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Telomerase activator made from plant extract: Any side effect?

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ABSTRACT

Telomerase is an enzyme that, during deoxyribonucleic acid (DNA) replication in eukaryotes, allows the length of the chromosome to be preserved by adding a specific structure at each end: the telomere. Although composed of deoxyribonucleotides such as the rest of the chromosome, the telomere is synthesized in a manner different from conventional DNA replication. Telomerases are ribonucleoproteins that catalyze the addition of a specific repeat sequence to the end of the chromosomes. The life expectancy of cells is directly dependent on the length of telomere, hence the existence of many products on the market whose function is to slow down the telomere shortening during cell division. A telomerase activator was used to study telomere length in this research. The telomerase activator used is a recent natural product in the market named TeloBooster®. This natural product is patent protected. A group of humans underwent a 4-years daily intake of TeloBooster®. At the end of the experiment, all subjects got an important increase in telomere length. It was confirmed that there was no alteration of human metabolism; after screening thirty biochemical and histological variables of all the subjects.

INTRODUCTION

Recent tests, particularly on mice, showed the efficiency of certain plants whilst determining that these plants had no carcinogenic effect (Yang, 2010). Similar work was also carried out in mouse and showed that no teratogenic incidence was generated (Bruno et al., 2011, 2012).

Uptil now, no studies have been conducted on a group of humans in order to highlight the appearance - if any- of side effects that could alter chemical and biological parameters in the blood. In order to study the modifications that a telomerase activator could have on the parameters of human physiology, a telomerase activator recently placed on the market and patented under the label of TeloBooster® (BOPI, 2015) was used in this research. This new product is made from natural plant extracts which existence is known from the highest antiquity (Smith and Stuart, 1973). The hypothesis put forward lies on an evidence that such practice coming from the old ages might have been abandoned if any bad side effects had been pointed out by consumers. But such assertion must be checked with the present scientific means in order to clear out any slight suspicion about the use of such a telomerase activator. The first step was to check the effectiveness of TeloBooster® on a group of humans in order to be certain that the second step could be undergone on a group with a relevant gain on telomere length. The TeloBooster® is labelled as a food supplement according to European regulation and the product complies with European Health Regulation (Official Journal of European Union, 2002). All compounds blended in the TeloBooster® are listed in its patent (BOPI, 2015) and they comply with European Policy on Food Supplements (JORF n°0073, 2011).

In this case, there is no need to either conducting again a special clinical trial to carry out proof of safety of the product (JORF n°0163, 2014) or asking for any allowance from authorities of drug administration to supply a human

group with the natural compounds blended in the TeloBooster®.

For deontology reasons, each member of the group signed a consent form to accept a daily intake of TeloBooster® and to undergo a blood test to quantify the length of their telomeres every year. All members of the group underwent a medical checking before entering in the global process and all of them were admitted to run the full program.

The purpose of the second step was to check thirty biological parameters in order to investigate any side effect after four years (2013-2016) of daily intake of TeloBooster®.

MATERIALS AND METHODS 1

First step: Impact of TeloBooster® on telomere length

The telomere length is measured by the High Throughput Quantitative Fluorescence *In Situ* Hybridization (HT-Q-FISH) technology (Canela et al., 2007), on interphase nuclei either on sections of tissue (Telomapping), blood cells or any cell type that can attach to a microscopic slide or Petri dish. Each telomere is hybridized with a fluorescent telomeric probe. Each probe recognizes a fixed number of telomeric sequences (base pairs).

For this reason, the intensity of the fluorescent signal of the telomeric probes is directly proportional to telomere length. Consequently, the values of fluorescence are transformed into telomere length values as well as the percentage of short telomeres in a population of cells (Hemann et al., 2001).

The HT-QFISH is a very well known technology (Poon and Lansdorp, 2001). Probes are PNA ones. These probes are not charged with phosphate groups so that binding between PNA and DNA is stronger than that of DNA/DNA or DNA/RNA duplexes (Slijepcevic, 2001). All analyses were performed by Life Length Laboratory in Barcelona (Spain).

Life length is one of the most famous companies in the world that can provide individuals with a scientifically rigorous estimate of its biological age based on the percentage of critically short telomeres measured in the blood as a substitute for the entire organism. The average variability of the samples reproduced has a coefficient of variation (CV) of about 5%. A human chromosome may contain 150 million nucleic acid pairs or "base pairs," (Chromosome size and number of genes, 2012) while the initial length of a telomere may be between 10,000 and 15,000 base pairs (Sven, 2003) or less of 1/10,000 of the length mean of the chromosome. Shortest telomeres are more important in old people than younger's (Harley et al., 1990; Cawthon et al., 2003; Hayflick, 1965). In order to take into account the percentage of shortest telomeres, the 20th percentile of telomere length is computerized along with all data coming from the analysis. The percentage of these short telomeres out of the whole cell population investigated is the main result to calculate the biological age of human beings.

