of formula I, II, or III. **Exemplary compounds of formulas I-III include Ginsenoside RH1**."

35. ***Ginsenoside rg1 enhances endothelial progenitor cell angiogenic potency and prevents senescence in vitro*.** Shi AW, et.a.l., **J Int Med Res**. 2011; This study investigated the effect of ginsenoside Rg1 on the functions of ex vivo cultivated endothelial progenitor cells (EPCs) and whether ginsenoside Rg1 prevented EPC senescence. β-Galactosidase and telomerase activities increased.

Relative telomerase activity increased significantly in the ginsenoside Rg1-treated group compared with the control group (*P* <0.01; Fig. 6).

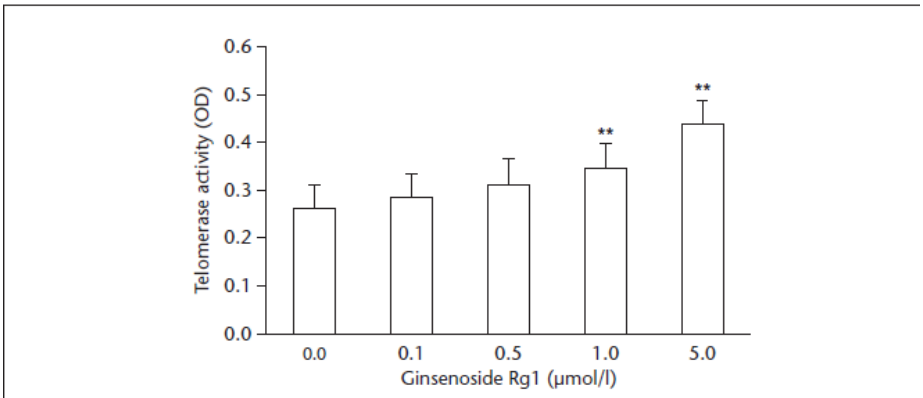


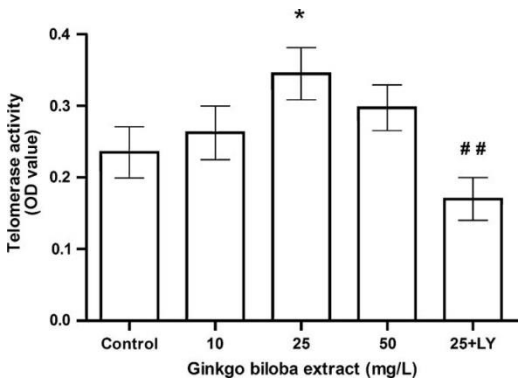
FIGURE 6: Effect of ginsenoside Rg1 on telomerase activity showing a dose-dependent increase in activity compared with the control group (data presented as the mean ± SD optical density [OD] [$n = 5$], $^{**}P < 0.01$ compared with vehicle control)

36. *Changes of telomere and telomerase in effect of ginsenoside Rg1 to delay hematopoietic stem cell senescence*; Zhou Y, et.al., **Zhongguo Zhong Yao Za Zhi. 2011 Nov.**; **OBJECTIVE:** To investigate the roles of telomere and telomerase in the effect of ginsenoside Rg1 to delay hematopoietic stem cell senescence. RESULT: It showed markedly decreased in the shortening of telomere length and reinforcing in the telomerase activity to Rg1 treated aged group and Rg1 delayed aged group. Activation of telomerase and prolonging of telomere length might be involved in the process of ginsenoside Rg1 to delay and treat the senescence of Sca-1(+) HSC.

C. *Ginkgo biloba*:

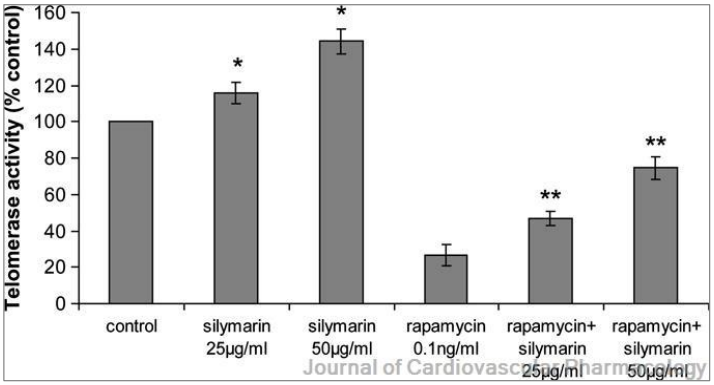
37. *Ginkgo biloba extract reduces endothelial progenitor-cell senescence through augmentation of telomerase activity*. Dong XX, Zhu CJ, et.al. **J Cardiovasc Pharmacol.** 2007 Feb; Our previous studies have shown that Ginkgo biloba extract increased endothelial progenitor-cell (EPC) numbers and functional activity. Ginkgo biloba extract significantly increased telomerase activity through the PI3k/Akt signaling pathway.

Ginkgo biloba **and Telomerase Activity**



D. Silymarin (from Milk Thistle Extract):

38. *Silymarin Inhibits Endothelial Progenitor Cells Senescence and Protects Against the Antiproliferative Activity of Rapamycin*, Parzonko A, Naruszewicz M., **J Cardiovasc Pharmacol.** 2010 Aug 31: We examined whether silymarin, a complex of flavonolignans with hepatoprotective and antioxidative properties, can protect EPCs against rapamycin-induced senescence. **Silymarin increased telomerase activity threefold**, reduced the number of senescent cells and increased EPC proliferative activity (up to 64%) in comparison with cells cultured with rapamycin alone. Cellular senescence is critically influenced by telomerase, which elongates telomeres, thereby counteracting telomere length reduction induced by cell division.



E. Resveratrol:

39. *Resveratrol reduces endothelial progenitor cells senescence through augmentation of telomerase activity by Akt-dependent mechanisms*, Xia L, et.al, . **Br J Pharmacol.** 2008 Oct: **KEY RESULTS:** Resveratrol dose dependently prevented the onset of EPCs senescence and increased the proliferation and migration of EPCs. Resveratrol significantly increased telomerase activity and Akt phosphorylation. CONCLUSIONS AND IMPLICATIONS: Resveratrol delayed the onset of EPC senescence and this effect was accompanied by activation of telomerase through the PI3K-Akt signalling pathway.

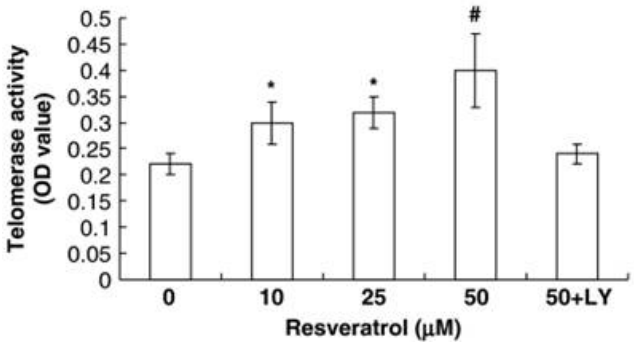
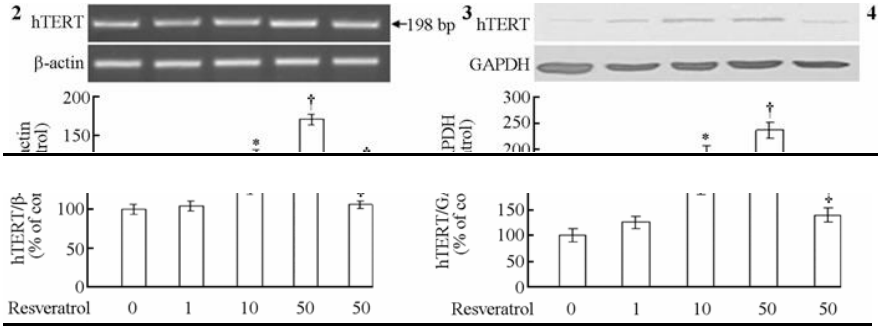


Figure 4 Resveratrol induces telomerase activity in endothelial progenitor cells (EPCs). Telomerase activity was measured by the telomeric repeat-amplification protocol (TRAP) assay. Data are $^{*}P<0.05$, $^{\#}P<0.01$ vs control.

40. ***Immortalization of epithelial progenitor cells mediated by resveratrol***, **Shay JW, Wright WE,** et.al., **Oncogene.** 2008 Apr 10: Resveratrol is considered an important nutrient implicated in prosurvival pathway induction. Our data support the pleiotropic effects of resveratrol by showing nanomolar concentrations of resveratrol initiate prosurvival effects by upregulating or reactivating telomerase in progenitor cells.

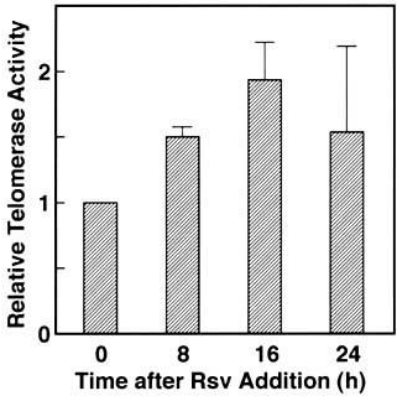
41. ***Resveratrol-induced augmentation of telomerase activity delays senescence of endothelial progenitor cells*****.** Wang XB, et.al.; **Chin Med J (Engl).** 2011 Dec; RESULTS: Resveratrol significantly increased telomerase activity. Resveratrol stimulates the expression of hTERT mRNA and hTERT protein in human EPCs. Thus, we speculate that resveratrol delays the onset of EPCs senescence, most likely through telomerase activation.

