Anti-aging and anti-tumor effect of FPP® supplementation

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Abstract

The beneficial effect of FPP® as antioxidant is known. Here we summarize recent data supporting future implementation of FPP® in tumor treatment and in controlling aging at the molecular level. We first showed that oral FPP® is able to control tumor growth and with inducing a potent and systemic anti-oxidant reaction (i.e. reduced ROS and increased GSH and SOD-1). Then we showed that FPP® is able to markedly increase the body anti-oxidant reaction together with increasing both telomerase activity in the blood and the telomeres length in bone marrow and ovary of treated mice as compared to the untreated mice.

Key Words: Tumor, Aging, Redox balance, Fermented Papaya Preparation.

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The Importance of fermented foods for health

Up to a century ago the Nobel prize Metchnikoff claimed that the longevity of some populations of Eastern Europe was due to the high quantity of food fermented in their diet.[1] This was supported by recent evidence showing that microbiota in the elderly is strongly influenced by diet, opening up that healthy ageing is associated with microbial diversity.[2,3]

Fermented Papaya Preparation (FPP®) (Immun'Âge®) is one of the fermented foods that have proven positive effects on brain health; FPP® is a product resulting from yeast fermentation of non-genetically modified *Carica Papaya* Linn, which is marketed as a natural dietary functional health supplement under the brand name of Immun'Âge®.[3-5] FPP® is a powerful antioxidant and nutraceutical adjuvant in combined therapies against various diseases,[6-13] including cancer.[6,9,14] The FPP® more documented actions are as a free radical regulator,[15] as immunomodulatory,[16-20] and as antioxidant.[21,22] In fact, FPP® has shown a powerful *in vitro* anti-oxidative activity on brain cells,[23], as well on *in vivo* experimental model of epilepsy consistently reducing neural release of epileptogenic monoamine.[24] Moreover, FPP® showed a clear action in reducing the derangement of oxidant/antioxidant balance at the brain level in elderly rats and in experimental ischemia-reperfusion model;[4,25,26] FPP® modulates oxidative DNA damage, protecting brain from oxidative damage in hypertensive rats and reducing genotoxic effect of H_2O_2,[27], and protecting the body from the aging-related diseases,[28-31] including neurodegenerative diseases.[31-33] However, a clear *in vivo* action of FPP® on the molecular signature of aging, such as telomerase activity and telomeres length has not been provided yet.

A role of FPP® in controlling cancer growth

Previous paper have shown that tumor microenvironment is a primary actor in inducing a sort of selective pressure leading to development of tumor cell clones armed at surviving in a very hostile microenvironment, in which extracellular acidity is conceivably a key actor.[34,35] However, tumor microenvironment is hostile also thanks to the progressive accumulation of oxidant species. For this reason we have explored the effectiveness of in vivo oral administration of FPP® in either preventing or treating cancer, using a mouse model of a very aggressive melanoma B16. The results have shown that treatment of mice with FPP® administered through both gavage and sublingual routes always induced a significant reduction of the tumor growth. However, the FPP® anti-tumor effect was clearly dependent on the duration of the treatment being the shortest treatment always the most effective. This result might be explained by the invasive and non-voluntary procedure of forcing the mice to have FPP® orally each day.[36]

A role of FPP® in controlling aging

We investigated the role of *in vivo* FPP® administration in the induction of an antioxidant action together with an