The first parameter that is taken into account is the Median Telomere Length (MTL) of the cell population for each subject. The second parameter to be taken into account lies into the 20th percentile of telomere length: as people age telomeres shorten more and more along the years so the 20th percentile is also a marker to quantify not only the efficiency of the telomerase activator but also the shortest telomere, not average telomere length, is critical for cell viability (Hemann et al., 2001).

RESULTS 1

Blood analysis was carried out (Figure 1) coming from the own telomeres of subject LABCO025. These data are from the blood sample that was analyzed using HT-QFISH technology. It is possible to capture and process images at a subcellular level. The image shows the nuclei of some cells from a blood sample of the subject LABCO025 (blue dots) and telomeres (red dots). Red dots of more intense color indicate longer telomeres and a smaller percentage of critically short telomeres.

From these Figures, the following data were extracted for each subject (Figures 2 and 3):

- Median telomere length (MTL, in kilobase pair kbp),
- The 20th percentile: that is the length of the upper limit at which 20% of the whole population of cells is contained.

But changes in the telomere length distribution spectrum are much more important than the simple measurement of MTL and the 20th percentile. A representation of the dispersion over the entire telomere length range shows that under TeloBooster®'s daily intake telomeres grow in size. As a result, there are fewer cells with short telomeres and more cells with long telomeres.

Finally, the telomere length distribution amplitude shifts to a significant increase in the cell population equipped with long telomeres (Figure 4). The cell population corresponding to the half a dose of TeloBooster® (Figure 4) is equipped with shorter telomeres than the population of cells corresponding to full daily intake of TeloBooster® (Figure 5)

MATERIALS AND METHODS 2

Second step: biological investigation through thirty parameters

The group undertook a blood sample analysis to know if

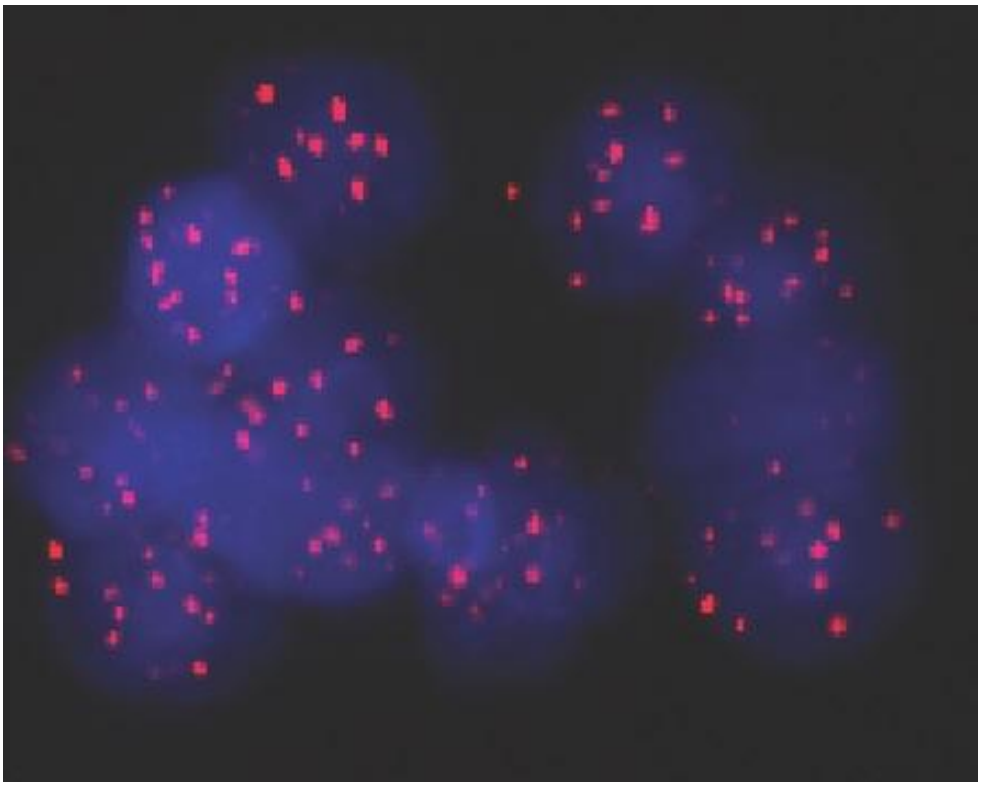

Figure 1. Fluorescent probes attached at the telomere of each cell are blinking on red color. Cells themselves are in pink color. The data are automatically processed in order to extract populations of cells according to the range of telomere length they are equipped with.