Figure 2. Induction of human telomerase reverse transcriptase (hTERT) mRNA in EPCs by resveratrol.
Figure 3. Effect of resveratrol on hTERT protein expression.



42. ***The effect of resveratrol on the Werner syndrome RecQ helicase gene and telomerase activity*****.** Watanabe T., et.al. **Curr Aging Sci.** 2011 Feb: In this study, we show that Rsv increases WRN promoter activity, and that its gene and protein expressions are accompanied by up-regulation of telomerase in HeLa S3 cells. These observations suggest that Rsv is an activator of telomerase and WRN without affecting cell death signals.

Activation of Telomerase by Rsv Treatment:

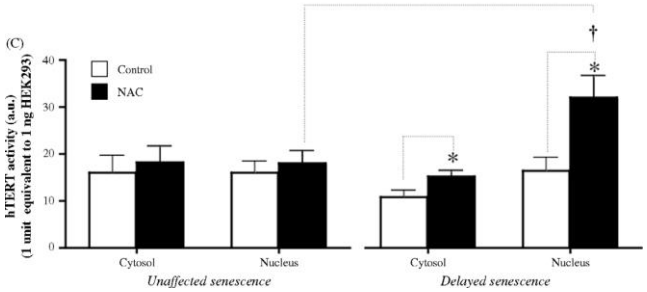


43. ***SIRT1 contributes to telomere maintenance and augments global homologous recombination.*** Blasco MA, et.al, **J Cell Biol.** 2010 Dec 27: Telomeres and Telomerase Group, Spanish National Cancer Centre: Our results indicate that SIRT1 is a positive regulator of telomere length in vivo and attenuates telomere shortening associated with aging, an effect dependent on telomerase activity. SIRT1 effects on telomere length are largely dependent on telomerase activity.

F. N-Acetyl L-Cysteine:

44. Chronic treatment with N-acetyl-cysteine delays cellular senescence in endothelial cells isolated from a subgroup of atherosclerotic patients*,* Voghel G**,** et.al. **Mech Ageing Dev.** 2008 May: Endothelial senescence may contribute to the pathogenesis of age-related vascular disorders**.** In a subgroup of NAC-treated EC (n=15) cellular senescence was significantly delayed, NAC decreased lipid peroxidation (HNE), activated the catalytic subunit of telomerase (hTERT) and inhibited telomere attrition. In conclusion, chronic exposure to NAC can delay senescence of diseased EC via hTERT activation and transient telomere stabilization, unless oxidative stress-associated cell damage has become irreversible.

Telomerase activity in normal EC is extremely low and was therefore detected with the very sensitive real-time-**TRAP assay. Fig. 7C shows that, in EC partially rescued from senescence, NAC increased nuclear hTERT activity by 95%**.



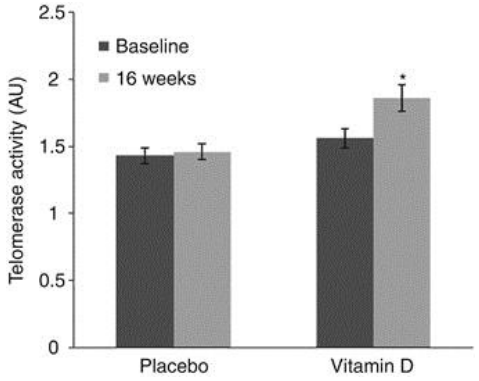
G. Vitamin D3:

45. ***Telomere/telomerase dynamics within the human immune system: Effect of chronic infection and stress,*** **Effros RB, Exp Gerontol. 2011 Feb-Mar**: "Finally, we have preliminary data showing that exposure to another hormone, 25-hydroxyvitamin D, upregulates telomerase activity in human T cells (Chou, Parish, and Effros, unpublished data.)"

46. ***Increased telomerase activity and vitamin D supplementation in overweight African Americans*****; H Zhu, et.al. International Journal of Obesity; 11 October 2011***:* Objective: We aimed to investigate whether vitamin D supplementation modulates peripheral blood mononuclear cell (PBMC) telomerase activity in overweight African Americans. Design: A double blind, randomized and placebo-controlled clinical trial was recently conducted. Subjects and Methods: African-American adults were randomly assigned to either the placebo, or the vitamin D group (equivalent to ~2000 IU per day) oral vitamin D3 supplementation.

Results: In the vitamin D group, PBMC telomerase activity increased by 19.2% from baseline to posttest ($P<0.0001$). PBMC telomerase activity in the placebo group did not change from baseline ($P=0.157$).

Conclusion: Vitamin D supplementation significantly increased PBMC telomerase activity in overweight African Americans. Our data suggest that vitamin D may improve telomere maintenance and prevent cell senescence and counteract obesity-induced acceleration of cellular aging.



II. Compounds in TELO-100 which are Documented to Increase the Production or Bioavailabilty of the Telomerase Activator Nitric Oxide:

A. L-Arginine

B. *Panax ginseng* and its Ginsenosides

C. *Ginkgo biloba* Extract

D. Resveratrol

E. Green Tea Extract [with EGCG]

F. Pycnogenol

G. Hydroxytyrosol

H. Icariin [from Horny Goat Weed]

A. L-Arginine:

47. ***Endothelial cellular senescence is inhibited by nitric oxide: Implications in atherosclerosis associated with menopause and diabetes*****; Nobel Laureate Louis J. Ignarro, Toshio Hayashi, et.al., Proc Natl Acad Sci U S A.** 2006 Nov 7; Treatment with NO donor and transfection with endothelial NO synthase (eNOS) into HUVECs ...increased telomerase activity. Treatment with L-arginine or L-citrulline of eNOS-transfected cells partially inhibited, and combination of L-arginine and L-citrulline with antioxidants strongly prevented, high glucose-induced cellular senescence.

48. ***L-arginine and antioxidant diet supplementation partially restores nitric oxide-dependent regulation of phenylephrine renal vasoconstriction in diabetics rats*****,** Coronel I, et.al, **J Ren Nutr**,2010 May: CONCLUSION: Restoration of this protective NO mechanism can be achieved by simultaneously stimulating NO synthesis and preventing the effects of ROS through the use of L-arginine and a combination of vitamins E and C as diet supplementation.

49. ***L-arginine attenuates high glucose-accelerated senescence in human umbilical vein endothelial cells***; **Zhong W**, et.al, **Diabetes Res Clin Pract.** 2010 Apr 14; L-arginine significantly attenuated these senescent alterations. Furthermore, high glucose induced a decrease in Akt and eNOS activity, and L-arginine prevented the decrease in activity.

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50. ***Modulation of endothelial nitric oxide by plant-derived products*****.** Schmitt CA, Dirsch VM, **Nitric Oxide.** 2009 Sep; In this article, we comprehensively review natural products and plant extracts known to positively influence eNOS activity and/or endothelial function in vitro or in vivo. We will discuss red wine, highlighting polyphenols, oligomeric procyanidins (OPC) and resveratrol as modulators of endothelial NO production. Other dietary products and their active components known to activate eNOS include cocoa (OPC), pomegranates (polyphenols), black and green tea (flavanoids, especially epigallocatechin gallate), olive oil (oleic acid and polyphenols). In addition, phytomedical preparations made from ginkgo, hawthorn and ginseng.

B. ***Panax ginseng*** **and its Ginsenosides:**

51. ***Modulation of endothelial nitric oxide by plant-derived products*****.** Schmitt CA, Dirsch VM, **Nitric Oxide.** 2009 Sep; Ginseng (Panax ginseng) root aqueous extract rapidly activated eNOS via the PI3K/Akt-pathway in HUVEC [240]. This effect might be mediated by the triterpen saponin ginsenoside Rg1, which induced eNOS phosphorylation.

52. ***Ginseng compounds: an update on their molecular mechanisms and medical applications***, Lü JM, et.al. **Curr Vasc Pharmacol.** 2009 Jul: Ginseng is one of the most widely used herbal medicines and is reported to have a wide range of therapeutic and pharmacological applications. **Ginsenosides**, the major pharmacologically active ingredients of ginseng, **have been shown to stimulate NO production in several systems.**

C. ***Ginkgo biloba*** **Extract:**

53. Modulation of endothelial nitric oxide by plant-derived products. Schmitt CA, et.al., **Nitric Oxide.** 2009 Sept.: An extract of Ginkgo biloba leaves, traditionally used in Europe for the treatment of central vascular diseases, increased eNOS expression, eNOS–Ser1177 phosphorylation and improved coronary artery circulation in patients with coronary artery disease.

D. Resveratrol:

54. ***Modulation of endothelial nitric oxide by plant-derived products.*** Schmitt CA, Dirsch VM, **Nitric Oxide.** 2009 Sep; Taken together, a number of in vivo and in vitro studies have shown improved vascular function in response to RV, which appeared to be at least partly due to increased NO availability.

