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Osato research institute

ori report
大里研究所®レポート

News & Activity Report

Pope Francis receiving FPP

Third audience in 2015

The president of Osato Research Institute (ORI), Yuki Hayashi, and his wife were invited for the 23rd World Day of the Sick in Vatican on February 11th, 2015. They had the great honor to be able to talk with Pope Francis and speak about the importance of preventive medicine and handed him a box of FPP (Immun'Âge).

The story with the Vatican began in June 2002 when Prof. Luc Montagnier (2008 Nobel Laureate in Physiology or Medicine) handed FPP directly to Pope John Paul II (suffering from Parkinson's) and recommended treatment for health recovery. In January 2012, the Osato team had the great honor for the second time to present FPP at the Vatican to Pope Benedict XVI. It was such an honorable and exciting news that we had the third time opportunity to present Immun'Âge to Pope this time.

Since 2012, Immun'Âge is sold in the Vatican pharmacy.

Second audience in 2012

First audience in 2002

The World Day of the Sick is a feast day of the Roman Catholic Church which was instituted on May 13th, 1992 by Pope John Paul II. Since, it is celebrated every year on the commemoration of Our Lady of Lourdes, for all believers seeks to be "a special time of prayer and sharing, of offering one's suffering".

Message from ORI director
Dr. Pierre Mantello

FPP and Inflammaging

Since you're born, you start a fight against your environment where you'll find stressors which are of very different origins. Environmental stressors could be physical, chemical or biological. Our body is equipped with defense systems in order to fight against these stressors. These natural systems of defense are organized in a network of defense functions or anti-stress responses which are playing a role of anti-aging mechanisms.

Naturally, majority of people want to live a healthy long life. To achieve this, goal factors influencing our lifespan are modifiable in order to protect ourselves against environmental stressors. Protection could be under our decision (modifications of our diet or of our bad habits, modification of our environment) or relative to our genetic equipment (different genetic polymorphisms make difference between individuals).

New medicines appear recently like predictive medicine which takes care of genetic analysis equipment allowing us to know our sensibility and by the way to the risk of having some diseases. This predictive medicine could help protect us by taking care of factors which could promote diseases at risk.

Preventive medicine by measurement of body parameters (oxidative stress parameters) which are linked with results of environmental stress allows us to protect our body by modifying habits like diet (alimentation, food supplement), by protecting us against sun or pollutants exposure.

In our network defense, our main systems are represented by our natural physiological immune and anti-oxidative systems.
Lifespan had been dramatically increased since the 20th century with progress in conventional medicine (drugs, vaccination, prophylaxis or hygiene).But progress had also come with increases of stressors like aerial pollution (industrial plants, cars…) as well as pollution inside food (pesticides in water or in food), radiations (electromagnetic fields cosmic radiation during long haul flights, Scans, X-rays or radiations due to atomic plant problems). Exhaustive activities like sport at high level or psychosocial stress due to heavy work are also stressors which are deleterious to our health.

Unfortunately, our defense systems are decreasing with age and are overtaken by these accumulations of stressors, leading to attacks resulting in acceleration of aging process. Among these attacks, we have to face particularly to a chronic systemic inflammation which we could call "Inflammaging". With societies which become 'more and more old', it is necessary to find solutions to protect us in order to stay healthy with age.

Predictive medicine allows us to change our habits in order to decrease risk of diseases, we are genetically more sensible. And preventive medicine allows us to measure results of protection we have taken. These protections we could take are of different origin. We could take care of our environment diminution of pollution exposure when it is possible or intake of food supplement which could help to counteract our diminution of defenses systems. FPP (Immun'Âge) as food supplement which is able to increase both of our main physiological systems, immune and antioxidative, is one of the best solution to help our body to stay healthy during aging. Osato Research Institute had

performed a lot of clinical studies with Immun'Âge and prove the potential of this food supplement to enhance the antioxidative and immune activity which protect our body and allow people to stay healthy during aging.

Inflammaging is the price to pay when we are getting older because keeping a good immune system during aging leads to a chronic production of inflammatory cytokines like TNF alpha, IL6 which are deleterious by creating a systemic chronic inflammation which is linked with oxidative stress.

Centenarians are able to maintain a low level of inflammatory cytokines and stay with a low systemic inflammation and keep a long healthy life. So maintaining a low level of inflammatory cytokines and keeping a low oxidative stress status is a key to stay healthy during aging. Immun'Âge which is able to decrease TNF alpha and IL6 (study LP) is a food supplement which protects us by maintaining a low level of inflammatory cytokines and could play an interesting role for anti-aging management by fighting against systemic inflammatory called "Inflammaging".

Immun'Âge is a food supplement which increases activity of the main antioxidative enzymes like SOD, Gluthatione peroxidase and numerous clinical studies support this property. Oxidative stress is an important factor in many chronic degenerative diseases linked with age like chronic hepatitis, atrophic gastritis, Alzheimer disease, Parkinson, Arteriosclérosis, and Cancers… Immun'Âge protects us by fighting against oxidative stress and could decrease risk of these degenerative diseases. During aging, our immune system is decreasing, clinical studies had proved that Immun'Âge is able to protect us against risks of infection by increasing the potential of our immune system.

A study recently made in Ohio State University has proved that Immun'Âge is able to enhances energy production (ATP) in mitochondria. This process of energy production is also decreasing during aging. Immun'Âge could protect our body against fatigue by helping energy production necessary for main body metabolisms. Immun'Âge is a unique food supplement able to protect us against decrease of our antioxidative and immune systems occurring during aging, but also able to protect us against "Inflammaging" (Chronic systemic inflammation increasing with age) and to protect us against aging weakness. With all these properties, Immun'Âge is one of the best candidate to maintain a healthy long life.

Dr. Pierre Mantello, Director of Osato Research Institute

EXPO MILANO 2015

Medical Convention for Prevention of Chronic Diseases

"The Medical Convention for Prevention of Chronic Diseases" was held on May 30 at Milano Expo 2015, as the only international congress over this six-month period. Prof. Chandan Sen from Ohio State University made a presentation on his clinical studies about the effect of FPP on Wound Closure in Type II diabetic patients and showed potentials of preventive medicine for treatment of chronic diseases. Many scientists from USA and Europe participated in this congress and the Health Minister of Vatican made a speech about the importance of Preventive Medicine. ORI sponsored this convention and Prof. Montagnier and the ORI president, Mr. Hayashi, also participated in it. On the day before his presentation, Prof. Sen received an interview by an Italian media and talked about FPP and explained that it is a great immune inducer and he uses it for his diabetic patients.
You can watch the interview here:
http://www.ori-japan.com/new/info/prof-chandan-k-senfppimmunage-2.html

Prof. Chandan Sen, making a presentation on his clinical studies for Type II diabetic patients


After the convention, we all enjoyed night at Milan Expo!


From left, Mr. Hayashi, Prof. Montagnier, and Prof. Belpomme of Paris University

At the entrance of the venue

H3C Health Sciences Innovation Conference in India

Ohio State University (OSU) and All India Institute of Medical Sciences (AIIMS) jointly hosted a Health Sciences Innovation conference in Mumbai, India, 15 - 17 January, 2015 with focus on the so-called "H3C", representing Health, Care, Commerce and Career. It was a marvelous meeting with Prof. Chandan Sen of OSU serving as the Conference Chair to explore the strategic relationship of government, industry and science for building a healthy society, in the presence of the Union Minister of Health & Family Welfare of India and the Mayor of Mumbai City.

ORI has enjoyed a long history of collaborative research relationship with the OSU, and agreed to their request for organizing the keynote lecture of Prof. Montagnier, 2008 Nobel laureate in Physiology or Medicine Prof. Luc Montagnier also co-chaired the FPP session with Mr. Hayashi, the ORI president, in which three presentations were made "the effect of FPP upon radiation exposure" by Prof. Fibach of Hebrew University, "the effect of FPP in Thalassemia" by Prof. Rachmilewitz of the Wolfson Medical Center, and also "FPP in the stimulation of respiratory burst function of innate immune cells in type Ⅱ diabetes patients" by Dr. Sashwati Roy of OSU. It is noted that researchers from different fields argued heatedly about the potential of FPP and the mechanism of its effect.


Keynote lecture of Prof. Montagnier

Front Page of the Abstract Book


Shri Jagat Prakash Nadda, the Honorable Union Minister of Health & Family Welfare of India (first right)


Prof. Montagnier (first right) and Mr. Hayashi (first left) as co-Chairmen and three presenters of FPP session (in the middle)

FPP Workshop 2014 held at ORI

On March 24, we held a workshop on the recent studies on FPP.

Firstly, Prof. Fibach made a presentation on the radio-protective effect of FPP on both animal and cell. Prof. Chandan showed FPP could enhance the immune system of diabetic patients.These two presentations are very significant to show the positive, balanced effects of FPP.

The former represents that FPP reduces oxidative damage and inflammation caused by radiation through stimulation of anti-oxidant system, while the latter shows that FPP generates free radical within a short period of time in type II diabetic patients by enhancing metabolic activity of macrophage and NADPH oxidase.

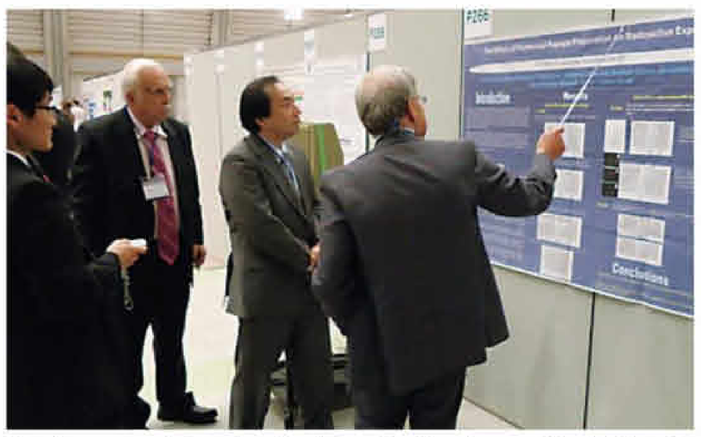
These effects are very much like the relationship of "a brake and a gas pedal" of a car. For inflammation, FPP functions as a brake by eliminating free radical for body defense. On the other hand, for weakened immune system, FPP functions as a gas pedal by accelerating free radicals to attack virus. It was a very significant workshop, showing effects of FPP which work like "two wheels of a car."

With workshop members at ORI

Presentation at SFRRI 2014 in Kyoto

The 17th Biennial Meeting of Society for Free Radical Research International (SFRRI 2014) was held at the Kyoto International Conference Center (ICCKyoto) from March 23 to 26, 2014.

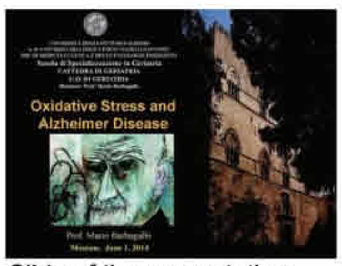
Prof. Eliezer A. Rachmilewitz and Prof. Eitan Fibach made a series of poster presentation on the effect of FPP on radioactive exposure in vivo and in vitro.


Poster presentation by Prof. Rachmilewitz and Prof. Fibach

Commemorative photograph after presentations

Presentation at the 2nd AMWC in Moscow

On June 1, 2014, Prof. Mario Barbagallo (University of Palermo, Italy) made a presentation on the effect of FPP on oxidative stress of Alzheimer patients, entitled "Oxidative Stress and Alzheimer Disease" in the 2nd Anti-Aging Medicine World Congress (AMWC) Eastern Europe held in Moscow. In the presentation, Prof. Barbagallo showed that FPP could significantly improve oxidative stress of Alzheimer patients.



Slide of the presentation

FPP Seminar at the 14th International Congress of Personalized Medicine

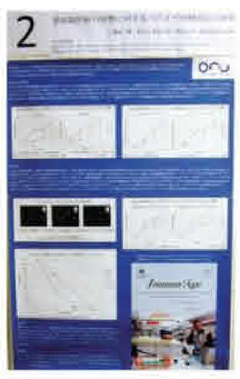
On June 2, 2012, "The 14th International Congress of Personalized Medicine" was held in Nasu, Tochigi, and the ORI director, Dr. Mantello, held a Luncheon Seminar.

