

Immun'Age

FPP (Fermented Papaya Preparation)

A NUTRITIONAL APPROACH TO AGING

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INTRODUCTION

FPP stands for Fermented Papaya Preparation, a process which was developed by the OSATO RESEARCH INSTITUTE in Japan. This process is used in the creation of *Immun'Age*, a papaya dietary supplement. *Immun'Age* is made with papaya, a tropical fruit from Hawaii, utilizing traditional Japanese fermentation methods and proprietary yeasts.

In 2001, the WHO (World Health Organization) reported that the Japanese have the longest life span in the world. The average life span of men is 77.64 years old and for women is 84.62 years. Much of this may be due to the Japanese diet, which is rich in fermented foods.

Papaya is well known throughout tropical countries as a healthy food in it's own right.

OSATO RESEARCH INSTITUTE has created *Immun'Age* (**FPP**) to combine these two wonderful elements, fermentation and the Papaya, for a natural approach to Anti-Aging. OSATO RESEARCH INSTITUTE brings to you a totally natural product manufactured under strict international quality rules: **ISO 9002** for production and packaging and **ISO 14001** for environmental regulations.

The **Non OGM** (Organism Non Genetically Modified) fruits origin is also certified.

Mr. Yuki Hayashi
President
Osato Research Institute and Osato International

GO THROUGH THE YEARS WITHOUT DAMAGE

For many centuries, the human quest for eternal youth has been a continual preoccupation. 20th century scientific progress has doubled the lifespan of humans and this duration is now quite in accordance with the one programmed in our genome (between 100 and 120 years).

However, scientific and technological progress has also provided us with new pathologies by the transformation of our environment (pollution, external stressors, carcinogens, etc.).

It seems to be a problem to live 120 years if one's quality of life were to be diminished by degenerative diseases, so if the 20th century has given us a longer life spans, the 21st century will bring us longer lives combined with good health.

**A better quality of life for all, that is the aim of Osato Research Institute.
Immun'Age (FPP) is the fruit of our anti-aging research.**

Dr. Pierre Mantello

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Director

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THE FIGHT AGAINST AGING

Three Causes of Aging

1) The Molecular Clock

Aging is recorded in the DNA software of our genomes. Recently, we have become aware of our “counter” at the DNA extremity of our cells: **the telomere**.

Normal human cells undergo a finite number of cell divisions and ultimately enter a non-dividing state called replicative senescence.

2) Immune and Endocrine Decline

Immune decline involves a decrease of immune system capacity of defenses (against infections, cancers, etc.). In parallel there is an endocrine decline with a decrease of different hormones produced by the adrenal, hypophyse, hypothalamus, thyroid, thymus, and pineal gland.

3) Oxidative Stress

Different stresses of our modern environment are due to:

- **Physical pollution:** UVA and UVB rays, noise, radiation
- **Aerial pollution:** tobacco and cigarettes exhaust gas, ozone, hydrocarbons, CO, NO², trichloroethylene, formolin, solvents, cadmium, lead tetra ethyl
- **Food pollution:** pesticides, detergents, oxidized fatty acids, pyrolyzed amino acids
- **Water pollution:** nitrates, heavy metals
- **Infections:** bacteria, viruses, parasites

All these stresses produce in our bodies heavy reactive molecules: oxygenated **free radicals**.

Normally, under healthy conditions, **free radicals are inactivated by antioxidative mechanisms:**

- anti-oxidative food molecules: Vitamins (A, C, E), Selenium, Zinc...
- enzymatic systems: Superoxide dismutase, Glutathione peroxidase, Catalase, Thioredoxin reductase...

These elements can become harmful when they are in excess, attacking our own cells, impairing our lipids and cells membranes, our DNA. Increase of these attacks induces incorrect codes of genomes involving degenerative cells:

- Skin cells aging (wrinkles, elasticity loss, spots...)
- Eyes aging (cataract, macula degeneration)
- Brain aging (Alzheimer's Disease, cerebral degeneration)
- Organs aging (Diabetes, cardiovascular diseases, arteriosclerosis, rheumatoid arthritis, muscle degeneration...)

Accumulation of these errors results in cell death (apoptosis).

The more frequent are these occurrences, the more aging is accelerated³³.

Two Ways of Fighting the Effects of Aging

The fight against our molecular clock is impossible, but we can fight aging by:

1) Fighting against **immune and endocrine system decline:**

- Endocrine supplements (which may be unsafe): DHEA, melatonin...
- Compounds which stimulate immunity

2) Fighting against **oxidative stress:**

- Improve one's way of life: environment (pollution), food (organic)
- Harmful ways of life (Sun exposure, alcohol, tobacco...)
- Antioxidant supplements:
 - A. Synthetic: vitamins (A,B,C, E), Selenium, Zinc
 - B. Natural: vegetables, fruits, grapes (flavonoids), papaya

***Immun'Age* (FPP), "... has outstanding properties for fighting against oxidative stress and stimulating the immune system."**

Professor Luc Montagnier

Discoverer of the HIV virus and President of the World Foundation for Aids

Research and Prevention

Paris, October 26, 2000

"Papaya is one of the richest sources of antioxidants and recently we have been learning that antioxidants play a very important role in protecting the body...We have compared five different fruits and two different vegetables, and we found papaya, a tropical fruit...is one of the richest sources of antioxidants, twenty times more powerful than Vitamin E."

Dr. Mark E. Weksler

Geriatric specialist, New York Weill Cornell Medical Center

Professor, Cornell University

Numerous worldwide studies have verified these properties, which has made *Immun'Age* a MAJOR ANTI-AGING food supplement effective on the two available ways of fighting against aging:

- **Acting against oxidative stress**
- **Improvement of immune system**

(These studies may be accessed at our website through the following link: www.osatousa.com > Literature & Articles > Abstract.)

I. WHAT IS *Immun'Age* (FPP)?

Definition and Composition

Immun'Age (FPP) is produced through a biotechnological process, under ISO 9002 & 14001 international quality regulations, by the fermentation of the tropical fruit papaya. *Immun'Age* is the first functional health food capable of controlling free radicals by scavenging hydroxyl radicals (the most dangerous among free radicals), vitalizing superoxide dismutase (SOD) activity in body metabolism² and improving immune status³⁴ (macrophage activator and improver of nitric oxide synthesis).