55. ***Therapeutic effect of enhancing endothelial nitric oxide synthase (eNOS) expression and preventing eNOS uncoupling***; Förstermann U, Li H., **Br J Pharmacol.** 2010 Dec 30: In recent years we have identified a number of small molecules that have the potential to prevent eNOS uncoupling and, at the same time, enhance eNOS expression. These include the polyphenolic phytoalex in trans-resveratrol. Such compounds enhance NO production from eNOS.

56. ***Effects of resveratrol and other wine polyphenols on vascular function: an update***, Gresele P, et.al. **J Nutr Biochem.** 2011 Mar; The mechanisms through which resveratrol and other wine polyphenols protect from ischemic cardiovascular events are many, but protection from oxidative stress and radical oxygen species production, a facilitating activity on nitric oxide production and activity and the ability to modulate the expression of adhesive molecules by blood cells and the vascular wall seem to be the most important.

57. ***Resveratrol recruits rat muscle microvasculature via a nitric oxide-dependent mechanism that is blocked by TNFα***. Wang N, et. al**.,** **Am J Physiol Endocrinol Metab.** 2011 Jan: In conclusion, resveratrol activates eNOS and increases muscle microvascular recruitment via an NO-dependent mechanism.

58. ***Effect of resveratrol on endothelial cell function: Molecular mechanisms***, Schmitt CA, et.al. **Biofactors.** 2010 Sep: We describe how RV enhances endothelial nitric oxide production.

59. ***Resveratrol: a multifunctional compound improving endothelial function***. Li H, Förstermann U.**,** **Cardiovasc Drugs Ther.** 2009 Dec: By stimulating eNOS expression, eNOS phosphorylation and eNOS deacetylation, resveratrol enhances endothelial NO production.

E. Green Tea Extract [with EGCG]:

60. ***Modulation of endothelial nitric oxide by plant-derived products*****.** Schmitt CA, Dirsch VM. **Nitric Oxide.** 2009 Sep; In BAEC, EGCG was shown to activate eNOS rapidly via the PI3K/Akt pathway. Another study demonstrated that both black and green tea, as well as pure-epicatechin and EGCG, increased NO production in HUVEC.

61. ***A constituent of green tea, epigallocatechin-3-gallate, activates endothelial nitric oxide synthase by a phosphatidylinositol-3-OH-kinase-, cAMP-dependent protein kinase-, and Akt-dependent pathway and leads to endothelial-dependent vasorelaxation*****.** Lorenz M, et.al. **J Biol Chem.** 2004 Feb.

62. ***Epigallocatechin gallate, a green tea polyphenol, mediates NO-dependent vasodilation using signaling pathways in vascular endothelium requiring reactive oxygen species and Fyn*****.** Kim JA, et.al. **Biol Chem.** 2007 May**:** We conclude that EGCG has endothelial-dependent vasodilator actions mediated by intracellular signaling pathways requiring reactive oxygen species and Fyn that lead to activation of phosphatidylinositol 3-kinase, Akt, and eNOS.

F. Pycnogenol

63. ***Pycnogenol, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans***. Nishioka K, et.al. **Hypertens Res**. 2007 Sep: These findings suggest that Pycnogenol augments endothelium-dependent vasodilation by increasing in NO production.

64. ***Antihypertensive effect of French maritime pine bark extract (Flavangenol): possible involvement of endothelial nitric oxide-dependent vasorelaxation,*** Kwak CJ, et.al. **J Hypertens.** 2009 Jan: It seems likely that the antihypertensive effect of Flavangenol is mediated by endothelial nitric oxide synthase activation.

G. Hydroxytyrosol

65. ***Hydroxytyrosol induces vascular smooth muscle cells apoptosis through NO production and PP2A activation with subsequent inactivation of Akt,*** *Zrelli H, et.al., **Planta Med.** 2011 Oct;* HT

enhanced nitric oxide (NO) production in a dose-dependent manner. Together, these findings indicate that HT could induce VSMCs apoptosis through NO production.

H. Icariin (from Horny Goat Weed):

66. ***Icariin delays homocysteine-induced endothelial cellular senescence involving activation of the PI3K/AKT-eNOS signaling pathway,*** Xiao-Hong D, et.al., **Pharm Biol**. 2013 Apr 5: Icariin, a flavonoid derived from Epimedium sagittatum, has been reported to increase production of nitric oxide (NO) and reduce reactive oxygen species (ROS) levels in human umbilical vein endothelial cells (HUVECs).

67. ***Icariin enhances endothelial nitric-oxide synthase expression on human endothelial cells in vitro,*** Xu HB, Huang ZQ, **Vascul Pharmacol.** 2007 July

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III. Compounds in TELO-100 which are Documented to Reduce Oxidative Stress:

A. ***Panax ginseng*** **and its Ginsenosides**
B. ***Ginkgo biloba*** **Extract**
C. Resveratrol
D. Green Tea Extract [with EGCG]
E. ***Pycnogenol*** **(French Maritime Pine Bark Extract)**
F. N-Acetyl L-Cysteine
G. Vitamin E
H. Folate
I. L-Arginine
J. Silymarin (Milk Thistle Extract)
K. Bacopa Monnieri
L. Horny Goat Weed (Icariin)
M. Vitamin D3
N. Hydroxytyrosol
O. Astaxanthin
P. Vitamin B6
Q. Vitamin B12

A. *Panax ginseng* and its Ginsenosides:

68. ***Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation in healthy participants: a randomized, double-blind, placebo-controlled trial*****.*** Kim JY, **Nutr J.** 2012 Jul 17; Plasma superoxide dismutase (SOD) activity after the 8-week KRG supplementation was significantly higher in the low-and high-dose groups compared to baseline. KRG supplementation may attenuate lymphocyte DNA damage and LDL oxidation by upregulating antioxidant enzyme activity.

69. ***Red ginseng abrogates oxidative stress via mitochondria protection*****.** Dong GZ, et.al. **BMC Complement Altern Med.** 2013 Mar 18;

70. ***Panax ginseng reduces oxidative stress and restores antioxidant capacity in aged rats*****.** Ramesh T, **Nutr Res.** 2012 Sep;

71. ***Ginseng compounds: an update on their molecular mechanisms and medical applications*****.** Lü JM, et.al. **Curr Vasc Pharmacol.** 2009 Jul: Ginsenosides, the major pharmacologically active ingredients of

ginseng, appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anti-cancer.

B. *Ginkgo biloba* Extract:

72. *Ginkgo biloba extract attenuates oxLDL-induced oxidative functional damages in endothelial cells*. Ou HC, et.al. **J Appl Physiol.** 2009 May;

73. *Ginkgo biloba leaves extract (EGb 761) attenuates lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and NF-κB-dependent matrix metalloproteinase-9 pathway*. Huang CH, et.al. **Phytomedicine.** 2013 Feb 15:

74. *Ginkgo biloba L. extract enhances the effectiveness of syngeneic bone marrow mesenchymal stem cells in lowering blood glucose levels and reversing oxidative stress*. Ren M, et.al. **Endocrine**. 2013 Apr;

75. *Mitochondrial effects of Ginkgo biloba* extract. Eckert A. Int Psychogeriatr. 2012 Aug; A growing volume of data confirms that Ginkgo biloba extract (GBE) reduces oxidative stress and improves mitochondrial respiration.

C. Resveratrol:

76. *Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases*. Carrizzo A, et.al., **Food Chem Toxicol**. 2013 Jul 18

77. *Resveratrol in mammals: effects on aging biomarkers, age-related diseases, and life span*. Marchal J, et.al. **Ann N Y Acad Sci**. 2013 Jul; Through its antioxidant, anticarcinogenic, and anti-inflammatory properties, resveratrol has become a candidate for drug development in the context of aging studies.

78. *Oxidative stress in vascular disease and its pharmacological prevention*. Förstermann U. et.al., **Trends Pharmacol Sci.** 2013 June:

79. *Prevention of diabetes-induced cardiovascular complications upon treatment with antioxidants*. Xu YJ, et.al**. Heart Fail Rev.** 2013 Feb 23: Antioxidants, N-acetyl-L-cysteine and **resveratrol,** have also been shown to attenuate the diabetes-induced cardiovascular complications. It has been indicated that the antioxidant therapy may be effective in a prevention strategy rather than as a treatment for CVD.

80. *Antioxidative effects of plant polyphenols: from protection of G protein signaling to prevention of age-related pathologies*. Jefremov V, **Ann N Y Acad Sci**. 2007 Jan: Resveratrol revealed significantly higher antioxidativity than curcumin or genistein.

D. Green Tea Extract [with EGCG]:

81. *Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients*. Bogdanski P, et.al. **Nutr Res.** 2012 Jun;

82. ***Epigallocatechin gallate, the major component of polyphenols in green tea, inhibits telomere attrition mediated cardiomyocyte apoptosis in cardiac hypertrophy*.**Sheng RG, et.al., **Int J Cardiol.** 2011 Oct 14: EGCG, quercetin and carvedilol, have potent antioxidant effects. EGCG, quercetin and carvedilol could prevent telomere attrition and telomere repeat-binding factor 2 (TRF(2)) loss remarkably.