He introduced researches conducted by ORI and explained the story with the Vatican, which began in June 2002 when Prof. Luc Montagnier handed FPP directly to Pope John Paul II and was followed by the second time to present FPP at the Vatican to Pope Benedict XVI in 2012.
He also reported that a project using FPP is now under way in collaboration with the Vatican. After this luncheon seminar, there was also a short lecture by ORI researcher.

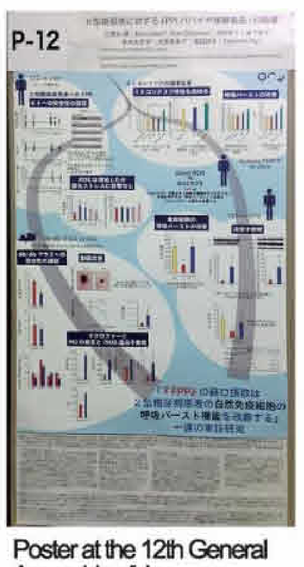

Dr. Pierre Mantello, speaking in the seminar

List of other Research Presentations

<2014> December: Poster Presentation at the 12th General Assembly of Japanese Society for Medical Use of Functional Food
November: Presentation at the 17th International Conference of FFC
September: Presentation at the meeting of the Japanese Society of Applied Glycoscience 2014
June: Poster Session and Booth Presentation at the 18th International Congress of Personalized Medicine
<2013> December: Poster Session at the 11th General Assembly of Japanese Society for Medical Use of Functional Food
September: Presentation at the meeting of the Japanese Society of Applied Glycoscience 2013
<2012> June: Booth Presentation at the 12th Scientific Meeting of Japanese Society of Anti-Aging Medicine



Poster at the 18th International Congress of Personalized Medicine on "Radio-protective effect of Fermented Papaya Preparation (FPP)"



Poster at the 12th General Assembly of Japanese Society for Medical Use of Functional Food on "Effect of FPP on Type II diabetics"


Presentation at Presentation at the meeting of the Japanese Society of Applied Glycoscience 2014

Booth at the 12th Scientific Meeting of Japanese Society of Anti-Aging Medicine

ORI Paris, UNESCO

In March 2015, Osato Research Institute opened a new office at UNESCO in Paris together with World Foundation Aids Research and Prevention Japan office.

The office is on the 15th floor and situated in the nice area in Paris with the beautiful view of the Eiffel Tower. We will work here to promote education on preventive medicine for young generation with UNESCO, in order to reduce medical costs in the aging society.

View of the Eiffel Tower from the office window!
We can be more enthusiastic for our mission.

ORI Paris
1,rue Miollis 75732 Paris Cedex 15

The ORI president, Mr. Hayashi, and the ORI director, Dr. Mantello, at UNESCO

UNESCO Youth FORUM —Four young ladies represented ORI—

The 8th UNESCO Youth Forum took place at UNESCO Headquarters in Paris, from 29 to 31 October 2013, and Osato Research Institute also participated in this forum together with several other global organizations and had a booth with the theme of reducing medical cost in aging society. The young participants of this Forum from all over the world had a precious opportunity to change their opinions to find solutions together under the overall theme "Youth and Social Inclusion: Civic Engagement, Dialogue and Skills Development". The 4 young ladies, representing ORI, Makiko Osato, Akiko Hayashi, Angela St. Pierre and Agathe Deniau, had an unforgettable experience in Paris.

Fabulous members of ORI team, spending time together for 3 days, From left, Maki, Angela, Agathe and Aki

Explaining about FPP to Ms. Irina Bokova, director-general of UNESCO

It is only opportunity for youth to make discussion at UNESCO conference hall.

Curie museum

The ORI president, Mr. Hayashi, and his wife were invited to the ceremony held on September 13, 2012 to celebrate the renovation of the Curie museum.
ORI helped the large screen display to get installed in the center of the museum under the large photo panel of the family of Mr. and Mrs. Curie so that visitors can see many photos and get information on their achievement, including the five Nobel Prizes awarded to them, by use of a touch panel screen.

In 2013, an article on the continuous support of Mr. Hayashi for the Museum appeared in the Journal of Curie Museum "LE JOURNAL DE L'INSTITUT CURIE".

『LE JOURNAL DE L'INSTITUT CURIE』

Article about ORI and Mr. Hayashi

Mr. and Mrs. Hayashi with grandchildren of Mrs. Curie, Hélène (female nuclear physicist) and Pierre (biophysicist)

Simms / Mann – UCLA Center for Integrative Oncology

On October 10, 2013, Mr. and Mrs. Hayashi visited the Simms / Mann - UCLA Center for Integrative Oncology at the UCLA's Jonsson Comprehensive Cancer Center. It was because UCLA started using FPP (Immun'Âge) at this center at the request of patients and asked them to make a presentation on the effect on FPP based on the clinical papers. Mr. Hayashi explained to Ms. Carolyn Katzin, Intergrative oncology specialist, about the anti-inflammatory effect by improving antioxidant function in a living organism as well as the effect on immune functions proven by numerous published clinical papers, to deepen the understanding that FPP is a fermented food bringing numerous benefits for cancer patients after their treatments. They left the center hoping that FPP will be able to be beneficial for patients.

With Ms. Carolyn Katzin, a very reputable U.S. intergrative oncology specialist, and her staff

FPP is sold for patients at the center in the category of Health and Immune Support.

With Ms. Marcia Britvan in front of the Simms/ Mann - UCLA Center for Integrative Oncology

Aston Martin Racing

Osato Research Institute (ORI) has been an official partner of Aston Martin Racing since 2005 and supporting health maintenance of drivers with FPP.

Aston Martin Racing has been participating in various motor races such as FIA World Endurance Championship (WEC) series including Nürburgring 24-Hour race and Le Mans 24 Hours.

Dr. Bez achieved class victory at 2015 Nürburgring 24hr race

Britcar DUNLOP 24 HOUR RACE 2015 at Silverstone circuit

2015 Le Mans 24 Hours

#97car and Driver Darren Turner at 2013 Six Hours of Fuji

ORI scholarship for young female driver, Alice Powell

ORI has been supporting Alice Powell with scholarship since she was a high school student. She takes FPP daily and before and after the races to take controls of her own health-care.

In 2012, she became 1st female ever to score a point with GP3 Grand Prix. In 2013, Alice flew to India with the Prime Minister David Cameron as part of a UK trade mission and stood in the center on the highest step of the F3 podium at Silverstone.

Alice in the machine with Immun' Âge logo

With the Prime Minister David Cameron

Podium of F3 Cup at Silverstone in 2013

GT4 challenge 2012

The ORI director, Dr. Mantello, participated in GT4 Challenge in 2011 and 2012 with Olivier Bouche by taking FPP. In 2012, they won 7 out of 8 rounds and became a champion of the season, although the total of their ages is 110 years old. The effect of FPP was proven even in the race field by these elder drivers.

Celebrating the victory around the Immun' Âge Osato V8

Project ORI Wine

ORI was asked by the local government office for advice on effective use of idled plots in Ono-town, which are increasing with aging of the farming societies, and in 2012, launched a project called "Project ORI WINE" aimed at making a good use of local elders as well as making life more enjoyable for them and started growing grapes.

Wine is said to be the oldest fermented food in the world and interesting in the view of Preventive Medicine.

Mature Pino Noir (right) and Chardonnay (left)

Vineyard made for effective use of the local idled plots

Supporting young talents at Whittier College

The ORI president, Mr. Hayashi, was appointed as a trustee of Whittier College in 2011. In commemoration of this appointment, ORI promoted new courses of preventive medicine supporting students to work on the problem of preventive health through the curriculums.

Whittier college president Sharon Herzberger (in the center)

Mr. Hayashi and his daughter with Sharon at her graduation ceremony of Whittier college

Oxygen Club of California (OCC) Meeting

From May 7th to 10th , 2014, OCC Meeting was held at the University of California Davis (UC Davis), which is near the Napa Valley and famous worldwide for Viticulture and Enology.

The meeting was held to understand the connection between food and human health at a molecular and cellular level and many studies were presented on how to balance oxidative stress by food which is a cause of chronic disease or illness. UC Davis has the Mondavi Center Studio Theater, which is named after Robert Mondavi, famous vineyard operator family of Opus One and serves as various world-renown musical concerts. ORI was requested by OCC to produce piano-duo concert by Mr. and Mrs. Ota.

The concert was held at the Mondavi Center on May 9. Their performance with two Steinway Model D concert grand pianos was so impressive. All the participants could enjoy the perfect harmony played by the couple.

From Left, Mrs. Hayashi, Mr. and Mrs. Ota, Prof. Lester Packer & his wife and Mr. Hayashi

Clinical Study : 2015

Does Oral Supplementation of a Fermented Papaya Preparation Correct Respiratory Burst Function of Innate Immune Cells in Type 2 Diabetes Mellitus Patients?

【Author】 Dickerson R, Banerjee J, Rauckhorst A, Pfeiffer DR, Gordillo GM, Khanna S, Osei K, Roy S.
【Organization】 Department of Surgery, Comprehensive Wound Center, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA
【Journal】 Antioxidants & Redox Signaling. 22(4):339-345, 2015

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 (Fig.1). 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 (Fig.2). Taken together, our observations lead to the hypothesis that FPP corrects inducible "respiratory burst" function in type 2 diabetes patients.

