



Clinical studies conducted on F.P.P.<sup>®</sup>  
- Fermented Papaya Preparation -

*Immun'Âge*<sup>®</sup>

BOOK  
OF  
ABSTRACTS

2019

# INTRODUCTION

*For twenty years scientific interest is more and more focused on free radicals and their involvement in the body.*

*Many studies had corroborated the preponderant part of free radicals in numerous pathologies as well as understanding mechanisms of aging.*

*FPP Fermented Papaya Preparation, research result of Osato Research Institute (O.R.I.) had also interested many worldwide researchers, on account of its anti-free radicals and immuno-stimulating properties.*

*FPP benefits and mode of action in organism had been studied over the last twenty years by many well-known researchers like: Pr. Montagnier L. (co-discoverer of AIDS virus and president of AIDS Research and Prevention World Foundation under the aegis of UNESCO), Pr. Packer L. of Berkeley University (California), Pr. Weksler M.E., Gerontologist of Cornell University (New York), Pr. Simonoff M. (CNRS, Bordeaux), Pr Marotta F. Roma, Pr. Rachmilewitz E.A. of Wolfson Medical Center Israël and Pr. Kishida T. of Research Center Louis Pasteur, Kyoto.*

*You will find in this book the abstracts of numerous studies on FPP.*

*To ease the reading, we have classified these abstracts in two summaries. The first one, general is sorted in chronological order and the second one by topics.*

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# GENERAL SUMMARY OF ABSTRACTS

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*Somanah J, Bourdon E, Rondeau P, Bahorun T, Aruoma OI.*  
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*Bertuccelli G, Marotta F, Zerbinati N, Cabeza A, He F, Jain S, Lorenzetti A, Yadav H, Milazzo M, Calabrese F, Tomella C, Catanzaro R*  
*Journal of Biological Regulators and Homeostatic Agents. 2014 Jan-Mar;28(1):53-63.* ..... 14

<b>The hidden phenomenon of oxidative stress during treatment of subclinical-mild hypothyroidism: a protective nutraceutical intervention</b> <i>Tomella C1, Catanzaro R, Illuzzi N, Cabeça A, Zerbini N, Celep G, Milazzo M, Sapienza C, Italia A, Lorenzetti A, Marotta F.</i> Rejuvenation Research. 2014 Apr;17(2):180-3 .....	14
<b>Novel concepts on functional foods and nutrigenomics in healthy aging and chronic diseases: a review of fermented papaya preparation research progress</b> <i>F. Marotta, G.S. Celep, A. Cabeça, A. Polimeni</i> Functional Foods in Health and Disease, 2012, 2(5):120-136 .....	15
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<b>Redox Balance Signalling in Occupational Stress: Modification by Nutraceutical Intervention</b> <i>F. Marotta, Y. Naito, F. Padrini, X. Xuewei, S. Jain, V. Soresi, L. Zhou, R. Catanzaro, K. Zhong, A. Polimeni and D.H. Chui</i> Journal of Biological Regulators & Homeostatic Agents, 2011 Apr-Jun; 25(2):221-9 .....	17
<b>Evolving concepts in nutrition: from functional foods to nutrigenomics: the paradigmatic example of fermented papaya preparation</b> <i>F. Marotta, A. Polimeni, P. Mantello</i> Approaches to Aging Control. Vol.15. September 2011 .....	17
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<b>Regulating Redox Balance Gene Expression in Healthy Individuals by Nutraceuticals: A Pilot Study</b> <i>F. Marotta, K. Koike, A. Lorenzetti, S. Jain, P. Signorelli, Y. Metugriachuk, P. Mantello, N. Locorotondo</i> Rejuvenation Research, 2010 Apr-Jun; 13(2-3):175-8 .....	18
<b>Decreased hemolysis following administration of antioxidant – fermented papaya preparation (FPP) to a patient with PNH</b> <i>H. Ghoti, H. Rosenbaum, E. Fibach, E. Rachmilewitz</i> Annals of Hematology, 2010, 89:429-430.....	19
<b>Applications and bioefficacy of the functional food supplement fermented papaya preparation</b> <i>O.I. Aruoma, Y. Hayashi, F. Marotta, P.Mantello, E. Rachmilewitz, L.Montagnier</i> Toxicology 278 (2010) 6–16.....	19
<b>Amelioration of Oxidative Stress in RBC from Patients with <math>\beta</math>-thalassemia Major and Intermedia and E-<math>\beta</math>-thalassemia Following Administration of Fermented Papaya Preparation</b> <i>E. Fibach, E.S. Tan, S. Jamuar, I. Ng, J. Amer and E.A. Rachmilewitz</i> Phytotherapy Research, 2010 Sep, 24(9):1334-8 .....	20
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<b>Fermented Papaya Preparation as Redox Regulator in Blood Cells of <math>\beta</math>-Thalassemic Mice and Patients</b> <i>Johnny Amer, Ada Goldfarb, Elizer A. Rachmilewitz and Eitan Fibach</i> Phytotherapy Research, (2008) 22, 820-828.....	21
<b>Nutraceutical Strategy in Aging. Targeting Heat Shock Protein and Inflammatory Profile through Understanding Interleukin-6 Polymorphism</b> <i>F. Marotta, K. Koike, A. Lorenzetti, Y. Naito, F. Fayet, H. Shimizu, and P. Marandola</i> Nutraceutical Strategy in Aging, New York Academy of Sciences, 1119:196-202, 2007 .....	21
<b>Oxidative-inflammatory damage in cirrhosis: Effect of vitamin E and a fermented papaya preparation</b> <i>Marotta F, Yoshida C, Barreto R, Naito Y, Fesce F, Packer L</i> Journal of Gastroenterology & Hepatology, 2007 May; 22(5):697-703 .....	22
<b>Nutraceutical Supplementation: Effect of a Fermented Papaya Preparation on Redox Status and DNA Damage in Healthy Elderly Individuals and Relationship with GSTM1 Genotype</b> <b><i>A randomized, placebo-controlled, cross-over study</i></b> <i>F. Marotta, M Weksler, Y Naito, C Yoshida, M Yoshioka, P. Marandola</i> Annals New-York Academy Science 2006 May; 1067:400-7 .....	23
<b>Relationship Between Aging and Susceptibility of Erythrocytes to Oxidative Damage: In View of Nutraceutical Interventions</b> <i>Marotta F, Pavasuthipaisit K, Yoshida C, Albergati F, Marandola P</i> Rejuvenation Res. 2006; 9(2):227-30. ....	24
<b>New and future prospects of protective potentials of Fermented Papaya Preparation (Immun'Âge FPP) in inflammatory and neurodegenerative chronic diseases</b> <i>M.E.Weksler, O.I. Aruoma, F. Marotta, P. Mantello</i> Entretiens de Bichat-Thérapeutique, Sep. 12, 2006.....	25
<b>Functional Foods as catalysts of the nutrition evolution into nutrigenomics: a scholastic example of a fermented papaya preparation (Immun'Âge)</b> <i>F. Marotta, E. Minelli, P. Marandola</i> Middle East Journal of Age and Ageing, 2005;3: 1-6 .....	26
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<b>Fermented Papaya interest on our health: benefits on oxidative stress and immunity</b> <b>Oxidative stress and chronic diseases</b> <i>Pr. Luc Montagnier, M. Brack, H. Chenal, P. Mantello</i> Entretiens de Bichat-Thérapeutique et Tables Rondes 2004; p.232-237 ISBN 2-7046-1675-2 .....	28
<b>Action of FPP on immune system cells</b> <i>Pr. Lester Packer</i> Entretiens de Bichat-Thérapeutique et Tables Rondes 2004 ; p.237-244 ISBN 2-7046-1675-2 .....	28
<b>FPP &amp; Gastroenterology : benefits of fermented papaya</b> <i>Dr. Francesco Marotta</i> Entretiens de Bichat-Thérapeutique et Tables Rondes 2004; p.244-252 ISBN 2-7046-1675-2 .....	28
<b>Improvement of Hemorheological Abnormalities in Alcoholics by an Oral Antioxidant</b> <i>F. Marotta, P. Safran, H. Tajiri, G. Princess, H. Anzulovic, GM Ideo, A Rouge, MG Seal, G. Ideo</i> Hepato-Gastroenterology 2001; 48:511-517 .....	29

**Cyanocobalamin Absorption Abnormality in Alcoholics is Improved by Oral Supplementation with a Fermented Papaya-derived Antioxidant**

*F. Marotta, H. Tajiri, R. Barreto, P. Brasca, GM Ideo, L Mondazzi, P. Safran, J Bobadilla, G. Ideo*

Hepato-Gastroenterology 2000; 47:1189-1194 .....29

**Ethanol-Related Gastric Mucosal Damage: Evidence of a Free Radical-mediated Mechanism and Beneficial Effect of Oral Supplementation with Immun'Age, a Novel Natural Antioxidant**

*F. Marotta, H. Tajiri, P. Safran, E. Fesce, G. Ideo*

Digestion 1999; 60:538-543. ISSN: 0012-2823 .....30

**Abstinence-Induced Oxidative Stress in Moderate Drinkers is Improved by Immun'Age**

*F. Marotta, I. Reizakovich, H. Tajiri, P. Safran, Barbi, G. Ideo*

Hepato-Gastroenterology 44:1360-1366 (1997), ISSN: 0172-6390 .....30

**Radio protective and Antioxidant Effects of Zinc Aspartate, and Fermented Papaya Preparation FPP in Children with Acute Myelo-Lympholeukemia**

*Korkina L., Afanas'ev I.B., Osato J.A. and al.*

Supplement to Nutrition Vol 11, N°5: 555-558, 1995 .....31

**Effects of dietary supplements on IFN producing capacity in humans**

*A, Kishi, K. Uno, Y. Matsubara, J.A. Osato, T. Kishida*

Journal of Interferon Research. Vol. 14 Supplement 1; 1994. ISSN: 0197-8357 .....31

**Effects of Bio-Normalizer (FPP) on Serum Components and Immunological Functions in Humans**

*Santiago L.A., Uno K., Kishida T., Miyagawa F., Osato J.A. and Mori A.*

Neurosciences, 20s:149-152, Apr 1994. ISSN: 0388-7448 .....32

**Effect of Bio-Normalizer (FPP) on the alcohol-induced changes in blood substances in human**

*Koide Y., Miyagawa F., Osato J.A., Santiago L.A. and Mori A.*

Neurosciences, 19s.1:85-88, 1993. ISSN: 0388-7448 .....32

*N.B. You can see in some publications Immun'Age - FPP, under other names such as Bio-Normalizer or Bio-Catalyzer ar No.11.*

# PUBLICATIONS

## Discovering the Health Promoting Potential of Fermented Papaya Preparation. Its Future Perspectives for the Dietary Management of Oxidative Stress During Diabetes

Jhoti Somanah, Manish Putteeraj, Okezie I. Aruoma and Theeshan Bahorun

The simplistic morphological characteristics of *Carica papaya* fruit or “pawpaw” should not be the cause for underestimating its potential as a nutraceutical. The market for papaya has been expanding at a staggering rate, partly due to its applicability as a biofortified product, but also due to its phytochemical properties and traditional health benefits. Papaya or formulations of fermented papaya preparation (FPP) display effective free radical scavenging abilities thought to be influenced by its phenolic, carotenoid, flavonoid, or amino acid profile. The antioxidant properties of FPP have been extensively reported in literature to potentially target a broad spectrum of free radical-induced diseases ranging from neurological impairments, such as senile dementia, to systemic diseases, to its interference at the cellular level and the support of normal biological ageing processes. FPP has thus been extensively investigated for its ability to exert cellular protective effects and reduce oxidative stress via the mitigation of genetic damage, reduction of lipid peroxidation, and enzymatic inactivation in specific diseases. The focus of this review is to appraise the potential of oxidative stress reduction strategies of FPP and discuss its holistic approach in disease prevention and management, with a particular focus on diabetes and cancer. However, with the current lack of information surrounding its mechanism of action, this review wishes to set the stage and aspire researchers to more profoundly investigate molecular pathways related to how FPP can unequivocally contribute to wellness in an aging population.