Analysis of compounds naturally present in 100g of *Immun'Age* (FPP):

Carbohydrate	90.7g	<u>Amino acids (HPLC)</u>	
Protein	0.3g	Arginine	16mg
Fat	non-detected	Lysine	6mg
Dietary fiber	non-detected	Histidine	5mg
Vitamin B6	17µg	Phenylalanine	11mg
Folic acid B9	2µg	Tyrosine	9mg
Niacin	240µg	Leucine	18mg
Iron	0.29mg	Isoleucine	9mg
Calcium	2.5mg	Methionine	5mg
Potassium	16.9mg	Valine	13mg
Magnesium	4.6mg	Alanine	12mg
Copper	14µg	Glutamic acid	37mg
Zinc	75µg	Serine	11mg
		Threonine	8mg
		Aspartic acid	27mg
		Tryptophan	2mg

In addition to these compounds there are other organic complex molecules naturally present in Papaya, which complement the properties of *Immun'Age*. Assays are in progress to determine the composition of these compounds.

Safety

Immun'Age has undergone the necessary tests to confirm and validate its safety for human consumption which includes the following:

Lethal Dose (LD50) Determination

The average lethal dose is the expected amount of a substance that will cause death in 50% of the population (experimental animal). The LD50 of *Immun'Age* (FPP) administered orally is 34.135 - 1.337 ± grams per kilogram body weight. It would require about 1700 grams or 1.7 kilos (570 times the basic dose) of *Immun'Age* to kill a 50-kg (110 pound) adult man.

Acute Toxicity Testing

Himedaka fish, which averaged 1.9 cm in length and 0.2 g in weight, were allowed to swim in 1,000 ppm *Immun'Age*, which is about 1-liter of water mixed with 1 g of *Immun'Age*. This test exhibited zero death rate after a lapse of 96 hours as evaluated by the Gifu Prefecture Public Health Test Center Foundation in Japan.

Heavy Metal and Harmful Compounds Analysis

The result of the chemical analysis made on *Immun'Age* revealed undetectable amounts of toxic heavy metals and harmful compounds. This was evaluated by the Gifu Prefecture Public Health Test Center Foundation in Japan.

Safe Interferon Modulation in Humans

This test was done & published by the Institut Pasteur de Kyoto³.

Immun'Age's modulation of interferon alpha and gamma production in humans was demonstrated after comparing it with two other food supplements-Labre and Spirulina A. *Immun'Age* can be a useful modality to improve a person's general condition and quality of life without side effects even on patients with impaired immune competence.

Effect on Liver Metabolism

Clinical studies done at the Russian Institute of Pediatric Hematology, Institut Pasteur de Kyoto (now Louis Pasteur Center for Medical Research, Japan) and Russian Research Center under the Russian Academy of Medical Sciences, among others, using toxicological parameters of the liver (e.g. SGOT and SGPT levels) showed that there were **no significant changes in the liver function⁴**.

Radioprotection and Antioxidant Protection Among Children During Medical Management of Acute Myeloleukemia and Lympholeukemia Clinical Trials

This study was done and published by the Russian Institute of Pediatric Hematology. Examination of children by pediatricians before, during and after completion of radiotherapy unequivocally demonstrated the radio protective and antioxidant effects of *Immun'Age* in patients with acute myelo- and lympholeukemia with **toxic side effects or adverse reactions similar to those of allergies⁵**.

Adjustment Reactions

Adjustment reactions are rare observations that come with *Immun'Age* use. These may take place during the repair process by *Immun'Age* on pre-existing and sub-clinical illness that otherwise do not exhibit symptoms. A few reactions like rashes, jaundice, malaise (especially in liver patients), pain in a diseased area (like in lead toxicity), changes in urine color and edema may be rarely observed. In such cases, the maintenance dose should be doubled for a few days until the symptoms disappear.

II. *Immun'Age* (FPP) AS A FUNCTIONAL FOOD

Immun'Age induces adaptive systems of redox regulation, immunomodulation and chelation of potentially harmful metal ions.

Quality of Life

Immun'Age improves the quality of life by alleviating the pain and discomfort caused by disease. Although it does not claim to provide a complete cure for serious health problems, statistics show that a greater number of patients' conditions were remarkably improved and their lives prolonged, casting no doubt that *Immun'Age* may indeed offer help. On the other hand, *Immun'Age* can also be taken for maintaining optimal health conditions and for slowing the cellular aging process⁶.

Priority to Restore Normal Cellular Functions

While conventional medicine in general acts to fight against specific pathogen agents and alleviate specific symptoms, *Immun'Age*'s main function is its physiologic ability to restore normal cellular functions in all the body by fighting against imbalance of the oxidant/pro-oxidant status and to improve overall immunity.

Individuality of Dose

Dosing of *Immun'Age* is highly flexible. Just because one is of a heavy build or seriously ill does not necessarily call for a large dose. It depends on each individual's physical constitution and clinical status. One should start with the basic dose of one packet a day and increase if necessary. Normally, one packet is enough. Sometimes, certain situations may call for 3 or 4 packets a day. Occasionally, you may even take a bombing dose to give a boost to your immune system. However, unlike medicines which can be toxic at increased doses, *Immun'Age* is absolutely safe because of its very low toxicity as evidenced by the LD50 determination conducted by the National Institute of Science and Technology of Japan⁷.

Benefits of Using *Immun'Age*

Chronic or debilitating illnesses like liver diseases, cancer, AIDS and others take a toll in the body's energy and defense reserves. The body fights against the infection but in so doing, exhausts much of its energy. The gross result is weakness and weight loss on the part of the patient. As a revolutionary functional food, *Immun'Age* replenishes the needed energy to enhance the body's defense systems and reverses the symptoms associated with these diseases.

Man is likewise subjected to a stressful and pressure-filled lifestyle because of work and personal problems, exposure to chemicals or drugs, noise and smoke pollution. Constant stress exerts a cumulative harmful effect of free radicals that contributes to general body weakness which in turn lowers our immune competence. This condition may trigger the onset of disease if allowed to continue unabated. *Immun'Age* has been observed and reported to reduce the effects of stress.

How Does *Immun'Age* Work?