Fig.1: FPP induces cellular ATP and NADPH production

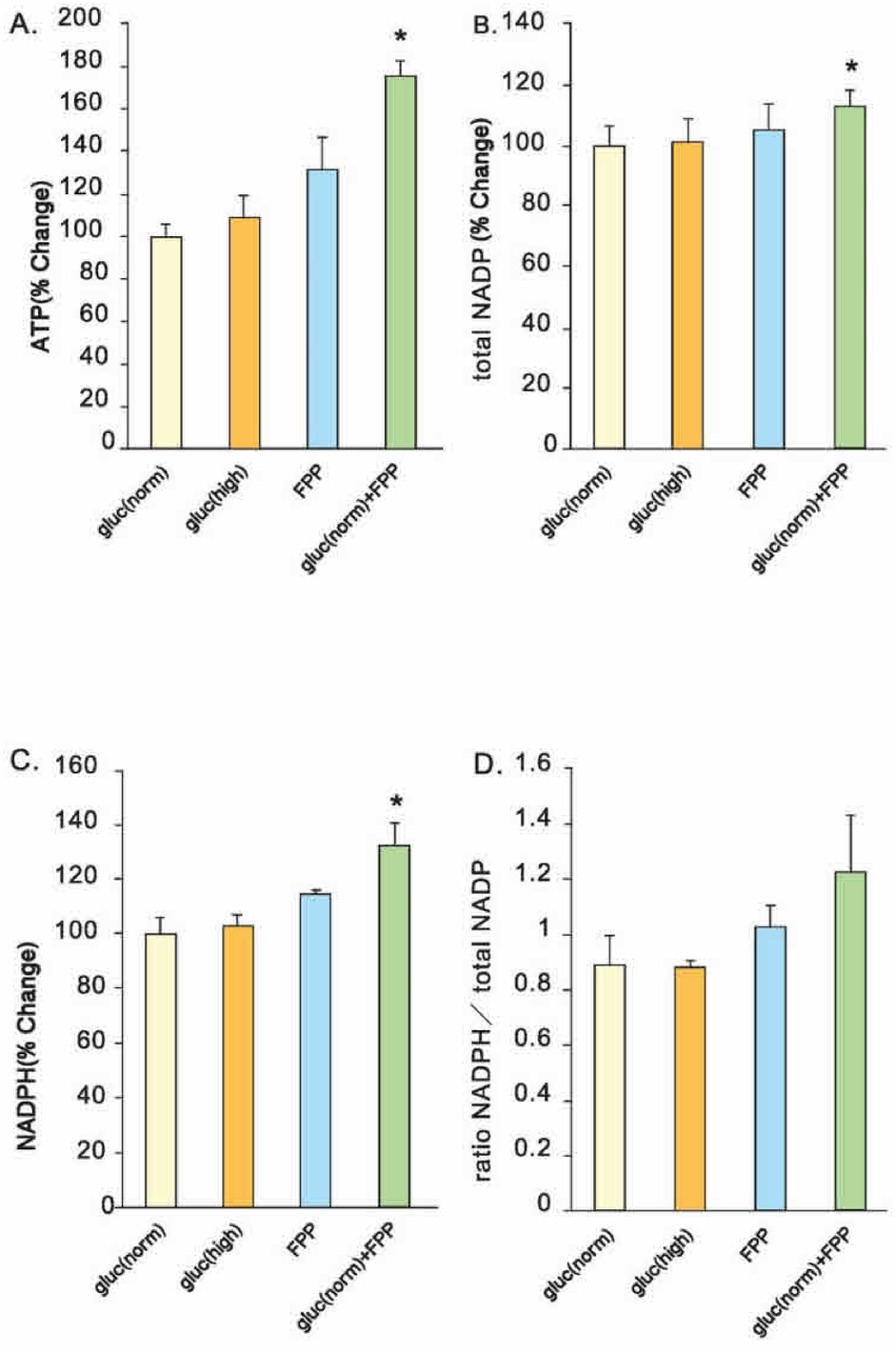
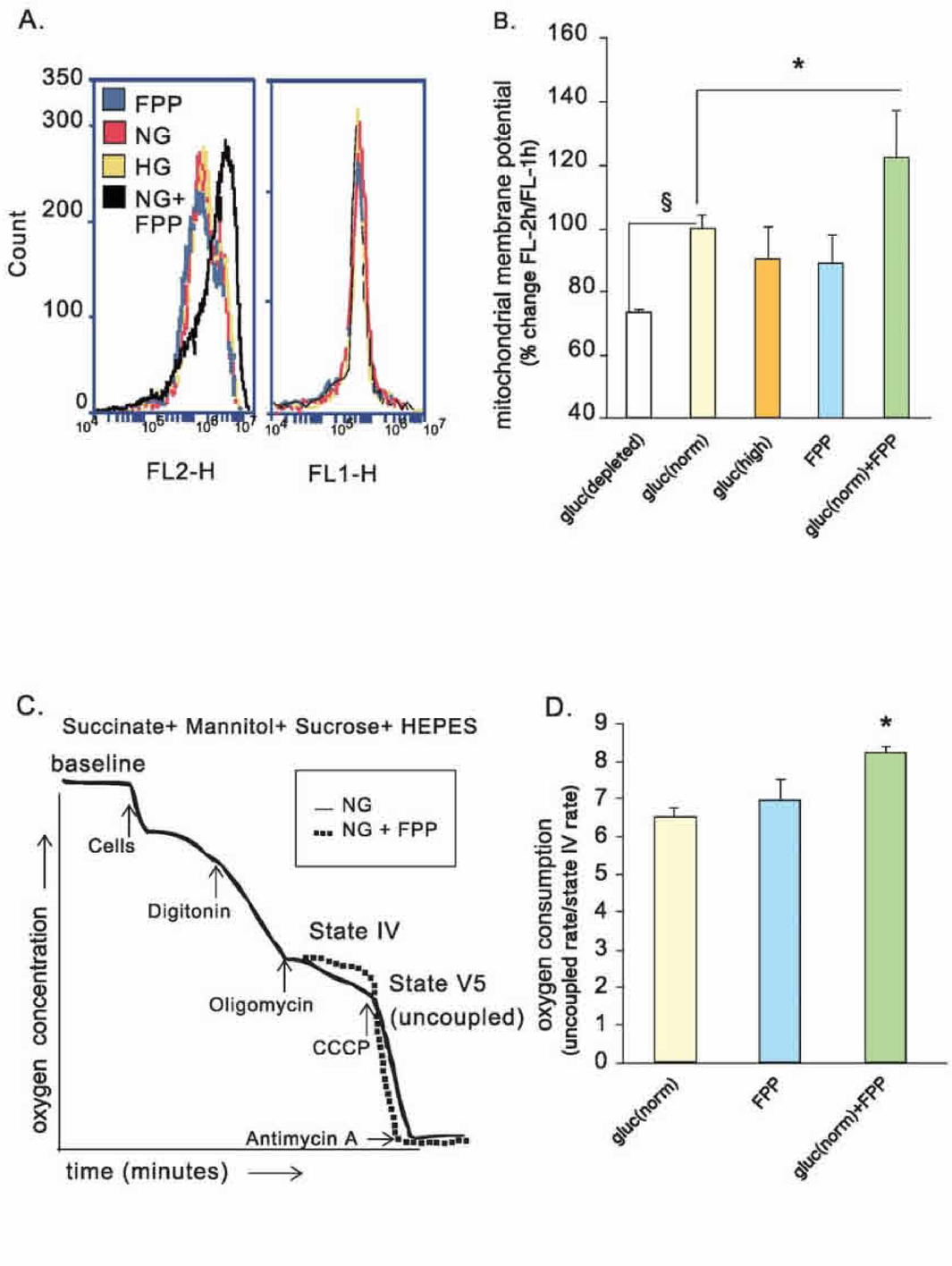


Fig.2: Elevated mitochondrial membrane potential and O_2 consumption in monocytes treated with FPP



gluc(norm): 2 mg/ml w/v glucose/GF media
gluc(high): 3.9 mg/ml w/v glucose/GF media
FPP: 2.9 mg/ml w/v FPP/GF media
gluc(norm): glucose free

Clinical Study : 2012

Correction of Aberrant NADPH Oxidase Activity in Blood-Derived Mononuclear Cells from Type II Diabetes Mellitus Patients by a Naturally Fermented Papaya Preparation

【Author】 Dickerson R, Deshpande B, Gnyawali U, Lynch D, Gordillo G.M, Schuster D, Osei K, Roy S.

【Organization】 Department of Surgery, Comprehensive Wound Center, Davis Heart and Lung Research Institute, The Ohio State University Medical Center, Columbus, Ohio, USA

【Journal】 Antioxidants & Redox Signaling. 17(3):485-491, 2012

Supplementation of standardized fermented papaya preparation (FPP) to adult diabetic mice improves dermal wound healing outcomes. Peripheral blood mononuclear cells (PBMC) from type II diabetes mellitus (T2DM) patients elicit a compromised respiratory burst activity resulting in increased risk of infections for the diabetic patients. The objectives of the current study were to determine the effect of FPP supplementation on human diabetic PBMC respiratory burst activity and to understand underlying mechanisms of such action of FPP. When stimulated with phorbol 12-myristate 13-acetate, the production of reactive oxygen species by T2DM PBMC was markedly compromised compared to that of the PBMC from non-DM donors. FPP treated ex vivo improved respiratory burst outcomes in T2DM PBMC (Fig.1). FPP treatment significantly increased phosphorylation of the p47phox subunit of NADPH oxidase (Fig.2B). In addition, the protein and mRNA expression of Rac2 was potently upregulated after FPP supplementation (Fig.2A). The proximal human Rac2 gene promoter is G–C rich and contains consensus binding sites for Sp1 and AP-1. While FPP had no significant effect on the AP-1 DNA binding activity, the Sp1 DNA binding activity was significantly upregulated in PBMC after treatment of the cells with FPP. This work provided first evidence that compromised respiratory burst performance of T2DM PBMC may be corrected by a nutritional supplement. FPP can correct respiratory burst performance of T2DM PBMC via an Sp-1-dependant pathway. Studies testing the outcome of FPP supplementation in diabetic patients are warranted.

Fig.1: Ex vivo supplementation of FPP corrects T2DM mediated compromised respiratory burst production by human PBMC

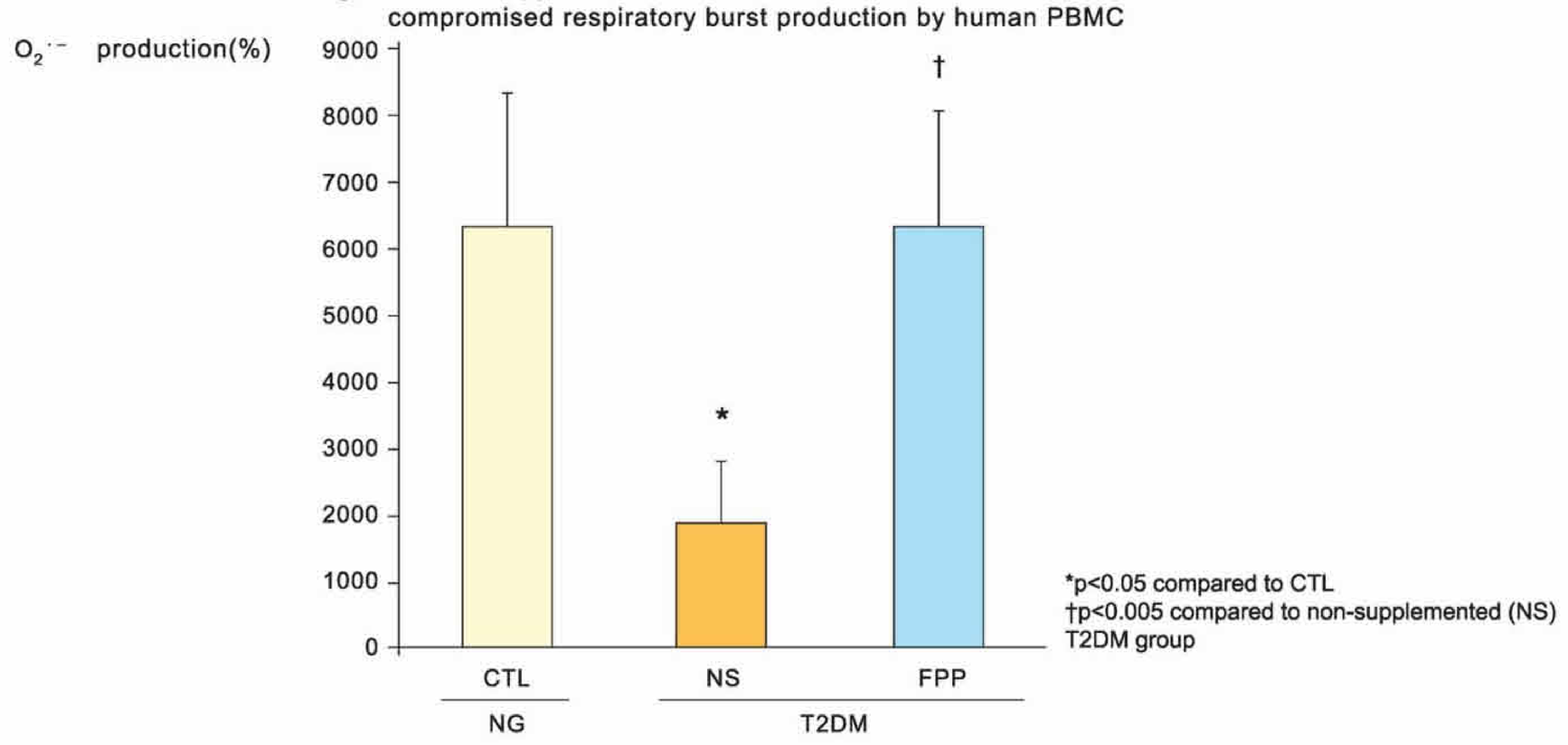
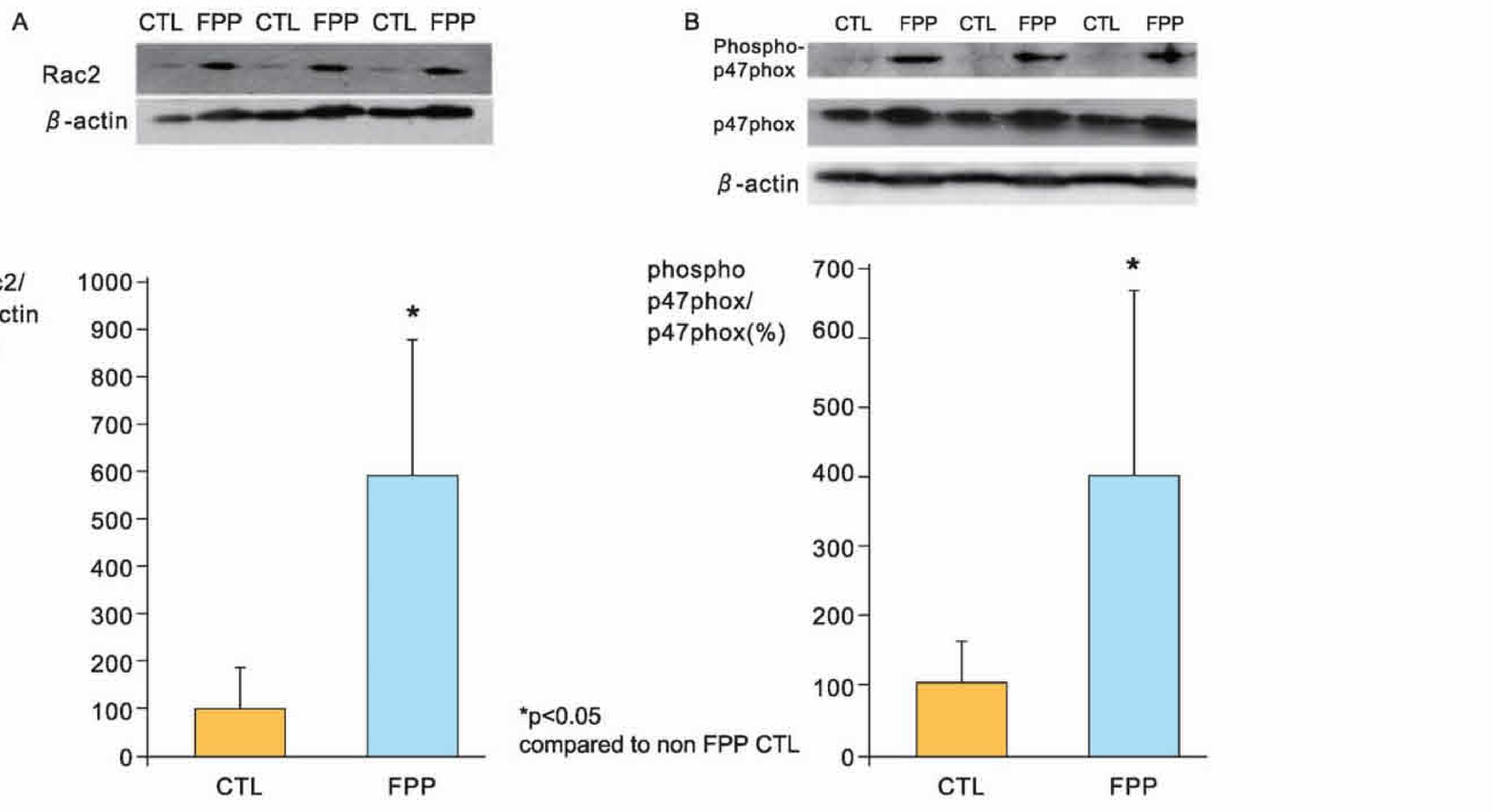