**Keywords:** *Carica papaya*; fermented papaya preparation (FPP); free radical scavenging; antioxidant; oxidative stress; anti-diabetic; anti-carcinogenic.

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### Oxidative stress in electrohypersensitivity self-reporting patients: Results of a prospective *in vivo* investigation with comprehensive molecular analysis

Philippe Irigaray, Daniela Caccamo and Dominique Belpomme

A total of 32 electrohypersensitivity (EHS) self-reporting patients were serially included in the present prospective study for oxidative stress and antioxidative stress response assessment. All thiobarbituric acid-reactive substances (TBARs) were measured in the plasma, particularly malondialdehyde (MDA) for lipid peroxidation; additional measurements included total thiol group molecules, reduced glutathione (GSH), oxidized glutathione (GSSG) for oxidative stress assessment and nitrotyrosine, a marker of peroxynitrite-induced oxidative/nitrosative stress. In addition, the activity of Cu-Zn superoxide dismutase (SOD1) was measured in red blood cells (RBCs) and glutathione reductase (GR) and glutathione peroxidase (GPx) in RBCs and plasma. Depending of the biomarker considered, 30-50% of EHS self-reporting patients presented statistically significantly increased TBARs, MDA, GSSG and NTT mean plasmatic level values in comparison with normal values obtained in healthy controls ( $P < 0.0001$ ). By contrast, there were no plasmatic level values above the upper normal limits for GSH, GSH/GSSG ratio, total glutathione (GluT) and GSH/GluT ratio, and values for these GSH-associated biomarkers were statistically significantly decreased in 20-40% of the patients ( $P < 0.0001$ ). Furthermore, in RBCs, mean SOD1 and GPx activities were observed to be statistically significantly increased in ~60% and 19% ( $P < 0.0001$ ) of the patients, respectively, while increased GR activity in RBCs was observed in only 6% of the patients. The present study reports for the first time, to the best of our knowledge, that overall ~80% of EHS self-reporting patients present with one, two or three detectable oxidative stress biomarkers in their peripheral blood, meaning that these patients-as is the case for cancer, Alzheimer's disease or other pathological conditions-present with a true objective new pathological disorder.

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## **A 2-year Double-Blind RCT Follow-up Study with Fermented Papaya Preparation (FPP) Modulating Key Markers in Middle-Age Subjects with Clustered Neurodegenerative Disease-Risk Factors**

Francesco Marotta, Massimiliano Marcellino, Umberto Solimene, Biagio Cuffari, Hariom Yadav, Alexander N Khokhlov, Aldo Lorenzetti, Amélie Mantello, Joseph Cervi and Roberto Catanzaro

In recent years a number of studies have reported the significant relationship between metabolic syndrome and neurodegenerative disease. There is accumulating evidence that the interplay of combined genetic and environmental risk factors (from diet to life style to pollutants) to intrinsic age-related oxi-inflammatory changes may be advocated for to explain the pandemic of neurodegenerative diseases. In recent years a specific Fermented Papaya Preparation (FPP) has been shown to significantly affect a number of redox signalling abnormalities in a variety of chronic diseases and as well in aging mechanisms either on experimental and on clinical ground. The aim of the present study was to evaluate FPP use in impending metabolic disease patients with potentially neurodegenerative disease clustered risk factors. The study population consisted of 90 patients aged 45-65 years old, with impending metabolic syndrome and previously selected as to be ApoE4 genotype negative. By applying a RCT, double-blind method, one group received FPP 4.5 g twice a day (the most common dosage utilized in prior clinical studies) while the other received an oral antioxidant cocktail (trans-resveratrol, selenium, vitamin E, vitamin C). Then, after 21 month treatment period, a selected heavy metal chelator was added at the dosage of 3 g/nocte for the final 3 months study treatment. The parameters tested were: routine tests oxidized LDL-cholesterol, anti-oxidised LDL, Cyclophilin-A (CyPA), plasminogen activator inhibitor-1 and CyPA gene expression. From this study it would appear that FPP, unlike the control antioxidant, significantly decreased oxidized-LDL and near normalizing the anti- Ox-LDL/Ox-LDL ratio ( $p < 0.001$ ) although unaffected the lipid profile per se. Moreover, only FPP decreased cyclophilin-A plasma level and plasminogen activator-inhibitor ( $p < 0.01$ ) together with downregulating cyclophilin-A gene expression ( $p < 0.01$ ). Insulin resistance was only mildly improved. Heavy metals gut clearance proved to be effectively enhanced by the chelator ( $p < 0.01$ ) and this was not affected by any of the nutraceuticals, nor it added any further benefit to the biological action of FPP.

**Keywords:** Fermented Papaya Preparation (FPP); Redox balance; Antioxidant; Neurodegenerative disease; Caviarlieri.

*Clin Pharmacol Biopharm.* 2017;6. pii: 170. doi: 10.4172/2167-065X.1000170. Epub 2017 May 18. PMID:31007971; PMCID:PMC6474671

## **Novel Nutrigenomics Avenues in Nutraceuticals Use: The Current Status of Fermented Papaya Preparation**

Amélie Mantello, Roberto Catanzaro, Fang He, Biagio Cuffari, Laura Bissi, Michele Milazzo,  
Aldo Lorenzetti and Francesco Marotta

Functional foods present a constantly growing research field, interrelating genomics, epidemiology and clinical investigations, followed by increased interest from the public and food supplement industry. As a matter of fact, the outcome of the implementation of functional foods is now amenable to be assessed by employing many of the most recent diagnostic tools.

Nutrigenomics is a relatively new discipline, which studies the genetic and epigenetic interplay with a nutrient or its functional component(s) in order to bring about a phenotypic modification of key cellular functions, such as, cell metabolism, differentiation or apoptosis. This represents one of the most expanding fields of research to unveil the health benefits of functional foods and their bioactive moieties which cannot be differentiated, as it happens in synthetic molecules devised by pharmaceutical industries.

Within this scenario, a specific functional food, i.e. fermented papaya preparation, coming from a controlled bio-fermentation process of papaya, is herewith reported and scientifically backed up by several experimental models and properly-designed clinical protocols.

The promising clinical health benefits provided by fermented papaya preparation are also discussed under the viewpoint of nutrigenomic mechanism understanding, and a significant antioxidant and effective transcriptomic property is described while ongoing investigations are warranted.

In general, this specific fermented papaya preparation represents a functional food, which closely meets the novel criteria of the new nutrigenomic-oriented strategic approach of preventive medicine, aimed to reduce the burden of chronic illnesses, while also offering potential adjuvant benefits within drugs regimens.

**Keywords:** Fermented papaya preparation, Functional food, Gene expression, Nutraceuticals, Nutrigenomics, Oxidative stress.

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## **Effect of a quality-controlled fermented nutraceutical on skin aging markers: An antioxidant-control, double-blind study**

Bertuccelli G, Zerbinati N, Marcellino M, Nanda Kumar NS, He F, Tsepakolenko V, Cervi J, Lorenzetti A, Marotta F

The aim of the present study was to determine whether oral supplementation with a fermented papaya preparation (FPP-treated group) or an antioxidant cocktail (antioxidant-control group, composed of 10 mg trans-resveratrol, 60 µg selenium, 10 mg vitamin E and 50 mg vitamin C) was able to improve the skin antioxidant capacity and the expression of key skin genes, while promoting skin antiaging effects. The study enrolled 60 healthy non-smoker males and females aged 40-65 years, all of whom showed clinical signs of skin aging. The subjects were randomly divided into two matched groups, and were administered FPP or antioxidant treatment of a 4.5 g/day sachet sublingually twice a day for 90 days in a double-blind fashion. The parameters investigated were: Skin surface, brown spots, skin evenness, skin moisturization, elasticity (face), redox balance, nitric oxide (NO) concentration, and the expression levels of key genes (outer forearm sample). As compared with the baseline (day 0) and antioxidant-control values, FPP-treated subjects showed a significant improvement in skin evenness, moisturization and elasticity. The two treatments improved the MDA and SOD skin concentrations, but only the FPP-treated group showed a higher SOD level and a significant NO increase, along with significant upregulation of aquaporin-3 and downregulation of the potentially pro-aging/carcinogenic cyclophilin-A and CD147 genes ( $P < 0.05$ ). Progerin was unaffected in both treatment groups. In conclusion, these findings suggest that orally-administered FPP showed a consistent biological and gene-regulatory improvement in the skin, as was also demonstrated in previous experimental and clinical trials testing other tissues, while common oral antioxidants had only a minor effect.

**Keywords:** antioxidant defence; fermented papaya preparation; gene expression; photoaging; skin aging; skin elasticity; skin moisturization

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## **Does oral supplementation of a fermented papaya preparation correct respiratory burst function of innate immune cells in type 2 diabetes mellitus ?**

Dickerson R, Banerjee J, Rauckhorst A, Pfeiffer DR, Gordillo GM, Khanna S, Osei K, Roy S.

Fermented papaya preparation (FPP) is a nutritional supplement reported to act as an antioxidant by scavenging reactive oxygen species (ROS) and removing "bad ROS," while inducing "respiratory burst" production of necessary "good ROS." We sought to investigate the safety of oral administration of FPP (9 g/day, 6 weeks) to T2D patients with regard to its effect on the hyperglycemia status of these patients. Peripheral blood was collected during a baseline visit, followed by subsequent collections both during and after supplementation. Induced "respiratory burst" ROS production was measured at each visit in addition to fasting blood glucose, lipid profile, glycated hemoglobin (HbA1c), and lipid/protein peroxidation. Oral FPP supplementation induced "respiratory burst" in peripheral blood mononuclear cells while not influencing other blood parameters studied. When human monocytic THP-1 cells were supplemented with sugar-based FPP, cellular ATP and NADPH concentrations were increased while matched glucose alone did not produce similar effects, suggesting a glucose-independent component of FPP to be responsible for increasing cellular energetics. THP-1 cells supplemented with FPP also exhibited higher mitochondrial membrane potential ( $\Delta\psi_m$ ) and oxygen consumption as compared with cells treated with glucose alone. Taken together, our observations lead to the hypothesis that FPP corrects inducible "respiratory burst" function in type 2 diabetes patients.