It is clear enough that after several clinical researches undertaken by world renowned scientists and clinicians, *Immun'Age* was found to possess properties like redox^{8,35} and trace element regulation, immunomodulation^{9,34} and metal ion chelation^{10,35}. These research efforts are still on going to discover other therapeutic properties of *Immun'Age*. For a better understanding of the properties of *Immun'Age's* and related research studies, the next three sections on basic concepts related to the immune system and free radicals will provide further information.

III. *Immun'Age* (FPP) AND THE IMMUNE SYSTEM

For the survival of all the organisms, a system which will recognize the **self** from the **non-self** (e.g. dust, pollens, microorganisms, drugs, chemicals, etc.) and will defend the body against these non-self agents is very vital. Fortunately, the body has a special system for combating the non-self, generally referred to as the immune system. Sometimes, however, aberration in the distinction of self from non-self occurs, leading the immune system to attack its own self (as in auto-immune diseases).

What is the Immune System ?

The immune system is a large and complex defense network of widely distributed elements in the body. The parts of the immune system can function individually or in coordination with one another so as to efficiently recognize, control, and kill foreign matters that gain successful entry into the body. There are two types of immunity, the natural and the specific immunity.

Natural or Non-Specific Immunity

This type of immunity is immediately mounted upon initial contact with the foreign agent and does not require memory of a previous encounter to initiate with the foreign agent for it to mount an effective immune response. This includes the following:

The Physiological Barriers

Skin

Intact skin is considered the body's first line of defense, providing a protective barrier against a wide variety of organisms.

Glands

In the skin, glands secrete enzymes, which help maintain acidity to prevent bacterial growth.

Mucous Membranes

They make up the lining of the nasal, oral and gastrointestinal tracts. These membranes are equipped with a system that causes the secretion of mucus which helps in trapping and expelling of the invading organism, hence, preventing the onset of infections.

Cilia Apparatus

The respiratory tract is lined up with cells bearing small "hairs" called cilia which function like a broom, sweeping debris and other foreign matter that can cause irritation which enable infectious organisms to colonize the lungs.

The Phagocyte System

This is composed of white blood cells called neutrophils, monocytes and macrophages which can kill invading foreign agents through the process of phagocytosis or cell- "eating". Phagocyte

cells produce free radicals during oxidative bursts that occur as part of the phagocyte process. Free radicals that are released by the phagocytes then destroy the invading organisms.

The Reticulo-Endothelial System

Phagocyte mononuclear cells in the lymph, liver, spleen, bone marrow, and lungs make up this system. This functions as a mechanical filter for invading microorganisms in the blood stream and makes phagocytosis more efficient.

The Natural Killer Cells

These are large granular lymphocytes distinct from T-cells and B-cells (see section on Specific or Adaptive Immunity) that are able to destroy a variety of target cells without prior stimulation. They can kill cells that have undergone malignant or cancerous transformation through a cytotoxic reaction. They possess an important role in immune-surveillance against tumor formation as well as virus-infected cells made more susceptible by soluble factors such as interferon.

The Complement System

This system is made up of 20 component proteins which are found in greatest concentration in the plasma, precursors for enzymes and which can be activated to promote destruction of bacteria and tumor cells. They also induce inflammation through which the action of phagocyte cells is enhanced to engulf foreign matters.

The Cytokines

These are substances produced by the cells of the immune system which affect the growth and activities of other cells. Such accessory factors serve to regulate various immune mechanisms without which, the fight against foreign antigens may be severely weakened. These include the following:

Interleukins

Among the numerous accessory factors, the interleukins are the best known and well-characterized, with several subsets produced by macrophages, T-lymphocytes, and other cells. They activate various cells of the immune system to grow, differentiate, or synthesize specific products.

Interferons

Glycoproteins (protein combined with a carbohydrate) released by a virus-infected cell, interferons (IFNs) cannot kill viruses on their own but instead can send signals to other cells to proliferate when virus infection ensues. There are three well-studied types of interferons, the alpha (α), beta (β), and gamma (γ). Interferons are produced by different cells, α -IFN are made by white blood cells, β -IFN from fibrous connective tissue, and γ -IFN by activated macrophages and T-lymphocytes. α and β -IFN can inhibit viral replication while γ -IFN may activate macrophages, natural killer cells, and other cells.

Specific or Adaptive Immunity

This involves antibodies and cells which can attack and destroy specific invading agents. In order for this type of immune response to reach maximum activity, previous exposure to the non-self agent is required. The immune response is relatively slow but the immunity conferred is long-lasting. The immune response can be antibody-mediated (humoral), cell-mediated (cellular), or both. Usually, an encounter with a foreign antigen like bacteria, viruses and other foreign matters elicits a complex variety of responses. The ability to respond to immunological stimuli resides mainly in lymphoid cells.

There are two main lymphocyte populations, which are:

T-cells

These are lymphocytes whose maturation requires processing by the thymus gland. Many subclasses exist with corresponding specific functions. Resistance to and from most microbial infections evolve from the cellular type immunity which they confer. They also provide defense against parasites, tumors, and grafted foreign cells. A well known example of this is the T-helper cells (which belong to one subclass of T-lymphocytes) which are suppressed in AIDS resulting in overwhelming infections and tumors.

B-cells

They are composed of lymphocytes, which unlike T-cells, do not require the thymus for maturation. Instead, they develop in the peripheral lymphoid tissue and in the bone marrow. They are the source of antibodies and as such, comprise the body's humoral immunity. Antibodies specifically attack foreign matters and tag them for destruction by the other components of the immune system. Antibody-mediated immunity is important in toxin-induced disorders, in some microbial infections, and in coping with some types of viral infections.

Balance of the Immune System

The immune system, as a whole, can be viewed as a dynamic network of components, each of which efficiently operates in coordination with each other so as to maintain a sensitive balance between the body and the environment. The upset of this balance is clearly shown in immunological-mediated diseases (such as auto-immune diseases on one end and AIDS on the other end of the spectrum) wherein the immune system may malfunction because of genetically determined defects or because of destructive attacks by pathogens, for example.

Evidence of Immuno-Modulation by *Immun'Age* (FPP)

Having been introduced to an overview of the immune system, the following explanations shall demonstrate the actions that *Immun'Age* exerts to enhance the immune system.