Fig.2: Rac2 and p-p47phox expression following FPP supplementation



Clinical Study : 2015

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

【Author】 Barbagallo M, Marotta F, Dominguez L J
【Organization】 Geriatric Unit, Department DIBIMIS, University of Palermo, Via del Vespro, 129, 90127 Palermo, Italy
【Journal】 Mediators of Inflammation. 2015

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 glycoxidation). 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 ± 1.1 years), 28 AD patients, and 12 controls (Table.1). Urinary 8-OHdG was measured to assess OS.Twenty AD patients were supplemented with FPP (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 ± 1.61 ng/mL versus 1.6 ± 0.12 ng/mL) (Fig.1). In AD patients FPP significantly decreased 8-OHdG (14.1 ± 1.7 ng/mL to 8.45 ± 1.1 ng/mL)(Fig.2), with no significant changes in controls. AD is associated with increased OS, and FPP may be helpful to counteract excessive ROS in AD patients.

Table 1: Clinical characteristics of study patients

	AD (group 1) baseline before FPP supplementation	AD (group 2) not supplemented	Controls without AD	
Age(years)	78.1±1.1	78.3±1.0	77.9±1.2	NS
8-OHdG(ng/mL)	14.1±1.7	12.5±1.9	1.6±0.12	<0.001
SBP(mmHg)	132.9±1.9	130.7±2.1	131.0±2.3	NS
DBP(mmHg)	78.6±1.1	77.7±1.2	77.9±1.2	NS
CHOL(mg/dL)	207.9±39	205.8±38	195.7±41	NS
TG(mg/dL)	127.5±47	118±57	112±49	NS
HDL(mg/dL)	43.8±12	47.9±14	47.6±13	NS
LDL(mg/dL)	136.8±35	128.9±40	127.7±41	NS
BMI	24.9±5.5	24.8±6.4	24.1±6.1	NS
MMSE	22.1±1.5	21.9±1.4	28.8±2.1	P<0.01

Fig 1: 8-Hydroxy-2'-deoxyguanosine (8-OHdG) level inpatients with Alzheimer's disease and in controls

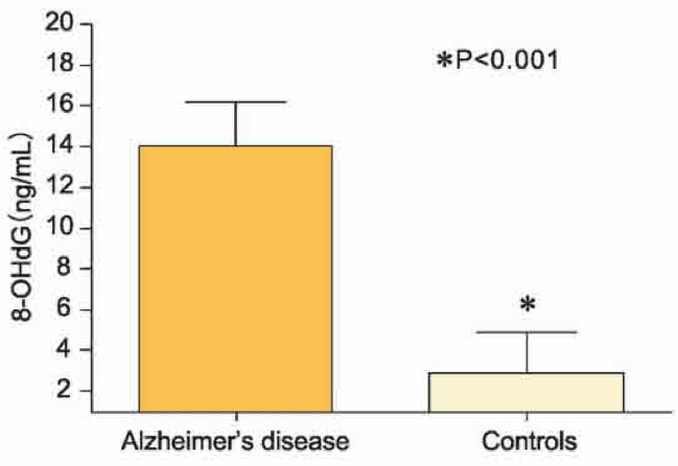
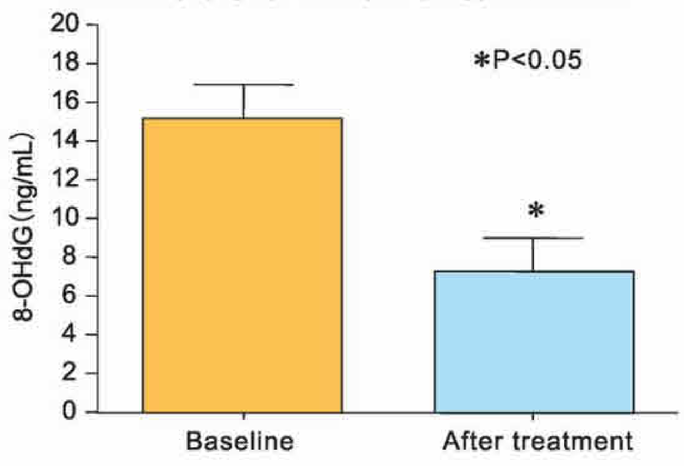


Fig 2:8-Hydroxy-2'-deoxyguanosine (8-OHdG) level in patients with Alzheimer's disease (group 1) before and after fermented papaya powder (FPP) supplementation



Clinical Study : 2015

Possible role of fermented papaya in the treatment of Parkinson's disease

【Author】 Nordera G.
【Journal】 TOUT SAVOIR POUR ÉVITER ALZHEIMER ET PARKINSON

Fermented Papaya Preparation (FPP), a product of Carica papaya Linn fermentation, is a nutraceutical supplement with favorable effects on immunological, hematological, inflammatory, and oxidative stress parameters in chronic and degenerative diseases. In a group of Parkinson's disease (PD) patients voluntarily taking FPP for 3 months we observed a reduction of motor scores of the Unified Parkinson Disease Rating Scale and an improvement in activity of daily living performance during treatment and a successive worsening of these parameters after FPP discontinuation. We follow prescribing FPP in clinical practice, associated with optimized dopaminergic therapy, with good outcomes in terms of tolerability and patient compliance and satisfaction with the treatment. Indeed, FPP has been shown to reduce the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of DNA damage induced by oxidative stress, in other neurodegenerative disorders, such as Alzheimer disease. Noteworthy, 8-OHdG levels are selectively increased in the substantia nigra, serum and CSF of PD patients. In a group of patients taking FPP for 3 to 6 months, who voluntarily underwent an oxidative stress panel analysis, we observed a reduction of 8-OHdG plasmatic levels. In 2011, a clinical study by Hirayama and colleagues pointed out a significant correlation between 8-OHdG levels and motor impairment assessed through UPDRS in PD patients. Further studies are warranted to clarify the effect of FPP on 8-OHdG levels and on motor and functional outcomes in PD.

Basic Study : 2015

The Antioxidant Effect of Fermented Papaya Preparation in the Oral Cavity

【Author】 Fibach E, Ginsburg I
【Organization】 The Hematology Branch, Hebrew University - Hadassah Medical Center, Jerusalem, Israel
【Journal】 Phytotherapy Research. 2015

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 10mg) 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 (Fig.1). 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 (Fig.2). 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.

Fig.1:Antioxidant activity of FPP alone or in the presence of mucin and albumin (a–b) as well as RBC and *C. albicans* (c–d). Each one alone or in combinations, were tested for their antioxidant activity by the H_2O_2–luminol-dependent chemiluminescence (LDCL) assay.

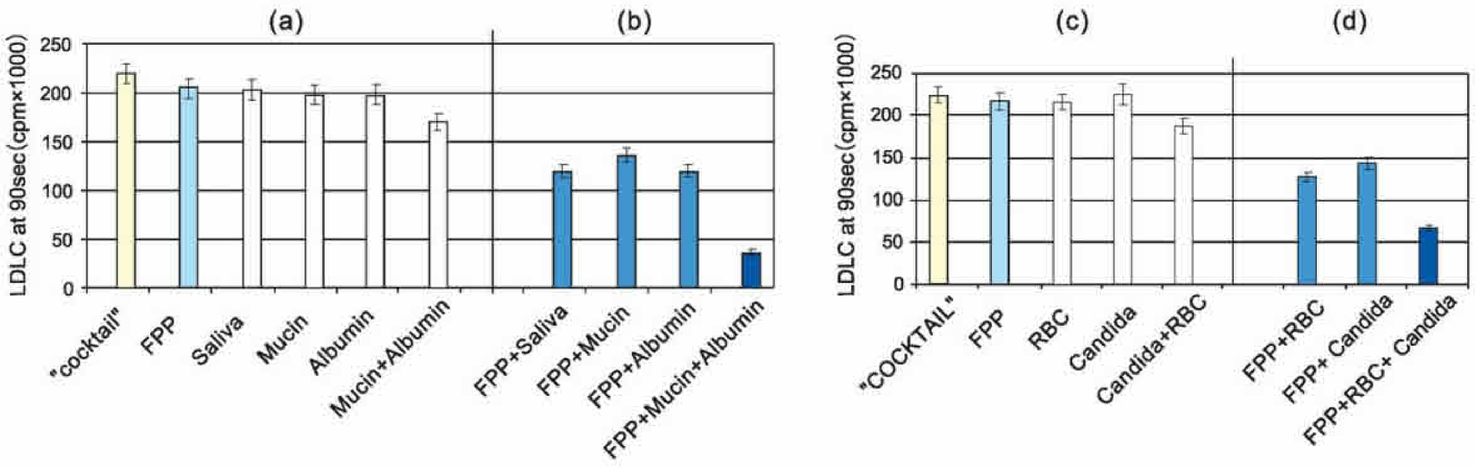
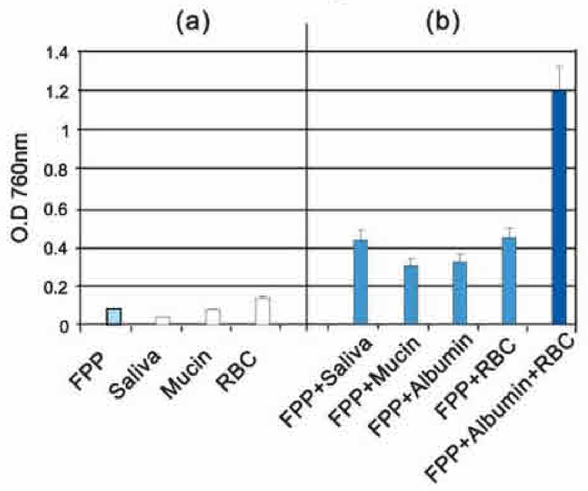


Fig. 2: The phenol content of FPP in the presence of saliva, mucin, albumin and RBC, separately (a) and in combinations (b), were measured by the Folin–Ciocalteu's assay.