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## The Antioxidant Effect of Fermented Papaya Preparation in the Oral Cavity

Fibach E, Ginsburg

Oxidative stress has been recognized to play important roles in various diseases, including of the oral cavity. However, nutritional supplementation of antioxidants to ameliorate the consequences of oxidative stress is debatable. One caveat is that oxidative status is often measured under non-physiological conditions. Here, we investigated the antioxidant potential of fermented papaya preparation (FPP), a product of yeast fermentation of *Carica papaya* Linn, under conditions that prevail in the oral cavity. Employing highly sensitive luminol-dependent chemiluminescence assays, we show that its antioxidant capacity was augmented by saliva (up to 20-fold,  $p < 0.0001$ , at 10 mg) and its components (mucin, albumin) as well as by red blood cells (RBC) and microorganisms present in the normal and pathological environment of the oral cavity. Polyphenols are major plant antioxidants. Using the Folin-Ciocalteu's assay, a very low amount of phenols was measured in FPP suspended in a salt solution. However, its suspension in saliva, albumin, mucin or RBC produced up to sixfold increase,  $p < 0.001$ , compared with the sum of polyphenols assayed separately. The results suggested that these enhancing effects were due to the solubilization of antioxidant polyphenols in FPP by saliva proteins and the binding to RBC and microorganisms, thus increasing their availability and activity.

**Keywords:** Antioxidants; *Carica papaya*; chemiluminescence; mucin; oral cavity; polyphenols; saliva

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## The Effect of Fermented Papaya Preparation on Radioactive Exposure

Fibach E, Rachmilewitz EA

Exposure to ionizing radiation causes cellular damage, which can lead to premature cell death or accumulation of somatic mutations, resulting in malignancy. The damage is mediated in part by free radicals, particularly reactive oxygen species. Fermented papaya preparation (FPP), a product of yeast fermentation of *Carica papaya* Linn, has been shown to act as an antioxidant. In this study, we investigated the potential of FPP to prevent radiation-induced damage. FPP (0-100  $\mu\text{g/ml}$ ) was added to cultured human foreskin fibroblasts and myeloid leukemia (HL-60) cells either before or after irradiation (0-18 Gy). After 1-3 days, the cells were assayed for: intracellular labile iron, measured by staining with calcein; reactive oxygen species generation, measured with dichlorofluorescein diacetate; apoptosis, determined by phosphatidylserine exposure; membrane damage, determined by propidium iodide uptake; and cell survival, determined by a cell proliferation assay. DNA damage was estimated by measuring 8-oxoguanine, a parameter of DNA oxidation, using a fluorescent-specific probe and by the comet assay. These parameters were also assayed in bone marrow cells of mice treated with FPP (by adding it to the drinking water) either before or after irradiation. Somatic mutation accumulation was determined in their peripheral red blood cells, and their survival was monitored. FPP significantly reduced the measured radiation-induced cytotoxic parameters. These findings suggest that FPP might serve as a radioprotector, and its effect on DNA damage and mutagenicity might reduce the long-term effects of radiation, such as primary and secondary malignancy.

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PMID: 26291738 [PubMed - indexed for MEDLINE]

## **Oxidative Stress in Patients with Alzheimer's Disease: Effect of Extracts of Fermented Papaya Powder**

Mario Barbagallo, Francesco Marotta, and Ligia J. Dominguez

Brain tissue is particularly susceptible to oxidative stress (OS). Increased production of reactive oxygen species (ROS), reduced antioxidant systems, and decreased efficiency in repairing mechanisms have been linked to Alzheimer's disease (AD). Postmortem studies in AD patients' brains have shown oxidative damage markers (i.e., lipid peroxidation, protein oxidative damage, and glycoxydation). Fermented papaya (FPP, a product of *Carica papaya* Linn fermentation with yeast) is a nutraceutical supplement with favorable effects on immunological, hematological, inflammatory, and OS parameters in chronic/degenerative diseases. We studied 40 patients (age  $78.2 \pm 1.1$  years), 28 AD patients, and 12 controls. Urinary 8-OHdG was measured to assess OS. Twenty AD patients were supplemented with FPP (Immunage, 4.5 grams/day) for 6 months, while controls did not receive any treatment. At baseline, 8-OHdG was significantly higher in patients with AD versus controls ( $13.7 \pm 1.61$  ng/mL versus  $1.6 \pm 0.12$  ng/mL,  $P < 0.01$ ). In AD patients FPP significantly decreased 8-OHdG ( $14.1 \pm 1.7$  ng/mL to  $8.45 \pm 1.1$  ng/mL,  $P < 0.01$ ), with no significant changes in controls. AD is associated with increased OS, and FPP may be helpful to counteract excessive ROS in AD patients.

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## **Relationship between fermented papaya preparation supplementation, erythrocyte integrity and antioxidant status in pre-diabetics**

Somanah J, Bourdon E, Rondeau P, Bahorun T, Aruoma OI.

Erythrocytes and their membranes are favorable models to study the relationship between diabetes and susceptibility of erythrocytes to oxidative stress damage. The recommendation for the use of fermented papaya preparation (FPP) as a functional food for dietary management of type 2 diabetes was evaluated by assessing its effect on the human antioxidant status and erythrocyte integrity on a multi-ethnic pre-diabetic population. The *in vivo* effect of FPP was compared with its *in vitro* free radical scavenging potentials. FPP exhibited potent *in vitro* free radical scavenging activities thought to be attributed to residual phenolic or flavonoid compounds. Low doses of FPP significantly reduced the susceptibility of human erythrocytes to undergo free radical-induced hemolysis. The intake of 6g FPP/day for a period of 14weeks was observed to significantly reduce the rate of hemolysis and accumulation of protein carbonyls in the blood plasma of pre-diabetics. That FPP consumption on a daily basis can strengthen the antioxidant defense system *in vivo* was clearly demonstrated by the marked increase of total antioxidant status in the FPP-supplemented pre-diabetics. That FPP maintains the integrity of erythrocytes could benefit the strategies to improve the quality of future blood products.

**Keywords:** Antioxidant; Blood product preservation; Erythrocyte hemolysis; Fermented papaya preparation; Oxidative stress; Type 2 diabetes

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*PMID: 24316314 [PubMed - indexed for MEDLINE]*

## **Iron supplementation in young iron-deficient females causes gastrointestinal redox imbalance: protective effect of a fermented nutraceutical**

Bertuccelli G, Marotta F, Zerbinati N, Cabeça A, He F, Jain S, Lorenzetti A, Yadav H, Milazzo M, Calabrese F, Tomella C, Catanzaro R

The aim of this study was to assess whether the concomitant supplementation of certified fermented papaya preparation (FPP, ORI, Gifu, Japan) together with iron supplementation could beneficially affect lipid peroxidation either systemically and at an intraluminal gut level in women with low iron stores. Treatment compliance and iron absorption was assessed as well. Fifty-two non-pregnant, fertile, non-smokers, healthy women with iron deficiency were recruited. The women were given iron supplements (100 mg Fe/d as ferrous sulfate) to be taken daily for 12 weeks (group A). Group B patients were also supplemented with 6g/day of a FPP. A detailed life style questionnaire was administered to all subjects. Iron, ferritin, transferrin receptors (Tf R) and malondialdehyde (MDA) in plasma were measured. The RBCs lysate was used for the estimation of superoxide dismutase (SOD) and glutathione peroxidase (GPx). The total and free iron concentration as well as analysis of oxidative stress in the feces was measured. FPP-supplemented subjects showed a significantly lower degree of gastrointestinal discomfort ( $p$  less than 0.05) and abolished the iron supplementation-induced increase of MDA ( $p$  less than 0.001) and the depletion of SOD and GPx ( $p$  less than 0.01). Moreover, the nutraceutical co-administration brought about a significant reduction of gut oxidative damage and lower fecal content of either total and free iron ( $p$  less than 0.05 vs group A). Overall, group B showed a better TfR/ferritin ratio response ( $p$  less than 0.05 vs group A). While iron supplementation maintains its clinical relevance considering the prevalence of iron deficiency among females, a careful clinical evaluation and a protective nutraceutical co-administration, as our data suggest with FPP, should be considered.

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PMID: 24750791 [PubMed - indexed for MEDLINE]*

## **The hidden phenomenon of oxidative stress during treatment of subclinical-mild hypothyroidism: a protective nutraceutical intervention**

Tomella C1, Catanzaro R, Illuzzi N, Cabeça A, Zerbinati N, Celep G, Milazzo M, Sapienza C, Italia A, Lorenzetti A, Marotta F.

Recent studies suggest that subjects with hypothyroidism under therapy with levothyroxine (L-T4) might develop oxidative stress. The aim of this study was to test a redox-balance modulator, fermented papaya-based nutraceutical (FPP), together with subclinical (SH) or mild hypothyroidism (MH) treatment in view of biochemical changes. A total of 60 females treated for SH-MH were divided into two matched groups and received either FPP 3 grams 1 sachet three times a day (t.i.d.) or placebo for 3 months. A significant baseline increase of all oxidative markers was observed in SH-MH ( $p < 0.05$  vs. control) and even more under T4 treatment ( $p < 0.05$ ). FPP caused a normalization of redox markers ( $p < 0.01$  vs. placebo). Thyroid supplementation accelerates mitochondrial oxygen consumption and oxidative stress, whereas a redox-modulator therapy is advisable, given the long-lasting treatment in such cases.

*Rejuvenation Research. 2014 Apr;17(2):180-3  
PMID: 24050492 [PubMed - indexed for MEDLINE]*

## **Novel concepts on functional foods and nutrigenomics in healthy aging and chronic diseases: a review of fermented papaya preparation research progress**

Francesco Marotta, Gulcin Sagdicoglu Celep, Anna Cabeça, Ascanio Polimeni

Functional foods are an emerging research field corresponding with genomics, epidemiological and clinical studies integrated with the food industry in accordance with the consumer demands. Consequently, the features of the functional foods are being discussed by various researchers and related institutions, and a common view has been pointed out about the availability and the nature of the components of functional foods. Recently, the outcomes of functional foods are being assessed by the help of all the available scientific tools. Genomic medicine is one of the most promising areas of research to reveal the benefits of functional foods and the bioactive ingredients. Nutrigenomics aims at studying the genetic and epigenetic interactions with a nutrient or the functional component in order to lead to a phenotype change and therefore to the cell metabolism, differentiation or even apoptosis. Papaya and its fermentation product are specific products derived from the technologically advanced and controlled environmental-friendly bio-fermentation process.

