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Leaky Gut Syndrome, Dysbiosis, Ama, Free Radicals, and Natural Antioxidants

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ABSTRACT : The functioning of the gastrointestinal (G.I.) system has wide-ranging influences on the body that go far beyond the G.I. tract. According to Ayurveda-the ancient natural health care system of India - proper diet and digestion are one of the major pillars of health. Altered digestive functioning can lead to the production of *Ama*, a toxic material that initiates and promotes disease processes throughout the body. Optimal functioning of the G.I. tract requires proper mucosal integrity and a balanced microflora. Compromised mucosal integrity which leads to 'leaky gut syndrome,' and imbalances in the microflora known as 'dysbiosis,' result in the formation of Ama. Ama is also produced at other levels of the physiology, including the cellular level. Excessive formation of free radicals contributes to the formation of Ama. A variety of free radicals and reactive oxygen species (ROS) are produced during cellular metabolism. Excessive amounts of these reactive molecules can cause damage, starting the disease process. They are believed to be causative agents in nearly every disease. The ability to control their concentrations may be helpful for the prevention and treatment of many disorders. Antioxidants 'scavenge' free radicals and ROS, and render them harmless. Antioxidants can be lipid- or water-soluble; some are produced in the body and others are obtained from food or dietary supplements. Natural antioxidants range from vitamins to enzymes to herbal mixtures. Powerful antioxidants are present in the bioflavonoids found in concentrated form in Ayurvedic herbal mixtures known as *Rasayanas*. The use of these Rasayanas will be helpful in neutralizing the excessive free radical activity that contributes to Ama formation. However, the accumulated Ama in the body will not be removed by the use of Rasayanas and antioxidants alone. Other Ayurvedic methodologies are required to eradicate accumulated Ama. Rasayanas are best utilized to neutralize ongoing damage to the physiology and regenerate the system.

Key words : Gastrointestinal system, leaky gut syndrome, dysbiosis, Ayurveda, Ama, Rasayanas, free radicals, antioxidants.

INTRODUCTION

Over the course of a lifetime, we will ingest 50-60 tons of macronutrients, micronutrients, chemicals, and toxins. This material provides the building blocks for every system of our body. Our ability to properly digest and metabolize these substances determines to a large extent the state of our health. Imbalance in the gastrointestinal (G.I.) system has implications that extend far beyond the G.I. tract. According to Ayurveda-the ancient natural health care system of India-proper diet and digestion are one of the major pillars of life[1]. An improper diet or inadequate digestive capacity results in undigested material in the body, leading to the production of *Ama*, a toxic material that blocks the channels of the body and initiates and promotes disease processes[2]. Optimal functioning of the G.I. tract requires proper mucosal integrity and a balanced microflora. Compromised mucosal integrity and disturbances in bacterial flora give rise to 'leaky gut syndrome' and 'dysbiosis,' which in turn result in the production of Ama.

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Free radicals and reactive oxygen species (ROS) are unstable molecules produced as a byproduct of cellular metabolism. They carry out many crucial functions in the body; however, if produced in excessive amounts, these reactive molecules can wreak havoc on cells and cause extensive damage. Free radical-damaged cellular material is involved in the production of Ama. Antioxidants 'scavenge' or 'quench' free radicals, rendering them harmless. There are hundreds of naturally - occurring antioxidants, some of which are produced in the body. Others must be obtained from food or dietary supplements. Bioflavonoids are a group of powerful free radical scavengers found in fruits, vegetables, herbs, and spices. They are present in concentrated form in Ayurvedic herbs. Herbal mixtures from Ayurveda known as *Rasayanas* have shown extraordinary antioxidant potency and will be helpful in neutralizing the excessive free radical activity that contributes to Ama formation. However, other Ayurvedic methodologies are also required to eradicate accumulated Ama from the body and restore optimal health.

Leaky Gut Syndrome :

Healthy cellular morphology in the G.I. tract, including proper functioning of the villi and tight cell junctions allows only fully digested material to be absorbed. Cellular damage resulting in altered villi and compromised cell junctions, permits the absorption of incompletely digested material (intermediate metabolites). This altered intestinal permeability is known as 'leaky gut syndrome,' which results in a host of problems locally in the G.I. tract as well as generalized in the organ systems. Significant permeability changes in the gut mucosa can have profound effects on anatomic and immunologic barriers to disease[3]. Leaky gut can lead to increased inflammatory cytokine production and a propagation of inflammation within the intestine[4]. It can also result in food allergies, malnutrition, dysbiosis, and toxic overload. These effects ultimately result in an elevated total toxic and antigenic burden that leads to systemic disease. There is evidence linking increased intestinal permeability with immune dysfunction, systemic disease, and multi-organ system failure[5]. The causes of leaky gut are :

- Inflammatory bowel disease (IBD) (Crohn's disease)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Altered commensal flora
- Small bowel bacterial overgrowth
- Celiac disease
- Infection
- Food allergies
- Peptic ulcer disease
- Chronic alcoholism
- Diarrhea
- Strenuous exercise
- Increasing age
- Nutritional depletion
- Poor dietary choices
- Stress and emotions
- Systemic disease
- Low stomach acid
- Exposure to toxins

Dysbiosis :

Microorganisms are ubiquitous and play a critical role in the functioning of the G.I. tract. More than 500 species of gut flora have been noted[6] and the number of bacteria present in the G.I. lumen are 10-fold greater than the number of cells in the human body[7]. The positive health effects of these bacteria include[8]:

- Energy salvage from carbohydrate fermentation
- Synthesis of B vitamins and K vitamins
- Production of short-chain fatty acids
- Lowering of pH
- Production of anti-microbial compounds
- Stimulation of the immune system.

Nearly 70% of the human immune system is localized in the digestive tract.

Dysbiosis is an imbalance in the microbial ecology of the gut, leading to G.I. dysfunction[9]. It may be due to a deficiency of beneficial species (e.g. *Lactobacillus*, *Bifidobacteria*), overgrowth of normal flora (e.g. small intestine bacterial overgrowth), or overgrowth of low virulence pathogens (e.g. *Klebsiella*, *Candida*). The causes of dysbiosis are:

- Impaired digestion
- Hypochlorhydria
- Antibiotics
- Ethanol
- NSAIDs
- Slow transit time, decreased peristalsis
- Impaired immune status
- Dietary factors (e.g. low fiber, excess meat)

The effects of intestinal dysbiosis are :

- G.I. symptoms (gas, bloating, constipation, diarrhea)
- Chronic intestinal inflammation, IBD
- Intestinal permeability defects
- Increased endotoxemia
- Systemic reactions to bacterial endotoxins and antigens
- Increased risk of cancer, hormonal imbalances

The profound effects of altered commensal flora are experienced by nearly 15% of the human population, who suffer from the functional G.I. disorder known as 'Irritable bowel syndrome (IBS)'.[10] Several chronic diseases have a high degree of overlap with IBS, including fibromyalgia, interstitial cystitis, and chronic fatigue syndrome[11].

