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Oxidative Stress and Chronic Degenerative Diseases - a Role for Antioxidants

ISBN 980-953-307-650-3
Book edited by:

Prof. Dr. José A. Morales-González
Área Académica de Farmacia, Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, México

Deadline for submitting chapter proposals (1-4 pages long): **April 17, 2012**
This book is planned to be published in **November 2012**

The book will be indexed in:

The topics covered in the edited book will include, but are not limited to:

- Chemical free radicals
- Antioxidants metabolism
- Radical scavengers
- Antioxidants
- Endogenous antioxidant defenses
- Exogenous antioxidant defenses
- Cell damage by free radicals
- Oxidative stress
- Adaptation, damage, repair and death by free radicals
- Lipid peroxidation
- Free radicals, oxidative stress and chronic degenerative diseases (liver cirrhosis, hypertension, diabetes, cancer, obesity, kidney diseases, neurodegenerative diseases)
- Aging and oxidative stress
- Disease and therapy: A role for antioxidants
- Health, nutrition and antioxidants
- Antioxidants in the prevention and treatment of chronic degenerative diseases (liver cirrhosis, hypertension, diabetes, cancer, obesity, kidney diseases, neurodegenerative diseases)
- Natural antioxidants
- Total antioxidant capacity

The role of natural antioxidants in cancer disease

Carmen Valadez-Vega[1], Luis Delgado-Olivares[1], José A. Morales González[1], Ernesto Alanís García[1], José Roberto Villagomez Ibarra[2], Esther Ramírez Moreno[1], Manuel Sánchez Gutiérrez[1], María Teresa Sumaya Martínez[3], Zuñiga Pérez Clara[1], Zuli Calderón Ramos[1].

[1]Institute of Health Sciences, Autonomous University of Hidalgo State, Ex-Hacienda de la Concepción, Tilcuautla, Hgo, Mexico. C.P.42080.
[2] Institute of Basic Sciences, Autonomous University of Hidalgo State, Km 4.5 Carretera Pachuca-Tulancingo, Ciudad del Conocimiento, Mineral de la Reforma Hidalgo, C.P. 42076
[3] Secretary of Research and Graduate Studies, Autonomous University of Nayarit, Ciudad de la Cultura "Amado Nervo", Boulevard Tepic-Xalisco S/N. Tepic, Nayarit, Mexico

1. Introduction

Cell oxidation can lead to the onset and development of a wide range of diseases including Alzheimer, Parkinson, the pathologies caused by diabetes, rheumatoid arthritis, neurodegeneration in motor neuron diseases, and cancer. Reactive species (RS) of various types are powerful oxidizing agents, capable of damaging DNA and other biomolecules. Increased formation of RS can promote the development of malignancy, and the 'normal' rates of RS generation may account for the increased risk of cancer development.

Oxidants and free radicals are inevitably produced during most physiological and metabolical processes, and the human body has defensive antioxidant mechanisms, these mechanisms vary according to the cell and tissue type and they may act antagonistically or synergistically. They include synthetic antioxidants and natural antioxidant as enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, as well as antioxidant such as vitamins, carotenoids, poliphenols and other naturals antioxidants which have taken great interest in last years.

There has been a great deal of interest recently in the role of complementary and alternative medicines for the treatment of various acute and chronic diseases. Of the various classes of phytochemicals, interest has focused on the anti-inflammatory and antioxidant properties of polyphenols found in various botanical agents. Plants vegetables and spices used in folk and traditional medicine have gained wide acceptance as one of the main sources of prophylactic and chemopreventive drug discovery and development.

Recently researches on medicinal plants has drawn global attention; large bodies of evidence have accumulated to demonstrate the promising potential of medicinal plants used in various traditional, complementary and alternate systems of treatment of human diseases. The plants are rich in a wide variety of secondary metabolites such as tannins, terpenoids, alkaloids, flavonoids, etc., which have been screened *in vivo* and *in vitro* and indicated antioxidant, and anticarcinogenic properties are used to developed drugs or dietary supplements.

Evidence suggests that plant kingdom is considered as a good candidate for chemoprevention and cancer therapy, due to the high concentration and wide variety of antioxidants such as resveratrol, genestein, beicalein, vitamin A, vitamin C, polyphenols, (-)-Epigallocatechin 3-gallate, flavonoids, polyphenols, gallic acid, glycosides, verbascoside, calceorioside, epicatechin, quersetin, curcumin, lovastatin, and many other kinds of compounds with capability to inhibit cell proliferation of different cancer cells *in vitro* and *in vitro*, such as colon cancer cells (HT-29, SW48, HCT116), breast (MCF7, MDA), cervix (HeLa, SiHa, Ca-Ski,C33-A), liver (Hep G2), skin (A 431), fibroblasts (3T3 SV40) and many others malignant cells; the studies had indicated that the antioxidants can be used efficiently as chemopreventive and as an effective inhibitor of cell proliferation, promoting cell apoptosis, increasing detoxification enzymes, inhibiting gene expression, and scavenger reactive oxygen species (ROS). For this reason many researchers are working with different kinds of natural antioxidants with the aim of finding those with greater capacity to inhibit the development of cancer, both *in vitro* as *in vivo*, since these compounds have submitted a high potential to be used not only in the treatment of this disease, if not also act as a good chemoprotective agents.