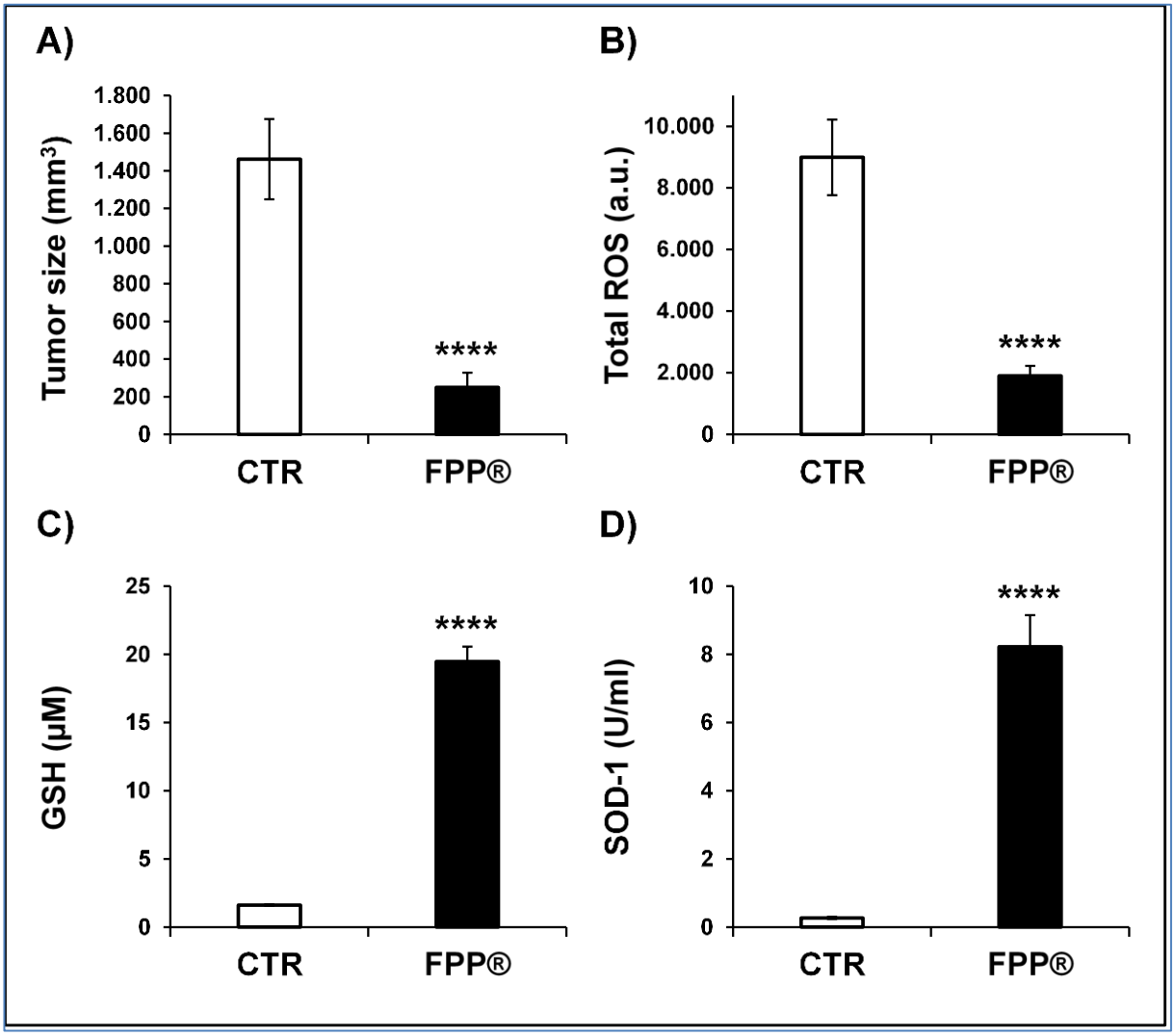

Fig 1. *FPP® antioxidant effect on C57/BL female mice tumor growth by measuring the blood levels of total ROS and antioxidant activity (GSH and SOD-1). The analyses were performed in control mice group (CTR group) and in mice groups treated with 200 mg/Kg/day of FPP® (FPP® group) starting 3 days before the inoculation up to the sacrifice. A) Tumor size (mm3). B) Total ROS levels (a.u). C) Total plasmatic glutathione (GSH, µM) activity. D) Total plasmatic superoxide dismutase-1 (SOD-1, U/ml) activity. Data are expressed as means ± SE. **** $p < 0.0001$*

anti-aging effect. Our results showed the effect of FPP® in inducing a clear systemic antioxidant reaction (higher of SOD-1 and GSH plasma levels) along with an increased telomerase activity and longer telomeres in both the bone marrow and the ovaries of the treated mice. This study also showed that FPP® was more effective when it starts at an early age as compared to late treatment.[37] Moreover, in both the bone marrow and the ovaries of the treated mice the number of cells harvested from those organs were significantly higher than in treated animals. Aging is characterized by a loss of fitness over time, with a series of molecular and macromolecular damages over the course of a lifetime. Faulty regulation of cellular processes could damage physiological integrity of cells and let to accumulation of damaged bioproducts. Among the various phenomena associated with aging, there is oxidative stress, characterized by the loss of balance of antioxidants/reactive oxygen species, with an accumulation of ROS at the cellular level. At the molecular level, there is a progressive shortening of the telomeres that, reached a threshold level, lead to cellular senescence and/or apoptosis. Crucial is the role of Telomerase, a polymerase that can elongate telomeres by de novo addition of TTAGGG sequence repeated in telomeres. Our results showed that the daily intake of FPP® significantly increased the levels of antioxidants in the blood and decreased the levels of total ROS, together