Probiotics :

Probiotics are live microorganisms that exert beneficial health effects on the host when administered in adequate amounts[12]. Probiotic bacteria have been utilized to treat leaky gut syndrome and dysbiosis.[9,12] Probiotic, meaning 'for life', is in opposition to 'antibiotic.' The most common probiotic bacteria are *Bifidobacterium*, *Lactobacillus*, and *Saccharomyces boulardii*. Probiotic supplementation has been shown to be of benefit in antibiotic-associated diarrhea, necrotizing enterocolitis,[13] cancer prevention,[14] health promotion, and prevention of *Helicobacter pylori* infection.[15]

Ama :

Ama is a concept of Ayurveda that can be understood as accumulated toxic substances at different levels of the physiology.[1,2] Leaky gut syndrome and dysbiosis contribute to the production of Ama. At the level of gross digestion, poorly digested food results in a thick, slimy material that lines the walls of the bowel, impeding absorption and assimilation of nutrients. Absorption of poorly digested material and intermediate metabolites, combined with free radical-damaged cellular material, cellular waste material, and toxins absorbed from the food supply and the environment, blocks the channels of the physiology at different levels, leading to various diseases and disorders. This toxic material (Ama) can be viewed as a foreign substance by the body and the immune system can react by forming antibodies to it, giving rise to antigen-antibody complexes and resulting in immune disorders.

At the cellular level, during functioning of the physiology there is accumulation of impurities and toxins. These impurities come from both inside and outside the body. From inside the body come internal metabolic and cellular waste products, such as free radical-damaged cells and tissues, and from outside come external impurities and toxins, such as herbicides, pesticides, pollutants, and toxins that occur naturally in food. All these impurities are collectively referred to as 'Ama' in Ayurvedic terminology.

Ama can accumulate at susceptible areas in the physiology, which vary from patient to patient. Ama in the blood vessels can be understood as the accumulation of lipids and other substances in the walls of the blood vessels, which causes plaque formation that results in blockage of blood flow. Ama in the joints can lead to development of arthritis. At the cellular level, damage from Ama can occur at various sites. Damage to the cell membranes results in the inability of exchange of substances, including nutrients, between the intracellular and extracellular environments. Damage to cell receptors hinders the action of hormones and other important biochemicals at the cellular level. Damage to mitochondria interferes with energy production at the cellular level. Damage to DNA causes mutation and can result in initiation of the cancer process. Cellular damage at these various sites results in the initiation of the disease process in most diseases and disorders. The extent of Ama and its symptoms can be graded (see Table 1).

TABLE NO. 1 : QUESTIONNAIRE TO ASSESS AMA IN PATIENTS :

Name :	**Date :**
Circle the appropriate response (1 = minimum; 5 = maximum)	
1. I tend to feel obstructed in the body (constipation, congestion in the head area, general feeling of non-clarity, or other).	1 2 3 4 5
2. When I wake up in the morning, I do not feel clear; it takes me quite some time to get really awake.	1 2 3 4 5
3. I tend to feel physically weak for no apparent reason.	1 2 3 4 5
4. I get the common cold or similar ailments several times a year.	1 2 3 4 5
5. I tend to feel heaviness in the body.	1 2 3 4 5
6. I tend to feel that something is not functioning properly in the body (breathing, digestion, elimination, or other).	1 2 3 4 5
7. I tend to be lazy, e.g. the capacity to work is there, but there is no inclination.	1 2 3 4 5
8. I often suffer from indigestion.	1 2 3 4 5
9. I tend to have to spit repeatedly.	1 2 3 4 5
10. Often, I have no taste for food, no real appetite.	1 2 3 4 5
11. I tend to feel tired or exhausted, mentally or physically.	1 2 3 4 5
11 - 25 Minimal 25 - 35 Mild 35 - 45 Moderate 45 - 55 Severe	

There are three types of Ama in the physiology. 'Common Ama' can be understood as improperly digested material in the bowel and the 'normal' formation of free radicals in the physiology, with resulting minor damage to the system. This damage is neutralized by antioxidants and other enzymes; proper nutrients from the diet; and polyphenols and bioflavonoids, which are found in concentrated form in Ayurvedic herbal Rasayanas. When this damage increases due to increased production of free radicals and other toxic metabolic byproducts in the physiology, resulting in cellular and tissue damage, this is called 'Ama Visha' (or reactive toxin). When exogenous substances such as pesticides, herbicides, other toxic chemicals, environmental pollutants, or excessive use of pharmaceuticals, vitamins, or minerals causes damage to the physiology, this is called 'Gara Visha' (toxic material resulting from the interaction of exogenous toxins within the physiology). The interaction of all these three forms of Ama produced in the physiology can cause DNA damage, resulting in serious illnesses, including cancer formation.

From the Ayurvedic point of view, Ama is produced from improperly digested material due to an imbalance in *Agni*. Agni is translated as 'fire' or 'flame.' It governs the metabolic and endocrine systems, and associated transformations in the physiology, e.g. digestion, metabolic transformations, and hormonal and biochemical changes. Agni is managed by governing principles of the physiology known as the *doshas*: *Vata*, *Pitta*, and *Kapha*. Thus, any imbalance in Vata, Pitta, and Kapha will produce an imbalance in Agni. No disease can manifest without a disturbance in Agni. Examples of Ama production, in relation to the doshas and Agni, are:

- Ama due to increased Vata with high Agni or low Agni
- Ama causing heaviness in the physiology - due to increased Kapha with low Agni
- Highly reactive Ama - due to increased Pitta with sharp Agni. This highly reactive Ama can turn into Ama Visha (see next section).

The primary source of Ama is the digestive system, but Ama can also be produced in the liver or at other tissue or cellular levels, depending on the etiological factor. Agni disturbance in the digestive system is responsible for the creation of Ama that leads to 80% of all disease processes.

Types of Ama :

- **Common Ama** - produced by Vata and Kapha imbalance. This type of Ama is nonreactive. Common Ama clogs the 'srotas' - the microcirculatory and macrocirculatory channels that carry nutritional substances and excretory products. This causes disturbance in Vata, Pitta, and Kapha, and leads to disease. By clogging the channels, Common Ama can create hyperactivity in the area involved, which can result in Common Ama being converted into reactive Ama (Ama Visha). This reactive Ama then creates disease. For example, if this process occurs in the liver, a toxic load could be created which would disturb liver functioning. In the kidneys, this process could produce abnormalities in kidney functioning. Detoxification would then be required to restore balance and normal functions.
- **Ama Visha** - produced when reactive Ama produced by Pitta interacts with the doshas and dhatus within the physiology. Ama Visha is highly reactive. It can damage various organs, produce autoimmune reactions, affect mental channels, produce lack of coordination between heart and mind, produce diarrhea, bronchial irritation, etc.
- **Gara Visha** - a type of reactive Ama produced when Common Ama reacts with external toxins, e.g. pesticides, herbicides, preservatives, environmental toxins, or excessive use of pharmaceuticals, vitamins, or minerals.

The combination of Common Ama, Ama Visha, and Gara Visha can be highly toxic and create very serious illnesses, including cancer.