Activation of Macrophages

Professor Lester Packer has shown in a study³⁴, that *Immun'Age* exerts both immunomodulatory and antioxidant activity in the macrophage cell line RAW 264.7.

In research done at the Vitamin Research Institute in Moscow, Russia in 1993, *Immun'Age* was found to stimulate in the neutrophils and macrophages, production of superoxide anion¹¹ which is a recognized essential in killing invading microorganisms through a step in the phagocytosis process known as the oxidative burst (see superoxide radicals).

Activation of Natural Killer Cells

At the Ehime University School of Medicine in Japan, it was discovered that oral administration of *Immun'Age* in tumor-bearing mice induced a significant elevation of the natural killer cell¹². This is a finding which suggests that *Immun'Age* can help in the dissolution of tumors.

Activation of Interferons

One month of oral administration of *Immun'Age* to human volunteers resulted in an increased mean rate of gamma interferon production. This was the finding of a study conducted at the Institut Pasteur de Kyoto¹³. Through interferons, as stated earlier, *Immun'Age* puts the immune system in a better combative stance against infections and diseases.

Activation of Lymphocytes

Among the myriad of actions of interferons is its stimulatory effect on lymphocytes. *Immun'Age* may induce T-cell and B-cell activities indirectly through its demonstrated action on interferons¹⁴.

Effect to Lung Phagocytes, RBC and WBC in Animal Models with Cobalt and Asbestos Induced Lung Injury

In a study done at the Russian State Medical University Laboratory of Occupational Lung Diseases, *Immun'Age* administration in experimental subjects who were exposed to cobalt and asbestos significantly ameliorated the inflammation by suppressing the destructive process caused by lipid peroxidation caused by oxygen radicals from pulmonary phagocytes. *Immun'Age* intake also stimulated the antioxidant activities of the RBC's and WBC's¹⁵.

IV. *Immun'Age* AGAINST FREE RADICAL DAMAGE

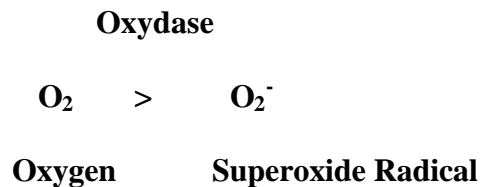
The human body needs oxygen in order to survive. However, oxygen utilizing cells produce a variety of free oxygen radicals involved in thousands of chemical reactions which accompany metabolic activity. For example, superoxide radicals result from mitochondrial, phagocyte and xanthine and alcohol dehydrogenase activities. Hydroxyl radicals may be formed during arachidonic acid metabolism. These go on continuously throughout all the cells and tissues, the levels of which can be modulated by the environment. The vast majority of free radicals are involved in the maintenance and functioning of the organism, e.g. the fertilization process, cell maturation and movement, cytokine production, and elimination of toxic products. They also play a major role in the defense against microbial and viral invasion as well as against tumor cells. These are among their roles as "good radicals". On the other hand, they can be considered as "bad radicals" when they become involved in a variety of disease pathogens as well as in the production of non-specific changes that can eventually result in malfunction, faster aging and death. The free radical status of an organism can be defined as the sum total of the changes, both "good" and "bad", produced by free radical reactions.

What are Free Radicals?

Free radicals are unique chemical molecules that have unpaired electrons in their orbit. Being so, they are very unstable, highly reactive, and potentially dangerous to the body, particularly to biomolecules such as proteins, lipids, carbohydrates, and DNA. Free radicals may cause irreversible damage to the normal structural and metabolic functions of these substances. The most common free radicals in the body are the following:

Superoxide radicals

Superoxide radicals are produced during energy metabolism in the cell either as a result of self-oxidation or by the action of enzymes such as oxidase. They are formed according to the following reactions:



Superoxide radicals are inactivated by an enzyme called superoxide dismutase (see section on superoxide dismutase) to form hydrogen peroxide according to these reactions:

SOD



The superoxide radical has two different mechanisms of action. It is the main agent in the bactericidal action of phagocytes through the process of oxidative burst. At the same time, it can be a harmful mediator in inflammation by damaging even the normal tissues of the body.

Hydroxyl radicals

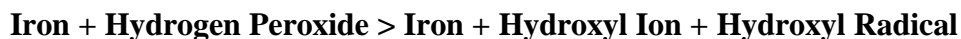
Hydroxyl radicals are formed in several ways. They can be generated through the hydrolysis or breakdown of water producing hydrogen radicals and hydroxyl radicals:

Hydrolyze



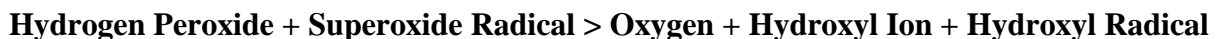
They can also be produced by the interaction of hydrogen peroxide with iron via the Fenton reaction:

Fenton Reaction



Another is through the Haber-Weiss reaction:

Haber-Weiss Reaction



Hydroxyl radicals are the most reactive free radicals and the main mediators of free radical damage in the body.

Nitric Oxide and Nitric Oxide Synthesis (iNOS)

Nitric oxide (NO•) is a soluble, free radical gas that plays an important role in the cellular pathophysiology. A key transducer of the vasodilator message from endothelium to the smooth muscle, it is a constituent in central and peripheral neuronal transmission and an active participant in the immune defense. Hence, modulation of the cellular and extra cellular concentration of NO• is very critical.

In vitro studies showed *Immun'Age's* various regulatory functions on the biological levels of NO•, such as scavenging NO• and promoting its production in a dose-dependent manner from peritoneal neutrophils and murine macrophage; enhancing the production of inducible nitric oxide synthase (iNOS); and stimulating regulatory effects on cellular redox status, especially under conditions where NO• is produced. This could have clinical relevance to the destruction of infectious bacteria or tumor cells during the host's defense process^{16,34}.

In an open randomized controlled clinical trial on the use of *Immun'Age* in adults suffering from insulin-dependent diabetes mellitus, short-term *Immun'Age* administration led to a significant improvement in the clinical conditions of patients and restored to normal levels the production of superoxide, NO• and glutathione (reduced and oxidized) in blood monocytes. These observations suggests a link between the free radical and antioxidant status in regulating blood circulation in diabetic-associated hypertension and probably underlie the remarkable improvement in vascular permeability and tonus to a rapid wound healing process using *Immun'Age*¹⁷.