Basic Study : 2013

The Inhibitory Effect of a Fermented Papaya Preparation on Growth, Hydrophobicity, and Acid Production of *Streptococcus Mutans*, *Streptococcus Mitis*, and *Lactobacillus Acidophilus*: Its Implications in Oral Health Improvement of Diabetics

【Author】 Somanah J, Bourdon E, Bahorun T, Aruoma OI
【Organization】 School of Pharmacy, American University of Health Sciences, Signal Hill, California 90755, USA
【Journal】 Food Science & Nutrition. 1(6):416-421, 2013

Fermented papaya preparation (FPP) is a "natural health product." The high incidence of dental caries, gingivitis, periodontitis, and oral microbial infection cases among patients with diabetes mellitus continues to prevail. The potential role of FPP against common oral microbiota (*Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus*) isolated from the human oral cavity was investigated using in vitro simulation models of dental plaque and caries. FPP showed an inhibitory effect against the growth (at 0.05 mg/mL: *S. mutans*: -6.9%; *S. mitis*: -4.47%, $P < 0.05$) (Fig.1), acid production (at 0.05 mg/mL: *S. mutans*: +6.38%; *L. acidophilus*: +2.25%)(Fig.2) , and hydrophobicity (at 50 mg/mL: *S. mutans*: 1.01%, $P < 0.01$; *S. mitis*: 7.66%, $P < 0.05$)(Fig.3) of tested microbiota. The results of this study suggest that low doses of FPP may be a suitable complement to good oral hygiene practice for the effective prevention of dental caries, plaque, and gingivitis. The functional application of FPP as a constituent of a balanced diet and active lifestyle can make a positive contribution to the oral health status and well-being of patients with diabetes.

Fig.1: Effect of FPP on the growth of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus*.
*/#P < 0.05 VS control.

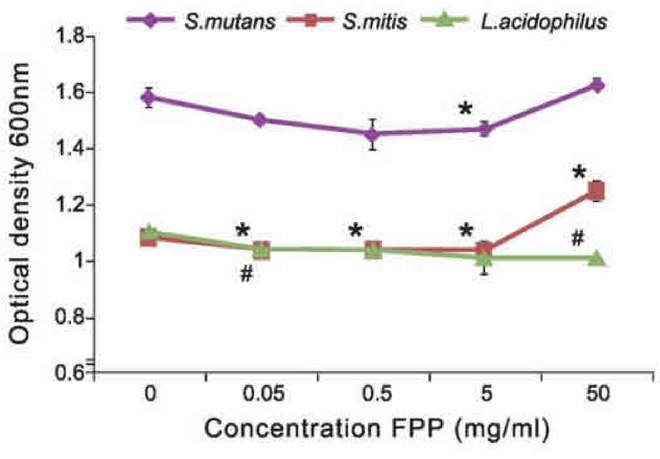


Fig.2: Effect of FPP on the acid production of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus*.

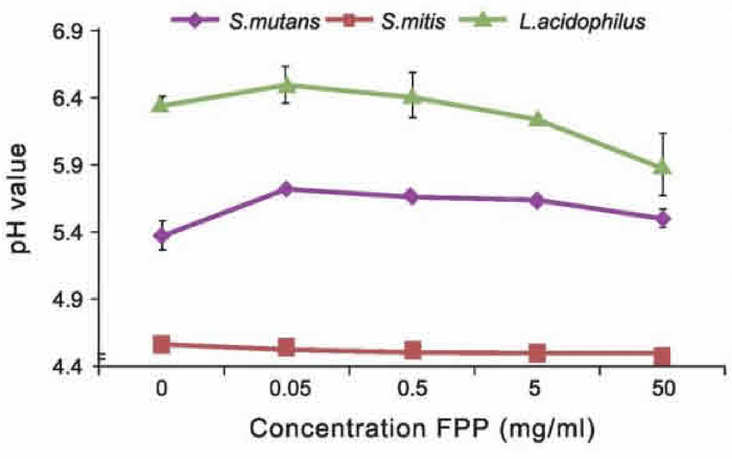
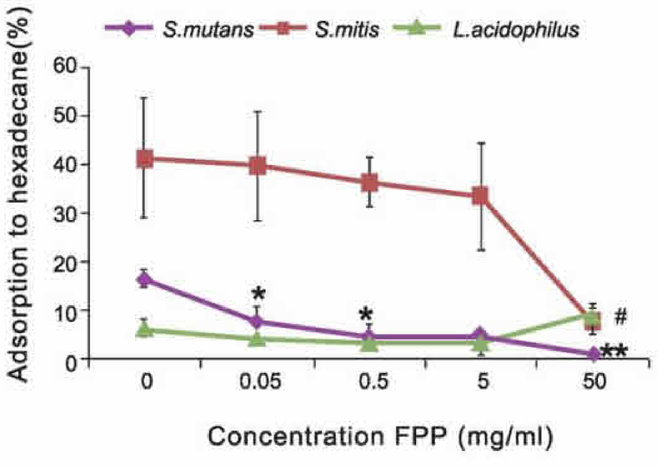


Fig.3: The effect of FPP on cell surface hydrophobicities of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus*.
*/#P < 0.05, **P < 0.01 vs control.



The Hidden Phenomenon of Oxidative Stress during Treatment of Subclinical-Mild Hypothyroidism: A Protective Nutraceutical Intervention

【Author】 Tomella C, Catanzaro R, Illuzzi N, Cabeca A, Zerbinati N, Celep G, Milazzo M, Sapienza C, Italia A, Lorenzetti A, Marotta F.
【Organization】 ReGenera Research Group for Aging Intervention, Milan, Italy
【Journal】 Rejuvenation Research.17(2):180-183, 2014

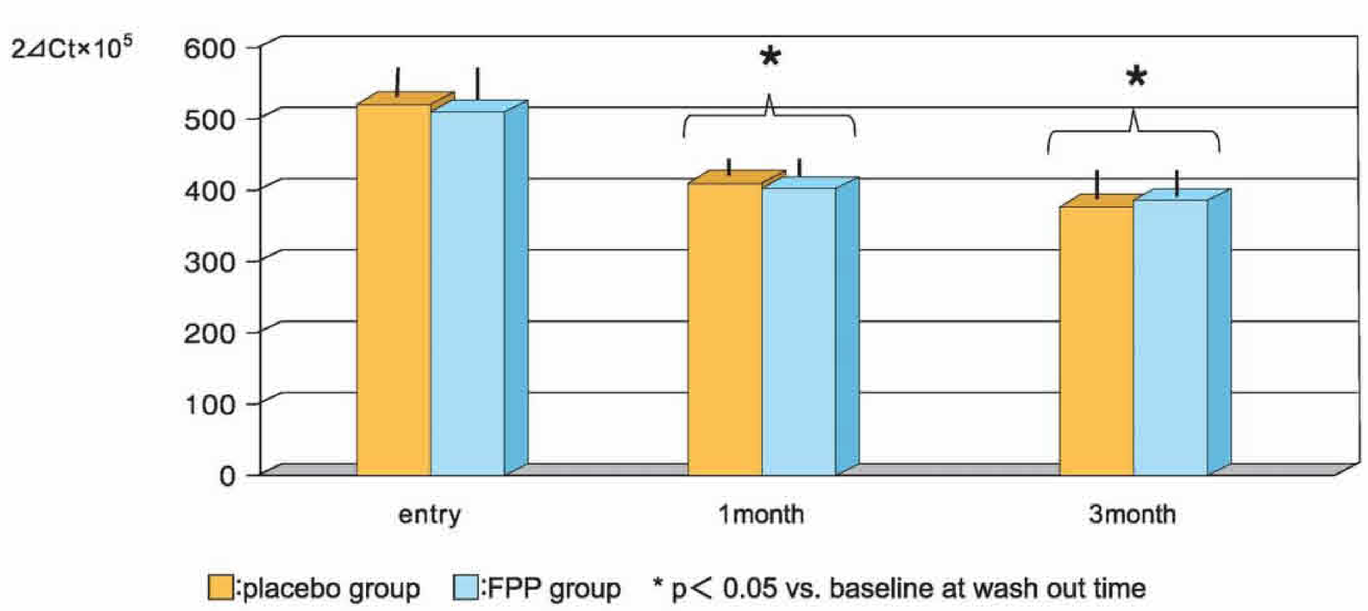
It is known that thyroid hormones are associated with the redox-balance homeostatic regulation. Indeed, thyroid dysfunctions increase lipoperoxides which is an autocatalytic mechanism leading to oxidative damage of cellular membranes. Increased ROS is also a feature of hyperthyroidism, this might be one of the reasons behind the discomfort and loss of working activity often experienced in these patients. Thus, the aim of the present study was to test a redox balance modulator, FPP, in association with treatment of SH or mild hypothyroidism (MH) in terms of: clinical symptom score, oxidative stress, lipid profile and gene expression involved in thyroid regulation. 60 generally healthy females, aged 18-55, presented with SH or MH were put on a 2-week wash-out period and then divided into two groups (30 each) matched as for age, routine biochemical status, dietary profile and thyroid status assessment. Both groups received similar medical treatment for their hypothyroidism. One group was given FPP 3g 1 sachet twice a day for 3 months (FPP group), while the other group was given a flavored sugar sachet as placebo (placebo group). A matched group of normal thyroid function subjects was our healthy control (HC). Lipid profile and thyroid hormone parameters remained unchanged and unaffected by FPP supplementation. As compared to HC a significant increase of all oxidative markers was observed in MH subjects ($p<0.05$) but not in SH. Treatment with T4 brought about a further increase ($p<0.05$ vs baseline) in MH and a significant increase also in SH subjects. While placebo was ineffective, FPP-supplemented individuals showed a significant normalization of redox markers in all tested subjects (Table.1). All 3 subjects in the FPP-treated group reporting a long-standing gastrointestinal discomfort often requiring to lower the dosage of the T3 therapy when cyclically being prescribed this in association to their established T4, reported a complete recovery. THS cased a significant down-regulation of TRα-1 mRNA ($p<0.01$ vs baseline) (Fig.1) but not of TRβ-1 genes and this pattern was unaffected by FPP. It appears that not only FPP can counteract the thyroid hormone-induced oxidative stress but it does not impair the physiological primary hormone-related receptors. Thus, FPP intervention might be an advisable integrative treatment to be associated to long-standing THS regimens.