Management of Ama :

In brief, the management of Ama according to Ayurveda begins with *Nidan Parivarjan* - identifying the etiological factors. The dosha that is the root cause of Ama is pacified through proper diet, daily routine, and behavior (*Achara Rasayana*), and balancing the predominant seasonal dosha. *Ama Pachana* (digesting Ama) is done using diet, spices, and herbs. After Ama Pachana, oil massage is added as well as *Shodhana* - detoxifying or clearing Ama from the physiology through proper diet, herbs, and Panchakarma.

Ama is a combination of free radical-damaged physiochemical and cellular material, combined with internal and external toxic material, which blocks the channels in the physiology. Natural antioxidants that scavenge free radicals are present in plants.[16] These include polyphenols, bioflavonoids, catechins, carotenoids, vitamin C, riboflavin, vitamin E, and low molecular weight compounds. These powerful antioxidants protect the plants from the damaging effects of the sun's radiation.[17] Bioflavonoids are present in their most concentrated form

in Ayurvedic herbal Rasayanas. The use of these Rasayanas will be helpful in neutralizing the excessive free radical activity that contributes to Ama formation. However, the accumulated Ama in the body will not be removed by the use of Rasayanas and antioxidants alone. Other Ayurvedic methodologies previously mentioned are required to remove accumulated Ama. Rasayanas are best utilized to neutralize ongoing damage to the physiology and regenerate the system. Rasayanas are most effective, when the body is free of Ama. The following sections describe free radicals and antioxidants, including the importance of Ayurvedic Rasayanas as powerful antioxidants.

Free Radicals and Natural Antioxidants :

The clinical presentation of any given disease is usually well known. However, the cellular and subcellular events that give rise to the characteristic signs and symptoms of a disease often remain obscure. In recent years, a great deal of research has taken place in the area of free radicals and reactive oxygen species (ROS). Free radicals and ROS are unstable molecules produced as a byproduct of cellular metabolism. They carry out many crucial functions in the body, ranging from fighting infection to controlling blood flow to maintaining mental alertness. However, if produced in excessive amounts, these reactive molecules can wreak havoc on cells and cause extensive damage. Although the exact mechanisms by which they contribute to the pathophysiology of disease are not fully elucidated, it is clear that free radicals and ROS are direct or indirect participants in the subtle beginings of the disease process[18,19]. It is now believed that they are either initiating or promoting agents in nearly every known disease[20]. They are also considered a major culprit in the aging process and the degenerative changes that accompany it.

Since free radicals and ROS appear to play such a prominent role in human disease, the ability to control their concentrations and behavior holds great promise for the prevention and treatment of a wide variety of diseases. The diverse array of interventions currently being investigated in this area includes natural antioxidants ranging from vitamins to enzymes to herbal mixtures that were formulated thousands of years ago. Antioxidants are unique in their ability to render free radicals and ROS harmless. They 'scavenge' or 'quench' free radicals before they can spread their destruction throughout the body. There are hundreds of naturally-occurring antioxidants, some of which are produced in the body. Others must be obtained from food or dietary supplements. Bioflavonoids are a group of powerful free radical scavengers found in fruits, vegetables, herbs, and spices. They are present in a concentrated form in Ayurvedic herbs. Herbal Rasayanas have shown extraordinary antioxidant potency[21]. Some of these herbal mixtures are Brahma Rasayana, Narasimha Rasayana, Amruthaprasham, Ashwagandha Rasayana or Ashwagandhadi Lehya, and Maharishi Amrit Kalash (MAK)[22,23].

In a recent study on a large cohort of postmenopausal women (161,808 participants), no overall association between multivitamin use and risk of several common cancers or cardiovascular disease was found. There was also no association between multivitamin use and total mortality. However, data are consistent in stating that diets high in fruits and vegetables are associated with a lower risk of cardiovascular disease and cancer[24]. This suggests that the phytochemicals present in fruits and vegetables have a better preventive effect on the physiology than synthesized vitamin supplements. Ayurvedic herbal Rasayanas, which contain concentrated phytochemicals, may be even more effective in preventing chronic disease, including cancer and cardiovascular disorders.

Free Radicals and Reactive Oxygen Species :

The Oxygen Paradox : Oxygen is the most abundant element in the earth's crust and atmosphere, comprising 49.2% by mass of all elements[25]. Although aerobic life currently dominates the planet, evolution began in the absence of molecular oxygen[26]. Only after the appearance of photosynthetic organisms about three billion years ago did molecular oxygen, a byproduct of photosynthesis, become a dominant chemical species[26]. Those organisms able to adapt to aerobic life evolved and flourished owing to benefits conferred by oxygen metabolism; however, elaborate cellular defenses evolved by necessity to protect the cell against the toxic effects of ROS[18]. The requirement of oxygen for viability, coexisting with the inescapable toxicities associated with its presence, is termed the 'oxygen paradox'[26,27]. A cell, then, is a dynamic entity placed in the paradoxical position of requiring oxygen to survive and yet risking injury and perhaps death as a result of its presence. Within each cell there exists an approximate equilibrium between the destructive forces of pro-oxidant metabolites and the antioxidant mechanisms that oppose these forces[26,28]. The term 'oxidative stress' is used to describe the disequilibrium that results when there is an excess of pro-oxidant forces[28]. Depending upon the magnitude and rate of application of an oxidative stress, a cell's adaptive capabilities may become overwhelmed, resulting in oxidative damage.

Early Research :

Free radical chemistry began at the end of the 19th century with the discovery that a newly-described class of chemical-free radicals-were responsible for fat spoilage, an extremely costly change occurring in stored fats and oils[29,30]. Free radical research was dominated in the early years by chemists concerned with food spoilage and polymerization reactions in rubber and plastics[29,31]. The hypothesis that free radicals were involved in important cellular functions and the pathophysiology of human disease met with skepticism until 1969 when McCord and Fridovich isolated the enzyme superoxide dismutase (SOD) from human cells[31,32]. Subsequent to this discovery, the field of free radical research in biological systems has become an intense and expanding area of investigation in both chemistry and biology.

Free Radical Chemistry :

A free radical is an atom, molecule, or molecular fragment that contains one or more unpaired electrons in its outer orbit[29,33]. It may carry a positive or negative charge, or it may be electrically neutral[33]. A compound becomes a free radical through either chemical oxidation-the loss of an electron, or through chemical reduction-the gain of an electron[34]. Free radicals may also be formed as a result of a particular type of covalent bond splitting called homolytic bond fission, in which both fragments retain an unpaired electron[29].

In chemical reactions, free radicals act as either oxidizing or reducing agents. When reacting with non-radical compounds, they may create new free radicals. A free radical may also initiate a chain reaction in which the original free radical is consumed and another free radical is created[33]. Owing to their unique chemical structure, free radicals are intrinsically unstable, highly reactive, and short-lived[29,35].

Molecular oxygen is not, by definition, a free radical; however, due to the unstable configuration of the electrons in its outer orbitals, oxygen behaves occasionally like two free radicals stuck together and is termed a 'biradical'[30]. Eventually, molecular oxygen, through its reactive metabolites-ROS-will oxidize all biological compounds[25].