How are Free Radicals Formed?

There are several ways by which free radicals are formed. Inside the body, oxygen radicals as well as hydroxyl radicals are generated during energy productions. Electromagnetic fields, ultraviolet rays, x-rays, ultrasound waves and irradiation produce free radicals in the body. Chemicals or drugs, or other elements from the environment, including smoke and other forms of air pollution can also lead to free radical formation. Once formed, these free radicals initiate their own reactions in which the chemicals they react with are also converted to free radicals.

With new free radicals being formed, a chain reaction is produced which further increases their potentially harmful effects in the body.

How Can Free Radicals Induce Damage ?

Among the main effects of free radicals are membrane lipid peroxidation, disulfide bond formation between proteins, and DNA damage.

Membrane lipid peroxidation

This occurs when free radicals attack the membranes which surround and protect our body cells. Free radicals destabilize the membranes, allowing faster cell and tissue deterioration.

Disulfide bond formation

Oxidation of thiols (R-SH) such as glutathione (GSH) produces thiol and oxygen radicals. Thiol radicals, although less reactive than hydroxyl radicals, might cause some biological problems. They are sulfur centered radicals (RSH), whose homolytic fission (cross-linking of sulfur molecules) reaction on proteins produces disulfide bond formation. This destabilizes the protein structure and destroys their metabolic functions in the body.

DNA damage

DNA can also be attacked by hydroxyl radicals during the exposure of an individual to electromagnetic, ultraviolet rays and x-rays. When the structure of DNA is altered due to free radical interaction, mutations and even death may occur on the offspring of an individual.

Free Radical Damage in the Body

Free radicals augment the body's resistance against diseases by destroying the invading organisms. However, when produced in excess, they may damage the different body components, resulting in illnesses. There is a growing number of diseases in which free radical reactions are involved. These "free radical pathologies" can be now classified into three groups:

1. Genetically-dependent (Fanconi's anemia, bloom syndrome)
2. Environmentally-associated (occupational diseases, intoxications, virus and bacterial infections)
3. Both genetically and environmentally associated (bronchial asthma, diabetes mellitus, cancer, cardio-vascular diseases, and many others)

Free radical injury is the term used to describe the damages caused by free radicals on the cells and tissues of the body. Examples of free radical injury in the body include the following:

Inflammation

Inflammation is a defense reaction of the body to injury, infection, irritation, irradiation and many other precipitating factors. During inflammation, bursts of oxygen-derived free radicals are released to leukocytes, a process that is fundamentally a protective response but which, may be potentially harmful if uncontrolled.

Microbial Killing

Microbes which gain access to the body are being killed and ingested by phagolysosomes of leukocytes. During this time, reactive superoxide and hydroxyl radicals are produced through oxidative bursts, occurring in milliseconds but are potentially toxic and highly damaging if unchecked.

Oxygen and other gas toxicity

Exposure to high oxygen and other gaseous concentrations may be harmful to living organisms and in some cases, lethal. The damaging effects of oxygen seems to be through oxidation of essential cellular components, like cell membranes, either by oxygen-derived free radicals or by other free radical intermediates.

Aging

The free radical theory of aging by Denham Harman proposes that normal aging results from the accumulation of deleterious damage to tissues by free radicals produced during normal aerobic metabolism. Therefore, ingestion of a balanced diet (antioxidant -oxidant) may minimize free radical reaction in the body.

Irradiation

The major constituent of living cells in water which when exposed to an ionizing radiation (such as x-ray or gamma ray) will result in hydroxyl radical production. These hydroxyl radicals are responsible for the damage to DNA and cell membranes.

Atherosclerosis

Peroxidation of low-density lipoprotein has been implicated in the pathogenesis of arteriosclerosis. This decreases the caliber (Lumen) of blood vessels leading to an increase in the arterial blood pressure (or hypertension) and other clinical complications manifested as diseases.

Alcohol intoxication

Alcohol intake produces many disorders in the body due to free radicals. Mucosal gastric damage, Cyanocobalamin absorption abnormalities (diminution of gastric intrinsic factor binding of B12), deterioration and hemorrhaging of erythrocytes (Lipoperoxidation).

Free Radical Defense and Regulation

An overload of free radicals can be dangerous to the human body. Otherwise, their reactivity is of great help in maintaining a disease-free body because they help in killing the invading microorganisms. Free radicals are carefully regulated in the human body through the following:

Free radical scavenging enzymes

Superoxide dismutase

Naturally found in the powerhouse of the human cells, (mitochondria) that converts superoxide radicals to hydrogen peroxide which is a less reactive form.

Catalase

Found in the micro bodies of the human cells, (peroxisomes) which decomposes hydrogen peroxide to water molecules to prevent formation of hydroxyl radicals.

Glutathione peroxidase

It catalyzes the ability of reduced glutathione (GSH) to release hydrogen from -SH to a hydroxyl radical or hydrogen peroxide to form water.

Thioredoxin

TRX plays a cytoprotective role against various oxidative stresses by radical scavenging activity. TRX can protect cells from TNF or anti-Fas antibody, hydrogen peroxide, activated neutrophils, and ischemic reperfusion injury³⁹.

Antioxidant molecules

Vitamins A, C, and E

Antioxidants like beta-carotene, ascorbic acid and alpha-tocopherol are proven to prevent oxidation caused by free radicals in *in vitro* and *in vivo* studies. Ideally these "...antioxidants must be supplied from natural sources like from fruits and vegetables rather than from supplements..." says Dr. Krinsky¹⁸. Most supplements are prepared chemically, unlike *Immun'Age*, which is naturally produced. Also the intake of vitamins and supplements, especially in high doses, is not without possible toxicities.

Taurine, bilirubin, and uric acid

These are three known natural antioxidant molecules found in the milk of lactating mother, in the liver and the kidneys respectively. Likewise, they can prevent free radical production.

Evidence of Free Radical Regulation by *Immun'Age*

The damaging effects of free radicals particularly hydroxyl radicals can be prevented or minimized¹⁹. The quest to lessen free radical damage and to regulate the production of superoxide radicals by balancing the good and bad effects of free radicals are continuously being explored in various on-going researches²⁰.