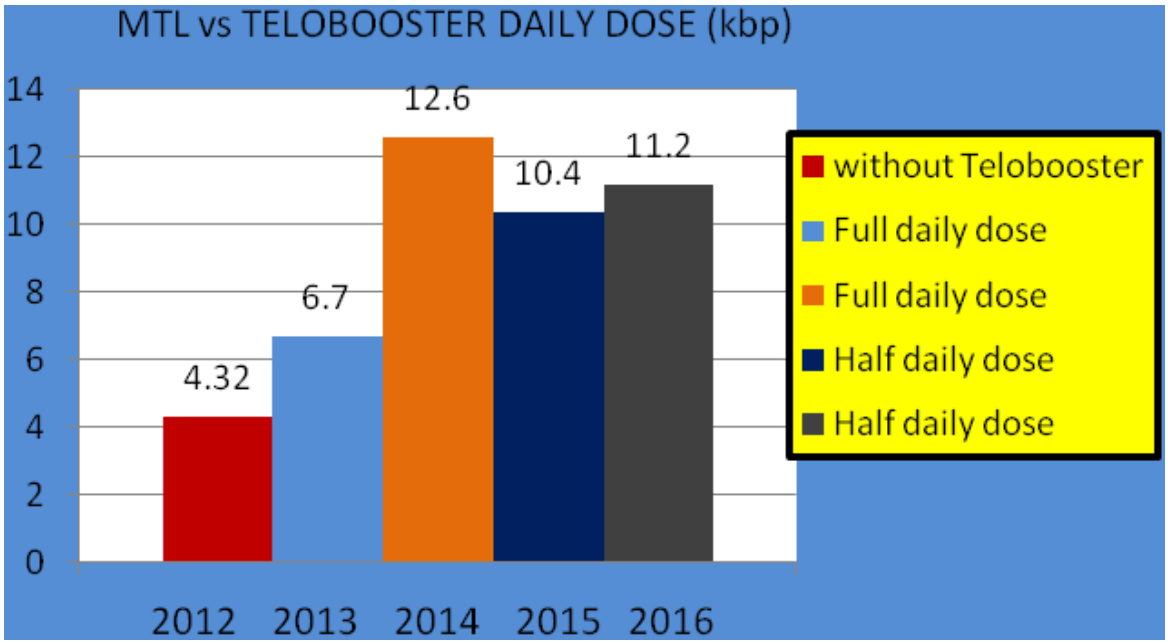

Figure 2. MTL over a 4-years daily intake of TeloBooster®. MTL is less important without any intake of TeloBooster®: the lesser the dose the lesser the MTL (subject Labco025).
X-axis: years (from 2012 to 2016): 2012 is the telomere length reference; Y-axis MTL in kilobase pair.

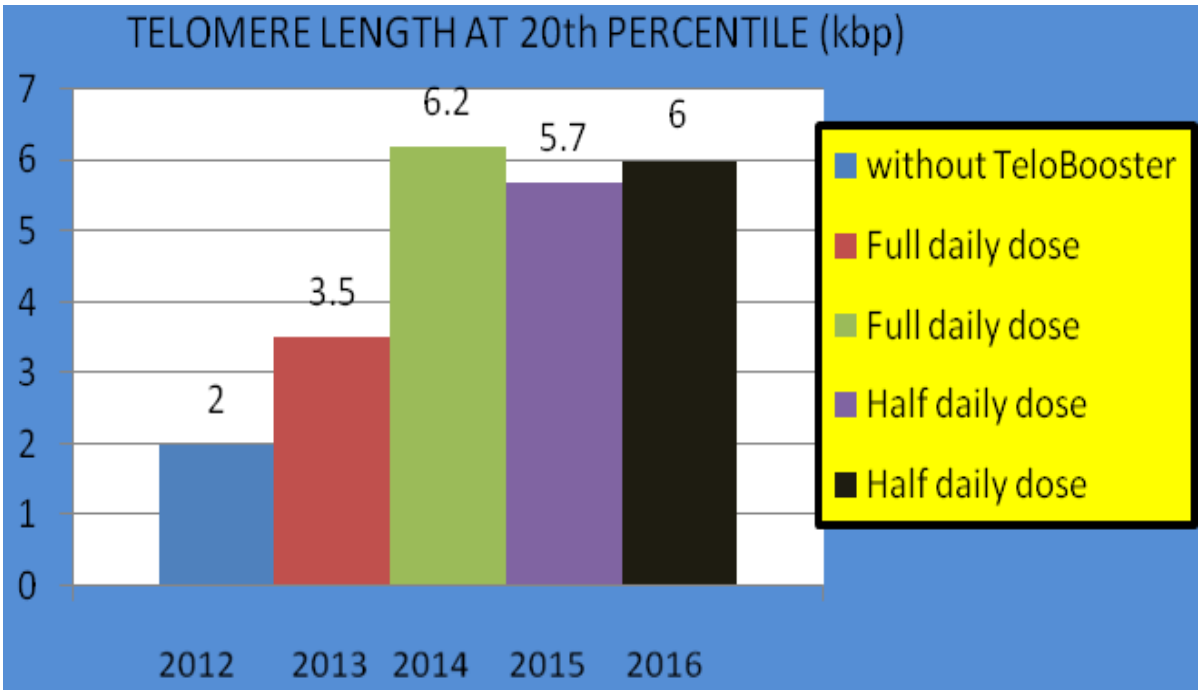

Figure 3. The bar chart displayed by the 20th percentile over a 4-years daily intake of TeloBooster® shows that short telomeres are less important (subject LABCO025).
X-axis, years (from 2012 to 2016): 2012 is the telomere length reference; Y-axis, upper limit for telomeres to reach 20% of the whole population of cells (in kilobase pair).