Table1 : Redox balance parameters

	Before T4	T4＋placebo	T4＋FPP
MDA(μmol/L)	0.26±0.19	0.73±0.21*	0.33±0.26**
L-HPX(nmol/L)	2.2±0.5	6.2±0.6*	3.1±0.8**
GPX(U/L)	634.2±91.6	688.5±102.2*	648.7±94.3**
SOD(U/L)	24.4±4.1	23.6±2.2	30.8±2.6**

MDA(malondialdehyde), L-HPX(lipid hydroperoxide),
GPX(glutathione peroxidase), SOD(Superoxide dismutase)
*$p<0.01$ vs. baseline at wash out time
**$p<0.05$ vs. placebo group

Fig.1: Thyroid Receptors TRα-1 gene expression: Effect of THS and supplementation



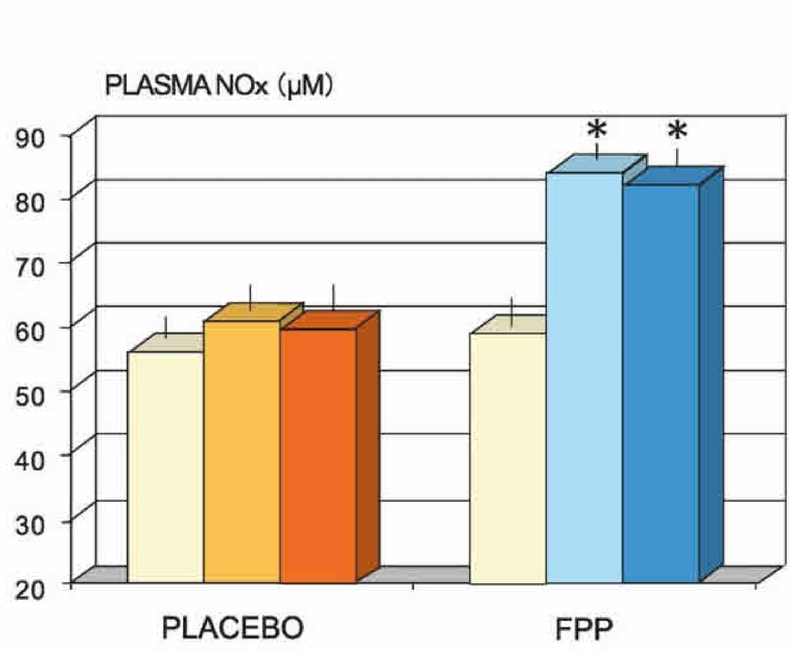
Clinical Study : 2012

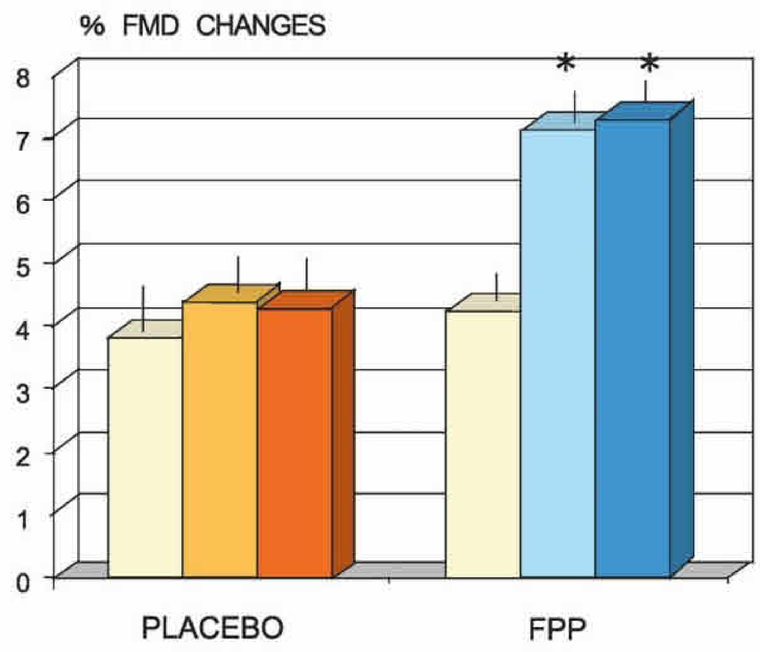
Cardioprotective Effect of a Biofermented Nutraceutical on Endothelial Function in Healthy Middle-Age Subjects

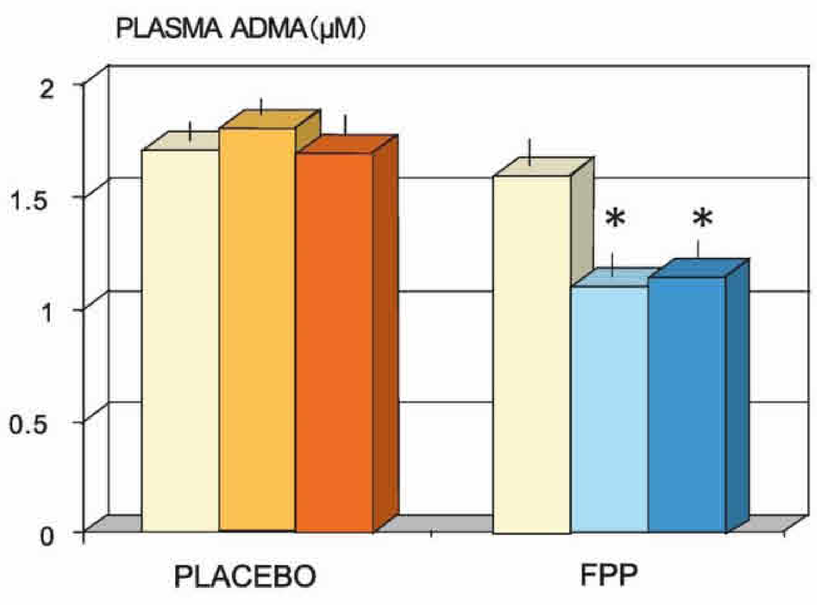
【Author】 Marotta F, Yadav H, Kumari A, Catanzaro R, Jain S, Polimeni A, Lorenzetti A, Soresi V.
【Organization】 ReGenera Res Group for Aging Intervention, Milan, Italy.
【Journal】 Rejuvenation Research. 15(2):178-181, 2012

The vascular endothelium is an active and relevant tissue which controls several important functions, including the regulation of vascular tone and maintenance of blood circulation, fluidity, coagulation and inflammatory responses. Endothelial function is influenced by numerous cardiovascular risk factors and is impaired in smokers although being otherwise healthy. Moreover, endothelial dysfunction is independently related to future cardiovascular events and the prognosis of cardiovascular diseases. NO is a fundamental endothelium-derived molecule and impaired endothelium dependent vasodilatation mediated by NO is a hallmark of endothelial dysfunction. Since, the availability of reactive oxygen species allows direct generation of cytotoxic radicals and NO inactivation, it has been shown that ADMA, an endogenous competitive inhibitor of NO synthase, is produced by methylation of arginine residues in intracellular proteins via arginine Nmethyltransferase and causes endothelial dysfunction and atherosclerosis. Thus, this study was aimed to test whether FPP, which has been previously shown to positively modulate NO, could positively affect the above parameters in a healthy subject cohort. All 42 participants were healthy middle-age subjects (42-57 years old, male/female: 27/15) and not taking any drugs or supplements. Subjects will be given FPP 3g three times a day for 6 weeks and tests were repeated at 3 and 6 weeks. Placebo group was given same quantity of flavored sugar. In result, either MDA, soluble CD40 ligand and hCRP were within normal limits in all subjects and were not changed by FPP consumption. In the interventional group overall FMD significantly increased from 4.2% to 7.3% ($p<0.05$ vs placebo). Few subjects had abnormal levels of 4HNE at baseline (outside the reference range given by the manufacturer) (3 in placebo group and 5 in FPP group) which didn't change the overall significance. However, only those subjects in FPP group normalized this value. A significant increase in plasma nitric oxide and a decrease in ADMA levels were detected after consumption of FPP ($p<0.01$). Although our data cannot be directly translated into an integrative therapeutic approach in cardiovascular patients, they may be worth consideration in view of a wider healthy aging perspective.

Fig.: Effect of FPP supplementation on plasma levels of NOx, ADMA and on percentage variations of FMD.







□:baseline values ■:3 weeks observation (FPP) ■:6 weeks observation(FPP)
■:3 weeks observation (Placebo) ■:6 weeks observation (Placebo) *p<0.01

Clinical Study : 2010

The Clinical Effects of Fermented Papaya Preparation (FPP) on Oxidative Stress in Patients with HbE/β –Thalassaemia

【Author】Jamuar SS, Tan ES, Sun L, Law HY, Lai AHM, Ng ISL.
【Organization】Genetics Service, Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore
【Journal】Proceedings of Singapore Healthcare.19(2)：101—106, 2010

The objective of this study is to assess the clinical effects of FPP treatment in patients with HbE/β-thalassaemia on RBC indices, oxidative stress and quality of life scores. Patients with HbE/β-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: Haemoglobin (Hb), mean corpuscular volume (MCV), reticulocyte count; production of reactive oxygen species (ROS), intracellular glutathione content (GSH), spontaneously and in response to oxidative stress; Quality of life (QoL) at the start and at the end of 12 weeks using health survey questionnaires. Seven patients (5 females and 2 males) were recruited to the study from January 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.(Fig,1 & 2) There was no significant difference in the Hb, MCV, reticulocyte count, clinical parameters or QoL scores. FPP was well tolerated by all the patients. 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 HbE/β-thalassaemia.

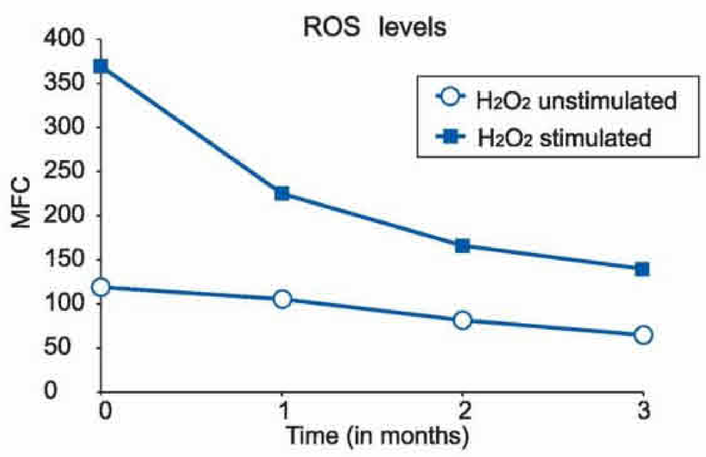


Fig.1:Mean reactive oxygen species (ROS) levels in H_2O_2 stimulated- and unstimulated-red blood cells after treatment with fermented papaya preparation.

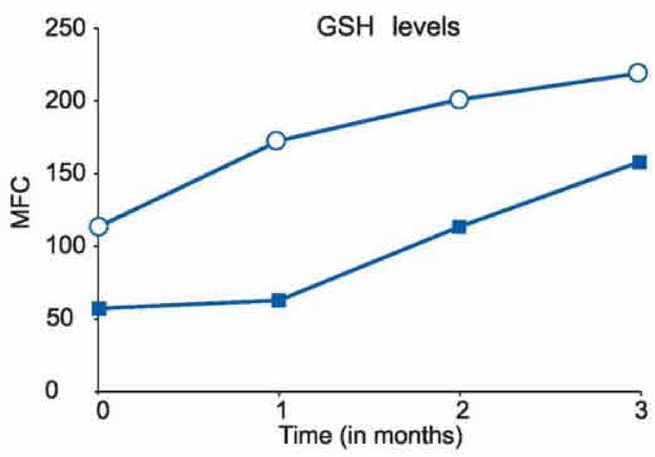


Fig.2: Mean glutathione (GSH) levels in stimulated- and unstimulated-red blood cells after treatment with fermented papaya preparation.