Free radical scavenging action

Among the many research studies that have been conducted so far on *Immun'Age* the detection of its free radical scavenging properties provided the earliest observation of scientific evidence on its beneficial effects in many illnesses. This research study was done at the Okayama University Medical School in Japan wherein *Immun'Age* was found to scavenge as much as 95% of hydroxyl radicals.

Furthermore, this scavenging action of *Immun'Age*, in another study from the same institution, was found to be thermo-stable at 100°C and acid-tolerant at pH 1.2. Thus, the ability of *Immun'Age* to scavenge free radicals is evident even under extremely varying and at times critical, conditions²¹.

Immun'Age in alcoholics is able to recover a normal absorption of cobalamine³⁷ and improve the gastric mucosal damage³⁶ by a local antioxidant effect (decrease of MDA and xanthine oxidase) and improves Glutathione synthase.

Prevention of lipid peroxidation

A number of researches studies done at the Okayama University Medical School which utilized animal models under widely varied conditions support the earlier studies which demonstrated the antioxidant defenses that *Immun'Age* provides²². As previously stated, free radicals may cause damage by attacking the lipids that make up the membranes of cells causing lipid peroxidation. This is evident by the apparent increase of measurements of thiobarbituric acid reactive substances (TBARS) which are products of peroxidative reactions.

In separate studies on aging, epilepsy, and liver injury using rat models, *Immun'Age* administration was shown to decrease the levels of TBARS which is indicative of decreased lipid peroxidation²³. The same findings were observed in a study on cerebral ischemia-reperfusion injury, this time using gerbils.

The aging process is strongly believed to involve free radicals and a decrease of superoxide dismutase (SOD) activity and level. The use of antioxidants for inhibition of free radicals as a strategy for the prevention and attenuation of aging has generated much interest. *Immun'Age* was shown to inhibit lipid peroxidation as well as increase the level of SOD. It therefore appears that the use of *Immun'Age* as an anti-aging regimen has a sound basis²⁴.

Free radical regulation

It is important to remember that free radicals are not detrimental in all instances. Generation of active oxygen species an indispensable to sustain life. For example, superoxide anion is an active oxygen species that plays an important role in the killing of microbes during phagocytosis. In the study conducted at the Vitamin Research Institute in Russia, *Immun'Age* was found to stimulate rather than inhibit the production of superoxide by phagocyte cells such as neutrophils and macrophages. In contrast, the production of harmful hydroxyl radicals was inhibited. All these finding suggest that *Immun'Age* is not simply a free radical scavenger but actually a free radical regulator²⁵.

V. FREE RADICALS AND THE IMMUNE SYSTEM

The decline of immune system function in aging persons and cancer patients may be attributed to increasing levels of free radicals. According to recent studies, the aging process is the sum of deleterious free radical reactions going on continuously throughout the cells, tissues and organs²⁶. Life span, therefore, appears to be largely determined by the rate of free radical-mediated cell degradation.

On the other hand, a number of antioxidants have been shown to enhance both humoral and cellular immune responses in the aged subjects, indicating that some endogenous free radical processes have adverse effects on the immune system. They also affect the cellular products involved in immunity, such as cytokines, and also interfere with cell division. It is reasonable to expect that the depression of the immune system caused by age and cancer may be ameliorated.

Similarly, a number of age-related free radical-mediated diseases may be decreased, and for the healthy individual, an active life span can be significantly increased through the selection of diet and free radical regulator supplementation.

VI. METAL ION CHELATION

1. A simple mixture of an iron salt and hydrogen peroxide, which can react with many organic molecules, provoke a whole series of free radical reactions. *Immun'Age* can sequester iron salts, scavenge hydrogen peroxide, thus halting further formation of more hydroxyl radical. This explains why *Immun'Age* is a potent hydroxyl radical scavenger²⁷.

2. Intratracheal injection of cobalt sulfate unto the rodents induces inflammation which effects were counteracted by *Immun'Age*. To wit, *Immun'Age* was shown to increase the survival rate and enhance the amount of endogenous antioxidants such as glutathione and superoxide dismutase in the erythrocytes and leukocytes²⁸.

3. *Immun'Age* exhibited an antagonistic action on the toxic effects of cisplatin (a platinum containing anticancer drug) by binding the metal and eliminating it from the body, thus minimizing the associated adverse reactions and side effects²⁹.

4. *Immun'Age* enhanced the release of lead from their bone storage in workers who cleared up the Chernobyl nuclear waste after the leakage with high doses of lead, which resulted in a statistically significant decrease of the main biochemical markers of lead toxicity³⁰.

VII. OTHER SCIENTIFIC INFERENCES OF *Immun'Age*

The numerous research studies chronicling what *Immun'Age* has done for users are documented. Altogether, they provide the confirmation of *Immun'Age's* beneficial effects. It can be inferred from these studies that *Immun'Age* is useful to help in fighting infection, tissue damage, and even cancer.

Infections

In earlier sections, *Immun'Age* has been shown to enhance the immune system, the body's natural defense against infections. Therefore, it has advantages over conventional antibiotics in certain ways. *Immun'Age's* actions against infections appear to be more physiologic or more attuned to the body's normal processes.

One study made by NIZO Food research (Ede Netherlands) show a significant liver protection by rats infected with pathogenic salmonella³¹.

Cancer

Immun'Age has demonstrated interesting and even astounding effects on cancer-afflicted persons. It appears that the disease can be downsized by the use of *Immun'Age*. The results are very promising. At present, the exact mechanisms in evaluating the total efficacy of *Immun'Age* vs. cancer have not yet been fully elucidated. However, some finished studies may provide initial answers.

To scientifically document *Immun'Age's* purported positive effect on cancer, several cases were studied. The results indeed suggest a potential cell-killing activity. This property of *Immun'Age* may be due to its stimulatory action on the natural killer cell activity as determined in study conducted at the Ehime University School of Medicine, Japan³². These NK cells have the ability to directly destroy tumor cells.

Very often, cancer patients are severely wasted due to depressed appetites. Toxohormone-L, a substance found in cancers, can significantly suppress food and water intake and hydrolyze or reduce the amount of body fats leading to significant weight loss. In an experiment at the Ehime University in Japan, *Immun'Age* was shown to inhibit the activity of toxohormone thus suggesting that it may be able to prevent weight loss in cancer patients. This may partly explain the repeated observation of good appetite of *Immun'Age* users.