Free Radical Production :

Researchers cite the following pro-oxidant species as important in the human physiology: the superoxide, hydroxyl, peroxy, and nitric oxide radicals; singlet oxygen; hydrogen peroxide; and hypochlorous acid[27,28] (Table 2). Singlet oxygen and hydrogen peroxide are not free radicals, but are highly reactive and capable of generating free radicals[36]. Hypochlorous acid is a potent chlorinating and oxygenating agent capable of degrading proteins and chlorinating purine bases in DNA[27,37].

TABLE NO. 2 : PRO-OXIDANT SPECIES :

Superoxide radical	Nitric oxide radical
Hydroxyl radical	Singlet oxygen
Peroxy radical	Hydrogen peroxide
Hypochlorous acid	

In health, over 98% of the oxygen consumed by a cell undergoes the stepwise addition of four electrons to form two molecules of water[36,38]. This complete (tetravalent) reduction of molecular oxygen is accomplished by the cytochrome oxidase system located within the mitochondria. The remaining 1-2% of oxygen escapes this pathway and undergoes a one-, two-, or three-electron reduction to produce the superoxide radical, hydrogen peroxide, or hydroxyl radical, respectively[18].

Free radicals are also generated in enzymatic and nonenzymatic reactions located in: lysosomes and peroxisomes; nuclear, endoplasmic reticular, and plasma membranes; and throughout the cytosol[36,37]. Approximately 10% of the reactions in which molecular oxygen acts as an electron acceptor generate free radicals[27]. In addition to endogenous sources, free radicals are also produced by environmental pollutants, pesticides, alcohol, tobacco smoke, anaesthetics, hyperoxic environments, ionizing radiation, certain wavelengths of light, and certain foods and drugs[39].

Free Radical Functions :

Under normal conditions, free radicals are continually produced as important intermediates in cellular metabolism; however, they are usually tightly bound to the active sites within the enzyme and cannot react with other cellular molecules[40]. Other physiologic functions of ROS are those associated with the inflammatory response. Neutrophils, when stimulated, have the ability to take up molecular oxygen during a respiratory burst to produce halogenated molecules that can kill bacteria and other pathogens[36]. Immune cells can also produce large amounts of nitric oxide and superoxide to kill bacteria and viruses, as well as tumor cells[41,42]. The disadvantage of these protective mechanisms is that the release of free radicals and ROS into the extracellular space can cause collateral tissue damage[43].

Free radicals are necessary for many other crucial functions. Nitric oxide in particular has proven to be a diverse biological mediator. It controls blood flow, regulates neurotransmission in the central and peripheral nervous systems, and modulates hormone release and

platelet aggregation. At low levels, some free radicals function as signaling molecules to turn genes on and off. In 1998, the Nobel Prize was awarded to scientists who discovered that nitric oxide functions as a signaling molecule in the cardiovascular system. Nitric oxide also helps control gastrointestinal motility[44,45].

Free Radical Damage :

During conditions of oxidative stress, a cell may experience an excessive free radical load; if cellular defenses are overwhelmed, oxidative damage results. Free radicals can react with and damage all major classes of biological molecules[26,29]. The following sections detail some of the cellular damage caused by oxygen-derived free radicals.

Lipids : Free radicals attack the double bonds in polyunsaturated fats within cellular membranes; this is known as lipid peroxidation[30]. A chain reaction may result that irreversibly destroys the fluidity and structural integrity of the membrane, resulting in the loss of secretory, enzymatic, cellular recognition, and other membrane functions, and leading ultimately to cell lysis[36]. The degradation products of these reactions can diffuse away from the site to cause cell edema, increased vascular permeability, and inflammation. Other diffusion products may alter low-density lipoprotein (LDL), enhancing its uptake into macrophages, which leads to foam cell formation and atherogenesis. In addition, some degradation products may damage nucleic acids, leading to mutagenesis and carcinogenesis[29,30,46].

Proteins : As the load of free radicals in a cell increases, damage to proteins may progress from site-specific lesions to fragmentation to crosslinking[26]. As a result, structural proteins such as elastin and collagen may be damaged. Protein function may also be altered, leading to enzyme dysfunction and inactivation. In addition, oxidized proteins such as lipofuscin accumulate during the aging process[26].

Nucleic Acids : Oxidation by free radicals causes two basic types of lesions in nucleic acids: strand breaks and base modification. Enzymes repair DNA strand breaks, but this results in decreased fidelity[26]. Consequently, the repaired DNA strand differs from the original in subtle but important ways. Such changes in DNA base sequence have clear implications for the pathogenesis of disease. In addition, free radicals may also attack and alter individual bases on a DNA strand, leading to mutagenesis and carcinogenesis[26].

Carbohydrates : Free radicals can cause depolymerization of polysaccharides, e.g. hyaluronic acid, resulting in the loss of structural and functional capabilities of these molecules[29]. In addition, damage to the carbohydrate portion of cell receptors can lead to the loss of various cellular functions. T-lymphocytes, in particular, appear to be susceptible to free radical damage[47]. As a result, the immune system may be compromised.

Free Radicals and Disease :

Free radicals and ROS clearly play a fundamental role in the etiology of a vast number of diseases (Table 3). The following sections discuss some of the diseases and disorders thought to be caused by free radicals.

TABLE NO. 3 : DISEASES AND DISORDERS IN WHICH FREE RADICALS AND ROS PLAY A SIGNIFICANT ROLE :

Adult respiratory distress syndrome	Environmental toxicity
Aging	Hepatitis
Alzheimer's disease	Hyperoxygenation syndrome
Atherosclerotic heart disease	Intestinal ischemia
Behcet's disease	Ionizing radiation side-effects
Cancer	Keloid formation
Carbon tetrachloride toxicity	Mucocutaneous syndrome
Cataracts	Myocardial infarction
Cerebral ischemia (stroke)	Paraquat toxicity
Chemotherapeutic agent-related toxicities	Parkinson's disease
Chronic bronchitis	Progressive systemic sclerosis
Crohn's disease	Pulmonary fibrosis
Dermatitis herpetiformis	Reperfusion injury
Diabetes mellitus	Retrolental fibroplasia
Eclampsia	Rheumatoid arthritis
Emphysema	Sunburn

Inflammatory Diseases : Free radicals are important mediators in the complex pathogenesis of acute and chronic inflammatory reactions[35]. During phagocytosis, they are released into the extracellular space where they cause direct tissue injury and alter structural macromolecules such as elastin, collagen, and hyaluronic acid[35]. In addition, they may react with a plasma component to produce a chemotactic substance that attracts more neutrophils to the site of inflammation. Rheumatoid arthritis is a case in point. Due to the free radical-mediated destruction of hyaluronic acid, synovial fluid loses its viscosity and joint cartilage becomes eroded[35]. Other diseases thought to be mediated by free radicals include connective tissue disease, inflammatory bowel disease, and immune deficiencies[48,49].