It has been well known for a long time that the natural anti-oxidant properties of papaya, mainly depending on vitamins A and C in addition to certain amino acids, were consistent both in the fruit and derived from the papain enzyme which is no longer present in the fermented product. In this article, functional foods in genomic medicine are discussed in review of the fermented papaya preparation research progress. Clinical evidences about fermented papaya as a functional food are reported as supported by various research protocols and experimental models. The benefits of fermented papaya preparation are also discussed in nutrigenomic basis and it is reported to have an important antioxidant and transcriptomic potential which deserves further investigation. As a conclusion, fermented papaya preparation represents a Functional Food highly compliant with the novel features of the new nutrigenomic-driven action plan strategy aimed to reduce the incidences of diseases and successful integration within specific pharmacological treatments.

**Keywords:** functional foods, fermented papaya preparation, nutrigenomics

*Functional Foods in Health and Disease 2012, 2(5):120-136*

## **Is There A Potential Application of a Fermented Nutraceutical in Acute Respiratory Illnesses? An *In-Vivo* Placebo-Controlled, Cross-Over Clinical Study in Different Age Groups of Healthy Subjects**

F. Marotta, Y. Naito, S. Jain, A. Lorenzetti, V. Soresi, A. Kumari, P. Carrera Basto, C. Tomella and H. Yadav

The role of oxidants in viral diseases is fairly complex because it includes metabolic regulation both of host metabolism and viral replication. However, a role for reactive oxygen species (ROS) and reactive nitrogen species (RNS) as mediators of virus-induced lung damage is supported by studies and antioxidants can thus be expected to act at many different levels. The aim of the present pilot study was to test an antioxidant nutraceutical approach on some relevant immunological parameters known to be affected in common seasonal respiratory tract infection. The study population consisted of 90 sedentary healthy patients, previously selected as being GSTM1-positive, divided into three groups: A) 20-40 years; B) 41-65 years; B) over 65 years. Each patients was administered a life style and dietary questionnaire. Subjects were supplemented for 6 weeks with either 9g/day (4.5g twice a day sublingually) of a fermented papaya preparation (Osato Research Institute, Gifu, Japan) or placebo. After a further month period of wash out, subjects were treated again in a crossover manner. Parameters checked were as follows: routine blood tests with WBC formula, saliva flow rate and secretory IgA and lysozyme production and redox gene expression of Phase II enzyme and SOD from upper airways cells (from nasal lavage). Salivary secretion rate showed an age-related decline and was significantly increased by FPP supplementation only in the youngest age-group ( $p < 0.05$ ). Subjects treated with FPP showed a significantly higher lever of IgA and lisozyme production., irrespective of age group while their baseline production was significantly lower in the oldest age-group as compared to the youngest one (C vs A,  $p < 0.05$ ). FPP treatment brought about a significant upregulation of all phase II enzyme and SOD gene expression tested in nasal lavage cells. In conclusion, FPP supplementation during 1 month resulted in higher salivary IgA and increase in phase II and SOD enzyme expression, i.e the most important antioxidant in the respiratory tract. The biological significance of these effects i.e., whether it will help reducing the whole respiratory oxidative stress in the human airway and, hopefully, the incidence and/or severity of URTI remains to be demonstrated in longer clinical trials.

*Journal of Biological Regulators & Homeostatic Agents* 2012 Apr-Jun; 26(2):285-94  
PMID: 22533427 [PubMed - indexed for MEDLINE]

## **Cardioprotective Effect of a Biofermented Nutraceutical on Endothelial Function in Healthy Middle-Aged Subjects**

Francesco Marotta, Hariom Yadav, Archana Kumari, Roberto Catanzaro, Shalani Jain, Ascanio Polimeni, Aldo Lorenzetti, and Vincenzo Soresi

We tested a biofermented nutraceutical (FPP) that has been previously shown to positively modulate nitric oxide (NO). Forty-two healthy middle-aged subjects were given 3 grams of FPP three times a day for 6 weeks, and tests were repeated at 3 and 6 weeks; the control group was given a placebo. Flow-mediated dilation (FMD) was measured together with NO compounds (nitrogen oxides [NOx]: NO<sub>2</sub> - + NO<sub>3</sub> -) plasma levels and asymmetrical dimethylarginine (ADMA). In the interventional group, overall FMD significantly increased from 4.2% to 7.3% ( $p < 0.05$  vs. placebo). A significant increase in plasma NO and a decrease in ADMA were detected after consumption of FPP ( $p < 0.01$ ). Although larger studies are awaited, it appears that, at least in healthy individuals, such nutraceutical intervention by positively acting on significant cardiovascular parameters can be considered in the armamentarium of a proactive age-management strategy.

*Rejuvenation Research* Volume 15, Number 2, 2012

## **Redox Balance Signalling in Occupational Stress: Modification by Nutraceutical Intervention**

F. Marotta, Y. Naito, F. Padriani, X. Xuewei, S. Jain, V. Soresi, L. Zhou, R. Catanzaro, K. Zhong,  
A. Polimeni And D.H. Chui

There is increasing evidence that psychosocial stress can be viewed as a system-wide derangement of cellular homeostasis, with heightened oxidative stress and triggered pro-inflammatory mechanisms. The aim of this study is twofold: a) to replicate findings that psychological stress increases oxidative damage and b) to determine whether a fermented papaya preparation known to exert significant protective antioxidant properties could buffer such increases in nuclear DNA damage while also inducing epigenetic protective mechanisms. Twenty-eight sedentary men and women (age range: 28-52), who reported living a stressful lifestyle but with an overall positive attitude, were recruited for this study. Chronic diseases as well as severe burnout and use of drugs for anxiety constituted exclusion criteria. Subjects were supplemented for 1 month with 9g/day (4.5g twice a day) of a certified fermented papaya preparation. All subjects were given a stress and sleep quality questionnaire together with a diet and life style assessment. Blood was collected at 2 and 4 week, erythrocyte and leukocyte were separated to assess redox balance and heme oxygenase-1 (HO-1) gene expression while bilirubin oxidized metabolites (BOMs) were tested in the urine. Stressed individuals showed a significant abnormality of redox status with increased MDA of erythrocyte and increased level of 8-OHdG in leukocyte and BOMs excretion ( $p < 0.05$ ). Nutraceutical supplementation brought about a normalization of such values already at the 2 week observation ( $p < 0.05$ ) together with a significant up-regulation of HO-1 ( $p < 0.01$ ). Taken together, the results of this study confirm that stressful occupational life per se, without any overt psychiatric illness, may be associated to increased oxidative stress. Supplementation with functional food affecting redox regulation may be part of the therapeutic armamentarium to be considered in this clinical setting.

*Journal of Biological Regulators & Homeostatic Agents 2011 Apr-Jun; 25(2):221-9*  
*PMID: 21880211 [PubMed - indexed for MEDLINE]*

## **Evolving concepts in nutrition: from functional foods to nutrigenomics: the paradigmatic example of fermented papaya preparation**

Marotta F, Polimeni A, Mantello P

FPP certainly represents a Functional Food, highly compliant with the novel features of the new nutrigenomic-driven action plan strategy aimed at disease risk reduction and successful integration within specific pharmacological treatments.

*Approaches to Aging Control. Vol 15. september 2011*

## **Effect of a fermented nutraceutical on thioredoxin level and TNF- $\alpha$ signalling in cirrhotic patients**

F. Marotta, D.H. Chui, S. Jain, A. Polimeni, K. Koike, L. Zhou, A. Lorenzetti, H. Shimizu And H. Yang

The aim of this study is to gain further insights into the possible nutraceutical effect on redox balance via thioredoxin (Trx) modulation and on the intrinsic susceptibility of monocytes to generate an inflammatory response. The study group consisted of thirty-two patients with compensated Child A-C, HCV-related cirrhosis. The patients were supplemented for 6 months with 6g/day of a certified fermented papaya preparation (FPP). Fifteen unsupplemented, age/gender-matched healthy subjects served as controls. The patients filled in a detailed diet-life style questionnaire, and blood samples were collected to test routine biochemistry, Trx, redox status (GSH, GSSG, GSH/GSSG ratio, 4-HNE and  $\alpha$ -tocopherol). Moreover, isolated monocytes were tested for *ex-vivo* LPS-stimulated TNF- $\alpha$  production and TNF- $\alpha$  mRNA. As compared to control, patients with liver cirrhosis showed a significantly higher serum level of Trx. A significant correlation occurred with GSH/GSSG ratio in Child B and C patients. FPP supplementation brought about a significant reduction of Trx with levels comparable to the ones of healthy controls. Ten patients Child C (31.2%) showed borderline low levels of  $\alpha$ -tocopherol while all cirrhotic patients, as a whole, showed a significantly abnormal redox balance. Supplementation with FPP did not modify  $\alpha$ -tocopherol depletion but significantly improved redox balance parameters. Patients with liver cirrhosis showed a significantly up-regulated TNF- $\alpha$  production in a time-dependent manner and this effect was more pronounced in more advanced stages of the disease and showed a significant correlation with  $\alpha$ -tocopherol level. Supplementation with FPP significantly, although partially, down-regulated TNF- $\alpha$  production from monocytes. Taken altogether, it would appear that the typical oxidative-inflammatory biochemical milieu of these patients is mirrored by a significant TNF- $\alpha$  up-regulation at a monocyte level while a targeted nutraceutical might be a potentially amenable intervention to be part of validated scheduled treatments.

*Journal Of Biological Regulators & Homeostatic Agents 2011 Jan-Mar; 25(1):37-45*  
PMID: 21382272 [PubMed - indexed for MEDLINE]

## **Regulating redox balance gene expression in healthy individuals by nutraceuticals: a pilot study**

Marotta F, Koike K, Lorenzetti A, Jain S, Signorelli P, Metugriachuk Y, Mantello P, Locorotondo N

We tested the effect of a fermented papaya preparation (FPP; ORI, Gifu, Japan) on redox balance gene expression in 11 healthy nonsmoker, teetotaler individuals subjected to a detailed dietary and lifestyle questionnaire who refrained from any multivitamin supplement or fortified food. Redox status was assessed by erythrocyte and plasma parameters together with related leukocyte mRNA (glutathione peroxidase [GPx], superoxide dismutase [SOD], catalase, 8-oxoguanine glycosylase [hOGG1]) before/after 6 grams of FPP supplementation. At 2 and 4 weeks after FPP administration, plasma parameters remained unchanged, whereas FPP significantly up-regulated all tested gene expression ( $p < 0.05$ ). Although post-transcriptional/translation protein modifications do occur and larger and longer studies are awaited, these preliminary data suggest that a transcriptomic modification of key redox and DNA repair genes may offer further insights when attempting to interrelate "nutragenomics" to clinical phenomena.