E. *Pycnogenol* (French Maritime Pine Bark Extract):

83. *Nutritional supplementation for type 2 diabetes: a systematic review*. Bartlett HE, Eperjesi F. **--Ophthalmic Physiol Opt.** 2008 Nov; Pycnogenol is one of the most potent natural antioxidants. Pycnogenol can readily cross the blood–brain barrier to provide antioxidant protection to central nervous system tissue. This property differentiates it from other known antioxidants.

84. ***A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology*** **,** Rohdewald P, **Int J Clin Pharmacol Ther.** 2002 Apr: PYC protects against oxidative stress in several cell systems by doubling the intracellular synthesis of anti-oxidative enzymes and by acting as a potent scavenger of free radicals. Other anti-oxidant effects involve a role in the regeneration and protection of vitamin C and E.

85. *The Antioxidant and Antigenotoxic Effects of Pycnogenol((R)) on Rats Treated With Cisplatin*. Aydin B, et.al. **Biol Trace Elem Res.** 2010 Jul 30: Pycnogenol(R) is known for its strong antioxidant and anti-inflammatory effects.

86. *Pycnogenol: a blend of procyanidins with multifaceted therapeutic applications*, D'Andrea G., **Fitoterapia**. 2010 Oct: Owing to the basic chemical structure of its components, the most obvious feature of pycnogenol is its strong antioxidant activity.

F. N-Acetyl L-Cysteine:

87. *Antioxidants Inhibit Nuclear Export of Telomerase Reverse Transcriptase and Delay Replicative Senescence of Endothelial Cells*, Haendeler J, Dimmeler, S., et.al., Circulation Research, 2004 April*:* Nuclear export of TERT protein, loss in the overall TERT activity, & the onset of replicative senescence were delayed by incubation with the antioxidant N-acetylcysteine.

88. ***Chronic treatment with N-acetyl-cysteine delays cellular senescence in endothelial cells isolated from a subgroup of atherosclerotic patients*.** Voghel G, et.al. **Mech Ageing Dev.** 2008 May; In a subgroup of NAC-treated EC (n=15) cellular senescence was significantly delayed, NAC decreased lipid peroxidation (HNE), activated the catalytic subunit of telomerase (hTERT) and inhibited telomere attrition.

89. *Delay in oocyte aging in mice by the antioxidant N-acetyl-L-cysteine (NAC)*. Liu J, et.al. **Hum Reprod.** 2012 Feb 21: Telomeres are particularly susceptible to ROS-induced damage. Previously, we have shown that antioxidant N-acetyl-l-cysteine (NAC) effectively rescues oocytes and embryos from ROS-induced telomere shortening and apoptosis in vitro. CONCLUSIONS: These data suggest that appropriate treatment with the antioxidant NAC postpones the process of oocyte aging in mice.

G. Vitamin E

90. *Diet, nutrition and telomere length,* Paul L, **J Nutr Biochem**. 2011 Mar 21: **2.6. Vitamins C and E**: Antioxidant properties of vitamin C and E are widely acknowledged. Intake of vitamin C and E either from diet or from multivitamins is positively associated with longer telomeres in a dose-dependent manner in women. In cells treated with vitamin E, there was a reduction in the ROS due to scavenging by the vitamin. This process may limit oxidative damage to telomeric DNA that would otherwise cause shortening of telomere length.

***91. Effect of Vitamin E Administration on the Elevated Oxygen Stress and the Telomeric and Subtelomeric Status in Alzheimer's Disease*.** Guan JZ, et.al.,**Gerontology.** 2011 Sep 7. Conclusions: AD patients showed an elevated Oxidative Stress (OS) marker level, and vitamin E lowered the OS level.

H. Folate:

92. ***Folate deficiency is associated with oxidative stress, increased blood pressure, and insulin resistance in spontaneously hypertensive rats*****.** Pravenec M, **Am J Hypertens.** 2013 Jan**;** In the current study, the low-folate diet was accompanied by significantly reduced activity of antioxidant enzymes.

93. Folic acid prevents depressive-like behavior and hippocampal antioxidant imbalance induced by restraint stress in mice. Budni J, et.al. **Exp Neurol.** 2013 Feb: Folic acid treatment restored the activity of the antioxidant enzymes and reduced lipid peroxidation in the hippocampus.

94. ***DNA and oxidative damages decrease after ingestion of folic acid in patients with type 2 diabetes*****,** Lazalde-Ramos BP, et.al. **Arch Med Res.** 2012; A positive correlation exists between oxidative stress produced by T2DM and DNA damage, so the use of an antioxidant such as folic acid in DM2 therapy is advisable for delaying complications due to T2DM-induced oxidative stress and DNA damage.

I. L-Arginine:

95. ***Beneficial effects of antioxidants and L-arginine on oxidation-sensitive gene expression and endothelial NO synthase activity at sites of disturbed shear stress*****.** Ignarro LJ, et.al. **Proc Natl Acad Sci U S A**, 2004 Dec 28.

J. Silymarin (Milk Thistle Extract):

96. ***Silymarin, the antioxidant component of Silybum marianum, prevents sepsis-induced acute lung and brain injury*****,** Toklu HZ, et.al.**, J Surg Res.** 2008: Potent antioxidant effects of silymarin.

97. Silymarin: a novel antioxidant with antiglycation and antiinflammatory properties in vitro and in vivo. Wu CH, et.al. **Antioxid Redox Signal.** 2011 Feb 1;

98. ***Silymarin: a review of its clinical properties in the management of hepatic disorders*****.** Wellington K, et.al., **BioDrugs.** Silymarin increases superoxide dismutase (SOD) activity of lymphocytes and erythrocytes, as well as the expression of SOD in lymphocytes.

99. ***Silymarin protects PBMC against B(a)P induced toxicity by replenishing redox status and modulating glutathione metabolizing enzymes--an in vitro study*****.** Kiruthiga PV, et.al. **Toxicol Appl Pharmacol.** 2010 Sep 1**:** Silymarin is one such compound used clinically and consumed as dietary supplement around the world for its strong anti-oxidant efficacy.

100. ***Silymarin modulates the oxidant-antioxidant imbalance during diethylnitrosamine induced oxidative stress in rats*****.** Pradeep K, et.al. Eur J Pharmacol. 2007 Apr 10.

K. Bacopa Monnieri:

101. A randomized controlled trial investigating the effect of Pycnogenol and Bacopa herbal medicines on cognitive, cardiovascular, and biochemical functioning in cognitively healthy elderly people: Stough CK, et.al. **Nutr J.** 2012 Mar 6; Bacopa Monniera: Chronic administration of *Bacopa* inhibits lipid peroxidation in the prefrontal cortex, striatum and hippocampus via a similar mechanism to vitamin E. These include: anti-oxidant (flavonoid) activity;

102. ***Neuroprotective effects of Bacopa monnieri in experimental model of dementia*****.** Saini N, **Neurochem Res.** 2012 Sep; BM administration attenuated oxidative damage, as evident by decreased LPO and protein carbonyl levels and restoration in activities of the antioxidant enzymes.

103. ***Pretreatment with Bacopa monnieri extract offsets 3-nitropropionic acid induced mitochondrial oxidative stress and dysfunctions in the striatum of prepubertal mouse brain*****.** Shinomol GK, et.al. **Can J Physiol Pharmacol.** 2012 May;

104. ***Neuromodulatory propensity of Bacopa monnieri leaf extract against 3-nitropropionic acid-induced oxidative stress: in vitro and in vivo evidences*****.** Shinomol GK, et.al. **Neurotox Res**. 2012 Aug:

105. ***Bacopa monnieri modulates antioxidant responses in brain and kidney of diabetic rats*****,** Kapoor R, **Environ Toxicol Pharmacol**. 2009 Jan; Administration of plant extract to diabetic rats showed significant reversal of disturbed antioxidant status and peroxidative damage.

L. Horny Goat Weed (Icariin):

106. ***Icariin reduces mitochondrial oxidative stress injury in diabetic rat hearts*****,** Bao H, Chen L. **Zhongguo Zhong Yao Za Zhi.** 2011 Jun.

M. Vitamin D3:

107. ***Vitamin D Supplementation Affects Serum High-Sensitivity C-Reactive Protein, Insulin Resistance, and Biomarkers of Oxidative Stress in Pregnant Women*****.** Asemi Z, et.al. J Nutr. 2013 Jul 24:

108. ***Vitamin D reduces deposition of advanced glycation end-products in the aortic wall and systemic oxidative stress in diabetic rats*****.** Salum E, **Diabetes Res Clin Pract**. 2013 May**:** Vitamin D supplementation may provide significant protection against oxidative stress-mediated vascular complications in diabetes.

109. ***Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells*****.** Bao BY, et.al. **Int J Cancer**. 2008 Jun 15: The antioxidative effects of vitamin D have been suggested by epidemiological and many in vitro and in vivo laboratory studies.