Hyperoxygenation Syndromes : Hyperoxia increases the production of free radicals in aerobic tissue[50]. The eyes and lungs appear to be the organs most susceptible to high concentrations of oxygen[37]. In addition to increased intracellular production of free radicals, the number of neutrophils sequestered in the lungs during hyperoxic states probably contributes to the lethal effects in lung tissue[35]. Neutrophil chemotaxis and the subsequent discharge of toxic oxygen radicals is

believed to be the common mediator of injury among the diverse clinical settings of adult respiratory distress syndrome, including aspiration, sepsis, burns, microembolism, and hyperoxia[35]. In addition, cytotoxic oxygen species are almost certainly the cause of tissue damage in retrolental fibroplasia[35].

Emphysema : The enzyme alpha-1-antitrypsin is the primary inhibitor of neutrophil-released proteolytic enzymes. Individuals who are genetically deficient in this enzyme and who smoke cigarettes are at a higher risk for developing emphysema early in life[35]. *In vitro* studies suggest that the tissue damage found in emphysema is promoted by free radical attack in two ways: first, neutrophils, when stimulated by bacteria or the particulate matter in cigarette smoke, release potent proteolysin; second, cigarette smoke contains a variety of oxygen- and carbon-based free radicals capable of inhibiting alpha-1-antitrypsin activity[35,37].

Reperfusion Injury : Injury caused by ischemia with subsequent reperfusion occurs almost exclusively during the reperfusion phase. This injury is promoted by oxygen-derived free radicals[26]. During the ischemic period, a cell undergoes a series of biochemical changes that cause free radical production. As the cell is reperfused, additional damage is caused by neutrophil activation and subsequent release of superoxide free radicals. Free radical-promoted reperfusion injury is thought to be important in a number of diseases and conditions, including myocardial infarction, elective cardioplegia (cardiopulmonary bypass), intestinal ischemia, cerebral ischemia and stroke, acute renal tubular necrosis, and circulatory shock [26, 35, 51, 52, 53].

Cancer : Carcinogenesis occurs in two stages: first, the initiation stage, during which a physical, chemical, or biologic agent directly causes an irreversible alteration in the molecular structure of DNA; and second, the promotion stage, during which the expression of the genes that regulate cell differentiation and growth is altered[35]. Free radicals are active in both the initiation and promotion stages of cancer, and therefore are important etiological agents in carcinogenesis[19,26]. In addition, chronic inflammation, with its many free radical-induced mechanisms, is well-known to be associated with cancer[35].

Atherosclerosis : The diffusion products of lipid peroxidation can structurally alter LDL. As a result, arterial endothelial cell receptors no longer recognize the altered lipoprotein and normal cellular LDL uptake is inhibited[27,54]. Instead, LDL is taken up by macrophages, leading to foam cell formation, an early event in the development of atherosclerotic plaque[55]. Arterial smooth muscle cells and endothelial cells may release free radicals that damage LDL within the arterial walls[35]. The lipid peroxidation products of free radical-damaged LDL are toxic to endothelial cells[56]. Endothelial cell damage is a major factor in the development of atherosclerotic plaque[35]. Other products of lipid peroxidation may affect the prostacyclin-to-thromboxane ratio, leading to the thrombotic episodes associated with atherosclerosis[35]. In addition, under certain conditions the free radical nitric oxide restricts blood flow, which can contribute to heart disease and stroke[57].

Environmental Toxicities : Free radicals are generated from a wide variety of exogenous sources. The damaging effects of ionizing radiation are enhanced by free radical mechanisms[37]. In addition, skin aging and other damaging effects due to excessive exposure to sunlight are caused by free radical production[58]. Ultraviolet radiation from sunlight causes the formation of singlet oxygen, which promotes the formation of free radicals[59,60]. The short-term effect of this free radical damage can be sunburn, while the long-term effect can be the formation of skin cancer.

Ozone is another oxygen-based molecule that promotes free radical formation[61,62]. This chemical is present in cigarette smoke and car exhaust fumes. It is harmful to the skin and when inhaled, can severely damage the oral cavity, nasal passages, and fluid lining in the lungs. Another free radical found in cigarette smoke and car exhaust fumes is nitric oxide. This free radical is also found in smog and it is believed to be a potent carcinogen. The carcinogenic and mitogenic properties of many industrial pollutants are due to the formation of free radicals and their subsequent interaction with nucleic acids[63,64].

The cellular metabolism of many drugs and chemicals also induces free radical production[63,65]. Hepatotoxicity due to carbon tetrachloride, lung damage caused by the pesticide paraquat, and cardiotoxicity caused by adriamycin are all free radical-induced injuries[35,37]. Other exogenous sources of free radicals include tobacco smoke and alcohol[66,67]. Tobacco smoke generates phenoxy free radicals and creates other free radicals in the body that damage cell membranes and crosslink proteins, leading to lung fibrosis and emphysema. Alcohol is metabolized to create the double free radical acetaldehyde, which can crosslink macromolecules in the liver. Certain foods are also sources of free radicals. These include smoked and barbecued foods, and peroxidized fats in meats and aged cheeses.[39]

Aging : In 1954, Dr. Denham Harman proposed the free radical theory of aging[68]. Dr. Harman was the first scientist to link biological oxidation occurring in the cells with the degenerative changes associated with the aging process. In the decades since Dr. Harman proposed his theory, much evidence has accumulated in support of it. Although a direct cause-and-effect relationship between aging and oxidative stress has not been demonstrated, it is clear that increased exposure to free radicals increases the rate of aging and, conversely, decreased exposure leads to a decreased rate of aging. It is also known that over time, free radical-damaged DNA and other oxidized macromolecules such as lipofuscin, accumulate in the cell and alter physiologic functions. Lipofuscin results from the process of lipid peroxidation. This age pigment accumulates in all the body's specialized cells, but is most pronounced in the brain and the heart. Lipofuscin accumulation is directly proportional to metabolic rate and inversely related to longevity[35].

NATURAL ANTIOXIDANTS

Antioxidant Defenses :

Aerobic cells have multiple defense mechanisms against free radical attack (Table 4). There are both enzymatic defense systems and non-enzymatic antioxidants. Free radicals are generated in both the aqueous and lipid portions of the intracellular and extracellular environments. Therefore, it is crucial for the body to have a combination of water-soluble and lipid-soluble antioxidants to provide the full range of protection (Table 5). Some antioxidants are synthesized by the body, whereas others must be obtained from food or food supplements (Table 6).