2. Antioxidants

The production of ROS during metabolism is an inevitable phenomenon associated at the process of the aerobic metabolism; on the other hand, we are exposed all the time to several exogenous sources of oxidants molecules for example environmental, pollutants factors and many dietary compounds, which increase its levels. The ROS participate in different cellular process, its intracellular levels are relatively low; however because that these are highly toxic when these increase its

concentration, is produced the phenomenon called Oxidative Stress (Sies, 1997), which can injure various cellular biomolecules causing serious damage to tissues and organs, resulting in chronic diseases (Delgado *et al.,* 2010). Oxidative damage can be prevented for the antioxidants, which are present into cell in low concentrations compared with the oxidants molecules (Utara *et al.,* 2009; Halliwell & Gutteridge, 2006).

Antioxidants are capable of donating electrons for stabilize the ROS and inhibit the detrimental effect, included both endogenous (synthetized by self-body) and exogenous molecules (those from external sources to de body) (Uttara et al., 2009). Endogenous antioxidants include the superoxide dismutase (SOD), that catalyze the reaction of dismutation of superoxide ($O2^{\bullet -}$) to hydrogen peroxide (H_2O_2), which is transformed in oxygen and water for the catalase (CT), also the peroxidase glutathione (GHX) can catalyze its reduction, however if in presence of transition metals as iron, by the Fenton reaction, the H_2O_2 can produce the radical hydroxyl ($OH^{\bullet -}$), the more reactive of the ROS, which can produce the majority of oxidative damage (Delgado *el at.,* 2010)

On the other hand, exogenous antioxidants can be of animal and vegetable source, however the vegetable origin are of great interest due they can contain major antioxidant activity (Katalinic *et al.,* 2006; Carlsen *et al.,* 2010). Different reports show that people with intake of diet rich in fruit and vegetables have an important reduction risk of development cancer principally for the content of antioxidants (La Vechia *et al.,* 2001). Among the vegetable antioxidants are vitamins E, C, β-carotene which are associated to diminished cardiovascular disease and risk of any cancer (Halliwell, 1996). On particular β-carotene and vitamin E can reduce breast cancer risk, vitamin C, β-carotene, and lutein/zeaxanthin have a protector effect against ovarian cancer, vitamin C, β-carotene and rivoflavin prevents of colorectal cancer. (La Vechia *et al.,* 2001), while, flavonoids plant phenolic and wine phenolic can inhibit lipid peroxidation and lipoxigenase enzymes, also any microelements can has antioxidant activity as Se, Zn, Mn, Cu (Halliwell, 1996; Delgado *et al.,* 2010).

On recent years has been growing the interest in the use of the natural antioxidants, for prevention or treatment of different diseases related to oxidative stress, however despite the wide information of beneficial effects of antioxidants in the prevention of cancer, today it is still questionable the use, because different reports shows that reduce the level of ROS may have counterproductive effects because raise of cancer risk, this may be due at that the ROS can produce apoptosis in malignant cells (Gago-Dminguez, et al., 2007; Perera & Bardeesy, 2011).

3. Natural antioxidants, molecular studies

Different types of natural antioxidants are presents in fruit and vegetables; they have interactions synergistic, which are important, for their activity and regenerative potential. For example, the ascorbate can regenerate to α-tocopherol (Han *et al.,*.2007; Packer *et al.,* 2001), and the ascorbate radical is regenerate for others antioxidants via thiol redox cycle. All interactions are known as "antioxidant network" (Packer *et al.,* 2001).

Vitamin E, is an antioxidant which penetrate rapidly through skin and is incorporated into of cellular membranes inhibiting the lipid peroxidation, specifically the α-tocotirenol, isoform of vitamin E, show more protection. Also vitamin E has antiproliferative properties interfering in signal transduction and inducing arrest cycle cell (Packer *et al.,* 2001).

Tumor Necrosis Factor–α (TNF-α), is a cytokine that, in normal conditions, induce inflammation, inhibition of tumors and apoptotic cell death. However when this suffer deregulation act as a breast tumor promoter, enhancing the proliferation of chemically-induced mammary tumors, (Rivas, 2008). Phenolic antioxidants can block the increase of TNF-α, at transcriptional level in the nucleus, which suggest that the molecular mechanism of phenolic antioxidants through control of cytokine induction (Ma & Kinner, 2002).

4. Oxidative stress and diseases

During the cellular metabolism the lysosomes, peroxisomes, endoplasmic reticulum and mitochondria being the latter the major source of ROS, such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$), in the process realized for obtain energy as ATP (Rabek *et al.,* 2003). There are others sources of oxidant molecules as: the pollution, environmental and some foods. On the last years, has been discovering that during aging the mitochondria increase the levels of production of ROS and the endogens antioxidant diminished, (Nyström 2005; Bohr *et al.,*, 1988). The ROS play an important role in the physiological process; however due their toxicity its levels must be controlled by the antioxidant endogenous system. But when increased the formation of ROS, is promoted the imbalance between these and the antioxidant molecules, phenomenon known as oxidative stress (OS) (Sies, 1997), the which can cause a oxidative damage of proteins, lipids and nucleic acids, macromolecules involved in the function cell, membranes integrity or keeping the genetic information (nucleic acids) (Gong *et al.,* 2012; Grimsrud *et al.,* 2008; Keller 2006).