N. Hydroxytyrosol:

110. ***Investigation into the biological properties of the olive polyphenol, hydroxytyrosol*****;** Rafehi H, et.al., **Genes Nutr**. 2012 Apr; Hydroxytyrosol has been shown to be a potent antioxidant and has anti-atherogenic and anti-cancer properties. This indicates that as well as being itself a potent antioxidant, hydroxytyrosol promotes the cells own defences against oxidative stress.

111. ***MnSOD activity regulates hydroxytyrosol-induced extension of chronological lifespan*****.** Sarsour EH, **Age (Dordr).** 2012 Feb**:** These results demonstrate that HT extends CLS by increasing MnSOD activity and decreasing age-associated mitochondrial reactive oxygen species accumulation**.**

112. ***The olive oil antioxidant hydroxytyrosol efficiently protects against the oxidative stress-induced impairment of the NObullet response of isolated rat aorta*****.** Rietjens SJ,et.al. **Am J Physiol Heart Circ Physiol.** 2007 Apr**:** The Mediterranean diet, which is abundant in antioxidants, is associated with a relatively low incidence of coronary heart disease. Olive oil and olives, which contain the antioxidants hydroxytyrosol. Hydroxytyrosol was found to be a potent OH(*) scavenger, which can be attributed to its catechol moiety.

113. ***Antioxidant and anti-atherogenic activities of olive oil phenolics*****.** Turner R, et.al. Int J Vitam Nutr Res. 2005 Jan;

114. ***Suppressive effects of hydroxytyrosol on oxidative stress and nuclear Factor-kappaB activation in THP-1 cells*****.** Zhang X, et.al. **Biol Pharm Bull.** 2009 Apr; HT significantly reduced LPS-stimulated NO production and ROS formation in a concentration-dependent manner. These findings suggest that HT has antioxidant activity to suppress intracellular oxidative stress.

O. Astaxanthin:

115. ***Astaxanthin protects ARPE-19 cells from oxidative stress via upregulation of Nrf2-regulated phase II enzymes through activation of PI3K/Akt*****.*** Li Z, et.al. **Mol Vis.** 2013 Jul 25: Astaxanthin is a carotenoid that shows significant antioxidant properties.

116. ***Impact of divergent effects of astaxanthin on insulin signaling in l6 cells*****.*** Ishiki M, et.al. Endocrinology. 2013 Aug: Astaxanthin [is] a carotenoid antioxidant. These findings indicate astaxanthin is a very effective antioxidant for ameliorating insulin resistance by protecting cells from oxidative stress generated by various stimuli including TNFα and palmitate.

117. ***Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease*****.** Pashkow FJ, et.al. **Am J Cardiol.** 2008 May 22**:** Results from multiple species support the antioxidant/anti-inflammatory properties of the prototype compound, astaxanthin.

P. Vitamin B6:

118. ***Oxidative damage and inflammation in obese diabetic Emirati subjects supplemented with antioxidants and B-vitamins: a randomized placebo-controlled trail*****.*** Gariballa S, et.al. **Nutr Metab (Lond).** 2013 Feb 4; Antioxidants supplementation with B-group vitamins enhances antioxidant capacity, and may have an anti-inflammatory effect in obese diabetic patients.

119. ***Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study*****.** Shen J, et.al. **Am J Clin Nutr.** 2010 Feb: Low vitamin B-6 concentrations are associated with inflammation, higher oxidative stress, and metabolic conditions in older Puerto Rican adults. Our data suggest that vitamin B-6 may influence cardiovascular disease risk through mechanisms other than [just] homocysteine**.**

120*. Vitamin B6: a long known compound of surprising complexity***.** Mooney S, et.al. **Molecules.** 2009 Jan 12; Recently it became clear that vitamin B6 is also a potent antioxidant that effectively quenches reactive oxygen species and is thus of high importance for cellular well-being.

Q. Vitamin B12:

121. ***Diet, nutrition and telomere length*****,** Paul L. 2.2. **Vitamin B12**: Vitamin B12 has strong antioxidant properties and has the effect of sparing the reactive oxygen species (ROS) scavenger glutathione, thus reducing oxidative stress.

IV. Compounds in TELO-100 which are Documented to Help Reduce Inflammation:

- **A. *Panax ginseng* and its Ginsenosides**
- **B. *Ginkgo biloba* Extract**
- **C. Silymarin (Milk Thistle Extract)**
- **D. Resveratrol**
- **E. Green Tea Extract [with EGCG]**
- **F. *Pycnogenol* (French Maritime Pine Bark Extract)**
- **G. L-Arginine**
- **H. N-Acetyl L-Cysteine**
- **I. Hydroxytyrosol**
- **J. Astaxanthin**
- **K. Bacopa Monnieri**

L. Vitamin D3
M. Vitamin B6

A. *Panax ginseng* and its Ginsenosides:

122. *Ginseng compounds: an update on their molecular mechanisms and medical applications*. Lü JM, et.al. **CurrVasc Pharmacol**. 2009 Jul; Ginsenosides, the major pharmacologically active ingredients of ginseng, appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anti-cancer.

123. *Ginsenoside Rh1 possesses antiallergic and anti-inflammatory activities*. Park EK, et.al. **Int Arch Allergy Immunol**. 2004 Feb; Ginseng (the root of Panax ginseng) has been reported to possess various biological activities, including anti-inflammatory and antitumor actions. In this study

124. *Anti-inflammatory mechanism of ginsenoside Rh1 in lipopolysaccharide-stimulated microglia*. Jung JS, et.al. J Neurochem. 2010 Dec;

125. *Differential effects of ginsenosides on NO and TNF-alpha production by LPS-activated N9 microglia*. Wu CF, et.al. **Int Immunopharmacol**. 2007 Mar; Ginsenosides, the main active components of ginseng; All ginsenosides studied potently suppressed TNF-alpha production in LPS-activated N9 cells. The significant suppressive effects of ginsenosides on proinflammatory responses of microglia implicate their therapeutic potential in neurodegenerative diseases accompanied by microglial activation.

126. *Inhibitory effect of ginsenoside Rg1 on lipopolysaccharide-induced microglial activation in mice*. Hu JF, et.al. **Brain Res.** 2011 Feb 16; Rg1 inhibited the inflammation mediated by LPS by suppressing NFκB and MAPK pathway, which provided the explanation for its therapeutic effect on neurodegenerative diseases.

B. *Ginkgo biloba* Extract:

127. *EGb761 inhibits inflammatory responses in human chondrocytes and shows chondroprotection in osteoarthritic rat knee*. Chen YJ, et.al. **J Orthop Res**. 2013 Jul; EGb761, a standardized extract of Ginkgo biloba leaves, holds an anti-inflammatory potency. Our results suggested that EGb761 exerts the anti-inflammatory effects on human articular chondrocytes and OA rats.

128. *Effects of Ginkgo biloba extract on inflammatory mediators (SOD, MDA, TNF-alpha, NF-kappaBp65, IL-6) in TNBS-induced colitis in rats*. Zhou YH, **Mediators Inflamm**. 2006; We concluded that the probable mechanisms of EGB ameliorated inflammatory injury in TNBS-induced colitis in rats by its modulation of inflammatory mediators and antioxidation.

129. *The effects of Ginkgo biloba extract on lipopolysaccharide-induced inflammation in vitro and in vivo*. Ilieva I, **Exp Eye Res.** 2004 Aug; The anti-inflammatory effect of 1 mg GBE was as strong as that of same dose prednisolone.

C. Silymarin (from Milk Thistle Extract):

130. *Silymarin: a novel antioxidant with antiglycation and antiinflammatory properties in vitro and in vivo*. Wu CH, et.al. **Antioxid Redox Signal**. 2011 Feb: Levels of oxidative and inflammatory biomarkers were also significantly decreased in SM-treated groups compared with the diabetic group.

131.. *Dietary supplementation of silymarin protects against chemically induced nephrotoxicity, inflammation and renal tumor promotion response*. Kaur G, Athar M, Alam MS. **Invest New Drugs**. 2010 Oct: Silymarin diet conferred a significant protection against Fe-NTA induced oxidative stress and inflammation…and decreased the expression of proinflammatory mediators.

D. Resveratrol:

132. ***Anti-inflammatory responses of resveratrol*****.** Das S, Das DK, **Inflamm Allergy Drug Targets**. 2007 Sep: Resveratrol exhibits potent anti-inflammatory activity.

133. ***Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation*****.** Zhang F, Liu J, Shi JS, **Eur J Pharmacol.** 2010 Jun 25; This minireview summarized the anti-inflammatory activities of resveratrol in the brain from both in vivo and in vitro studies.

134. ***Anti-inflammatory compound resveratrol suppresses homocysteine formation in stimulated human peripheral blood mononuclear cells in vitro*****.** Schroecksnadel K, et.al., Clin Chem Lab Med. 2005: Apart from its strong antioxidant properties, resveratrol has also been demonstrated to act as an anti-inflammatory agent.

135. ***Protective effects of resveratrol on calcium-induced oxidative stress in rat heart mitochondria*** Gutiérrez-Pérez A, **J Bioenerg Biomembr**. 2011 Mar 30. Trans-resveratrol is a nutraceutical with known antioxidant, anti-inflammatory, cardioprotective, and anti-apoptotic properties.