TABLE NO. 4 : ANTIOXIDANT DEFENSES :

Enzymatic	Nonenzymatic
Superoxide dismutase	Vitamin C, Vitamin E
Glutathione system	Alpha lipoic acid
Catalase	Coenzyme Q10
	Carotenoids
	Polyphenols and bioflavonoids, including herbal mixtures

TABLE NO. 5 : WATER-SOLUBLE AND LIPID-SOLUBLE ANTIOXIDANTS :

Water-soluble	Lipid-soluble
Glutathione	Vitamin E
Alpha lipoic acid	Alpha lipoic acid
Vitamin C	Coenzyme Q10
Polyphenols and bioflavonoids, including herbal mixtures	Polyphenols and bioflavonoids, including herbal mixtures

TABLE NO. 6 : SOURCE OF ANTIOXIDANTS :

Synthesized by the Body :
Superoxide dismutase
Glutathione system (except for selenium)
Catalase
Alpha lipoic acid
Coenzyme Q10
Obtained from Food or Food Supplements:
Vitamin C, Vitamin E
Coenzyme Q10
Alpha lipoic acid
Carotenoids
Polyphenols and bioflavonoids, including herbal mixtures
Selenium (part of glutathione system)

Antioxidant Enzymes :

Enzymes dismantle free radicals without being altered in the process. This makes them thousands of times more effective, molecule for molecule, than many nonenzymatic antioxidants, which are rendered useless after scavenging just one free radical. Relatively high numbers of these enzymes are in circulation at all times and moreover, they are inducible-large amounts can be created rapidly in response to a sudden increase in free radical levels.

Superoxide Dismutase (SOD) : This enzyme catalyzes a two-step reaction in which the superoxide radical undergoes dismutation to yield hydrogen peroxide and molecular oxygen. Other antioxidant enzymes then dismantle hydrogen peroxide. High levels of SOD are correlated with a reduction in the occurrence of cancer[69]. SOD also protects against the toxic effects of high oxygen levels in the lungs[37]. Research has shown that burn victims who can induce high levels of SOD recover more quickly than those who cannot[17].

Glutathione System : This powerful antioxidant system involves glutathione, several enzymes, and selenium. The glutathione peroxidase enzyme uses an electron from a molecule of glutathione to disarm lipid peroxide. The glutathione is then supplied with a replacement electron by the enzyme glutathione reductase. Glutathione can also be recycled by alpha lipoic acid and it is able to regenerate vitamin C. Glutathione is water-soluble and is produced in the body by the enzyme glutathione synthetase. It is made from three amino acid molecules-cysteine, glutamic acid, and glycine - and four selenium atoms. A hereditary deficiency of glutathione synthetase leads to premature death from oxidative damage to the brain[70].

Glutathione is crucial for protection of liver function. It aids in the liver's detoxification of pollutants, drugs, alcohol, and other potentially poisonous substances[71]. By attaching onto these toxins, glutathione makes them more water-soluble so they can then be flushed out of the body through the kidneys. It also protects against liver cancer. Administration of glutathione caused regression of liver tumors in 81% of experimental lab animals[72].

Glutathione is also required for healthy immune function. A laboratory study on immune cells of men aged 65-84 years showed that addition of glutathione to these cells stimulated production of both interleukin-1 (IL-1) and interleukin-2 (IL-2)[73]. IL-1 is involved in the inflammatory response required to fight infection, and IL-2 is involved in the growth of new immune cells. Glutathione also increased the proliferation of lymphocytes.

Each molecule of glutathione contains four selenium atoms. This trace mineral is therefore a crucial component of the glutathione system. The body obtains selenium through food and water. Food sources include garlic, onions, wheat germ, broccoli, and red grapes. However, the selenium content in these foods and in water varies throughout the world, due to variations in selenium content in the soil. This can have serious health consequences for those people living in low-selenium regions. Studies have shown that these individuals have a much higher incidence of cancer, whereas people living in selenium-rich areas have the lowest incidence of cancer. The same holds true for heart disease¾people living in areas that have the lowest levels of selenium in the soil have a much greater risk of fatal heart disease, whereas people who live in regions with high selenium content have significantly lower rates of death from heart disease. Selenium is vital to the body's antioxidant defense system[74].

Catalase : This enzyme has the valuable role of breaking down hydrogen peroxide into water and oxygen. However, it is only available within subcellular organelles known as peroxisomes. These organelles create hydrogen peroxide as a byproduct of their normal activities, therefore high concentrations of catalase are required just to keep the peroxisomes functioning properly.

Nonenzymatic Antioxidants :

There are thousands of naturally-occurring nonenzymatic antioxidants. Some are produced in the body, while others are available only through food or food supplements. Many of these antioxidants work together synergistically to enhance the power of one another. For example, there is a dynamic interaction between Vitamin C, Vitamin E, Coenzyme Q10, and Alpha lipoic acid. They work together to regenerate one another after quenching a free radical. This cooperation is vital to the efficiency of these antioxidants since, unlike enzymes, they do not have the ability to disarm free radicals one after another. In fact, once they have quenched a free radical, they become a weak free radical themselves and must be regenerated by another antioxidant.

The carotenoids function as helper antioxidants to decrease free radical levels in the body. Beta-carotene is the most well-known antioxidant in this category. Polyphenols are another category of antioxidants[75,76]. These phytochemicals (plant-based chemicals) give fruits and berries their striking colors[75]. The polyphenol known as Resveratrol has strong antioxidant properties and is thought to be responsible for the beneficial effects of red wine consumption on heart disease[77]. Bioflavonoids are a subgroup of polyphenols comprised of several thousand phytochemicals. These potent antioxidants are found in their most concentrated form in herbs. The following sections discuss the nonenzymatic antioxidants in more detail.

Vitamin C : Since our body does not produce Vitamin C, we must obtain it from food or food supplements. It is present in many fruits and vegetables, as well as some herbs. Good sources include citrus fruits, tomatoes, cranberries, red peppers, broccoli, and the herb from India called Amla berry, also known as Indian gooseberry. Vitamin C is water-soluble and functions in the cytosol, bloodstream, and intercellular spaces. It aids in the construction of connective tissue, helps regulate lipid levels in the blood, assists in iron absorption, and is involved in the synthesis of various brain chemicals. As an antioxidant, it scavenges the hydroxyl radical, superoxide radical, and singlet oxygen. Vitamin C regenerates Vitamin E, and can in turn be recycled by Vitamin E, glutathione, Alpha lipoic acid, and bioflavonoids[20].

Vitamin C is critical for enhancing immune function. Its concentration in immune cells is 20-100 times higher than in blood. In lab experiments, it has been shown to suppress the replication of viruses such as the rhinovirus, which causes a stuffy nose. Studies have also shown that Vitamin C supplements decrease the incidence of tonsillitis and bronchitis in schoolchildren [20, 78, 79].

Vitamin C has also been shown in numerous studies to reduce the incidence of cancer. There is a direct correlation between increased intake of fruits and vegetables high in Vitamin C content and lowered incidence of cancer of the esophagus, mouth, stomach, and pancreas[80]. Conversely, low levels of Vitamin C in the blood have been correlated with bladder cancer. In lab animals supplemented with Vitamin C, bladder tumors were prevented[39]. Vitamin C supplements have also been shown to reduce the risk of heart disease and stroke[81,82].

A current controversy surrounding Vitamin C and other antioxidants involves their use in reducing the toxic side effects of chemotherapy and radiation. Oncologists fear that antioxidants might inhibit the pro-oxidant effects of these cancer treatments. Research shows that this fear is unwarranted. In a laboratory study, Vitamin C augmented tumor kill and did not protect cancer cells[83]. Further evidence comes from the results of two clinical studies on patients undergoing aggressive chemotherapy, which revealed that supplementation with the herbal mixture MAK decreased the toxic side effects but did not interfere with the efficacy of the treatment [84, 85].