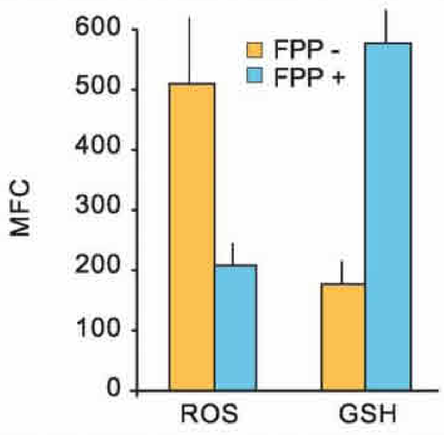
Clinical Study : 2011

Oxidative Stress Contributes to Hemolysis in Patients with Hereditary Spherocytosis and can be Ameliorated by Fermented Papaya Preparation

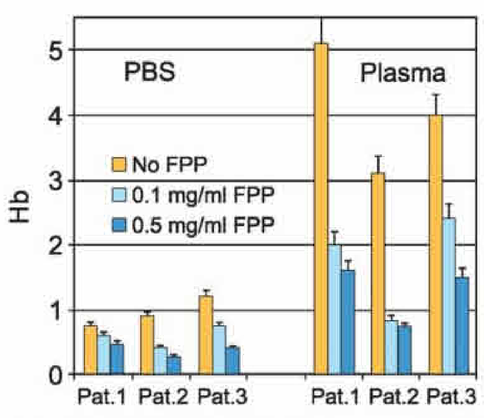
【Author】Ghoti H, Fibach E, Dana M, Shaban MA, Jeadi H, Braester A, Matas Z, Rachmilewitz E.
【Organization】Department of Hematology, Edith Wolfson Medical Center, Holon, Israel
【Journal】Ann Hematol. 90(5):509-513, 2011

Hereditary spherocytosis (HS) is a genetic disorder of blood cells (RBC) skeleton, where RBC have a shortened survival due to primary deficiency in membrane proteins. Secondary protein deficiencies resulting from oxidative stress are often observed and may be involved in the clinical manifestations of the disease, mainly hemolysis. In the present study, we questioned the role of oxidative stress in HS and evaluated the effects of an antioxidant, fermented papaya preparation (FPP), a biofermentation product of Carica papaya, on HS-RBC, both in vitro and in vivo. Using flow cytometry techniques, we showed that RBC derived from 17 HS patients of seven families generate more reactive oxygen species, membrane lipid peroxides, and less reduced glutathione than normal RBC. Following in vitro incubation of HS-RBC from seven patients with FPP, oxidative stress markers were significantly reduced.Similar results were obtained following treatment with FPP for 3 months of 10 adult HS patients, as well as decreased tendency to undergo hemolysis. The hemoglobin levels increased by >1 g/dl, mean corpuscular hemoglobin concentration decreased by >1 g/dl, and the reticulocyte count decreased by 0.93%. Concomitantly, lactic dehydrogenase decreased by 17% and indirect bilirubin by 50%. A significant decrease in malondialdehyde was also detected. These data indicate that oxidative stress plays an important role in the pathophysiology of HS which can be ameliorated by an antioxidant such as FPP. Additional clinical trials with FPP and other antioxidants are warranted.

Fig: The in vitro effect of FPP on oxidative stress and hemolysis of HS-RBC



A) RBC from HS patients were diluted in PBS and incubated for 2h with or without 0.1 mg/ml FPP. The cells were then assayed for ROS and GSH. The results are expressed as the average MFC of 17 patients.



B) RBC from three HS patients were diluted in PBS or in their autologous plasma and incubated overnight at 37℃ with the indicated concentrations of FPP. The cells were then centrifuged, and the Hb concentration in the supernatant was measured.

C) RBC from one HS patient were diluted in PBS and incubated overnight with or without 0.1 mg/ml FPP. Hemolysis is present in the absence of FPP (left tube) but not following incubation with FPP (right tube)

Summaries of papers

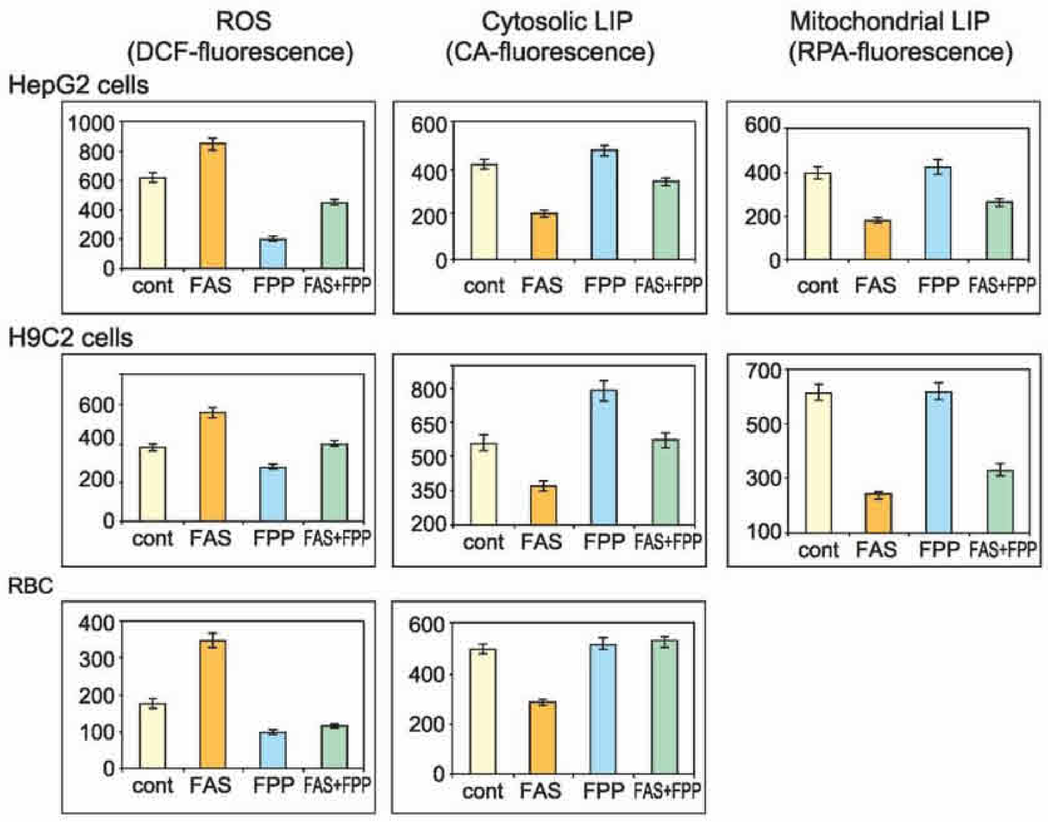
Basic Study : 2012

The Antioxidant Effect of Fermented Papaya Preparation (FPP) Involves Iron Chelation

【Author】 Prus E and Fibach E.
【Organization】 Department of Hematology, Hadassah - Hebrew University Medical Center, Jerusalem, Israel
【Journal】 Jounal of Biological Regulators & Homeostatic Agentes. 26(2):203-210, 2012

Iron-overload is a major clinical problem in various diseases. Under this condition, serum iron which surpasses the binding capacity of transferrin is present as non-transferrin bound iron (NTBI) and cellular unbound Labile Iron Pool (LIP) is increased. LIP participates in generation of free radicals, including reactive oxygen species (ROS). Increased ROS, with concomitant decrease in anti-oxidants, results in oxidative stress and toxicity to the liver, heart and other tissues, causing serious morbidity and eventually mortality. Therapeutic iron chelation reduces the LIP and thereby ameliorates oxidative stress-mediated toxicity. Many food-derived antioxidants have the capacities to scavenge ROS and chelate iron. We have reported that fermented papaya preparation (FPP) has ROS scavenging effect on blood cells in vitro or in vivo (in thalassemic patients and experimental animals). We now investigated FPP's iron chelating effect - its ability to prevent (and revert) LIP accumulation. Liver- and heart-derived cells, and RBCs were exposed to NTBI in the form of ferrous ammonium sulfate and the effect of FPP on their LIP content and ROS generation was measured by flow-cytometry. The results indicated that FPP reduces LIP and ROS, and suggest that its antioxidant mechanism is related, at least in part, to iron chelation.

Fig: The effects of iron and FPP on cellular LIP and ROS.



HEPG2 cells, H9C2 cells and RBCs were first stained for 15-min with DCF, CA-AM or RPA as indicated, washed and incubated for 1-hr with FAS (20 mM), FPP (50 mg/ml), both, or none (cont). Cells were then washed with PBS and analyzed by flow cytometry. The data are presented as the MFI (mean ± SD) of 4 experiments. The results show that in all cells tested FAS increased the DCF fluorescence, indicating an increase in ROS generation, and decreased the CA-fluorescence, indicating an increase in the cytosolic LIP. In HEPG2 and H9C2 cells, FAS also decreased the RPA-fluorescence, indicating an increase in the mitochondrial LIP. FPP ameliorated all these effects of iron.

Clinical Study : 2014

Iron Supplementation in Young Iron-Deficient Females Causes Gastrointestinal Redox Imbalance: Protective Effect of a Fermented Nutraceutical

【Author】 Bertuccelli G, Marotta F, Zerbinati N, Cabeca A, He F, Jain S, Lorenzetti A, Yadav H, Milazzo M, Calabrese F, Tomella C, and Catanzaro R.
【Organization】 ReGenera Research Group for Aging Intervention, Milan, Italy
【Journal】 Jounal of Biological Regulators & Homeostatic Agentes. 28(1):53-63, 2014

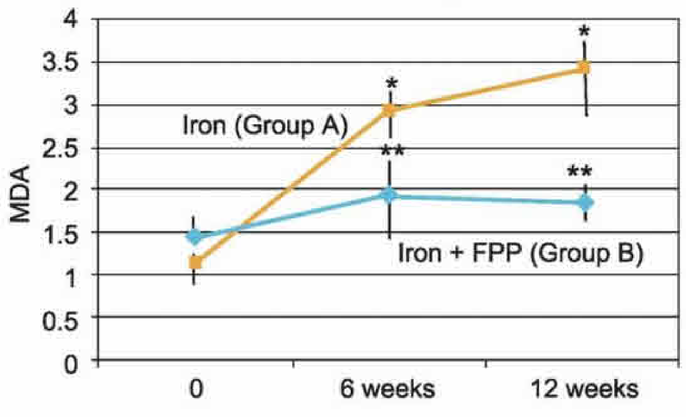
The aim of this study was to assess whether the concomitant supplementation of certified fermented papaya preparation (FPP, ORI, Gifu, Japan) together with iron supplementation could beneficially affect lipid peroxidation either systemically and at an intraluminal gut level in women with low iron stores. 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 supplemented also with 6 g/ day of a FPP. A detailed life style questionnaire was administered to all subjects. Iron, ferritin, transferrin receptors (TfR) 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 in group B showed a significantly lower degree of gastrointestinal discomforts ($p< 0.05$) and abolished the iron supplementation-induced increase of MDA ($p< 0.001$) (Fig.1) and depletion of SOD and GPx ($p< 0.01$). Moreover, the nutraceutical co-administration brought about a significant reduction of gut oxidative damage (Fig.3) and lower fecal content of total and free iron ($p< 0.05$ vs group A) (Fig.2). Overall, group B showed a better TfR/ferritin ratio response ($p< 0.05$ vs group A). While iron supplementation maintains its clinical relevance considering that 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.