Immun'Age may play yet another role in cancer prevention. It has demonstrated an ability to exert an anti-genotoxic potential, in a separate study done at the Research Center for the Natural Sciences in UST. In this way, it may be able to prevent mutation by reducing or inhibiting the destruction of chromosomes caused by tumor-producing substances.

VIII. CONCLUSION

Environmental degradation is now a grim reality whose pace is hastened by harmful agents such as chemicals and pathogens that cause disease. To stay healthy, the body should be equipped with natural defense mechanisms that provide protection against physical damage and injury. Based on the preceding discussions, we can conclude that *Immun'Age* indeed enhances the immune system and helps in alleviating free radical-mediated illnesses. Its over-all effect comes from its ability to balance the human body's condition optimally as naturally as possible.

Although numerous research studies have been concluded and are now available to support these claims, the Osato Research Institute is still pursuing further studies in the hope of shedding more light on *Immun'Age's* capacity to improve the quality of life for all.

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IX. FOOTNOTE REFERENCES

1. Free Radical Scavenging Action of Fermented Papaya Preparation (*Immun'Age*) and it's by-product
Santiago, L.A., Osato, J.A., Hiramatsu, M., Edamatsu, R., Mori, A.,
Free Radical Biology and Medecine, Volume 11 Number 4, 1991; pp. 379-383.
2. Age-related Increases in Superoxide Dismutase Activity and Thiobarbituric Acid-reactive Substances : Effect of Fermented Papaya Preparation (*Immun'Age*) in Aged Rat Brain
Santiago, L.A., Osato, J.A., Liu, J., Mori, A.,
Neurochemical Research, Volume 18 Number 6, 1993; pp. 711-717
3. Effects of Dietary Supplement 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: 0917-8357
4. *Immun'Age* (Fermented Papaya Preparation) Approaches in Management of Patients with Diabetes Mellitus and Hepatitis
Korkina, E. Samochatova, M. Balabolkin, and I. Afanaslev
Institute of Pediatric Hematology and Center of Diabetes, Russia
In proceedings of the International Workshop on Nutritional Approach to Aging and Disease Final Program and Abstract Book (Gifu, Japan, 1 - 3 August, 1995)
5. Radioprotective and Antioxidant Effect of Zinc Aspartate et Fermented Papaya Preparation (*Immun'Age*) in Children with Acute Myelo and Lympholeukemias
Korkina, E., Osato, J.A., Chivilyeva, I., Samochatova, E., Afanas'ev, I.
Supplement to Nutrition, Volume 11 Number 5, 1995
6. A Randomized Double-Blind-Placebo-Controlled Clinical Trial on the Effect of Fermented Papaya Preparation (*Immun'Age*) on Liver Cirrhosis
Samar-Sy, O.M., Espiritu, A .C., Osato, J.A.
Philippine Journal of Internal Medecine, Volume 25 Number 4, 1997 ; pp. 189-194
7. Redox Immune-modulators (RIMs) for Natural Products May Mitigate Delocalized Free Radical Damage for Opportunistic Infections in the AIDS-related Complex : A Initial Clinical Glimpse Using Fermented Papaya Preparation (*Immun'Age*)
Marietta Corpio-Baccay and others
(unpublished data)
8. The Effect of a Naturally Sourced Antioxidant Product Fermented Papaya Preparation (*Immun'Age*) on Patients with IDDM or NIDDM
L.G. Korkina, E.A. Ostrachovich, I.B. Deeval, and I.B. Afanaslev
In proceedings of the 2nd International Conference on Natural Antioxidants and Anticarcinogens in Nutrition, Health and Disease (Helsinki, Finland, June 24 - 27, 1998)

9. Regulation of Inducible Nitric Oxide Synthase Expression in IFN- γ treated Macrophages by Fermented Papaya Preparation (*Immun'Age*)

H. Kobuchi; L. Packer

Oxidants and Antioxidants in Biology 5-8 Feb., 1998 pp. 128-129

10. Prooxidant Effects of Transition Metal (Iron and Copper) in Biological Systems

I.B. Afanaslev; L.G. Korkina; J. Aaseth

6th Nordic Symposium on Trace Elements in Human Health and Diseases

Roskilde, Denmark; Abstract, p.21; June 29 – July 3, 1997

11. Fermented Papaya Preparation (*Immun'Age*) as a modulator of Phagocytosis and Free Radical Production by Murine Inflamed Neutrophils and Macrophages

Osato, J.A., Afanasev, I. and others

Physical, Chemical, Biological and Medicine Volume 2 1995; pp.87-95

12. Studies on the Biological Activities of Fermented Papaya Preparation (*Immun'Age*)

Okuda, H., Ohmionami, H., Zhou, A., Matsuura, Y., Osato, J.A., Santiago, L.A.

Clinical report, Volume 27 Number 11, 1993; pp 47-56

13. Effects of *Immun'Age* (Fermented Papaya Preparation) of IFN Producing Capacity in Humans

Kishi, K. Uno, Y. Matsubara, J.A. Osato and T. Kishida (I.Pasteur Kyoto)

Journal of Interferon Research, Volume 14, Supplement 1, 1994

14. Effects of *Immun'Age* (Fermented Papaya Preparation) on Serum Components and Immunological Functions in Humans

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

Neurosciences Volume 20 (Supplement) 1994; pp.149-159

15. Natural Occuring Oral Chelators Against Lead and Cobalt Toxicity

Korkina, L.G. and others

Chelating Agents in Pharmacology, Toxicology and Therapeutics

Symposium. Pilsen. Czech Republic; Plzensky Lebarsky Sbornik, 1996; pp 11-14

16. Mechanism of Antioxidant Activity of Natural Food Supplements

I.B. Afanaslev; J.A. Osato; L.G. Korkina

International Symposium on Antioxidant Food Supplements in Human Health. Oct.16-18

17. Fermented Papaya Preparation (*Immun'Age*) Approaches in Management of Patients with Diabetes Mellitus And Hepatitis

L. Korkina; E. Samochatova; M. Balabolkin; I. Afanaslev

Final Program and Abstract Book International Workshop on Nutritional

Approach to Aging and Disease 1-3 Aug., 1995 p.23

18. Preventions, Healing with Vitamins, **Alice Feinstein**, Pennsylvania: Rodale Press, Inc, 1996

p4

19. Free Radical Scavenging Action of Fermented Papaya Preparation (*Immun'Age*) and it's by-product

Santiago, L.A., Osato, J.A., Hiramatsu, M., Edamatsu, R., Mori, A.,
Free Radical Biology and Medicine, Volume 11 Number 4, 1991; pp. 379-383.