Proteins are responsible of different cell process (enzymatic, hormonal, structural support), the protein oxidation produce disulfide crosslinks, nitration o tyrosine residues, and carbonylation, resulting in loss of structure and function of the proteins

and fragmentation (Berlett *et al.,* 1997; Nunomura *et al.,* 2006). But as the chaperons are susceptible to oxidative damage, allowing the accumulation of misfolding proteins (RobeK *et al.,* 2003) increasing its susceptibility to proteases degradation (Roche and Romero, 1994), however also the proteasome suffer oxidation and its activity is diminished which make that the aggregates accumulate in the cell. Aggregates are has been associated with aging and various pathologies as cancer neurodegenerative disorders, Parkinson, Huntington and Alzheimer (Nyström, 2005)

Brain is the organ with high oxygen consume, have high levels of fatty acids, iron and low antioxidants defenses. This is an organ with major susceptibility to damage oxidative (Uttara, *et al.,* 2009), producing neurodegeneration that result in different disease as Parkinson, Alzheimer, Dow syndrome, autism, bipolar disorder and epilepsy (Dal-Pizzol *et al.*, 2009; Delgado *et al.,* 2010), and the cognitive alteration, known as mild cognitive impaired (MCI), which is produced in preferentially brain regions involved in regulating cognition, contributing to development to dementia (Keller 2006). Similar processes occur during aging, resulting in the genetic response for increase the levels of antioxidants enzymes and chaperon proteins (Lee *et al.,* 2000). The reductions of the oxidative stress cause the improvement of long-term memory (Pieta *et al.,* 2007).

Polyunsaturated fatty acids (principal compounds of the membranes) are susceptible to peroxidation are affecting the integrity of membranes of organelles of cellular membrane and respiratory chain affecting cell viability. The lipid peroxidation produced aldehydes as 4-hydroxy-2 *E*-nonenal, which is toxic and that is involved in alterations in Alzheimer´s disease and DNA damage causing mutations associated to development of cancer (Gago-Dominguez *et a*l., 2007; Cejas *et al.*, 2004).

The ribosomal RNA and transfer RNA constitute the majority stable species of cellular RNA which have a major rate of oxidation that DNA. The major modification for oxidation into of RNA is 8-hidroxyguanine (8-oxoG) which in normal conditions are present three times more in no ribosomal that in ribosomal RNA's, however when the cell are exposure at H_2O_2, the concentration of 8-oxoG in ribosomal RNA increase at the same levels in both RNA's (Nunomura et al., 2006). The oxidation of the RNA can diminish the capacity of replace oxidation of proteins (Keller, 2006; Gong *et al.,* 2012) and inhibition of protein synthesis, cell cycle arrest and death cell. The oxidation RNA is involved in development of cancer, viral infections of AIDS and hepatitis (VIH-1; HCV; Price *et al.,* 2005; Waris & Siddiqui, 2005) and neurological diseases. Has been observed that region in the brain that suffer RNA oxidation is dependent of each neurological disease. On Alzheimer's disease there are an increase oxidation RNA in hippocampus and cerebral neocortex, while that in Parkinson' disease the oxidation is localized in the *sustancia nigra* (Numomura *et al.,* 2006).

The more important damage caused for oxidative stress are the DNA modifications, which can result in permanent mutations, due to that oxidative damage too, affecting the proteins involved in the repair the harm or reduce oxidative stress (endogenous antioxidant), so oxidative damage to DNA can be the cause of development of various diseases as cancer (Bhor *et al.,* 1998; Halliwell, 2007).

On the other hand, high fat diets induce obesity and insulin resistance resulting increase the ROS production, which modify the activity sympathetic in the brain that contribute to the rise in blood pressure and increase the insulin resistance and the obesity (Ando and Fujita, 2009). The obesity is the principal factor in the development of metabolic syndrome due to that people with obesity have a deficient antioxidant defense and an increase production of ROS (Skaliky *et al.,* 2008; Echart *et al.,* 2009; Li *et al.,* 2009), which lead to the spoilage and subsequently cell death, resulting in a damage to tissues and organs causing serious health problems as insulin resistance (Ando *et al.,* 2004), diabetes mellitus and hypertension (Maritm *et al.,* 2003; Katsuyuki *et al.,* 2009). Moreover during metabolic syndrome the NAD(P)H oxidase, the major source of ROS in various tissues, is up-regulated, resulting in increase of ROS production and several antioxidants enzymes (SOD isoforms, GPX, and heme oxygenase) are down-regulation(Roberts *et al.,* 2006). This enzyme in specific the isoform type 4 (NOX4) is implicated in the damage for oxidative stress during the cerebral ischemia (Kleinschnitz *et al.,* 2010).

The scientific literature has been showing that oxidative stress is involved in the development of wide range of disease as heart diseases, Hutchinson-Gilford syndrome or progeria, hypertensive brain injury, muscular dystrophy, multiple sclerosis, congenital cataract, retinal degeneration, retinopathy of premature, autoimmune diseases, rheumatoid arthritis, cardiovascular abnormalities, nephrological disorders, emphysema, stroke, rheumatoid arthritis, anemia, hepatitis, pancreatitis, aging, premature wrinkles and dry skin, endothelial dysfunction, dermatitis, between others (Markesbery, 1997; *Andreazza, et al.,2009;* Tsaluchidu, *et al.,2008 ;* Medina-Ceja, *et al., 2007*; Dal-Pizzol *et al.,* 2009; Pieta *et al.,* 2007).