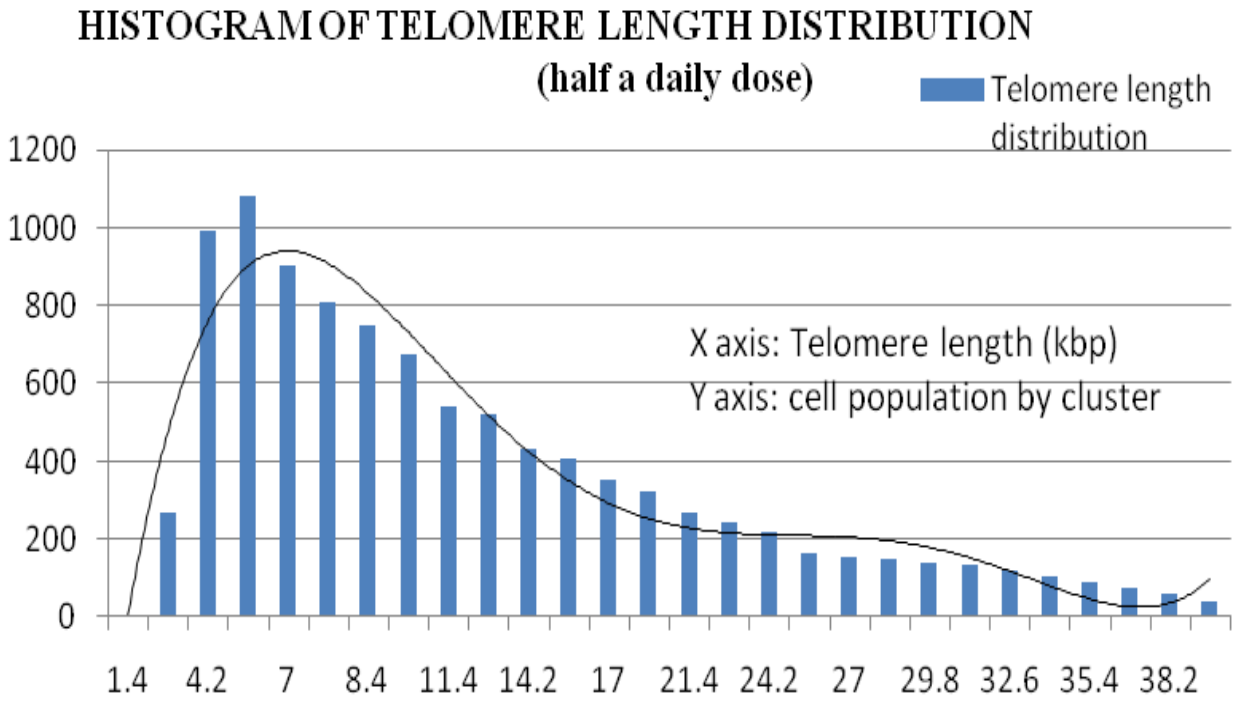

Figure 4. The spectrum of telomere length is ranging from 1.4 to 39.6 kbp since the subject LABCO025 took half a daily intake of TeloBooster®.
X-axis, telomere length (kilobase pair); Y-axis, population of cells corresponding to the group belonging to each range of telomere length (absolute values).