*Rejuvenation Research 2010 Apr-Jun; 13(2-3):175-8. PMID: 20370494 [PubMed - indexed for MEDLINE]*

## Decreased hemolysis following administration of antioxidant - fermented papaya preparation (FPP) - to a patient with PNH

Hussam Ghoti & Hanna Rosenbaum & Eitan Fibach & Eliezer A. Rachmilewitz

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disease (HSC), characterized by intravascular hemolysis due to inactivating mutation of the X-linked PIG-A gene in an HSC; the gene product is essential for the synthesis of glycosylphosphatidylinositol (GPI) anchor molecules. Intravascular hemolysis is a major cause of anemia in PNH. Two surface proteins, CD55 and CD59, which regulate complement activation on the cell surface are GPI-linked, and their deficiency explains the hyper-susceptibility of PNH red blood cells (RBC) to complement-mediated lysis, intravascular hemolysis, and release of free hemoglobin (Hb). Hb has a vasculotoxic potential, directly impairing endothelial function and generating inflammatory and oxidative stress. Cell-free Hb disintegrates into heme and globin, and the iron from heme catalyzes the formation of reactive oxygen species (ROS) causing damage to various components of the cell. Flow cytometry analyses of RBC, platelets, and polymorphonuclear cells from patients with PNH disclosed a significant increase in ROS, while reduced glutathione was decreased. Oxidative stress was more profound in cells derived from the pathological clone with a CD55–CD59 phenotype. Increased membrane lipid peroxidation was also documented in PNH RBC. Consequently, there is evidence for increased oxidative stress in PNH, which might play a significant role in the pathophysiology of the disease. Indeed, *in-vitro* treatment of PNH-RBC with antioxidants decreased their hemolysis. Therefore, there is a rationale for treatment with antioxidants in order to reduce the oxidative stress and improve its clinical manifestations in PNH patients. One antioxidant is fermented papaya preparation (FPP), a natural health food product obtained by yeast biofermentation of *carica papaya*, which decreases oxidative stress both *in-vitro* and *in-vivo*.

*Annals of Hematology* (2010) 89:429–430. PMID: 19756600 [PubMed - indexed for MEDLINE]

## Applications and bioefficacy of the functional food supplement fermented papaya preparation

Okezie I. Aruoma, Yuki Hayashi, Francesco Marotta, Pierre Mantello, Eliezer Rachmilewitz, Luc Montagnier

Fermented papaya preparation (FPP) (a product of yeast fermentation of *Carica papaya* Linn) is a food supplement. Studies in chronic and degenerative disease conditions (such as thalassemia, cirrhosis, diabetes and aging) and performance sports show that FPP favorably modulates immunological, hematological, inflammatory, vascular and oxidative stress damage parameters. Neuroprotective potential evaluated in an Alzheimer's disease cell model showed that the toxicity of the  $\beta$ -amyloid can be significantly modulated by FPP. Oxidative stress trigger apoptotic pathways such as the c-jun N-terminal kinase (JNK) and p38-mitogen activated protein kinase (MAPK) are preferentially activated by pro-inflammatory cytokines and oxidative stress resulting in cell differentiation and apoptosis. FPP modulated the H<sub>2</sub>O<sub>2</sub>-induced ERK, Akt and p38 activation with the reduction of p38 phosphorylation induced by H<sub>2</sub>O<sub>2</sub>. FPP reduces the extent of the H<sub>2</sub>O<sub>2</sub>-induced DNA damage, an outcome corroborated by similar effects obtained in the benzo[a]pyrene treated cells. No genotoxic effect was observed in experiments with FPP exposed to HepG2 cells nor was FPP toxic to the PC12 cells. Oxidative stress-induced cell damage and inflammation are implicated in a variety of cancers, diabetes, arthritis, cardiovascular dysfunctions, neurodegenerative disorders (such as stroke, Alzheimer's disease, and Parkinson's disease), exercise physiology (including performance sports) and aging. These conditions could potentially benefit from functional nutraceutical/food supplements (as illustrated here with fermented papaya preparation) exhibiting anti-inflammatory, antioxidant, immuno-stimulatory (at the level of the mucus membrane) and induction of antioxidant enzymes.

*Toxicology* 278 (2010) 6–16. PMID: 20870007 [PubMed - indexed for MEDLINE]

## Amelioration of Oxidative Stress in RBC from Patients with $\beta$ -thalassemia Major and Intermedia and E- $\beta$ -thalassemia Following Administration of Fermented Papaya Preparation

Eitan Fibach, Ee-Shien Tan, Saumya Januar, Ivy Ng, Johnny Amer and Eliezer A. Rachmilewitz

In  $\beta$ -hemoglobinopathies, such as  $\beta$ -thalassemia (thal) and sickle cell anemia, the primary defects are mutations in the  $\beta$ -globin gene. However, many aspects of the pathophysiology are mediated by oxidative stress. Fermented papaya preparation (FPP), a natural health food product obtained by biofermentation of *carica papaya*, has been shown to limit oxidative stress both *in-vitro* and *in-vivo*. We studied the effect of FPP on two groups of  $\beta$ -thal patients:  $\beta$ -thal, major and intermedia, (in Israel) and E- $\beta$ -thal (in Singapore). The results indicated that in both groups FPP treatment increased the content of reduced glutathione (GSH) in red blood cells (RBC), and decreased their reactive oxygen species (ROS) generation, membrane lipid peroxidation, and externalization of phosphatidylserine (PS), indicating amelioration of their oxidative status, without a significant change in the hematological parameters. Since the turnover of the erythron is relatively slow, it is possible that longer duration of treatment, probably with the addition of an iron chelator, is required in order to achieve the latter goals.

**Keywords:** hemoglobinopathies, thalassemia, erythrocyte, free radicals, antioxidants, flow cytometry.

*Phytotherapy Research. 2010 Sep, 24(9):1334-8. PMID: 20127662 [PubMed - indexed for MEDLINE]*

## The Clinical Effects of Fermented Papaya Preparation® (FPP®) on Oxidative Stress in Patients with HbE/ $\beta$ –Thalassaemia

Saumya Shekhar Januar, Ee Shien Tan, Li Sun, Hai Yang Law, Angeline HM Lai, Ivy SL Ng

**Background:** Red blood cells (RBC) of patients with thalassaemia are under continuous oxidative stress. Fermented papaya preparation® (FPP®) has been shown to have an antioxidative effect and is postulated to reduce the oxidative stress on RBC.

**Objective:** To study the clinical effects of FPP treatment in patients with HbE/ $\beta$ -thalassaemia on RBC indices, oxidative stress and quality of life scores.

**Method:** Patients with HbE/ $\beta$ -thalassaemia who do not receive regular blood transfusion were included in the study and were given FPP® daily (3gm 2 times a day) for 12 weeks. Peripheral blood samples were obtained at the initiation of the study and at 4-weekly intervals thereafter for a period of 12 weeks. The following parameters were measured:

1. Haemoglobin (Hb), mean corpuscular volume (MCV), reticulocyte count;
2. Oxidation studies: production of reactive oxygen species (ROS) and intracellular glutathione content (GSH), spontaneously and in response to oxidative stress;
3. Quality of life (QoL) at the start and at the end of 12 weeks using health survey questionnaires.

**Results:** Seven patients (5 females and 2 males) were recruited to the study from January 2006 to April 2006. Median age of the study population was 19 years (range 4 to 27yrs). In vitro analyses showed production of significantly less ROS and more GSH following treatment. There was no significant difference in the Hb, MCV, reticulocyte count, clinical parameters or QoL scores. FPP® was well tolerated by all the patients.

**Conclusion:** Although oxidative stress parameters were decreased, FPP® did not have any significant effect on the Hb levels or QoL. Longer studies on larger sample size are required to study the long-term clinical effect of FPP® on clinical parameters in patients with Hb E/ $\beta$ -thalassaemia.

**Keywords:** antioxidants, erythrocytes, haemoglobin, thalassaemia

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## **Fermented Papaya Preparation as Redox Regulator in Blood Cells of $\beta$ -Thalassemic Mice and Patients**

J. Amer, A. Goldfarb, E. A. Rachmilewitz and E. Fibach

Many aspects of the pathology in  $\beta$ -hemoglobinopathies ( $\beta$ -thalassemia and sickle cell anemia) are mediated by oxidative stress. Fermented papaya preparation (FPP) was tested for its antioxidant effects: the scavenging effect was determined spectrophotometrically in a cell-free system using 2'-7'-dichlorofluorescein-diacetate (DCF). Both spontaneous and H<sub>2</sub>O<sub>2</sub>-induced DCF oxidations were decreased by FPP in a dose-dependent fashion. Using flow cytometry, it was shown that *in-vitro* treatment of blood cells from  $\beta$ -thalassemic patients with FPP increased the glutathione content of red blood cells (RBC), platelets and polymorphonuclear (PMN) leucocytes, and reduced their reactive oxygen species, membrane lipid peroxidation and externalization of phosphatidylserine. These effects result in (a) reduced thalassemic RBC sensitivity to hemolysis and phagocytosis by macrophages; (b) improved PMN ability to generate oxidative burst – an intracellular mechanism of bacteriolysis, and (c) reduced platelets tendency to undergo activation, as reflected by fewer platelets carrying external phosphatidylserine. Oral administration of FPP to  $\beta$ -thalassemic mice (50 mg/mouse/day for 3 months) and to patients (3 g x 3 times/day for 3 months), reduced all the above mentioned parameters of oxidative stress ( $p < 0.001$  in mice and  $p < 0.005$  in patients). These results suggest that FPP, as a potent antioxidant, might alleviate symptoms associated with oxidative stress in severe forms of thalassemia.

*Phytotherapy Research* 22, 820-828 (2008). PMID: 18384199 [PubMed - indexed for MEDLINE]

## **Nutraceutical Strategy in Aging Targeting Heat Shock Protein and Inflammatory Profile through Understanding Interleukin-6 Polymorphism**

F. Marotta, K. Koike, A. Lorenzetti, Y. Naito, F. Fayet, H. Shimizu and P. Marandola

The aging process is paralleled by two- to fourfold increases in plasma/serum levels of inflammatory mediators, such as cytokines and acute-phase proteins. In this study, we assessed the inflammatory profile and polymorphism of healthy elderly subjects and the fluence of a nutraceutical supplement. Forty elderly, generally healthy subjects were recruited, divided into two matched groups, and given either a fermented papaya preparation 9 g/day by mouth or the same amount of placebo. Treatments were carried out in a cross-over manner with a 3-month supplementation period followed by a 6-week washout period between treatments. Ten healthy young subjects served as controls. Interleukin-6 (IL-6) promoter -174 G/C polymorphism genotype was determined together with blood levels for redox status, proinflammatory cytokines, high sensitivity C-reactive protein, and serum 70 kDa heat shock protein (Hsp70) concentrations. Tumor necrosis factor- $\alpha$  and IL-6 were higher in elderly subjects ( $P < 0.05$  versus young controls). The concentration of Hsp70 inversely correlated with markers of inflammation in -174 G/C-negative subjects ( $r = 0.62$ ,  $P < 0.05$ ). Nutraceutical intervention normalized the inflammatory parameters ( $P < 0.05$ ) with a rise of Hsp70 ( $P < 0.05$ ). This suggests that healthy elderly individuals may have a proinflammatory profile playing as a downregulating factor for inducible Hsp70, particularly if -174 G/C-negative. A nutraceutical intervention seems able to beneficially modulate such a phenomenon.