136. ***Resveratrol differentially modulates inflammatory responses of microglia and astrocytes*****.** Lu X, **J Neuroinflammation.** 2010 Aug 17: Resveratrol is a natural polyphenolic compound that has cardioprotective, anticancer and anti-inflammatory properties. These results further suggest that resveratrol exerts anti-inflammatory effects in microglia and astrocytes by inhibiting different proinflammatory cytokines and key signaling molecules.

E. Green Tea Extract [with EGCG]:

137. ***Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients*****.** Bogdanski P, **Nutr Res**. 2012 Jun;

138. ***Anti-inflammatory effects of dietary phenolic compounds in an in vitro model of inflamed human intestinal epithelium*****.** Sergent T,et.al. **Chem Biol Interact.** 2010 Dec 5; Phenolic compounds (PCs) are considered to possess anti-inflammatory. In conclusion, this study provides evidence that genistein and EGCG downregulate the inflammatory response in inflamed intestinal epithelial cells.

F. Pycnogenol (French Maritime Pine Bark Extract):

139. ***Pycnogenol: a blend of procyanidins with multifaceted therapeutic applications*** D'Andrea G, **Fitoterapia**. 2010: Between 65% and 75% of Pycnogenol are procyanidins. Pycnogenol is now utilized throughout the world as a nutritional supplement and as a phytochemical remedy for chronic inflammation.

140. ***Treatment options in myocarditis: what we know from experimental data and how it translates to clinical trials*****.** Matsumori A, **Herz.** 2007 Sep: Pycnogenol suppresses the expression of pro-inflammatory cytokines…and improves inflammation.

141. ***Therapeutic efficacy of pycnogenol in experimental inflammatory bowel diseases*****.** Mochizuki M, Hasegawa N., **Phytother Res**. 2004 Dec; These results suggested that pycnogenol ameliorates TNBS-induced inflammation by radical scavenging activity.

142. ***A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology*****.** Rohdewald P, **Int J Clin Pharmacol Ther.** 2002 Apr: Anti-inflammatory activity has been demonstrated in vitro and in vivo in animals.

143. ***The Antioxidant and Antigenotoxic Effects of Pycnogenol on Rats Treated With Cisplatin*****.** Aydin B,et.al, **Biol Trace Elem Res**. 2010 Jul 30: Pycnogenol is known for its strong antioxidant and anti-inflammatory effects.

G. L-Arginine:

144. ***L-arginine as a nutritional prophylaxis against vascular endothelial dysfunction with aging*****.** Heffernan KS, et.al, **J Cardiovasc Pharmacol Ther**. 2010 Mar; The ability of L-arginine to modulate the vascular inflammatory and systemic hormonal milieu, which in turn may have a positive effect on vascular endothelial function.

H. N Acetyl L-Cysteine:

145. ***The effects of N-acetylcysteine and ozone therapy on oxidative stress and inflammation in acetaminophen-induced nephrotoxicity model*****.** Ucar F, et.al., **Ren Fail.** 2013; RESULTS: NAC significantly decreased MDA and TNF-α levels. Our results showed that NAC reduced inflammation.

146. ***N-acetylcysteine administration is associated with reduced activation of NF-kB and preserves lung dendritic cells function in a zymosan-induced generalized inflammation model*****.** Wang HW, et.al. **J Clin Immunol.** 2013 Apr; **RESULTS:** NAC treatment resulted in: significant improvements.

I. Hydroxytyrosol:

147. ***Hydroxytyrosol is the major anti-inflammatory compound in aqueous olive extracts and impairs cytokine and chemokine production in macrophages*****.** Richard N, et.al. **Planta Med.** 2011 Nov; HT…reflecting strong anti-inflammatory activity.

148. ***Hydroxytyrosol inhibits pro-inflammatory cytokines, iNOS, and COX-2 expression in human monocytic cells*****.** Zhang X, Cao J, Zhong L, **Naunyn Schmiedebergs Arch Pharmacol**. 2009 Jun; In this study, our aim was to examine the anti-inflammatory mechanism of HT.

149. ***Mediterranean diet polyphenols reduce inflammatory angiogenesis in human vascular endothelial cells: a potentially protective mechanism in atherosclerotic vascular disease and cancer*****,** Scoditti E, et.al., **Arch Biochem Biophys.** Our findings reveal that olive oil and red wine polyphenols reduce inflammatory angiogenesis in cultured endothelial cells.

J. Astaxanthin:

150. ***Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease*****.** Pashkow FJ, et.al**., Am J Cardiol.** 2008 May 22; Results from multiple species support the antioxidant/anti-inflammatory properties of the prototype compound, astaxanthin.

151. ***Astaxanthin, cell membrane nutrient with diverse clinical benefits and anti-aging potential*****.** Kidd P., **Altern Med Rev**. 2011 Dec; Astaxanthin, a xanthophyll carotenoid, blocked oxidative DNA damage, lowered C-reactive protein (CRP) and other inflammation biomarkers.. The concentrations used in these cells would be attainable in humans by modest dietary intakes.

K. Bacopa Monnieri:

152. ***Amelioration of age associated neuroinflammation on long term bacosides treatment*****.** Rastogi M, et.al. **Neurochem Res**. 2012 Apr; Bacopa monnieri (L.) is a revered medicinal plant of traditional Indian system of medicine. The results of the present study demonstrated the significant attenuation of age dependant elevation of pro inflammatory cytokines.

153*. A randomized controlled trial investigating the effect of Pycnogenol and Bacopa herbal medicines on cognitive, cardiovascular, and biochemical functioning in cognitively healthy elderly people*: Stough CK, et.al. **Nutr J.** 2012 Mar 6: Bacopa Monniera has been used in traditional Ayurvedic medicine for various indications including inflammation…*Bacopa* appears to have multiple modes of action. These include: anti-oxidant (flavonoid) activity; and anti-inflammatory effects.

L. Vitamin D3:

154. *Higher serum vitamin D concentrations are associated with longer leukocyte telomere length [LTL] in women*. Richards JB, et.al. **Am J Clin Nutr.** 2007 Nov; Vitamin D is a potent inhibitor of the proinflammatory response and thereby diminishes turnover of leukocytes. CONCLUSION: Our findings suggest that higher vitamin D concentrations, which are easily modifiable through nutritional supplementation, are associated with longer LTL. Given that vitamin D displays antiinflammatory properties, we hypothesized that it may attenuate the rate of LTL attrition.

***155. Vitamin D: its role and uses in immunology*. H. F. DELUCA and M. T. CANTORNA, *The FASEB Journal*.** 2001; The vitamin D hormone stimulates transforming growth factor TGFß-1 and interleukin 4 (IL-4) production, which in turn may suppress inflammatory T cell activity.

156. *Diet, nutrition and telomere length* Paul L 2.5. Vitamin D also reduces the expression of inflammation mediators interleukin- 2 and interferon gamma. These anti-inflammatory and antiproliferative properties of vitamins D limit the turnover of cells, thus potentially reducing their telomere length attrition.

157. *1,25-dihydroxyvitamin D3 protects against macrophage-induced activation of NFκB and MAPK signalling and chemokine release in human adipocytes*. Ding C, Wilding JP, Bing C. **PLoS One.** 2013 Apr 24. In conclusion, vitamin D3 could be anti-inflammatory in adipose tissue, decreasing macrophage-induced release of chemokines and cytokines.

158. Regulatory effects of 1,25-dihydroxyvitamin D3 on vascular smooth muscle cells. Tukaj S, et.al. **Acta Biochim Pol.** 2012: Many reports indicate that the biologically active vitamin D metabolite - 1,25-dihydroxyvitamin D(3) plays an essential role in the regulation of the inflammation process. The results of our study suggest that 1,25(OH)(2)D(3) may serve as a natural anti-inflammatory agent.

M. Vitamin B6:

159. *Oxidative damage and inflammation in obese diabetic Emirati subjects supplemented with antioxidants and B-vitamins: a randomized placebo-controlled trial.* Gariballa S, et.al. **Nutr Metab (Lond).** 2013 Feb 4; CONCLUSIONS: Antioxidants supplementation with B-group vitamins enhances antioxidant capacity, and may have an anti-inflammatory effect in obese diabetic patients.

160. *Plasma pyridoxal-5-phosphate is inversely associated with systemic markers of inflammation in a population of U.S. adults*. Sakakeeny L, et.al. **J Nutr.** 2012 Jul**;** Low vitamin B-6 status, based on plasma concentrations of pyridoxal-5-phosphate (PLP), has been identified in inflammatory diseases. This study further supports our hypothesis that inflammation is associated with a functional deficiency of vitamin B-6. We discuss 2 possible roles for PLP in the inflammatory process.

161. *Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study*. Shen J, et.al. **Am J Clin Nutr.** 2010 Feb; **CONCLUSIONS:** Low vitamin B-6 concentrations are associated with inflammation, higher oxidative stress, and metabolic conditions in older Puerto Rican adults. Our data suggest that vitamin B-6 may influence cardiovascular disease risk through mechanisms other than [just] homocysteine.