20. Effect of Fermented Papaya Preparation (*Immun'Age*) on Free Radical Production by Human Blood Neutrophils, Erythrocytes and Rat Peritoneal Macrophages

Osato, J.A., Korkina, L., Santiago, L.A., Afanas'ev, I.B.
Nutrition, Volume 11 Number 5 (Supplement) 1995

21. Stability of the Hydroxyl radical Scavenging Components of the Health Food Fermented Papaya Preparation (*Immun'Age*)

Osato, J.A., Korkina, L., Santiago, L.A., Afanas'ev, I.B.
Medical Science Research, Volume 20, 1992; pp.27-28

22. Fermented Papaya Preparation (*Immun'Age*) Quenched Free Radicals and Inhibited Lipids Peroxidation in Iron-induced Epileptic Focus in Rats

Santiago, L.A., Osato, J.A., Hiramatsu, M., Mori, A.
Oxygen Radicals, 1992; pp 405-408

23. Decrease Release of Monoamine Metabolites in Iron-induced Epileptic Focus in Rat following administration of Fermented Papaya Preparation (*Immun'Age*)

Santiago, L.A., Osato, J.A., Kabuto, H., Mori, A.
Medical Science Research Volume 21 Number 4, 1992; pp 139-141

24. Age-related Increase in Superoxide Dismutase Activity and Thiobarbituric Acid Reactive Substances: Effect of Fermented Papaya Preparation in Aged Rat Brain

Santiago, L.A., Osa to, J.A., Liu, J., Mori, A.
Neurochemical Research, Volume 18 Number 6, 1993; pp 711-717

25. Free Radical Regulatory and Immunomodulatory Effect of Fermented Papaya Preparation

Osato, J.A., Afanas'ev, I., Korkina, L., Santiago, L.A., Mori, A.
Nutrition, Lipids, Health and Disease, Chapter ,1995; pp 45-58

26. Free Radicals in Biology and Medecine

Halliwell Barry and Gutteridge John
2nd Edition New York: Oxford University Press Inc, 1996 ; pp 454-455

27. Fermented Papaya Preparation (*Immun'Age*) Quenched Free Radicals and Inhibited Lipids Peroxidation in Iron-induced Epileptic Focus in Rats

Santiago, L.A., Osato, J.A., Hiramatsu, M., Mori, A.
Oxygen Radicals, 1992; pp 405-408

28. Antioxidant Action of Fermented Papaya Preparation (*Immun'Age*) on Abestos and Cobalt-Induced Lung Injury

Osato, J.A., Afanas'ev, I., Takamizawa, K., Korkina, L.
Oxidants and Antioxidants in Biology, 1995: p 110

29. Effects of Fermented Papaya Preparation (*Immun'Age*) Alone or in Combination with Anticancer Drugs on Cancer Cells: A preliminary study
Ortega, R., Simonoff, M., Osato, J.A., Santiago, L.A.
 Conference on Oxidative Stress and Redox Regulation I Pasteur Paris
 May 21-24, 1996; p 230.
30. The Fermented Papaya Preparation (*Immun'Age*) Clinical Efficacy Against Lead Intoxication
Kundiev Yuri and others
31. Effect of Fermented Papaya Preparation on the Resistance of Rats against Infection of Salmonella
NIZO Food Research Netherlands
 NIZO-Rapport E 2000/72 pp 1-24
32. Studies on the Biological Activities of Fermented Papaya Preparation (*Immun'Age*)
Okuda, H., Ohmionami, H., Zhou, A., Matsuura, Y., Osato, J.A., Santiago, L.A.
 Clinical report, Volume 27 Number 11, 1993; pp 47-56
33. Analysis of Free Radicals in Biological Systems
Favier A.E., Cadet, J., Kalyanaraman, B., Fontecave, M., Pierre, J-L.
 Berlin Birkhäuser ,1995
34. Mode of Action of a Fermented Papaya Preparation (*Immun'Age*) on NO synthesis and TNF- a Secretion in the Mouse Macrophage Cell Line RAW 264.7
G. Rimbach Y.C. Park; Q. Guo; L. Packer and coll.
 Life Science 67 (2000); pp 679-694
35. Ferric Nitritotriacetate Induced DNA and Protein Damage: Inhibitory Effect of a Fermented Papaya Preparation (*Immun'Age*)
G.Rimbach, Qiong Guo, Takashi Akiyama, Seiichi Matsugo, Hadi Moini, Fabio Virgili and Lester Packer
 Anticancer Research 20: 2907-2914 (2000)
36. Ethanol-Related Gastric Mucosal Damage: Evidence of a Free Radical-Mediated Mechanism and Beneficial Effect of Oral Supplementation with Fermented Papaya Preparation (*Immun'Age*), a Novel Natural Antioxidant
F. Marotta, H. Tajiri, P. Safran, E. Fesce, G. Ideo
 Digestion 1999; 60: 538-543
37. Cyanocobalamin Absorption Abnormality in Alcoholics is Improved by Oral Supplementation with a Fermented Papaya-derived Antioxidant (*Immun'Age*)
F. Marotta, H. Tajiri, R. Barreto, P. Brasca, GM Ideo, L Mondazzi, P. Safran, J Bobadilla, G. Ideo
 Hepato-Gastroenterology 2000; 47:pp 1189-1194

38. 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

Hepato-Gastroenterology 2001; 48: pp 511-517

39. Redox Regulation of Gene Expression and Transcription Factors in Response to
Environmental Oxidants

Hiroshi Masutani, Akira Nishiyama, Yong-Won Kwon, Yong-Chul Kim, Hajime Nakamura, Junji Yodoi

Environmental Stressors in Health and Disease. Chap 6 ; pp 115-134
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