*Ann. N.Y. Acad. Sci.* 1119 : 196-202 (2007). PMID: 18056967 [PubMed - indexed for MEDLINE]

## Oxidative-inflammatory damage in cirrhosis: Effect of vitamin E and a fermented papaya preparation

Francesco Marotta, Chisato Yoshida, Rafael Barreto, Yasuhiro Naito, Lester Packer

**Background and Aim:** Oxidative DNA damage occurs as an early event in hepatitis C virus (HCV) infection and is an indication of the potential for carcinogenesis. The aim of this study was to test a novel antioxidant/immunomodulator in patients with HCV-related cirrhosis.

**Methods:** The study group consisted of 50 patients with HCV-related cirrhosis with transaminase values less than twofold increased (alanine aminotransferase [ALT] < 80 IU/L). Patients underwent a standardized food-vitamin composition assessment and were assessed for dietary intake, nutritional status and iron level. Patients were randomly allocated into two groups and then given either  $\alpha$ -tocopherol 900 IU/day or 9 g/day of a fermented papaya preparation (FPP, Immun-Age, Osato Research Institute, Gifu, Japan) at bedtime for 6 months. Ten healthy subjects served as controls. Patients were checked monthly for: routine tests, redox status (reduced glutathione, glutathione peroxidase, oxidized glutathione, malondialdehyde), plasma  $\alpha$ -tocopherol, 8-hydroxy-deoxy-guanidine (8-OHdG) level in circulating leukocyte DNA and serum levels of cytokines.

**Results:** Patients with cirrhosis showed a significant imbalance of redox status (low antioxidants/high oxidative stress markers) ( $P < 0.005$  vs controls). Neither treatment regimen affected transaminases as a whole. However, vitamin E supplementation almost normalized ALT only in the limited vitamin-E-deficient subgroup. A significant improvement of redox status was obtained by both regimens. However, only FPP significantly decreased 8-OHdG and the improvement of cytokine balance with FPP was significantly better than with vitamin E treatment ( $P < 0.05$ ).

**Conclusions:** Although the present data seem to suggest a potential supportive role of antioxidants/immunomodulators as FPP in HCV patients, more studies are needed to substantiate their effect on the natural history of the disease.

**Keywords:** antioxidants, cytokines, fermented papaya preparation, liver cirrhosis, oxidative stress

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# **Nutraceutical Supplementation: Effect of a Fermented Papaya Preparation on Redox Status and DNA Damage in healthy elderly individuals and relationship with GSTM1 Genotype.**

## ***A randomized, placebo-controlled, cross-over study***

F. Marotta, M Weksler, Y Naito, C Yoshida, M Yoshioka, P. Marandola

### **Summary**

Our study group consisted of 54 elderly patients without major invalidating diseases who were randomly divided in two fully matched groups. Group A was given a certified fermented papaya preparation 9g/day by mouth while group B received placebo. Treatment was carried out in a cross-over manner with a 3 months supplementation followed by a 6-week washout period. Blood samples were withdrawn at entry and on a monthly basis to check routine parameters, redox status and 8-OHdG in circulating leukocyte DNA. Polymorphism analysis of GSTM1 was carried out too. GSTM1 genotype was null (-) in 40% and 46% of group A and B, respectively. GSTM1 (-) smokers had a significantly higher level of plasma DNA adducts and leukocytes level of 8OHdG than the GSTM1 (+) counterpart ( $p < 0.01$ ). There was a weak correlation between cigarette smoked/day and DNA adduct ( $r: 0.61, p < 0.05$ ) which also correlated with antioxidants concentrations but only in GSTM1 (-) smokers ( $p < 0.01$ ). FPP-supplemented group showed a significant enhancement of the antioxidant protection ( $p < 0.01$  vs A) within the subgroups with GSTM1 (-) and of plasma DNA adduct, irrespective of the GSTM1 genotype. Only GSTM1 (-) subgroup was the one which, under FPP treatment improved lymphocyte 8OHdG ( $p < 0.01$ ). Such preliminary data show that FPP is a promising nutraceutical improving antioxidant defense in elderly patients even without any overt antioxidant deficiency state while help explaining some inconsistent results of prior interventional studies.

### **Introduction**

Reactive oxygen species have been implicated in the pathogenesis of many chronic diseases since they may cause a different degree of DNA damage and other biological molecules. Such DNA damage can account for the genetic changes that take place along with the progression from cancer-predisponent abnormalities to precancerous lesions and, eventually, to anaplastic cancerous growth and metastasis dissemination. On the other hand, it is known that, even without any overt disease, oxidative damage to DNA, proteins, and lipids accumulates with age and contributes to degenerative diseases and the aging phenomenon by disrupting cellular homeostasis. Moreover, this population is more prone to depleted antioxidant defenses due to poor/improper intake while a number of elderly may concomitantly suffer from a subclinical impaired gut absorption ability. In this respect, a study conducted among 490 geriatric patients has showed that over 40% had indeed an occult malabsorption. To make the field of interventional nutrition even more complex, although intriguing, the post-genomic era has opened new avenues in the study of specific genotype-modulated understanding of the interrelationships between food, food components and xenobiotics exposure with each single individual response. As an example, quite interestingly, Palli et al. has recently suggested that the effect of dietary antioxidants in reducing DNA adducts is dependent by the detoxifying activity of GSTM1 isoenzyme. This finding is of great practical relevance and may help explaining some contradictory or inconclusive results of studies tackling the issue of antioxidants and genomic abnormalities when considering that GSTM1 gene deficiency has been shown to occur in approximately half of the populations of various ethnic origins, mostly Caucasian, Japanese and white americans. GSTM1 deficiency has been shown to increase DNA adduct formation and cytogenetic damage. Indeed, the glutathione S-transferases (GST) represent a crucial enzymatic system of the cellular mechanism of detoxification by protecting cells against reactive oxygen metabolites due to the conjugation of glutathione with electrophilic compounds. GST enzymes are involved in the metabolism of xenobiotics that include environmental carcinogens, reactive oxygen species and chemotherapeutic agents. Associations of GSTM1 and/or GSTT1 null genotypes with bladder, lung, and colorectal cancer, as well as head and neck squamous cell carcinoma have been reported and represent an area of growing intensive research.

The aim of the present study was to test in an healthy elderly population whether a novel functional food, endowed by a number of bench-validation studies proving its potent antioxidant and NO-modulating properties, could beneficially affect some redox status abnormalities which are likely to take place with advancing age while trying to get further insights into the meditative role of GSTM1 genotype status.

*Annals. N. Y. Acad. Sciences. 2006 May;1067:400-7. PMID: 16804018 [PubMed - indexed for MEDLINE]*

## **Relationship Between Aging and Susceptibility of Erythrocytes to Oxidative Damage: In View of Nutraceutical Interventions**

Marotta F, Pavasuthipaisit K, Yoshida C, Albergati F, Marandola P

Twelve (12) healthy elderly subjects were divided into two groups: (a) those given an antioxidant/NO-modulating fermented papaya preparation (FPP) 9 g/day for 4 weeks, and (b) a placebo group. No protein/lipid distribution in erythrocytes (RBC) membranes was noted among different ages and treatments. Higher RBC concentration of malondialdehyde and nitric oxide synthase were found in the elderly ( $p < 0.05$  versus "young" controls), whereas superoxide dismutase was unaltered. Such abnormalities were prevented by FPP supplementation ( $p < 0.01$ ). RBC and RBC ghosts showed an enhanced susceptibility to lipid peroxidation by using cumene hydroperoxide ( $p < 0.01$  versus young) but FPP supplementation significantly protected intact RBC ( $p < 0.05$ ). These preliminary data suggest that nutraceuticals with antioxidant/NO-regulating properties significantly protect from RBC oxidative damage, and are potential weapons for the aging process and chronic and degenerative diseases.

*Rejuvenation Research. 2006; 9(2):227-30. PMID: 16706649 [PubMed - indexed for MEDLINE]*

## **New and future prospects of protective potentials of Fermented Papaya Preparation (Immun'Age FPP) in inflammatory and neurodegenerative chronic diseases**

M.E.Weksler, O.I. Aruoma, F. Marotta, P. Mantello

### **Aging, Oxidative Stress and Alzheimer's Disease**

Considerable evidence has been obtained that free-radical damage is evident in patients with AD. Preliminary evidence suggests that anti-oxidants that reduce free radical stress can limit the generation of A $\beta$  that would be expected to delay the development and/or the progression of AD. Finally, animal studies suggest that gene therapy directed at suppressing the expression of iNOS may prevent the generation of cerebral A $\beta$  plaques.

The availability of means to measure free radical damage in patients with MCI or AD is now available. Thus, the two most promising therapeutic means of preventing free radical damage - anti-oxidant administration or gene therapy directed at the enzymes responsible for the synthesis of reactive oxygen or nitrogen species - can be documented in patients with MCI or AD using surrogate markers of free radical brain damage that appear in the CSF and/or the blood.

*Marc E. Weksler, M.D.*

*Entretiens de Bichat Thérapeutique, Sept 2006*

### **Fermented Papaya Preparation, Dietary Antioxidants and Neuroprotective Potentials.**

The outcome of ongoing clinical trials with FPP will help to unequivocally endorse the clinical benefits in patients with chronic inflammatory and neuroinflammatory diseases and for the management of degenerative aging, hence maintaining the fountains of youth in the older population.

*Okezie I. Aruoma*

*Entretiens de Bichat Thérapeutique, Sept 2006*

### **“Inflammaging” and Redox regulation: FPP role**

Aging and chronic diseases have both oxidative and inflammatory manifestations which we have to counteract in order to avoid their deleterious consequences at a cellular and molecular level. These manifestations are widely linked to a real auto amplification vicious circle.

Human immune-senescence is characterized by complex modifications where clonal immunity decrease when innate ancestral immunity is widely preserved. Immuno-inflammatory response to continuous different environmental stresses lead to production of numerous mediators like pro-inflammatory cytokines as well as production of reactive oxygen species which have auto-stimulating properties.

In many chronic inflammatory syndromes, it is proved that oxidative stress by oxidative mediator production either due to a diminution of antioxidative systems and /or due to a lack of essential antioxidative nutriment, is a factor generating or at least contributing to maintenance of immune and inflammatory response with dysfunction or destruction of cells.