Vitamin E : This antioxidant is actually a group of molecules that includes four tocopherols and four tocotrienols. Although the most well-known form of Vitamin E is d-alpha-tocopherol, all members of this group have important health benefits. Vitamin E is the body's primary fat-soluble antioxidant. It can recycle Vitamin C and can in turn be regenerated by Vitamin C, Alpha lipoic acid, Coenzyme Q10, and bioflavonoids. The best food sources for Vitamin E are those high in vegetable fats, such as nuts and wheat germ. Other sources include lettuce and other green leafy vegetables.

Vitamin E is found in all cell membranes and functions aggressively in this lipid environment to quench free radicals and prevent the massive lipid peroxidation that results from a free radical chain reaction speeding along the membrane. This process of lipid peroxidation can ultimately result in atherosclerosis-hardening of the arteries-which can lead to heart disease.

Vitamin E has become known as the anti-aging antioxidant[20]. Laboratory experiments have shown that Vitamin E can decrease lipid peroxidation in the brain[20,86]. It may also be able to prevent or delay the onset of Alzheimer's disease by protecting brain cells from oxidative damage[87]. In cell culture, Vitamin E prevented formation of the age pigment lipofuscin[88] and doubled the lifespan of human lung cells[89]. In a clinical study of older people, it enhanced the immune response[90]. Vitamin E also decreases the risk of developing cancer [91, 92, 93]. A possible mechanism for this may be its ability to inhibit Protein kinase C activity, which involves activation of enzymes that stimulate tumor growth[94].

Although the tocopherols are the most well-known forms of Vitamin E, the tocotrienols are valuable antioxidants in their own right. In a long-term clinical study, tocotrienol intake decreased carotid stenosis[95]. Tocotrienols from rice bran have cholesterol-lowering effects[96]. Tocotrienols also reduce levels of thromboxane, a clotting factor associated with increased risk of heart attack and stroke[97]. Tocotrienols may also be effective against breast cancer. In a laboratory study, they inhibited the growth of both estrogen-positive and estrogen-negative breast cancer cells[98].

Alpha lipoic acid : This powerful antioxidant is produced by the body and helps break down sugar for production of energy. Alpha lipoic acid is also present in foods such as potatoes, carrots, beets, and yams. As an antioxidant, Alpha lipoic acid is unique in several important ways. First, it is both water-soluble and fat-soluble, so it can function in all areas of the cell. Second, it can recycle multiple other antioxidants, including Vitamin C, Vitamin E, Coenzyme Q10, and glutathione. Third, it can recycle itself-an amazing ability that no other antioxidant has[99].

Research has shown that Alpha lipoic acid provides a wide range of protection for the body. It protects the brain against stroke-related oxidative injury by crossing the brain/blood barrier and functioning directly in the brain cells. It also boosts glutathione levels, which are important for protection of the brain. Alpha lipoic acid increases glutathione levels in the lens of the eye as well, which helps to prevent cataracts[100]. Another benefit of this antioxidant is its ability to protect the heart from oxidative damage that occurs when the heart is deprived of oxygen and then reperfused. Alpha lipoic acid also reduces crosslinking of proteins, an aging process associated with heart disease, cataracts, arthritis, and Alzheimer's disease.

The liver is another organ that Alpha lipoic acid protects. It can counteract the fatal effects of mushroom poisoning by the *Amanita phalloides* mushroom, which normally would destroy the liver within a short period of time[101]. Alpha lipoic acid has also been used successfully to treat Hepatitis C[102].

In Europe, Alpha lipoic acid has been utilized for decades for treating the complications of diabetes. In several studies conducted in Germany, diabetic patients

with peripheral nerve damage had marked improvement in their symptoms after taking Alpha lipoic acid[20,103]. Another study showed that treatment with Alpha lipoic acid actually stimulated the regeneration of nerve fibers. This occurred after three weeks of taking 600 mg of Alpha lipoic acid daily, and resulted in a significant reduction in the pain and numbness associated with neuropathy[104].

Coenzyme Q10 (CoQ10) : This fat-soluble antioxidant is a cofactor that works with enzymes in the body to produce fuel. CoQ10 is produced in the body and is found in all cell membranes. It is also available from certain foods. Foods with the highest content of CoQ10 are wheat germ, soy, spinach, broccoli, fish, vegetable oils, grapeseed oil, and rice bran. CoQ10 regenerates Vitamin E and is regenerated by Alpha lipoic acid. It is most abundant in the mitochondria, the energy-producing organelles inside the cell. When energy is produced, free radicals are created as a byproduct, so it is crucial to have adequate levels of CoQ10 to quench these free radicals before they cause damage. CoQ10 has been found useful in the treatment of heart patients with various ailments such as cardiomyopathy, high blood pressure, angina, and valve disorders[105,106,107]. CoQ10 is also effective in treating gum disease[108].

Carotenoids : These natural pigments give fruits and vegetables their bright colors, with a spectrum ranging from red, orange, and yellow, to dark green and purple. Three of the carotenoids-Alpha-carotene, Beta-carotene, and cryptoxanthin-are converted into Vitamin A in the body. Vitamin A is involved in maintaining vision and is required for healthy skin. It is used in skin care products to treat acne and reduce wrinkles, and it also protects against skin cancer.

Beta-carotene is the most common carotenoid in our diet. It is an efficient quencher of singlet oxygen and also works effectively against many other free radicals and ROS[109,110]. In spite of this, research on Beta-carotene has yielded conflicting results. Some studies have shown Beta-carotene use to be beneficial, whereas other studies have yielded negative results[111,112,113,114]. However, one consistent finding is that a diet rich in foods containing Beta-carotene is beneficial[115,116]. Another area in which positive results have been obtained is immunity-the use of Beta-carotene has shown increased immune function[117].

Lycopene is the carotenoid that makes tomatoes red. It appears that it may help protect men against prostate cancer[118]. A diet rich in spinach and collard greens reduces the risk of developing age-related macular degeneration-a leading cause of blindness in older people. Spinach and collard greens contain the carotenoids lutein and zeaxanthin, which are also found in high concentrations in the macula region of the eye[119].

Polyphenols and Bioflavonoids : Plants have extensive exposure to the sun's radiation and high levels of oxygen are generated as a byproduct of photosynthesis. This combination results in a proliferation of free radicals and ROS. Plants therefore have a high concentration of antioxidants to provide the protection they require. Research is now discovering that some of these plants may in turn protect the health of humans.

The phytochemicals-plant chemicals-that exhibit antioxidant properties are part of a large group of molecules called polyphenols. There are more than 8000 polyphenols currently identified. These can be divided into at least ten different classes based on their chemical structure. They range from simple molecules such as phenolic acids, to highly polymerized structures such as tannins. Polyphenols are ubiquitous in plant-derived foods and beverages. They are found in fruits, vegetables, cereal grains, legumes, nuts, tea, coffee, cocoa, beer, wine, etc. The astringency and bitterness of foods and beverages is due to their polyphenol content. These substances are also pigments that give the beautiful blues and reds to fruits, berries, and wine.