5. Cancer

Cancer is an unnatural cell growth, where they can loss their natural function and spread through of the blood, at all the body. Breast cancer is the more commonly diagnosed in industrialized countries and has the highest death toll (Maxmen, 2012). Oxidative stress is involved in the process development of cancer and tumors; due to that ROS can damage the macromolecules as lipids which react with metals (as free iron and copper) and produce aldehydes and synthesize malondialdehyde inducing mutations (Noda and Wakasugi *et al.,* 2001) or cause breaks in the double chain, produce modifications in guanine and thymine bases, and sister chromatid exchanges (Brown and Bicknell, 2001), which can affect

the activities of signal transduction, transcription factors and genes tumor suppressor as p53, which is a gene important in apoptosis and cycle cellular control. This inactivation can increase expression of proto-oncogenes (Noda and Wakasugi *et al.,* 2001) which can produce major damage. Oxidative damage or genetic defects that result in some defect enzymes incapable of repair the mutations increase the age-dependent cancer incidence (Halliwell, 2007).

On the other hand, treatments with anticancer drugs and radiation, increase the ROS and a decrease in antioxidants, for produce a state of severe oxidative stress, and cause apoptosis, resulting in side effects (Noda & Wakasugi *et al.,* 2001); while persistent oxidative stress at sublethal levels can result in resistance to apoptosis (Brown & Bicknell, 2001).

Some microorganisms, as bacteria and virus are involved, via oxidative stress, in the process of production of some cancers, as for example Helicobacter pylori, induce gastric cancer and colon cancer, through the production of $SO^{\bullet -}$ (Noda & Wakasugi *et al.,* 2001). It has been proposed that lower antioxidant activity increase the risk of developing cancer, so that the ingestion of antioxidants can prevent the cancerogenesis. However is not clear the decrease of antioxidants levels, in as much as in freshly cancerous tissue the levels of MnSOD are elevated, so that some investigators have proposed that this antioxidant enzyme is involved in tumor invasion, therefore it is possible that antioxidants have a role as prooxidants. Another point to consider is that when increasing the level of 8-oxodG in DNA, the cancer rates do not increase (Noda & Wakasugi *et al.,* 2001; Halliwell, 2007). However, the oxidative stress is a factor for cancer and other diseases, but not the only factor for diseases, also are involved other, like genetic factors (genetic predisposing).

6. Antioxidants and cancer

Human beings are constantly bombarded by exogenous factors such as ultraviolet rays, tobacco smoke and many others agents that cause oxidative stress, such stress can also arise from drugs that are used in medical practice. On the other hands under physiological conditions normal aerobics metabolism gives rise to active and potentially dangerous oxidants in cells and tissues, these endogenous sources of oxidative stress include those derived from activities of mitochondria or microsomes and peroxisomes in the electron transfer system and those from the enzyme NADPH present in macrophages and neutrophils as a mechanism of protection against infection. Various reducing substances in the human body control the status of oxidation-reduction (redox), and a continuing imbalance in favor of oxidation causes various problems when it exceeds the capacity of such control (Noda & Wakasug, 2000).

Otto Warburg was the first scientist to implicate oxygen in cancer (Warburg, 1956) as far back as the 1920s. However, the underlying mechanism by which oxygen might contribute to the carcinogenic process was undetermined for many years. The discovery of superoxide dismutase in 1968 by McCord and Fridovich (1968) led to an explosion of research on the role of reactive oxygen in the pathologies of biological organisms. Reactive oxygen has been specifically connected with not only cancer but also many other human diseases (Allen & Tresini, 2000; Hippeli *et al.,* 1999). For many years, research in oxidative stress focused primarily on determining how ROS damage cells by indiscriminate reactions with the macromolecular machinery of a cell, particularly lipids, proteins and DNA. Is well known in great detail how ROS react with lipids leading to the peroxidation of biological membranes and resulting in necrotic lesions (Gille & Sigler, 1995) and how ROS react with the nucleotides of DNA leading to potential mutations (Cadet *et al.,* 1997; Gille & Sigler, 1995; Upham & Wagner, 2001).

When produced in excess, ROS (some of which are free radicals) can seriously alter the structure of biological substrates such as proteins, lipids, lipoproteins, and deoxyribonucleic acid (DNA), they have a huge range of potential actions on cells, and one could easily envisage them as anti-cancer (e.g. by promoting cell-cycle stasis, senescence, apoptosis, necrosis or other types of cell death, and inhibiting angiogenesis) or as pro-cancer (promoting proliferation, invasiveness, angiogenesis, metastasis, and suppressing apoptosis).

Active oxygen may be involved in carcinogenesis through two possible mechanisms: the induction of gene mutations that result from cell injury and (Floid *et al*., 1986) the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress (Mates *et al*., 1999). Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals, is now apparent and it is known that tumor suppressor genes such as p53 and cell cycle-related genes may suffer DNA damage. In addition, oxidized lipids react with metals to produce active substances (e.g., epoxides and aldehydes) or synthesize malondialdehyde, which has the potential to induce mutation. Active oxygen species act directly or indirectly via DNA damage on gene expression (DNA binding of transcription factors) and signaling at the cellular level.

Markers for oxidative stress can be divided into three categories: 1) formation of modified molecules by free radical reactions; 2) consumption or induction of antioxidant molecules or enzymes; 3) activation or inhibition of transcription factors. Targets of

free radicals include all kinds of molecules in the body. Among them lipids, nucleic acids and proteins are the major targets. Since free radicals are usually generated near membranes (cytoplasmic membrane, mitochondria or endoplasmic reticulum), lipid peroxidation is the first reaction to occur. Lipid peroxidation products can be detected as classical thiobarbituric acid (TBA)-reactive substances. Recently, detection of 4-hydroxy-2-nonenal (HNE) or malondialdehyde (MDA) is favored because of their high specificity (Esterbauer *et al.,* 1991); aldehydes are end-products of lipid peroxidation, but they are still reactive with cellular proteins (Toyokuni, 1998).