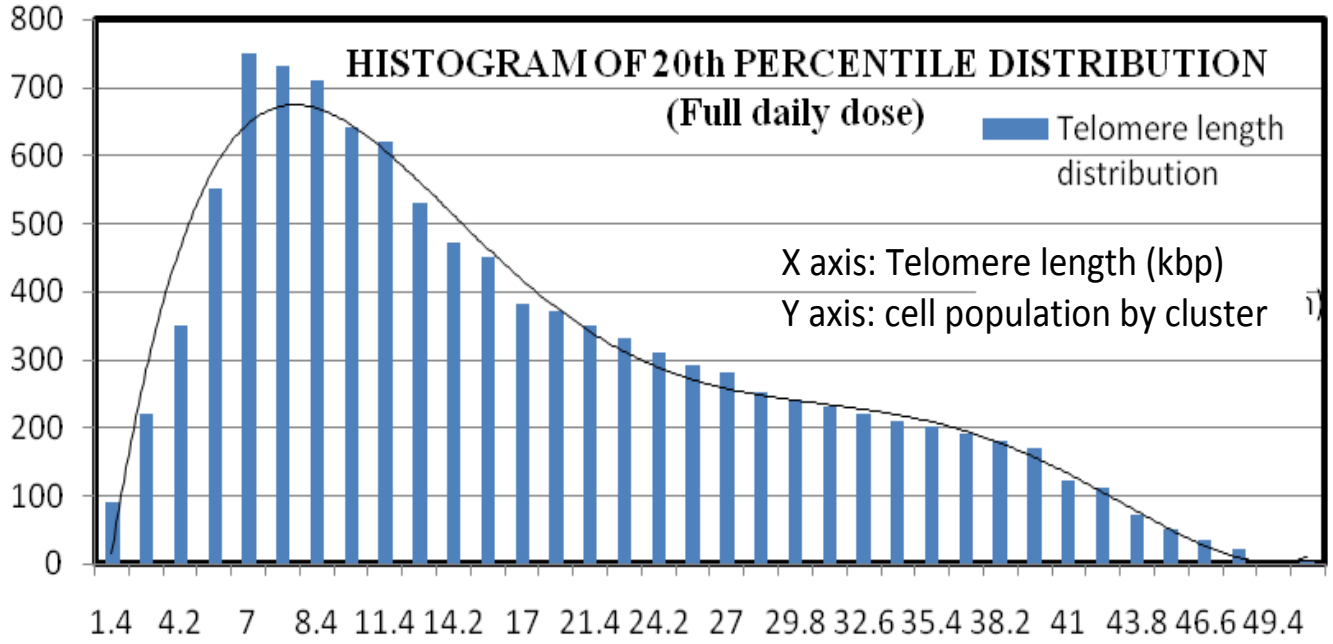

Figure 5. The spectrum of telomere length ranged from 1.4 to 49.4 kbp since the subject LABCO025 took a full daily intake of TeloBooster®.
X-axis, telomere length (kilobase pair); Y-axis, population of cells corresponding to the group belonging to each range of telomere length (absolute values).

any side effect was occurring after a 4-years treatment with TeloBooster®. All analyses were undertaken in France on behalf of these laboratories:

• Laboratoire d'Analyses Médicales, Mornant, France.
• Selarl Genis Bio, Brignais, France.

For each analysis there are two physiological results to comply with:

• One maximum value for each parameter which is the maximum acceptable parameter;
• One minimum value for each parameter which is the minimum acceptable parameter.

In order to make the bar chart easily understandable, all results have been normalized. All data coming from the group have been sorted regarding the maximum and the minimum value for each parameter. An average value is carried out and they are compared to the theorical highest and lowest acceptable values.

For lowest normalized values results to be acceptable, it must be higher than 5 (5 is the lowest threshold) and must be lesser than 1 (1 is the highest threshold) for highest normalized values. References range and critical values are those proposed by University of California, San Francisco (UCSF Departments of Pathology & Laboratory Medicine, 1998).

List of thirty biochemical and histological parameters

Each parameter is linked to the tag number in brackets displayed in results section on strip charts.

Hemogramme

• The cells that circulate in the bloodstream are generally divided into three types: white blood cells [leukocytes (1)], red blood cells [erythrocytes (2)] and platelets [thrombocytes (13)]. Abnormally high or low counts may indicate the presence of many forms of disease, and hence blood counts are amongst the most commonly performed blood tests in medicine, as they can provide an overview of a patient's general health status (Mayo Clinic, 2014).
• Neutrophil granulocytes (8): may indicate bacterial infection. May also be raised in acute viral infections (Zucker-Franklin et al., 1988). Because of the segmented appearance of the nucleus, neutrophils are sometimes referred to as "segs." The nucleus of less mature neutrophils is not segmented, but has a band or rod-like shape. Less mature neutrophils, those that have recently been released from the bone marrow into the bloodstream are known as "bands" or "stabs". Stab is a German term for rod (Witko-Sarsat et al., 2000).