Inflammaging observed during aging is also responsible of a positive regulation of wide responses to molecular and cellular level stresses which lead to molecular and cellular injury accumulation.

Redox regulation control of organism is essential to limit deleterious effects in chronic diseases as well as in aging.

Three studies realized with FPP have shown protection potential of this food supplement in different therapeutic schemas even by patients suffering from hepatitis C or for prevention of oxidative damages by elderly people in good health.

*F.Marotta*

*Entretiens de Bichat Thérapeutique, Sept 2006*

## **Functional Foods as catalysts of the nutrition evolution into nutrigenomics: a scholastic example of a fermented papaya preparation (Immun'Age)**

F. Marotta, E. Minelli, P. Marandola

### **Functional Food: a recent history dating back in time**

"Functional Foods" represent an emerging opportunity and they will certainly play a consistent and important role in future too. Such a new perspective entirely depends on the growing attention paid by nutritionists to the development of new innovating solutions aiming at acting on organic systems as well as on more general topics relating to consumer good health conditions. Differently from the past, when mainly retrospective epidemiological studies or empirical experiences were carried out on single nutrients, such a new and growing interest by the scientific community follows research deeply oriented to clinics supplemented by an accurate study on nutrients, genomics and single nutritional requirement diagnostics. Already in 1993, Nature published a report "Japan is exploring limits between food and medicine". Clearly the success of "Functional Foods" depends also on the food industry capacity of developing new effective products which on the one side meet consumers requests and on the other must have positive effects on health, supported and validated by scientific research and therefore far beyond a simplistic claiming of positive properties, as recently underlined in a meeting, organized by a not profit non governmental international association.

### **Definition and demanded features**

Such a new philosophy in the last few years lead to constant changes in the Functional Food definition which an authoritative scientific European panel defined as followed in 1999 "A nutrient can only be easily considered functional if it was satisfactorily proved that it can positively change one or more target functions, besides nutritional effects, as to consistently improve health, well-being while reducing any affection risk. A Functional Food should ideally be a nutrient and should not change its efficacy when entering into a diet, it should not be either a pill or a capsule". It was then agreed that, from a practical viewpoint, a Functional Food should comply with the following features:

- 1) a natural food;
- 2) a food which was simply supplemented by a component;
- 3) a food which was no longer holding a component;
- 4) a food which the nature of one of more components had been changed;
- 5) a food which one or more component availability had been changed;
- 6) a combination of the previous features.

It was then underlined how, besides its nutritional properties or physiological effects, it is mandatory to offer a consistent safety profile of its administration. Such a condition is nothing but a prerequisite to further develop any Functional Food. From the recommendations of such an European commission, it is possible to come to the conclusion that "The design and development of a Functional Food is a key factors, besides a scientific challenge, which should be mainly based on consistent scientific knowledge in terms of target functions and their possible modulations by nutritional components". And therefore it is furthermore stressed that "Functional Foods are not universal, therefore a nutritional-specific approach would be no longer suitable, but rather a basic scientific approach would only apply".

It is important to underline a new concept within nutrition on the role played by Functional Foods science, which is the only one to be followed to get to useful clinical interferences.

An ancient Chinese proverb specifies that "medicine and food are isogenic" and it is not by chance that in 1984, in Japan, a unique national study group was set up, sponsored by the Ministry of Education, Science and Culture (MESC), aiming at exploring the interface between nutrition and science. Scientists in time studied and defined a series of foods and nutrients which were officially listed in the category "foods to be specifically administered for health-care", stressing and recognizing their nutritional value, after undergoing a consistent bio-fermentation process. Such a classification is still a legally-binding tool against media communication of wrongly defined natural products, misleading or simply recalling data from the literature but not followed by specific validations of the product itself.

*Middle East Journal of Age and Ageing 2005; 3: 1-6*

## The Aging/Precancerous Gastric Mucosa: A Pilot Nutraceutical Trial

F. Marotta , R. Barreto , H. Tajiri , J. Bertuccelli , P. Safran , Yoshida and E. Fesce

The aim of this study was to test the effect of antioxidant supplementation on enzymatic abnormalities and free radical-modified DNA adducts associated with premalignant changes in the gastric mucosa of elderly patients with HP-negative atrophic gastritis (CAG). Sixty patients with atrophic gastritis and intestinal metaplasia underwent a nutritional interview and a gastroscopy with multiple biopsy samples in the antrum that were processed for histology and for assaying: alpha-tocopherol, MDA, xanthine oxidase (XO), ornithine decarboxylase (ODC), and 8-OHdG. Patients were randomly allocated into three matched groups and supplemented for 6 months with (1) vitamin E, 300 mg/day; (2) multivitamin, two tablets t.i.d.; and (3) Immun-Age 6 g/day nocte (ORI, Gifu, Japan), a certified fermented papaya preparation with basic science-validated antioxidant/immunomodulant properties. Ten dyspeptic patients served as controls. Histology and biochemistry were blindly repeated at 3 and 6 months. CAG patients showed a significantly ( $P < .05$ ) increased level of mucosal MDA and XO concentration that were reverted to normal by each supplementation ( $P < .05$ ). All supplements caused a significant decrease of ODC ( $P < .01$ ), but Immun-Age yielded the most effective ( $P < 0.05$ ) and was the only one significantly decreasing 8-OHdG ( $P < 0.05$ ). These data suggest that antioxidant supplementation, and, namely, Immun-Age, might be potential chemopreventive agents in HP-eradicated CAG patients and especially in the elderly population.

KEYWORDS: oxidative stress; atrophic gastritis; ODC activity; 8-OHdG; antioxidants

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## **Fermented Papaya interest on our health: benefits on oxidative stress and immunity**

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ISBN 2 – 7046-1675-2

### **Oxidative stress and chronic diseases,**

Pr Luc Montagnier, M. Brack, H. Chenal, P. Mantello

Oxidative stress (excess of free radicals) is involved in many chronic diseases related to environmental factors. It is therefore logical to suggest to patients suffering from these diseases the use of appropriate antioxidants, in extra conventional treatment and also for prevention.

From a simple blood test, specific tests permit to assess various parameters of oxidative stress and antioxidant capacity of the body. We can thus make rational use of antioxidants to correct observed abnormalities.

Tested as controlled clinical trials, new antioxidant and immunostimulant preparations, such as the fermented papaya extract (FPP) and vitamin C stabilized glutathione, suggest beneficial results. When used as a preventive measure, it can be assumed that the recovery to normal values of antioxidant parameters reduce the risk of developing these disorders, paving the way for a new medicine both prospective and preventive.

*ISBN 2 – 7046-1675-2 - pages 232-236*

### **Action of FPP on immune system cells**

Pr Lester Packer

Healthy aging and prevent disease through the use of micronutrients is an area of increasingly interest for public health and biomedical research.

Diseases related to our lifestyle could be avoided in most cases. The most important factors affecting health are prevention of oxidative stress and improvement of antioxidant and immune systems.

FPP, fermented papaya preparation, has an antioxidant action in vitro and in vivo. In macrophages and neutrophils, the FPP induced the production of nitric oxide, superoxide and cytokines.

A strong anti-oxidant activity and a powerful immune system are essential properties for healthy aging and effectively fight infections and diseases; FPP has these properties.

*ISBN 2 – 7046-1675-2 - pages 237-244*

### **FPP & Gastroenterology: benefits of fermented papaya.**

Pr Francesco Marotta (Milan)

Four published clinical studies, conducted double-blind against placebo, showed the beneficial effect of FPP on biological disturbances encountered in moderate drinkers or in alcoholics.

The antioxidant power of the FPP is primarily responsible for the protective effects on the gastric mucosa, improved rheological disturbances (decreased lipid peroxidation) and a normalization of the absorption of vitamin B12.

Other effects on hepatitis C have shown promising results.

*ISBN 2 – 7046-1675-2 - pages 244-251*

## Improvement of Hemorheological Abnormalities in Alcoholics by an Oral Antioxidant

F. Marotta, P. Safran, H. Tajiri, G. Princess, H. Anzulovic, GM Ideo, A Rouge, MG Seal, G. Ideo

It has been shown that alcohol might impair erythrocyte (RBC) membrane fluidity and lipid composition. In particular, low-molecular thiol concentration has been pointed out as a main step of such derangement. The aim of this study was to test the effect of a novel acid-resistant antioxidant on the haemorrheological parameters in alcoholics.

Thirty alcoholics (150g ethanol/day for 3 or 5 years) were randomly, double-blindly allocated into 2 groups which were given for 2 weeks 18g/day of FPP (obtained from biofermentation of Carica Papaya, Osato Research Foundation, Gifu, Japan) dissolved in 5ml of water at bedtime and 3 hours prior examination or placebo devoid of any antioxidant property.

On the examination day blood samples were taken for routine tests, alcohol, acetaldehyde, plasma GSH and erythrocyte (RBC)-malondialdehyde (MDA). Hemorheological studies were as follows: blood and plasma viscosity, whole blood filterability, RBC-membrane fluidity by electron spin resonance, RBC-aggregation index by photometric rheoscopy and RBC-deformability by ektacytometry (laser diffraction analysis).

As compared to controls, alcoholics on placebo treatment showed no change of plasma viscosity but a significantly higher RBC-MDA, blood viscosity ( $p < 0.05$ ) and lower plasma GSH, whole blood filterability and RBC membrane fluidity ( $p < 0.01$ ).

No relationship appeared between biochemical tests and membrane fluidity. FPP group showed a significant recover to control values of either blood viscosity and whole blood filterability ( $p < 0.01$ ) and a partial although significant improvement of RBC-membrane fluidity ( $p < 0.05$ ), RBC-MDA and plasma GSH.

As compared to control, RBC aggregation decreased in alcoholics ( $p < 0.05$ ) and was not affected by FPP. However, FPP significantly improved ( $p < 0.05$ ) the reduced RBC deformability observed in alcoholics ( $p < 0.05$  vs control) and which correlated to RBC-MDA ( $r: 0.62$ ,  $p < 0.05$ ).

These data suggest that an effective antioxidant supplementation is able to improve the hemorheology in alcoholics either by directly affecting the ethanol related lipoperoxidation and xanthine oxidase system activation and/or by modifying RBC membranes characteristics.

*Hepato-Gastroenterology 2001; 48:511-517. PMID: 11379344 [PubMed - indexed for MEDLINE]*

## Cyanocobalamin Absorption Abnormality in Alcoholics is Improved by Oral Supplementation with a Fermented Papaya-derived Antioxidant

F. Marotta, H. Tajiri, R. Barreto, P. Brasca, GM Ideo, L Mondazzi, P. Safran, J Bobadilla, G. Ideo

**Backgrounds / Aims:** Thirty alcoholic patients and 24 teetotaler dyspeptic patients were considered and underwent baseline blood chemical evaluation and the Schilling test.