Exposure to free radicals from a variety of sources has led organisms to develop a series of defense mechanisms, which involve: (i) preventative mechanisms, (ii) repair mechanisms, (iii) physical defenses, and (iv) antioxidant defenses. Enzymatic antioxidant defenses include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT). Non-enzymatic antioxidants are represented by ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), glutathione (GSH), carotenoids, flavonoids, tannins, triterpepenoids, saponins, glycosids,steroids and other antioxidants (Gupta & Sharma, 2012). Under normal conditions, there is a balance between both the activities and the intracellular levels of these antioxidants: this balance is essential for the survival of organisms and their health

7. Antioxidants in cancer assays

Humans have evolved with antioxidant systems to protect against free radicals and ROS. These systems include some antioxidants produced in the body (endogenous) and others obtained from the diet (exogenous) (Chen *et al.,* 2012). The first include (a) enzymatic defenses, such as *Se*-glutathione peroxidase, catalase, and superoxide dismutase, which metabolize superoxide, hydrogen peroxide, and lipid peroxides, thus preventing most of the formation of the toxic HO·, and (b) nonenzymatic defenses, such as glutathione, histidine-peptides, the iron-binding proteins transferring and ferritin, dihydrolipoic acid, reduced CoQ10, melatonin, urate, and plasma protein thiols, with the last two accounting for the major contribution to the radical-trapping capacity of plasma. The various defenses are complementary to each other, since they act against different species at different cellular compartments. However, despite these defense antioxidants (able either to suppress free radical formation and chain initiation or to scavenge free radical and chain propagation), some ROS still escape to cause damage. Thus, the body antioxidant system is provided also by repair antioxidants (able to repair damage, and based on proteases, lipases, transferases, and DNA repair enzymes (Varma *et al.*, 1995; Pietta, 2000).

Owing to the incomplete efficiency of our endogenous defense systems and the existence of some physiopathological situations (cigarette smoke, air pollutants, UV radiation, high polyunsaturated fatty acid diet, inflammation, ischemia/ reperfusion, etc.) in which ROS are produced in excess and at the wrong time and place, dietary antioxidants are needed for diminishing the cumulative effects of oxidative damage over the life span (Wayner *et al.,* 1987; Halliwell, 1994). Well known naturals antioxidants derived from the diet like vitamins C, E, A, and carotenoids, which have been studied intensively (Sies, 1997). Besides these antioxidant in plants might account for at least part of the health benefits associated with vegetable and fruit consumption (Pietta, 2000).

Plants vegetables and spices used in folk and traditional medicine have gained wide acceptance as one of the main sources of prophylactic and chemopreventive drug discovery and development (Matés *et al.,* 2011; Ebenezer *et al.,* 2011)

Some reports indicate that the prevalence of use of complementary and alternative medicine by cancer patients had been estimated range of 7% to 64% (Akar, 1995; Akinpule, 1999; Hladik *et al.,* 2005). At the present time, many cancer patients combine some forms of complementary and alternative therapy with their conventional therapies (Akinpule, 1999; Hladik *et al.,* 2005). A recent survey of patients in a comprehensive cancer center placed the use of vitamin and minerals at 62.6%; of these patients, 76.6% combined the use of vitamins and minerals with conventional chemotherapy (Hladik *et al.,* 2005, Drisco *et al.,* 2003).

These kind of patients use complementary and alternative therapies for a variety of reasons(Ernst & Cassileth, 1998; Boom *et al*., 2000); to improve quality of life (77%), improve immune function (71%), prolong life (62%) or relieve symptoms (44%) related to their disease (Ernst, 1998). Only 37.5% of the survey patients expected complementary and alternative therapies to cure their disease. Whatever the reasons, alternative therapy use is on the rise and this includes megavitamin, mineral, natural substances cocktails during chemotherapy administration; these cocktails include antioxidants such as the commonly consumed antioxidants vitamin E (mixed tocopherols and tocotrienols), vitamin C, β-carotene (natural mixed carotenoids), polyphenols, tannins, terpenoids, alkaloids, flavonoids, vitamin A and many others. Controversy exists about the use of antioxidants with chemotherapy, but increasing evidence suggests a benefit when antioxidants are added to chemotherapy (Riordan *et al*., 1995; Riordan *et al*., 2000; Prasad *et al*., 2001; Weijl et al., 1997; Lamson & Brignal, 1999; Schmitt & Lowe, 1999; Prasad *et al*., 1999; Chinery *et al*.,1997; Drisco *et al*., 2003)

It is widely accepted that a diet rich in fruits and plants are rich sources of different kinds of antioxidants, phenolic compounds are the most studied and have been recognized to possess a wide range of properties including antioxidant, antibacterial, anti-inflammatory, hepatoprotective and anticarcinogenic actions.(Akah & Ekekwe, 1995; Akinpelu, 1999; Jisaka *et al*.,1993;

Mejía, *et al.*, 2005)). Many of the biological functions of flavonoids, phenolic, catechins, curcumin, resveratrol and genistein compounds have been attributed to their free radical scavenging, metal ion chelating and antioxidant activities (Seef *et a*l., 2001; Winslow & Krol, 1998). Antioxidant phenolic agents have been implicated in the mechanisms of chemoprevention which refers to the use chemical substances of natural origin or synthetic to reverse, retard or delay the multistage carcinogenesis process (Ebe nezer *et al*., 2011)