- Lymphocytes (11): Higher with some viral infections such as glandular fever and also raised in chronic lymphocytic leukemia (Shanshal et al., 2012). Can be decreased (Alimonti et al., 2003) by HIV (Human immunodeficiency virus infection). In adults, lymphocytes are the second most common White Blood Cell (WBC) type after neutrophils (Mayo Clinic, 2014).
- Monocytes (12): may be raised in bacterial infection, tuberculosis, malaria, Rocky Mountain spotted fever, monocytic leukemia, chronic ulcerative colitis and regional enteritis (Ziegler-Heitbrock et al., 2010; Ziegler-Heitbrock, 2007).
- Eosinophil granulocytes (9): increased in parasitic infections, asthma, or allergic reaction (Hogan et al., 2008).
- Basophil granulocytes (10): may be increased in bone marrow related conditions such as leukemia or lymphoma (Grattan et al., 2003; Voehringer, 2009).
- Mean corpuscular volume (MCV) (5): the average volume of the red cells. Anemia is classified as microcytic or macrocytic if the MCV value is above or below the expected normal range; anemias are classified as normocytic if the MCV is within the expected range. Other conditions that can affect MCV include thalassemia, reticulocytosis, alcoholism, chemotherapy, Vitamin B12 deficiency, and/or Folic acid deficiency (Tønnesen et al., 1986).
- Hemoglobin (3): a low level of Hemoglobin is a sign of anemia (Janz et al., 2013).
- Hematocrit (4): or packed cell volume (PCV) this is the fraction of whole blood volume that consists of red blood cells (Purves et al., 2004).
- Mean corpuscular hemoglobin concentration (MCHC) (6): the average concentration of hemoglobin in the cells (William K.et al., 2004).
- Mean corpuscular hemoglobin (MCH) (7): the average amount of hemoglobin per red blood cell (Medlineplus Medical Encyclopedia, 2016).

Blood chemical analysis

- Blood urea nitrogen (BUN) (14): is an indication of renal (kidney) health. The main causes of an increase in BUN are: high protein diet, decrease in Glomerular Filtration Rate (GFR) (suggestive of renal failure) and in blood volume (hypovolemia), congestive heart failure, gastrointestinal hemorrhage, fever and increased catabolism. The main causes of a decrease in BUN are severe liver disease, anabolic state, and syndrome of inappropriate antidiuretic hormone (Mayo Clinic, 2014).
- Serum creatinine (15): is an important indicator of renal health because it is an easily measured byproduct of muscle metabolism that is excreted unchanged by the kidneys (Taylor, 1989). Creatinine itself is produced via a biological system involving creatine, phosphocreatine (also known as creatine phosphate), and adenosine triphosphate (ATP, the body's immediate energy supply).
- Uric acid (16): is a product of the metabolic breakdown of purine nucleotides. High blood concentrations of uric acid can lead to gout. The chemical is associated with other medical conditions including diabetes and the formation of ammonium acid urate kidney stones (Cirillo et al., 2006).
- Glycemia (17): means the presence, or the level, of glucose in one's blood (Capes et al., 2001).
- A triglyceride (TG, triacylglycerol, TAG, or triacylglyceride) (18): is an ester derived from glycerol and three fatty acids. As a blood lipid, it helps enable the bidirectional transference of adipose fat and blood glucose from the liver. There are many triglycerides: depending on the oil source, some are highly unsaturated, some less so (Lampe et al., 1983).
- Cholesterol H.D.L. (19), cholesterol total (20), cholesterol L.D.L. (21): is an organic molecule. It is a sterol biosynthesized by all animal cells because it is an essential structural component of animal cell membranes that is required to maintain both membrane structural integrity and fluidity. Cholesterol also serves as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D (Hanukoglu, 1992).

Blood ionogram

- Sodium (22): is an essential nutrient that regulates blood volume, blood pressure, osmotic equilibrium and pH (Pohl et al., 2013). Unusually low or high sodium levels in humans are recognized in medicine as hyponatremia and hypernatremia. These conditions may be caused by genetic factors, physical factors associated with ageing or illnesses involving vomiting or diarrhea.
- Potassium (23): is essential for many body functions, including muscle and nerve activity (Pohl et al., 2013). The electrochemical gradient of potassium between the intracellular and extracellular space is essential for nerve function; in particular, potassium is needed to repolarize the cell membrane to a resting state after an action potential has passed. Lower potassium levels in the extracellular space cause hyperpolarization of the resting membrane potential. This hyperpolarization is caused by the effect of the altered potassium gradient on resting membrane potential as defined by the Goldman equation. As a result, a greater than normal stimulus is required for depolarization of the membrane to initiate an action potential. In the heart, hypokalemia causes

hyperpolarization in the myocytes' resting membrane potential. The more negative membrane potentials in the atrium may cause arrhythmias because of more complete recovery from sodium-channel inactivation, making the triggering of an action potential less likely. In addition, the reduced extracellular potassium (paradoxically) inhibits the activity of the I_{Kr} potassium current and delays ventricular repolarization. This delayed repolarization may promote reentrant arrhythmias (Mount and Zandi-Nejad, 2012).

- Chloride anions (24): are essential to a large number of species, humans included (Thomas et al., 2002). Often hyperchloremia does not produce any symptoms. However, hyperchloremia is sometimes associated with excess fluid loss such as vomiting and diarrhea. Hypochloremia (or Hypochloraemia) is an electrolyte disturbance in which there is an abnormally low level of the chloride ion in the blood. It can be associated with hypoventilation, chronic respiratory acidosis.
- CRP (25): as C-reactive protein is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments (Pepys and Hirschfield, 2003).