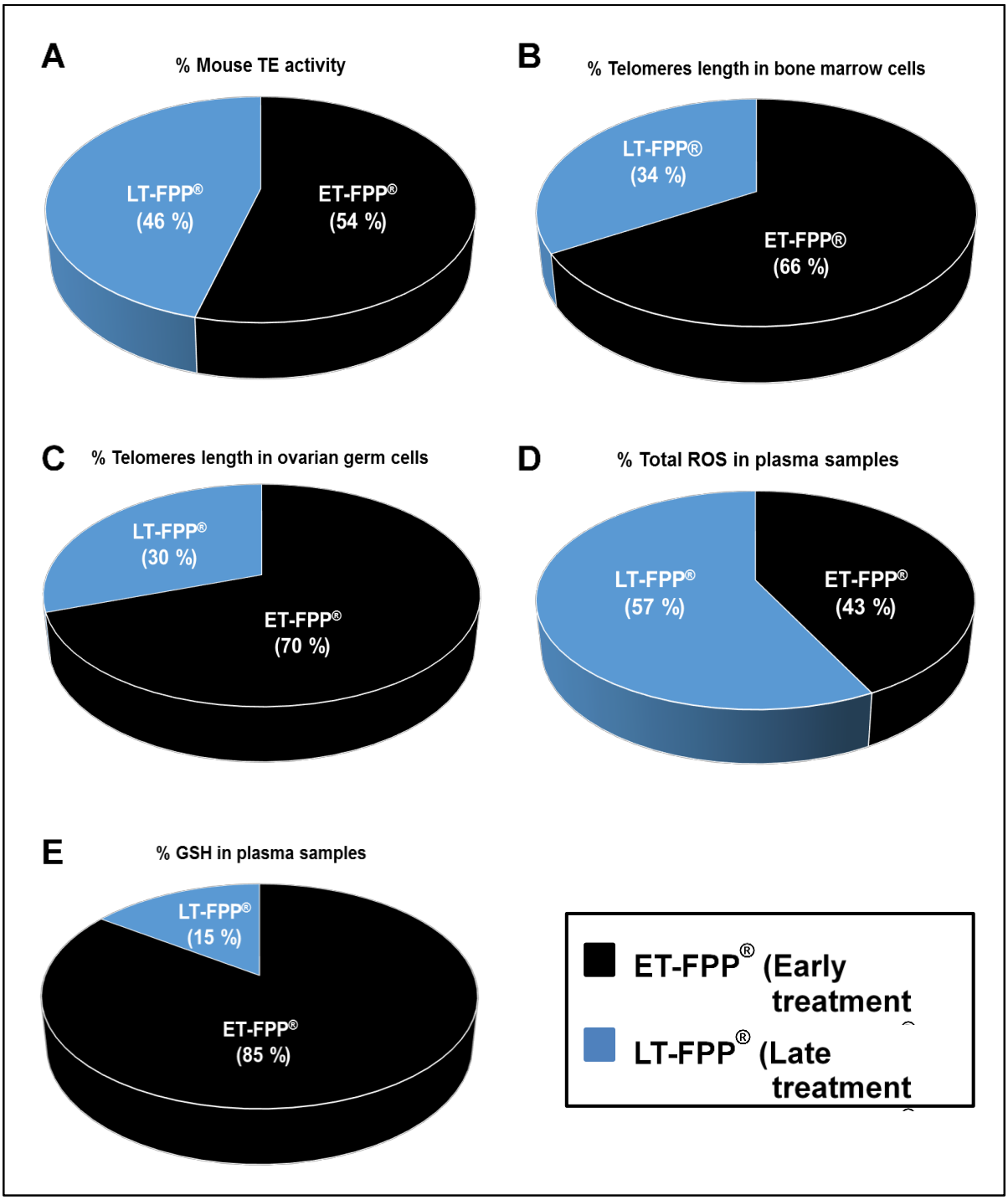

Fig 2. *Anti-aging effect of FPP® in C57BL/6J female mice comparing early (ET-FPP®) and late (LT-FPP®) treatments. A) Mouse Telomerase (TE) activity. B) Telomeres length in bone marrow cells. C) Telomeres length ovarian germ cells. D) Total ROS in plasma samples. E) Glutathione (GSH) in plasma samples. Data are expressed as % between CTR and FPP® groups.*

with a clear anti-aging effect as shown by the length of telomeres and telomerase quantification in FPP® treated mice. In our experiment, we have shown that although papaya has an effect even in beginning treatment later in life, the early treatment is far more effective. This is conceivably due to the fact that the anti-aging action of FPP® in maintaining telomeres length and mitigating progressive age-related shortening, is reduced when at a later age the telomeres have reached a shorter length. Similarly considering the redox balance, in ET-FPP®

mice we have much higher antioxidants levels and a greater reduction of ROS than in LT-FPP® mice.
All in all this review would like to emphasize the importance of an as early as in our life daily intake of a very potent anti-oxidant compound, such as FPP® , in order to possibly control the aging process and avoid the development of malignant tumors. The results we have summarized suggest also that the FPP® treatment may prolong the fertility period at least in the females, being the cellularity of the ovaries significantly increased by the treatment, in turn suggesting that the use of FPP® may be helpful in preventing or treating infertilities.

List of acronyms

FPP® - Fermented Papaya Preparation

SOD-1 - SuperOssidoDismutase-1

GSH - Gluthatione

Author's contributions

Mariantonia Logozzi played a main role in the conception, study design, and data acquisition, Davide Mizzoni and Rosella Di Raimi participated in analyses of data; Stefano Fais played a main role in the study design, drafting and finalizing the manuscript.

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Conflict of Interest

The authors declare they have no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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