It has been shown that dietary phytochemicals can interfere with each stage of carcinogenesis development (Surth, 2003; Middleton *et al*., 2000). As in the case of direct antioxidant effects, dietary polyphenols, are most likely to exert their chemopreventive effects in the gastrointestinal tract where they are present in the highest concentrations.(Halliwell, 2008; Halliwel, 2000; Martinez, 2005; Li *et al*., 2009) Indeed, studies have shown that various polyphenol-rich fruits and vegetables are particularly effective in protecting against several kind of cancer development.(Martinez,2005; Li *et al*.,2009; Hu, 2011). Dietary polyphenols may exert their anticancer effects through several possible mechanisms, such as removal of carcinogenic agents, modulation of cancer cell signaling and antioxidant enzymatic activities, and induction of apoptosis as well as cell cycle arrest. Some of these effects may be related, at least partly, to their antioxidant activities (Hu, 2011). They may exert protective effects against cancer development, particularly in the gastrointestinal tract where they will be at highest concentration. In fact, many studies have shown that various polyphenol-rich fruits and vegetables are particularly effective in protecting against colon cancer development (Martinez, 2005; Li *et al*., 2009)

At the cellular level, there is good evidence that polyphenols present in tea, red wine, cocoa, fruit juices, and olive oil, at some level it can stimulate carcinogenesis and tumor development (Middleton *et al*.,2000). For example, they may interact with reactive intermediates (Duthie *et al.,* 1999) and activated carcinogens and mutagens (Calomme *et al.,* 1996)], may modulate the activity of key proteins involved in controlling cell cycle progression (Plaumann *et al*., 1996) and influence the expression of many cancer-associated genes (Van *et al*., 2005). Perhaps most notably, the *anticancer properties of green tea flavanols have been reported in animal models (*Khanet *al., 1988), human cell lines (Takada et* al., 2002), as well as in human intervention studies (Inoue *et al*., 2001). On the other hand, green tea consumption has been proposed to significantly reduce the risk of cancer of the biliary tract (Takada *et al*., 2002), bladder (Rieger-Christ *et al*., 2007), breast (Leong *et al*., 2008) and colon (Larsen *et al*., 2009). Many of the anti-cancer properties associated with green tea are believed to be mediated by the flavanol, epigallocatechin gallate (EGCG), which has been shown to induce apoptosis and inhibit cancer cell growth by altering the expression of cell cycle regulatory proteins and the activity of signaling proteins involved in cell proliferation, transformation and metastasis (Khan *et al*., 2006). In addition to flavonoids, phenolic alcohols, lignans and secoiridoids (all found at high concentration in olive oil) are also thought to induce anti-carcinogenic effects (Owen *et al*., 2000) and have been reported in large intestinal cancer cell models (Llor *et al*., 2003), in animals (Bartoli *et al*., 2000; Solanas *et al*., 2002) and in humans (Owen *et al*., 2000). These effects may be mediated by the ability of olive oil phenolics to inhibit the initiation, promotion and metastasis in human colon adenocarcinoma cells (Gill et al., 2005; Hashim *et a*l., 2008) and to down-regulate the expression of COX-2 and Bcl-2 proteins that have a crucial role in colorectal carcinogenesis (Llor *et al.*, 2003; Vauzour *et al*., 2010)

in vivo studies had demonstrate that many natural compounds found in plants and fruits have the capability to inhibit many kinds of human an animal cancer. Vitamins like C, E and A had demonstrated can diminish cervical, bladder, prostate, intestine, skin and other kinds of gastrointestinal. Cancer and have the capability to inhibit ROS production in patients (Fuchs-Tarlovsky *et al*., 2011; Fukumura *et al*., 2012; Mazdak *et al*., 2012Thapa *et al*., 2012; Szpetna *et al*., 2012; Jayaprakash *et al*., 2012; Slagayar, 1995), and had been demonstrate that this vitamins can inhibit progression and pathogenesis on colorectal cancer (Bhagat *et al*., 2011). In animal models vitamins showed promise for chemopreventive agents for several kinds of gastrointestinal cancer (Jayaprakash *et al.,* 2011).

The use of a combination of vitamins, selenium, β-carotene, essential fatty acids, coenzyme Q_{10}, in patient with breast cancer and it was observed that during the study any patient died, any patient showed signs of further distant metastases, quality of life was improved and six patients showed apparent partial remission (Lockwood *et al*., 1994). Human studied had demonstrate that consume of total antioxidants in the diet (fruits and vegetables) is inversely associated with the risk of distal gastric cancer (Mauro *et al*., 2002). Antioxidants, especially poliphenols have been found to be promising agents toward cervical cancer, including induction of apoptosis, growth arrest, inhibition of DNA synthesis and modulation of signal transduction pathway, and they can interfere with each stage of carcinogenesis initiation, promotion and progression to prevent cancer development (Di Domenico *et al*., 2012).

Camelia sinensis tea which contain a great quantity of polyphenols (epichatechin, (-) epigallocatechin-3-galato) is the most widely consumed beverage in the world and had been demonstrated that the consumption of this beverage has shown to afford protection against chemical carcinogen-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast and colon carcinogenesis in specific bioassay models, the properties of the tea polyphenols make them effective chemopreventive agents against the initiation, promotion and progression stage of multistage carcinogenesis (Kariyar *et al.,* 1997). Rosmanic acid had demonstrate to have potent anticancer and apoptotic effect in mouse induced skin cancer (Sharmila *et al*., 2012), curcumin, (-)-epigallocatechin-3-gallate and lovastatin in combination were able to suppress