Table: Baseline values of relevant biochemistry examinations: effect of iron and iron plus FPP supplementation

		Plasma Iron (μg/dl)	Ferritin (μg/dl)	sTfR (μg/ml)	RBC SOD (U/L)	RBC GPx (U/g Hb)
Group A	Baseline	66.8±12.3	9.8±2.6	3.8±0.9	23.3±4.4	34.7±8.1
	12weeks	104.8±17.8*	18.9±3.7*	3.4±1.1*	16.1±3.5*	21.2±4.4*
Group B	Baseline	71.2±10.6	9.2±4.3	3.9±0.8	21.9±2.8	36.1±7.3
	12weeks	126.6±21.3*	21.6±3.8*	3.3±0.7*	20.6±4.2**	31.3±8.1**

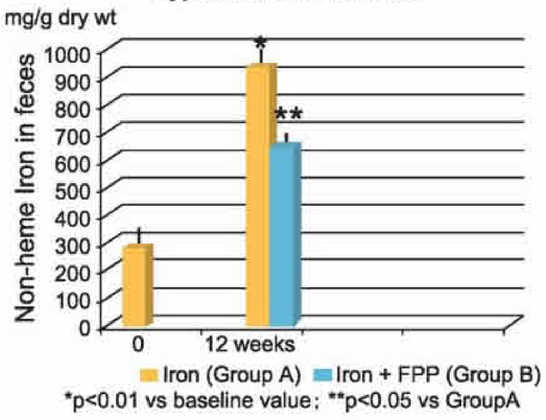
*p<0.01 vs baseline value; **p<0.05 vs groupA

Fig1: Plasma time-course MDA level in subjects administered iron therapy



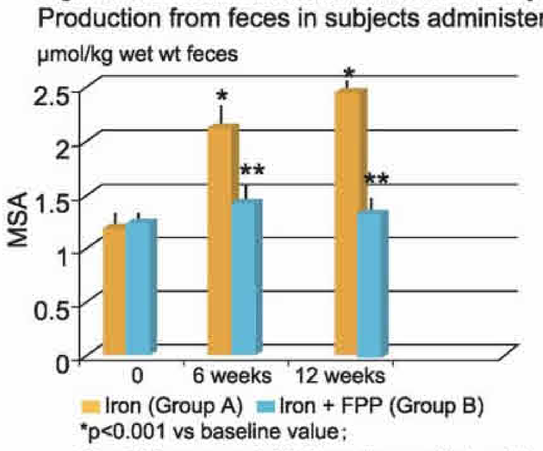
*p<0.001 vs baseline value; **p<0.01 vs GroupA

Fig2: Level of non-heme iron in feces of hyposideremic females



*p<0.01 vs baseline value; **p<0.05 vs GroupA

Fig3: Time-course variation of in vitro Assay of Free Radical Production from feces in subjects administered iron therapy



*p<0.001 vs baseline value;
**p<0.01 vs groupA MSA: methanesulfinic acid

Clinical Study : 2014

Relationship between Fermented Papaya Preparation Supplementation, Erythrocyte Integrity and Antioxidant Status in Pre-diabetics

【Author】Somanah J, Bourdon E, Rondeau P, Bahorun T, Aruoma OI.
【Organization】School of Pharmacy, American University of Health Sciences, Signal Hill, CA 90755, USA
【Journal】Food and Chemical Toxicology.65:12–17, 2014

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-ethnical 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 (Table.1). The intake of 6 g FPP/day for a period of 14 weeks was observed to significantly reduce the rate of hemolysis and accumulation of protein carbonyls in the blood plasma of pre-diabetics (Fig.1 & 2). 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.

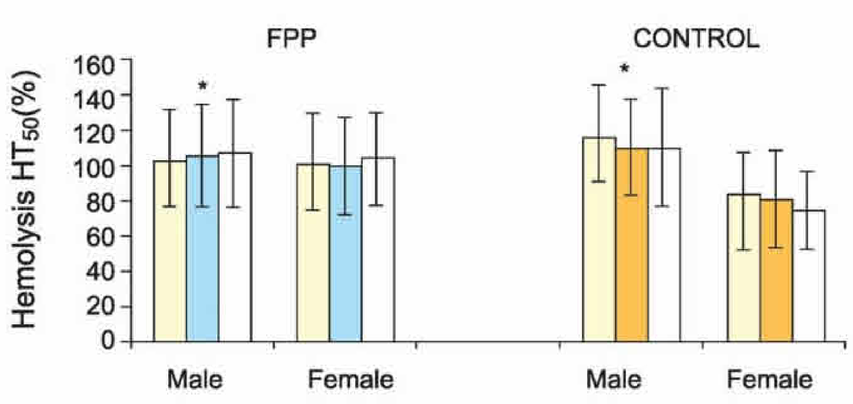


Fig. 1 : The effect of FPP on hemolysis half-time (HT_{50}) in a pre-diabetic population under the FPP (male, n = 22; female, n = 15) and control regimes (male, n = 25; female, n = 26). Data is expressed as mean percentage, where error bars represent standard deviation. Significance: *p < 0.05 vs. baseline value.

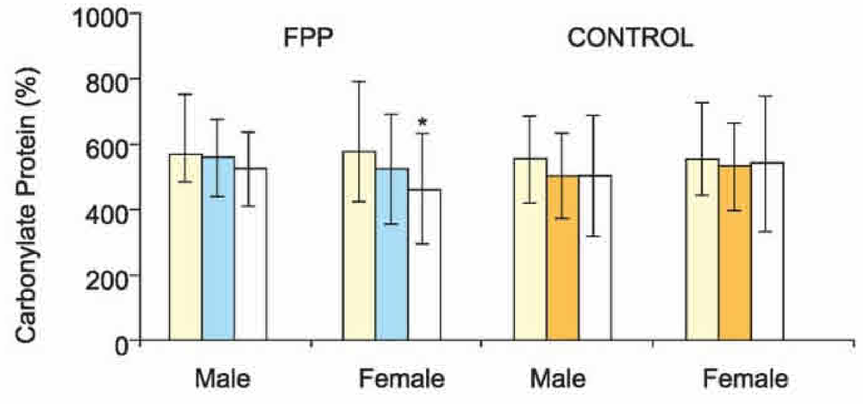


Fig. 2 : The effect of FPP on the accumulation of carbonylated proteins in a prediabetic population under the FPP (male, n = 23; female, n = 18) and control regimes (male, n = 30; female, n = 28). Data is expressed as mean percentage where error bars represent standard deviation. Significance: *p < 0.05 vs. baseline value.

Table 1: The effect of fermented papaya preparation(FPP) on the rate of free radical-induced hemolysis of human erythrocytes

Hemolysis (HT_{50})						
Concentration of FPP (μg /ml)	Control	200	400	600	800	1000
HT_{50}(%)	100	144.61±7.49**	135.78±6.38*	121.17±20.12	112.67±18.80	111.39±8.71

HT_{50} denotes the time taken (in min) for 50% hemolysis to occur compared to a control (1% NaCl). Values are expressed as mean percentage ± standard deviation (n = 3).
*p<0.05 vs. control. **p<0.01 vs. control

Review : 2012

Functional Foods in Genomic Medicine: a Review of Fermented Papaya Preparation Research Progress

【Author】Marotta F, Catanzaro R, Yadav H, Jain S, Tomella C, Polimeni A, Mantello P.
【Organization】ReGenera Research Group, Milan, Italy
【Journal】Acta Biomed. 83(1):21-29,2012

"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, the leading journal Nature published a report "Japan is exploring limits between food and medicine" (Swinbanks 1993). Clearly the success of "Functional Foods" depends on the food industry capacity too of developing new effective products which on the one side meet any consumer request and on the other must have positive effects on health, supported and validated by scientific research and therefore far beyond simple positive properties, as recently underlined in a meeting, organised by a no profit non governmental international association.
(www.actabiomedica.it)

Basic Study : 2015

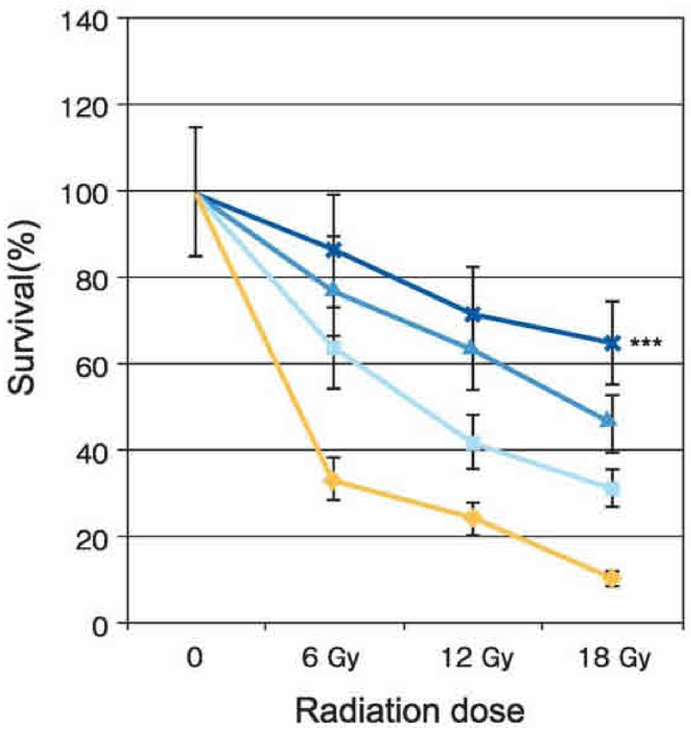
The Effect of Fermented Papaya Preparation on Radioactive Exposure

【Author】Fibach E and Rachmilewitz E
【Organization】 Department of Hematology, Hadassah - Hebrew University Medical Center, Jerusalem, Israel
【Journal】 Radiation Research. 184:304-313, 2015

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 μg/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.

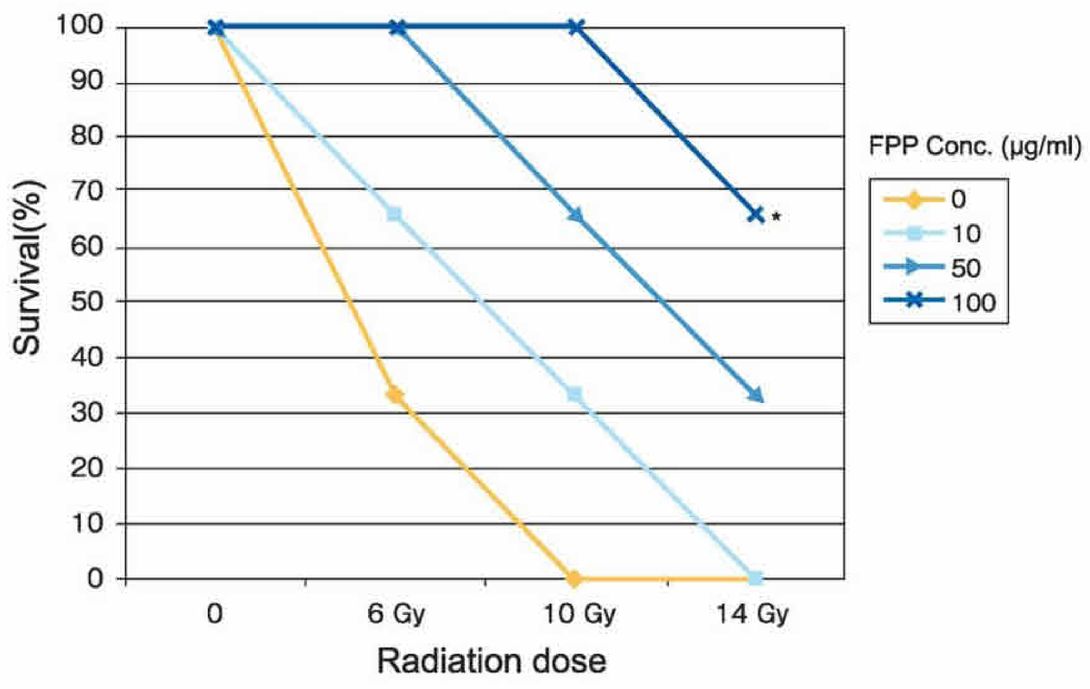
Fig: The in vitro and in vivo effect of FPP on radiation-induced toxicity
Survival rate after radiation exposure of different dose

Fig. A : in vitro Cultured normal human foreskin fibroblasts
2 days after irradiation



***p < 0.05 (Statistical differences between 18Gy irradiated cells, treated with 100μg/ml FPP compared with untreated cells)

Fig. B : in vivo Mice 3 weeks after irradiation



*p < 0.001 (Statistical differences between 14Gy irradiated mice, treated with 100μg/ml FPP compared with untreated mice)

Osato research institute

Publisher:Osato Research Institute
Supervisor:Dr.Pierre Mantello
Address:1956 Inatomi Ono-cho Ibi-gun Gifu 501-0501 JAPAN
Tel:+81(585)34-3830 Fax:+81(585)34-3833
http://www.ori-japan.com E-mail:osato@ori-japan.com