**Methodology:** During gastroscopy, biopsy samples were taken to assay: routine histology, malonyldialdehyde, vitamin E and glutathione concentration and for testing vitamin B12 – Intrinsic Factor binding. Examinations were repeated after 1 week supplementation with FPP (Fermented Papaya Fermentation)

**Results:** Plasma malonyldialdehyde level and lipid hydroperoxides concentration as well as either malonyldialdehyde and xanthine oxidase concentration in the gastric mucosa in alcoholics were significantly decreased after FPP supplementation.

Gastric mucosal glutathione was markedly depressed in alcoholics and partly recovered after FPP supplementation. Although the alcoholics showed a normal intrinsic factor secretion in the gastric juice, they exhibited a markedly depressed intrinsic factor-cobalamin binding on the “ex vivo” study. Moreover, nearly 23% of them had an abnormal Schilling test. Both these impairments reverted to normal after FPP supplementation.

**Conclusions:** It can be postulated that the antioxidative action played by FPP, possibly due to its availability substrates for glutathione synthesis as well as to its effects on local antioxidative burst from neutrophil, is able to recover a normal cobalamin absorption.

**Ethanol-Related Gastric Mucosal Damage:  
Evidence of a Free Radical-Mediated Mechanism and Beneficial Effect of Oral  
Supplementation with Immun'Age (FPP), a Novel Natural Antioxidant**

F. Marotta, H. Tajiri, P. Safran, E. Fesce, G. Ideo

Twenty-two healthy teetotal volunteers underwent gastroscopy during which biopsy samples from the antrum and body were taken for chemiluminescence assay, routine histology, and for malonyldialdehyde, xanthine oxidase and glutathione determination. Subjects were divided into 2 groups which, in a double-blind fashion, were randomly and orally given either (a) FPP (Fermented Papaya Preparation) 9 g at bedtime and 3 h prior examination, or (b) flavored sugar 9 g as placebo. During the second gastroscopy 40 ml of 80% ethanol were sprayed perendoscopically. Gastroscopy with biopsy was repeated 60 min later. As compared to the placebo group, subjects given FPP showed significantly reduced gastric mucosal damage at endoscopy and the histological level. When considering the placebo group, ethanol administration brought about a significant increase in the luminol-amplified chemiluminescence response in gastric mucosa as compared to the baseline value which was correlated with the histological score. The mean chemiluminescence value in the FPP group was significantly lower than in the placebo group. Ethanol ingestion brought about a significant increase in xanthine oxidase and malonyldialdehyde together with a decreased glutathione concentration. FPP significantly prevented such changes. The present data suggest that the natural antioxidant FPP when given orally promotes an effective protection against ethanol-induced gastric mucosal damage.

*Digestion* 1999; 60:538-543

**Abstinence-Induced Oxidative Stress in Moderate Drinkers  
Is Improved by Immun'Age (FPP)**

F. Marotta, Reizakovich, H. Tajiri, P. Safran, G. Ideo

The aim of this investigation was to study the oxidative phenomena which take place in the early recovery phase after alcohol withdrawal. Further, the effect of a novel antioxidant, i.e. FPP, in such clinical setting was studied. Forty-six alcoholics (HBV and HCV negative) with moderate drinking habits (daily ethanol intake: >80g - <120g) were enrolled and divided in two groups given either placebo or 9g/nocte of FPP by mouth for one week. Patients agreed to stop alcohol intake and daily blood sampling was obtained for routine tests and to check plasma and erythrocyte level of MDA, SOD, GPX and hydro peroxide level. Groups were comparable as for initial routine blood biochemical and antioxidant parameters (selenium, a tocopherol, ascorbic acid and erythrocyte GPX), as well as smoking habit. Two patients on FPP were later excluded for protocol violation. FPP prevented the early increase of plasma TBARS observed in placebo group enabling a near-to-normal level also of erythrocyte MDA already on the fourth day. FPP also prevented the significant drop of erythrocyte GPX and the transient decrease of plasma SOD observed in placebo group. Despite alcohol withdrawal, plasma lipid hydro peroxide remained significantly elevated in placebo group but this phenomenon was rapidly improved by FPP. These data suggest that a pro-oxidative condition with an avid consumption of SOD and glutathione still takes place once alcohol ingestion is stopped while confirming the enhanced susceptibility to oxidative stress due to derangement of structural membrane lipids in patients with alcohol-related liver disease. FPP is able to significantly prevent free radical-mediated lipoperoxidative changes occurring soon after alcohol withdrawal while fastening the recovery mechanisms. Alcoholics would potentially benefit from increased dietary supplementation of truly effective natural free radicals scavengers, such as FPP.

*Hepato-Gastroenterology* 44:1360-1366, 1997. PMID: 9356856 [PubMed - indexed for MEDLINE]

## **Radio protective and Antioxidant Effects of Zinc Aspartate and Fermented Papaya Preparation F.P.P. in Children with Acute Myelo- Lympholeukemia**

Korkina L.G., Osato J.A., Afanas'ev I.B., and al.

The combined use of irradiation and chemotherapy is a fundamental principle in modern cancer management, especially in children. The only limitation is that cytotoxic drugs enhance the radiation damage to normal tissues. Radiation therapy can induce acute and late reaction of normal tissue. Although acute radiation injury is mostly expressed in the rapidly proliferating tissues such as skin, mucous membranes, spermatogonia and hematopoietic cells, the late deleterious effects of irradiation occur in the central nervous system. The encephalopathy syndrome has been documented in about 50% of children with acute lympholeukemia (ALL) subjected to cranial and spinal cord irradiation for 4 to 8 weeks. This includes headache, somnolence, anorexia, nausea, vomiting and sometimes unconsciousness. As the injury following the ionizing irradiation exposure is the most spectacular example of free radical-mediated pathology, it is not surprising that radioprotective agents usually possess free-radical scavenging properties. Earlier, we showed that FPP, a non-toxic natural food supplement is a powerful immunomodulator that stimulates macrophages and lymphocytes to produce  $\alpha$ -TNF and interferons. In addition, FPP exhibits free-radical scavenging and antioxidant activities. Therefore, it seems interesting to study the effects of the zinc-aspartate and FPP administration to children suffering from acute myelo and lympholeukemia in order to prevent the late encephalopathy syndrome.

Examination of children by pediatricians during and after the completion of clinical trial (19 ALL, 9 AML) has shown that there were no toxic side effects, allergic reactions, or other adverse events during the Unizinc and FPP administration.

Data of these study suggest that the strong protocol treatment of lympho- and myeloproliferative malignancies caused the suppression of main intracellular antioxidant enzymes and drastically induced hydroxyl radical release from leukocytes which can be the source of the central nervous system oxidative damage induced by therapeutic irradiation. Unizinc can treat such deleterious effects of irradiation by the inhibition of oxygen radical overproduction by circulated leukocytes. The reasons for beneficial radio protective effects of FPP seem to be more complex. Besides its pronounced free-radical scavenging activity, FPP appears to increase the organism potency to be adapted to oxidative stress, inducing glutathione synthesis and/or preventing glutathione oxidation and enhancing MnSOD activity in leukocytes, especially in patients. Probably, FPP stimulates MnSOD indirectly, inducing  $\alpha$ -TNF production by myelocytic leukocytes. Collectively, zinc aspartate and FPP could be regarded as essential components of supportive care of cancer patients after intensive irradiation course.

*Supplement to Nutrition Vol 11, N°5: 555-558, 1995*

## **Effects of dietary supplement on IFN producing capacity in humans**

A. Kishi, K. Uno, Y. Matsubara, A. Osato, T. Kishida

We studied the effects of oral administration for one month of dietary supplements such as *Labre*, *FPP* and *Spirulina A* on IFN producing capacity of the whole blood of human individuals. *Labre* is a newly isolated *Lactobacillus brevis* sp. Coagulans from *suguki* pickles. FPP is a nutraceutical product of the fermentation of herbal plants. *Spirulina A* consists mainly of *Spirulina* alga. IFN- $\alpha$  producing capacity was determined by bioassay and IFN- $\gamma$  producing capacity by time-resolved immunofluoroassay. The increased levels of IFN- $\alpha$  and IFN- $\gamma$  production were observed in the *Labre* group and in the FPP group, respectively, but no change of IFN production was seen in the *Spirulina* group. IFN- $\alpha$  and IFN- $\gamma$  producing capacities are considered to be useful parameters of immunological functions. Therefore, it is suggested that the enhancement of these immunological functions improves the general condition and the quality of life of patients with impaired immune competence without any side effects.

*Journal of Interferon Research. Vol. 14 Supplement 1, 1994*

## **Effects of Bio-Normalizer (FPP) on Serum Components and Immunological Functions in Humans**

Santiago L.A., Uno K., Kishida T., Miyagawa F., Osato J.A. and Mori A.

We studied the effect of the one-month administration of FPP on the immunological, hematological, biochemical, and antioxidant functions of the blood and serum of 14 healthy and unhealthy subjects, and observed an increased mean rate of interferon- $\gamma$  production in both groups while a downtrend then uptrend or vice-versa were noted in the production of interferon- $\alpha$ , 2-5A synthetase activity, and phytoagglutinins or concanavalin A-stimulated proliferative activity. The exceptionally high levels of GOT and GPT and the lipid components in three unhealthy subjects were significantly decrease after 14 days of treatment. The thiobarbituric acid-reactive substances increase while the superoxide dismutase activity didn't change. The ability of FPP to increase interferon- $\gamma$  producing capacity provides greater resistance for lymphocytes or helper T cells to combat infections and diseases.

*Neurosciences, Vol.20s: 149-152, 1994*

## **Effect of Bio-Normalizer (FPP) on the alcohol induced changes in blood substances in human**

Koide Y., Miyagawa Y., Osato A., Santiago L.A. and Mori A.

The amount of glucose and superoxide dismutase (SOD) in the blood has been known to undergo changes during alcohol intake. To determine the effects of FPP on these substances, a group of male subjects was allowed to drink alcohol. In addition, half of the group was given FPP and the other one was not fed with FPP. Measurement of the aforementioned substances was made at three time points: before alcohol intake and then 40 and 120 minutes after drinking. The blood sugar level of those who did not receive FPP was significantly reduced 120 minutes after alcohol intake while the activity of the protective anti-oxidant enzyme SOD was found to decrease 40 minutes after drinking. However, during the second measurement, the SOD activity was found to be increased. On the other hand, those who received FPP had no change in glucose level after alcohol intake. The SOD activity was initially high, most probably due to the enhancing action of FPP on this enzyme, a finding supportive of what we found in our previous study. Moreover, the activity level 40 minutes after drinking remained high and was significantly higher than that shown without FPP. This indicates that FPP has a potential to increase the SOD activity and to prevent the decrease of SOD activity due to alcohol drinking. These findings provide evidences about the protective action of FPP against alcohol-induced changes in blood substances in humans.

*Neurosciences, 19s.1: 85-88, 1993*