esophageal cancer in mouse (Ye et al., 2012), melatonin demonstrate diminishing the development and mortality of mouse implanted with murine hepatoma cells MN22a (Gamalei *et al*., 2011). It was demonstrated that beta-ionone, a precursor of carotenoids, ameliorated the lung carcinogenesis, which is attributed to the antiproliferative and antioxidant potential through free radical scavenging properties (Asokkumar *et al.*, 2012), α-tocopherol showed down-regulation of expression of stress activated genes PKC-α,c-Myc and lactato deshydrogenase A in cancerous mice decreasing cancer cell proliferation (Sharma *et al*., 2012). Rosmanic acid had suggest suppress oral carcinogenesis by stimulating the activities of detoxification enzymes, improves the status of lipid peroxidation and antioxidants, and down regulates the expression of p53, and bcl-2 during 7,12 dimethylbenz(a)anthracene induced oral carcinogenesis in hamster (Anusuya *et al.,* 2011), in same way methanolic extract of fennel seed had exhibited an antitumoral affect by modulating lipid peroxidation and augmenting the antioxidant defense system in Ehrlich ascite carcinoma bearing mice with o without exposure to radiation (Mohamad *et al.,* 2011). Silymarin, a natural flavonoid from the seed of milk thistle, had indicated chemopreventive action against 1,2-dimethylhydrazine plus dextran sodium sulfate induced inflammation associated colon carcinogenesis (Toyoda-Hokaiwado, *et al.*, 2011). Quercetin a flavonoid found in many naturals foods had demonstrate to exerts a direct oro-apoptotic affect in tumour cells and can indeed block the growth of several cancer human cell lines an different phases of the cell cycle, which have been demonstrate in several animal models (Gibellini *et al*., 2011). Methanolic extact of *Indigofera cassioides* was evaluated in their antitumor activity on ehrich ascite carcinoma bearing mice, and the extract showed a potent antitumoral effect against tumor cells, due preventing lipid peroxidation and promotes the enzymatic antioxidant defense system in animals (Kumar *et al*., 2011). Brucine a natural plant alkaloid had been reported to possess cytotoxic and antiproliferative activities and also had showed to be a potential agent antimetastatic and anti-angiogenic agent (Agrawal *et al.,* 2011).

In vitro assay had demonstrated that the mechanism antioxidant action, according to Halliwell (2008), can include (1) suppressing reactive oxygen species formation either by inhibition of enzymes or chelating trace elements involved in free radical production; (2) scavenging reactive oxygen species; and (3) upregulating or protecting antioxidant defenses. Flavonoids have been identified as fulfilling most of the criteria described above. Thus, their effects are twofold. 1. Flavonoids inhibit the enzymes responsible for superoxide anion production, such as xanthine oxidase (Hanasaki *et al*., 1994) and protein kinase C (Ursini *et al.,* 1994). Flavonoids have been also shown to inhibit cyclooxygenase, lipoxygenase, microsomal monooxygenase, glutathione *S*-transferase, mitochondrial succinoxidase, and NADH oxidase, all involved in reactive oxygen species generation (Korkina *et al.,* 1997; Brown *et al.,* 1998). A number of flavonoids efficiently chelate trace metals, which play an important role in oxygen metabolism. Free iron and copper are potential enhancers of reactive oxygen species formation, as exemplified by the reduction of hydrogen peroxide with generation of the highly aggressive hydroxyl radical (Pietta, 2000).

On the other hand In vitro studies had shown that compounds present fruits and vegetables, such as resveratrol, genestein, baicalein, and many others, are attractive candidates for improved chemotherapeutic agents (Fox *et al*., 2012); resveratrol in combination with platinum drugs and oxaliplatin demonstrated that resveratrol administrated 2 h before platinum drugs may sensitize the ovarian cancer cells to platinum, inducing apoptosis and providing a means of overcoming resistance (Nessa *et al.*, 2012)

Ren et al. (Ren *et al.*, 2011) demonstrated that (-)epigallocatechin-3-galte induce reduction in IM9 myeloma cells and that their activity was dose and time dependent manner to induce apoptotic cell death; and this natural metabolite combinated with curcumin and lovastatin had the ability to suppress esophageal cancer cells growth (Ye *et al.*, 2012). In multilla berries was found that their high levels of polyphenols, flavonoids, flavonols and their antioxidants have strong ability to reduce viability of cancer colon HT-29 and SW480 cells lines (Fils *et al*., 2012). Baicalein, a flavonoid found in several plants was evaluated their anticancer activity on cutaneous squamous carcinoma cell line, A431, found that this compound reduce the migration and invasiveness of the cells through the inhibition of Ezrin expression, with leads to the suppression of tumor metastasis (Wu *et al*., 2011).

In beans had been found that contains several compounds with cytotoxic activity on animals and humans cells lines (C33-A, SW480, 3T3), which can be attributed to the antioxidant and damage in DNA caused by tannins, saponins, lectins, and others compounds found in the seed (Mejía *et al*., 2005; Valadez-Vega *et al*., 2011; Valadez-Vega *et al*, 2011).