There is a large body of scientific research accumulated on polyphenols. These antioxidants are free radical scavengers and chelators of metal ions that can initiate hydroxyl radical production and catalyze lipid peroxidation. Polyphenols include both water-soluble and lipid-soluble antioxidants. They can regenerate Vitamin C and Vitamin E. Epidemiologic studies have demonstrated a correlation between increased consumption of polyphenol antioxidants and reduced risk of heart disease and certain types of cancer[75].

Resveratrol is a polyphenol found in high concentration in the skin of grapes. It has strong antioxidant and anti-inflammatory properties, and has been shown to prevent tumor initiation, promotion, and progression[77]. One of its mechanisms of action may be its ability to inhibit the cyclooxygenase-2 (COX-2) enzyme, which stimulates tumor cell growth and suppresses immune surveillance[120]. Resveratrol also protects LDL from oxidation and prevents platelet aggregation, both important factors in the prevention of heart disease[121,122].

The antioxidant efficiency of polyphenols varies greatly and is strongly dependent on their chemical structure. Bioflavonoids constitute the group of polyphenols that have the greatest antioxidant potency. They are highly effective scavengers of hydroxyl and peroxy radicals[75]. More than 5000 different bioflavonoids have been identified. All of them are antioxidants, but some are stronger than others. Bioflavonoids have been researched heavily. They have been shown to have antibiotic properties and to be anti-diarrheal, anti-ulcer, anti-inflammatory, anti-allergic, anti-hemorrhagic, anti-thrombotic, and vasoprotective[123,124]. They decrease high blood pressure, decrease levels of LDL, and increase levels of high-density lipoprotein (HDL). In addition, they are potent inhibitors of LDL oxidation. Bioflavonoids also exert an anticarcinogenic effect through several different mechanisms: they protect DNA from oxidative damage, inactivate carcinogens, inhibit the expression of mutant genes and the activity of enzymes involved in activation of procarcinogens, and activate enzymes for breakdown of toxins[75].

Rasayanas : Herbal mixtures have been used worldwide for thousands of years as therapeutic agents to prevent and treat disease. The herbs in Ayurvedic Rasayanas generally contain a variety of polyphenols, bioflavonoids, catechins, and carotenoids, as well as Vitamin C, Vitamin E, and a large number of low molecular weight compounds. These chemical constituents have a wide variety of biological activities, including antioxidant, antiplatelet, lipid-lowering, fibrinolytic, anti-tumor, anti-inflammatory, anti-microbial, allergy - reducing, asthma-reducing, etc.[16,39] Bioflavonoids are present in their most concentrated form in herbs. It is now known that complex mixtures of bioflavonoids have a synergistic effect that yields a benefit greater than the sum of the individual components. This is clearly evidenced by an abundance of research conducted on various Rasayanas such as Brahma Rasayana, Narasimha Rasayana, Amruthaprasham, Ashwagandha Rasayana or Ashwagandhadi Lehya, and Maharishi Amrit Kalash (MAK). Rasayanas are Ayurvedic preparations that are used for slowing the aging process, inducing homeostasis, improving immunity, and preventing various disorders. Research on these Rasayanas has shown that they are very powerful antioxidants. They can also enhance immunity, prevent cancer, prevent chemotherapy (including cyclophosphamide)-induced toxicity and radiation-induced toxicity, inhibit LDL oxidation, prevent platelet aggregation, and/or reduce the severity of experimental atherosclerosis [23, 125].

MAK is a full-spectrum antioxidant that can protect both the aqueous and lipid portions of the cell. It has significant antioxidant properties[22, 126]. MAK has been researched extensively in laboratory, animal, and clinical settings, and found to have a wide range of beneficial properties. In laboratory and animal studies, MAK prevented and treated breast cancer,[127,128] prevented metastasis of lung cancer,[129] caused nervous system cancer cells (neuroblastoma) to regain normal cell functioning,[130] potentiated neuronal differentiation in pheochromocytoma cells,[131] inhibited the growth of skin cancer cells (melanoma),[132] and prevented liver cancer[133]. In laboratory and clinical studies, MAK has been shown to reduce the toxic side-effects of chemotherapy and maintain glutathione peroxidase levels, without reducing the efficacy of the cancer treatment [84, 85, 134, 135].

MAK also reduces several risk factors for heart disease. It prevented human platelet aggregation[136] and reduced atherosclerosis in laboratory animals by 53%[137]. In clinical studies on patients with heart disease, MAK reduced the frequency of angina, improved exercise tolerance, and lowered systolic blood pressure and lipid peroxide levels[138,139]. A study on hyperlipidemic patients showed that MAK increases the resistance of LDL to oxidation[140].

Several studies have also shown that MAK significantly enhances immune functioning [141-146]. It also has anti-aging effects-it improved age-related visual discrimination in older men[147] and in animal studies has been shown to rejuvenate the antioxidant defense system of the aging central nervous system[148-151] and enhance cholinergic enzymes in the aging brain[152].

Rasayanas have been used in India for more than 5,000 years. The ancient medical texts assert that they promote longevity, stamina, immunity, and overall well-being. Modern research is bearing out these claims.

CONCLUSION

A healthy gastrointestinal system is crucial to the overall health of the body. If the mucosal integrity is compromised, leaky gut syndrome will result. If there is an imbalance in the microflora, this dysbiosis will result in dysfunction of the G. I. tract. Leaky gut syndrome and dysbiosis lead to the creation of Ama, which can disseminate and initiate disease processes throughout the body. Probiotics are beneficial live bacteria that have been used to treat leaky gut syndrome and dysbiosis. Ama can also be created at the level of the liver or at other tissue or cellular levels. Excessive free radical activity can result in production of Ama at the cellular

level. Powerful natural antioxidants that scavenge free radicals are present in the bioflavonoids found in concentrated form in Ayurvedic herbal Rasayanas; however, other Ayurvedic methodologies are also required to eradicate accumulated Ama from the body. Rasayanas are best utilized to neutralize ongoing damage to the physiology and regenerate the system, thereby ensuring optimal health.

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हिन्दी सारांश

आम, फ्रीरेडिकल्स एवं प्राकृतिक एण्टीऑक्सिडन्ट्स

हरि शर्मा

अन्नवह संस्थान की कार्यप्रणाली का शरीर की अनेक गतिविधिओं पर प्रभाव होता है। आयुर्वेद में आहार और पाचन को आयु एवं स्वास्थ्य का महत्त्वपूर्ण आधार माना गया है। आधुनिक विज्ञान के अनुसार फ्रीरेडिकल्स एवं रिएक्टिव ऑक्सिजन स्पिसिज शरीर में विभिन्न विकारों को जन्म देते हैं। आयुर्वेद मतानुसार आम सभी रोगों का मूल कारण है। आयुर्वेदिक रसायन औषधियाँ एवं प्राकृतिक एण्टीऑक्सिडन्ट्स इनकी चिकित्सा में उपयुक्त होते हैं। प्रस्तुत लेख में इन सभी घटकों का विस्तार से वर्णन किया गया है।

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