Blood enzymology

- Liver transaminases [AST (26) or SGOT and ALT (27) or SGPT]: are useful biomarkers of liver injury in a patient with some degree of intact liver function. Most liver diseases cause only mild symptoms initially, but these diseases must be detected early. Hepatic involvement in some diseases can be of crucial importance (Oh et al., 2001).

Blood immunology

- Brain natriuretic peptide (BNP), now known as B-type natriuretic peptide (28) or Ventricular Natriuretic Peptide (still BNP): is secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). BNP can also be used for screening and prognosis of heart failure (Niederkofler et al., 2008).

Blood hormonology

- The thyroid hormones (Walter and Emile, 2012) triiodothyronine (T_3) (29) and its prohormone, thyroxine (T_4) (30): are tyrosine-based hormones produced by the thyroid gland that are primarily responsible for regulation of metabolism (Cooper, 1989). They act to increase the basal metabolic rate, affect protein synthesis, help regulate long bone growth (synergy with growth hormone) and neural maturation, and increase the body's sensitivity to catecholamines such as adrenaline. The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism. Numerous physiological and pathological stimuli influence thyroid hormone synthesis (Brix et al., 2011).

RESULTS 2

All the 30 parameters show a full compliance with the normalized and official limit of blood sample values: after a 4-years daily intake of TeloBooster®; there is no detectable side effect (Figures 6 and 7).

DISCUSSION

The results obtained in part I confirmed the literature: the results obtained *in vitro* on human fibroblasts showed the effect of the activation of telomerase on the life expectancy as well as the elongation of the telomeres on a human group (Caterini, 2016). Not only that there is a significant reduction in the percent short telomeres but that the global median telomere length (MTL) increased significantly for all human subjects.

Similarly, studies in mice showed that an increase in telomerase activity slows tissue aging (Mariela et al., 2011) without increasing the risk of cancer (Bruno et al., 2011 Bruno et al., 2012). Nevertheless, various collateral effects are reported in the literature. In particular, activation of telomerase on cytomegalovirus (CMV) seropositive subjects results in a decrease in the cytotoxic (CD8 + / CD28_) T cells (Calvin et al., 2011).

Some studies link the length of telomeres with a decrease in the likelihood of favoring certain types of cancer (Harley, 2002) or show the correlation between short telomeres and the existence of breast cancer in women (Beatriz et al., 2011). All these links between telomere lengthening and biological parameters of living beings lead us to carry out a second step of results (RESULTS 2) in order to check thirty biological and physiological parameters on a human group after a 4-years TeloBooster® daily intake.

As a result, all parameters are included in the reference ranges and critical values allowed by the Lab Manual for Clinical Laboratories (UCSF Departments of Pathology & Laboratory Medicine, 1998). It means that a daily intake of a telomerase booster made from plants like