V. Compounds in TELO-100 which are Documented to Help Inhibit TNF-alpha:

A. ***Panax ginseng*** **and its Ginsenosides**
B. ***Ginkgo biloba*** **Extract**
C. **Silymarin (Milk Thistle Extract)**
D. **Resveratrol**
E. **Green Tea Extract [with EGCG]**
F. ***Pycnogenol*** **(French Maritime Pine Bark Extract)**
G. **N-Acetyl L-Cysteine**
H. **Bacopa Monnieri**
I. **Hydroxytyrosol**
J. **Vitamin D3**
K. **Vitamin B6**
L. **Vitamin B12**

A. *Panax ginseng* and its Ginsenosides:

162. ***In vitro inhibitory effect of protopanaxadiol ginsenosides on tumor necrosis factor (TNF)-alpha production and its modulation by known TNF-alpha antagonists*****.*** Cho JY, et.al. Planta Med. 2001 Apr; **Abstract:** Ginsenosides are the major principles of Panax ginseng. In this report, Rb1, and Rb2 strongly suppressed TNF-alpha production in RAW264.7 cells.

163. ***Ginsenoside Rh1 suppresses inducible nitric oxide synthase gene expression in IFN-gamma-stimulated microglia via modulation of JAK/STAT and ERK signaling pathways*****.**Jung JS, Kim DH, Kim HS. **Biochem Biophys Res Commun.** 2010 Jun 25**;** In the present study, we found that ginsenoside Rh1 suppresses NO, ROS, and TNF-alpha production in IFN-gamma-stimulated BV2 microglial cells. Rh1 inhibited the mRNA and protein expression of iNOS and TNF-alpha.

B. *Ginkgo biloba* Extract:

164. ***Effects of Ginkgo biloba extract (EGb 761) and quercetin on lipopolysaccharide-induced signaling pathways involved in the release of tumor necrosis factor-alpha*****.*** Wadsworth TL, McDonald TL, Koop DR., **Biochem Pharmacol.** 2001 Oct 1; Pretreatment with Ginkgo biloba extract (EGb 761) inhibited the in vivo production of TNF-alpha.

C. Silymarin [from Milk Thistle Extract]

165. ***Effect of silymarin administration on TNF-α serum concentration in peritoneal dialysis patients*** Nazemian F,et.al. **Phytother Res.** 2010 Nov;,Silymarin suppresses the induction of TNF-α and it was hypothesized that silymarin could decrease the serum concentration of TNF-α in peritoneal dialysis patients.

166. ***Inhibitory effect of silibinin on tumour necrosis factor-alpha and hydrogen peroxide production by human monocytes*****.** Bannwart CF, et.al., **Nat Prod Res.** 2010 Nov : Silibinin is a chemically defined flavonoid and the main active component of silymarin, a polyphenolic complex from Silybum marianum. Significant inhibition of TNF-α production: These results suggest that silibinin exerts antioxidant and anti-inflammatory properties on human monocytes through an inhibitory effect on TNF-α production.

167. ***Effects of plant-derived polyphenols on TNF-alpha and nitric oxide production induced by advanced glycation endproducts*****.** Chandler D, **Mol Nutr Food Res**. 2010 Jul; TNF-alpha expression was only reduced by apigenin, diosmetin and silymarin;

D. Resveratrol:

168. ***Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation*** Bereswill S, et.al. **PLoS One.** 2010 Dec 3 BACKGROUND: The health beneficial effects of Resveratrol, Curcumin and Simvastatin have been demonstrated in various experimental models of inflammation. FINDINGS: pro-inflammatory cytokine expression (IL-23p19, IFN-γ, TNF-α, IL-6, MCP-1) was found to be significantly lower in the ileum of treated animals.

169. ***Dietary supplementation of resveratrol attenuates chronic colonic inflammation in mice.*** Sánchez-Fidalgo S, et.al., **Eur J Pharmacol.** 2010 May 10: Resveratrol: the polyphenol caused substantial reductions of the rise of pro-inflammatory cytokines, TNF-alpha.

E. Green Tea Extract [with EGCG]:

170. ***Green tea catechins improve human forearm vascular function and have potent anti-inflammatory and anti-apoptotic effects in smokers.*** Oyama J, et.al. **Intern Med.** 2010; The plasma concentration of 8-OHdG, IL-6, TNF-alpha, and soluble Fas decreased significantly for two weeks in the high dose group.

F. Pycnogenol

171. ***French maritime pine bark extract inhibits viral replication and prevents development of viral myocarditis.*** Matsumori A, Higuchi H, Shimada M, **J Card Fail.** 2007**:** French maritime pine bark extract (Pycnogenol) revealed diverse anti-inflammatory actions by an inhibition of NF-kappaB-dependent gene expression. Gene expression of tumor necrosis factor were significantly suppressed in the hearts of mice treated with Pycnogenol.

172. ***Pycnogenol inhibits tumor necrosis factor-alpha-induced nuclear factor kappa B activation and adhesion molecule expression in human vascular endothelial cells*****.** Peng Q, Wei Z, Lau BH, **Cell Mol Life Sci.** 2000 May: Pretreatment with pycnogenol exhibited a concentration-dependent suppression of TNF-alpha-induced activation of NF-kappa B.

G. N Acetyl L-Cysteine:

173. ***N-acetylcysteine treatment normalizes serum tumor necrosis factor-alpha level and hinders the progression of cardiac injury in hypertensive rats*****.** Bourraindeloup M, et.al. **Circulation**. 2004 Oct 5; NAC treatment, which replenished cardiac glutathione, normalized serum TNF-alpha level. These findings suggest that TNF-alpha antagonism may be achieved by glutathione supplementation**.**

174. ***N-acetylcysteine inhibits TNF-alpha, sTNFR, and TGF-beta1 release by alveolar macrophages in idiopathic pulmonary fibrosis in vitro*****.** Cu A, et.al. **Sarcoidosis Vasc Diffuse Lung Dis**. 2009 Jul: NAC suppressed the production of TNF-alpha.

175. ***Tumor necrosis factor alpha and glutathione interplay in chronic heart failure.*** Adamy C,et.al., **Arch Mal Coeur Vaiss.** 2005 Sep; Oral administration of the glutathione precursor, N-acetylcysteine (NAC), was shown to hinder pathways of TNF alpha harmful signaling.

H. Bacopa Monnieri:

176. ***A comparison of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi [Bacopa monnieri]*****,** Yamada K, et.al., **J Ethnopharmacol.** 2011 Sep 1; Here, we investigated the potential for two herbs commonly found in India, Ashwagandha and Brahmi (Bacopa monnieri): TNF-α production in rats receiving dietary herbal supplements was significantly lower compared to the control animals.

I. Hydroxytyrosol:

177. ***Effect of olive oil phenols on the production of inflammatory mediators in freshly isolated human monocytes.*** Rosignoli P, et.al. **J Nutr Biochem.** 2013 Aug; In this study, the ability of olive oil phenols to influence the release of superoxide anions (O2-) and tumor necrosis factor α (TNFα): these results suggest that the health effects of olive oil phenols may be related to their ability to modulate the production of pro-inflammatory molecules.

178. ***Effects of antioxidant polyphenols on TNF-alpha-related diseases*****.** Kawaguchi K,et.al. **Curr Top Med Chem**. 2011: A proinflammatory cytokine, tumor necrosis factor α (TNF-α), plays a pivotal role in the pathogenesis of chronic and auto-immune diseases. The present review shows that the intake of polyphenols contained in natural sources, such as hydroxytyrosol, are able to modulate chronic inflammatory diseases.

J. Vitamin D3:

179. ***Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women.*** Peterson CA, Heffernan ME**, Inflamm (Lond).** 2008 Jul 24: Linear regression models revealed a significant inverse relationship between serum 25(OH)D and TNF-alpha concentrations. CONCLUSION: Serum 25(OH)D status is inversely related to TNF-alpha concentrations in healthy women.

K. Vitamin B6:

180. ***Vitamin B(6) supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis.*** Huang SC,et.al. **Eur J Clin Nutr**. 2010 Sep; RESULTS: In the group receiving vitamin B(6), plasma IL-6 and TNF-alpha levels significantly decreased at week 12. CONCLUSIONS: A large dose of vitamin B(6) supplementation (100 mg/day) suppressed pro-inflammatory cytokines (that is, IL-6 and TNF-alpha) in patients with RA.

181. ***Abnormal vitamin B6 status in rheumatoid cachexia. Association with spontaneous tumor necrosis factor alpha production and markers of inflammation*****.** Roubenoff R, et.al. Arthritis Rheum. 1995 Jan; OBJECTIVE: To compare vitamin B6 levels in rheumatoid arthritis (RA) patients and healthy control subjects. Plasma levels of pyridoxal-5'-phosphate (PLP) were lower in the RA patient group. In multivariate analyses, PLP was inversely associated with tumor necrosis factor alpha (TNF alpha) production by peripheral blood mononuclear cells.

L. Vitamin B12:

182. ***High tumor necrosis factor-alpha levels in cerebrospinal fluid of cobalamin-deficient patients*****.** Scalabrino G, et.al. **Ann Neurol.** 2004 Dec: In human CSF, as in human serum and the rat central nervous system, decreased Cbl concentrations are concomitant with an increase in TNF-alpha.

183. ***Vitamin B12 deficiency, tumor necrosis factor-alpha, and epidermal growth factor: a novel function for vitamin B12*****?** Miller JW.**, Nutr Rev.** 2002 May: Vitamin B12 deficiency was recently shown to be associated with elevated levels of tumor necrosis factor-alpha.

184. ***Human cobalamin deficiency: alterations in serum tumour necrosis factor-alpha and epidermal growth factor*****.** Peracchi M, et.al. **Eur J Haematol**. 2001 Aug; CONCLUSIONS: In humans, as in rats, cobalamin concentration appears to be correlated with the synthesis and release of TNF-alpha, because cobalamin deficiency is accompanied by overproduction of TNF-alpha.

VI. Compounds in TELO-100 which are Documented to Help Reduce Homocysteine Levels:

A. **Vitamin B12**
B. **Vitamin B6**
C. **Folate**
D. **N-Acetyl L-Cysteine**
E. **Resveratrol**

A. Vitamin B12:

185. ***A Natural Product Telomerase Activator as Part of a Health Maintenance Program: Metabolic & Cardiovascular Response*****, Harley C, Raffaele J, et.al., Rejuvenation Research, June 29, 2013:** It is likely that folate and vitamins B12 and B6 in the supplement packs played a significant role in the decline in homocysteine.

186. ***Multivitamin use and telomere length in women*****, Xu Q, Cawthon RM, et. al.: Am J Clin Nutr. 2009 Jun;** Vitamin B-12 supplement users (*n* = 52) had a longer telomere length than did nonusers (5.9% difference; *P* = 0.03)... [This difference (345 bp) corresponds to ≈12.3 y of age-related telomere loss since each year of age was associated with a 28-bp shorter telomere in the study sample.]

187. ***Diet, nutrition and telomere length*****,** Paul L**. J Nutr Biochem.** 2011 Mar 21: 2.2. **Vitamin B12**: Methylation of homocysteine to form methionine, the precursor of SAM, is catalyzed in a vitamin-B12-dependent reaction. Women who use vitamin B12 supplements have longer telomeres than nonusers .

188. ***B Vitamins and Antioxidants Intake is Negatively Correlated with Risk of Stroke in Iran*****.** Hariri M, et.al. **Int J Prev Med.** 2013 May; Folic acid, vitamin B6, and vitamin B12 are all cofactors in homocysteine metabolism.

189. ***Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment*****.** Douaud G, et.al**. Proc Natl Acad Sci U S A.** 2013 Jun 4: One approach is to modify nongenetic risk factors, for instance **by lowering elevated plasma homocysteine using B vitamins.**

190. ***Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration.*** Gopinath B, et.al. **Am J Clin Nutr.** 2013 Jul; OBJECTIVE: In this cohort study, we aimed to investigate associations between intakes and serum concentrations of folate and vitamin B-12 on serum tHcy.

191. ***One year B and D vitamins supplementation improves metabolic bone markers.*** Herrmann W, et.al. **Clin Chem Lab Med.** 2013 Mar 1; Median total homocysteine (tHcy) was high at baseline (group A: 12.6, group B: 12.3 µmol/L) and decreased by B vitamins (group A) to 8.9 µmol/L (29.4%).

B. Vitamin B6:

192. ***Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment*****.** Douaud G, et.al**. Proc Natl Acad Sci U S A.** 2013 Jun 4: One approach is to modify nongenetic risk factors, for instance by lowering elevated plasma homocysteine using B vitamins.

193. ***One year B and D vitamins supplementation improves metabolic bone markers.*** Herrmann W, et.al. **Clin Chem Lab Med.** 2013 Mar 1; Median total homocysteine (tHcy) was high at baseline (group A: 12.6, group B: 12.3 µmol/L) and decreased by B vitamins (group A) to 8.9 µmol/L (29.4%).

194. ***Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial*****.** de Jager CA, et.al. **Int J Geriatr Psychiatry. 2012 Jun**; The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo.

C. Folate:

195. ***Telomere length in peripheral blood mononuclear cells is associated with folate status in men*****.** Paul L, et.al.,**J Nutr.** 2009 Jul; Telomere length is epigenetically regulated by DNA methylation, which in turn could be modulated by folate status. When plasma folate concentration was above the median, there was a positive relationship between folate and telomere length. We propose that folate status influences telomere length by affecting DNA integrity and the epigenetic regulation of telomere length through DNA methylation.

196. ***Diet, nutrition and telomere lengt*****h** Paul L**, J Nutr Biochem.** 2011 Mar 21. **2.1. Folate:** Association between plasma concentration of the B vitamin folate and telomere length has been reported in men and women. Impairment of remethylation of Hcy to methionine due to inadequate levels of folate will result in elevated Hcy concentrations. Thus, plasma total Hcy (tHcy) functions as a marker of folate status. Increase in plasma tHcy is linked to decrease in telomere length.

197. ***Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration.*** Gopinath B, et.al. **Am J Clin Nutr.** 2013 Jul; **OBJECTIVE:** In this cohort study, we aimed to investigate associations between intakes and serum concentrations of folate and vitamin B-12 or serum tHcy and 10-y AMD incidence**.**

198. ***Nutrition throughout life: folate*****.** McNulty H, **Int J Vitam Nutr Res.** 2012 Oct; Folate is required for one-carbon metabolism, including the remethylation of homocysteine to methionine; thus elevated plasma homocysteine reflects functional folate deficiency.

D. N-Acetyl L-Cysteine:

199. ***Lowering homocysteine levels may prevent cardiovascular impairments? Possible therapeutic behaviors*****.** Cacciapuoti F.**, Blood Coagul Fibrinolysis.** 2012 Dec; Some nutraceuticals, such as N-acetyl cysteine, reduce both Hcy serum concentration and cardiovascular risk.

200. ***Therapy of hyperhomocysteinemia in hemodialysis patients: effects of folates and N-acetylcysteine*****.** Perna AF, **J Ren Nutr.** 2012 Sep; NAC therapy induces a significant additional decrease in homocysteine removal during dialysis.

E. Resveratrol:

201. ***Effects of resveratrol on blood homocysteine level, on homocysteine induced oxidative stress, apoptosis and cognitive dysfunctions in rats*****.** Koz ST, **Brain Res.** 2012 Nov 12; Resveratrol significantly decreased serum levels of homocysteine.

202. ***Anti-inflammatory compound resveratrol suppresses homocysteine formation in stimulated human peripheral blood mononuclear cells in vitro*****.** Schroecksnadel K, et.al.**Clin Chem Lab Med.** 2005; In this study resveratrol suppressed homocysteine formation in a dose-dependent manner. The data suggest that resveratrol may prevent homocysteine accumulation in the blood by suppressing immune activation cascades.

VII. Compounds in TELO-100 which are Documented to Help Reduce Cortisol Levels:

A. ***Ginkgo biloba* Extract**
B. **Green Tea Extract [with EGCG]**
C. **Vitamin D3**
D. **Vitamin B6**

A. *Ginkgo biloba* Extract:

203. ***Reduction of rise in blood pressure and cortisol release during stress by Ginkgo biloba extract (EGb 761) in healthy volunteers*****.** Jezova D, **J Physiol Pharmacol.** 2002 Sep; The standardized extract of Ginkgo biloba (EGb 761): This study provides evidence that EGb 761 has an inhibitory action on blood pressure and it may influence cortisol release in response to some stress stimuli.

B. Green Tea Extract [with EGCG]:

204. ***Effect of green tea polyphenols on behavioral performances in psychological stress in rats*****.** Chen W, et al. **Wei Sheng Yan Jiu.** 2007 Sep; Serum cortisol levels in SMG and SHG [both green tea product groups] were decreased than that of SCT [control group].

205. ***Effects of epigallocatechin-3-gallate on behavioral impairments induced by psychological stress in rats*****.** Chen WQ, et.al., **Exp Biol Med.** 2010 May; This study was conducted to explore the effects of epigallocatechin-3-gallate **(**EGCG) on cognitive performances in psychological stress rats. Stress control group had increased contents of cortisol.

C. Vitamin D3:

206. ***1,25-dihydroxyvitamin D3 modulation of adipocyte glucocorticoid function*****.** Morris KL, et.al. **Obes Res.** 2005 Apr; We conclude that 1,25-dihydroxyvitamin D3 directly regulates adipocyte 11beta-HSD 1 expression and, consequently, local cortisol levels.

D. Vitamin B6:

207. ***Modulation of gene expression by vitamin B6*****.** Oka T. **Nutr Res Rev.** 2001 Dec; The physiologically active form of vitamin B6, pyridoxal 5'-phosphate (PLP): Recent studies have shown that, apart from its role as a coenzyme, PLP acts as a modulator of steroid hormone receptor-mediated gene expression. Specifically, elevation of intracellular PLP leads to a decreased transcriptional response to glucocorticoid hormones.

208. ***Nutritional and botanical interventions to assist with the adaptation to stress*****.** Kelly GS. **Altern Med Rev.** 1999 Aug; The systemic effects of stress include increased levels of stress hormones such as cortisol. Based on human and animal research, it appears a variety of nutritional substances - such as vitamin B6, may allow individuals to sustain an adaptive response and minimize some of the systemic effects of stress.