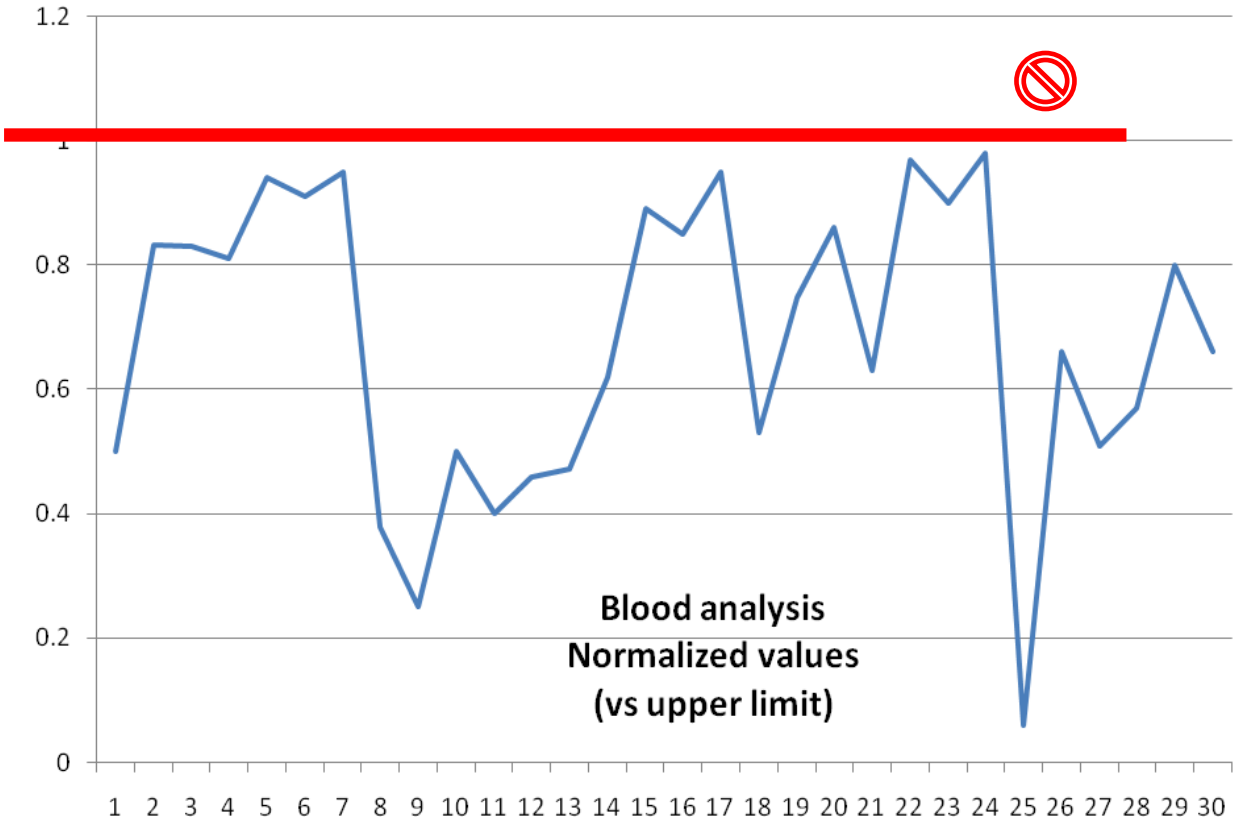

Figure 6. Distribution for the 30 blood parameters after a 4-years daily intake of TeloBooster®.
Of the allowed range, there is not a value above.

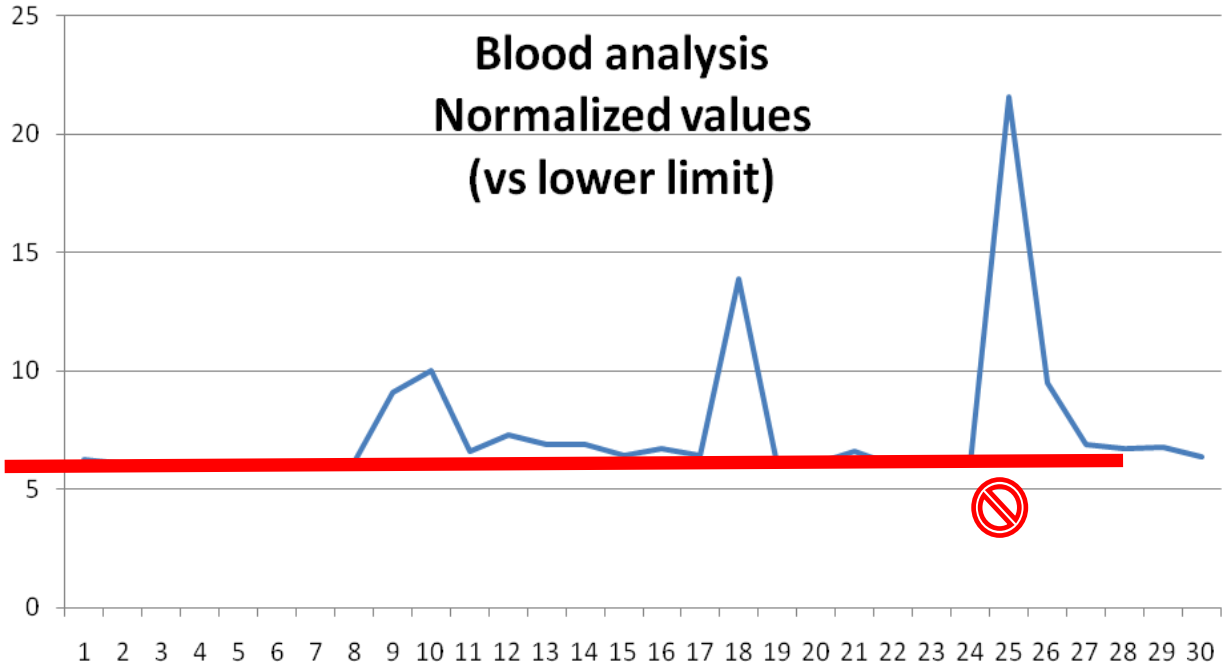

Figure 7. Distribution for the 30 blood parameters after a 4-years daily intake of TeloBooster®.
There is not a value below the allowed range.

TeloBooster® formula (BOPI, 2015) brings a lot of profits including an increase of median telomere length, a shrink in shortest telomere leading to a longer life expectancy (Bruno et al., 2011).

For pre-menopausal women, a protection against breast cancer for women may be provided by longer telomere length reinforced by low dietary intake of antioxidants or antioxidant supplements (Jing et al., 2009). Most of all, there is no bad side effect after a 4-years daily intake of a telomerase activator made from plants like the TeloBooster® product.

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