Melastoma malabathricum showed to have the ability to inhibit proliferation of Caov-3, HL-60, CEM-SS, MCF-7, HeLa and MDA-MB-231 cells lines indicating that the leaves of this plant possess potential antiprolifevative and antioxidant activities that could be attributed to its high content of phenolic compounds (Zakaria *et al.*, 2011). Melatonin, a naturally occurring compound, have showed cytotoxic activity to toward transformed fibroblasts 3T3-SV40 (Valadez-Vega *et al*., 2011) and murine hepatoma cells MN22a, and it was showed that the sensitivities of both cells types to lysis by killer cells fell sharply (Gamalei *et al*., 2011).The potent antioxidant activity of *Kalanchoe gracili*s (L.) DC steam due at the polyphenolic compound found in this medicinal plant show to have the ability to inhibit the proliferation of HepG2 cell (Lai *et al.*, 2011) and the flavonoids found in *Rosa canina* L. are responsible for the antiproliferative activity in HeLa, MCF7 and HT-29 cancer cells lines (Tumbas *et al.,* 2012). Analysis of a fruits of *Phelaria macrocarpa* (Boerl.) Scheff, and *Olea europaea* L., indicated that all part of the fruit have cytotoxic activity against HT-29, MCF-7, HeLa, BPH-1 and Chang cells, indicating that these fruits are

a sources of bioactive compounds potent as an antioxidants and antioxidant agents, suggesting its possible use and adjuvant agent in the treatment of cancer (Hendra *et al*., 2011; Acquaviva *et al.,* 2012).

Calluna vulgaris extract had showed a photoprotective effect on human keratinocytes (HaCaT) exposed to ultraviolet B (UVB) radiation (Perde-Schreple *et al*., 2011), *Cachrys pungens jan* had been analyzed on human tumor cell line, amelanotic melanoma, and was found that their extract contains antioxidant, such as coumarins, which are responsible to their cytotoxicity on A375 cells (Menichini *et al*., 2012). *Inonotus obliquus* and *Peperomia pellucida*, plants used as a folk remedy for treatment of cancer were evaluated on several kinds of tumor cells lines and was found that these plants contains several antioxidants such as lanosterol, inotodios, ergosterol, phytol, 2-naphthalenol, decahydro hexadecanoic acid, methyl ester and 9,12 octadecadienoic acid, indicating that this antioxidant compounds are responsible for the anticarcinogenic activity of the plants extract (Sun *et al*., 2011; Wei *et al.,* 2011). Extract of *Indigofera cassioides* had indicate present antioxidant activity, preventing lipid peroxidation and promoting enzymatic antioxidant defense system, and also showed potent antitumoral and cytotoxic affect against EAC, DLA, HeLa, Hep-2, HepG-2, MCF-7, Ht-29 and NIH 3T3 cells (Kumar *et al.,* 2011)

Hesperetin, hesperetin analogue, carnocine and resveratrol had been evaluating for their antioxidant and anticarcinogenic activity on HT-29, HCT116 and mouse skin carcinogenesis, their studies demonstrate that these compounds can inhibit cell proliferation, induce apoptosis, affect glycolysis, decrease tumor (Sivagami *et al.*, 2012; Iovine *et al.,* 2012; George *et al.,* 2011). Honey, a natural product common used around the word, contain antioxidant properties and preventive effect against disease, Chrysin is a natural flavone commonly found un honey and had been demonstrated this compound induce apoptosis in PC-3 cells (Samarghandia *et al.,* 2011); fennel seeds (*Foeniculum vulgare*) present an antioxidants which have the anticancer potential against HepG2 and MCF-7 cells lines (Mohamad *et al*., 2011). Had been indicated that compounds such as quersetin, flavonoids, brucine have chemopreventive action against osteosarcoma cell line (MG63), C6 glioma cells and Erlich ascites cells and that they can be used as anticancer, antigenotoxic agents, and can induce apoptosis (Toyoda *et al.,* 2011; Seibert *et al.,* 2011; Agrawal *et al.*, 2011).

8. Conclusion

Oxidative stress causes injury to cells, induces gene mutation, and is involved in carcinogenesis and other degenerative diseases by influencing intracellular signal transduction and transcription factors directly or indirectly. The state of oxidative stress in carcinogenesis and tumor bearing conditions is an intricate one in which various substances are involved in complex interactions.

The data discussed in this paper show that the biological effects of antioxidants in humans and animal can be controversial, because the antioxidant action depend of the oxidative status of cells, antioxidants can be protective against cancer; since ROS induce oxidative carcinogenic damage in DNA, antioxidants can prevent cancer in healthy people harboring increased levels of ROS.

Oxidative stress as cause and effect is not the only factor in development of cancer, it is important to take into account that there are other factors involved in its development, such as genetic predisposition, eating habits, environment, and so on. Since ROS in moderate concentrations act as indispensable mediators of cancer-protective apoptosis and phagocytosis, in people with a low ROS level, an excess of antioxidants can block these cancer-preventive mechanisms. High doses of antioxidants can reduce the ROS level in people who over produce ROS and protect them against cancer and other ROS-dependent morbid conditions.

For people with a low ROS level, high doses of antioxidants can be deleterious, suppressing the already low rate of ROS generation and the ROS-dependent cancer preventive apoptosis. Screening and monitoring the human population regarding the ROS level can transform antioxidants into safe and powerful disease-preventive tools that could significantly contribute to the nation's health.

Many in vivo and in vitro studies, to evaluate the capability of antioxidants against cancer, as chemopreventive or therapeutically agents, had been conduced employing natural antioxidants from fruits and vegetables which are mainly supplied through food, which often do not give enough input so that they function as chemoprotectors, that is why humans are forced to consumer antioxidants in a manner more direct, either in the form of tablet, pill or any other forms to supply the levels that the body requires of these compounds to protect it against cell damage caused by oxidation reactions and in this. way reduce the risk of certain kinds of cancer, specially from the epithelial surface and in the upper part of the body, such as breast, lung, kidney, liver, intestine, and many others which had been well documented. However further investigations are expected before to better understanding the function of many antioxidants and be used to the prevention and treatment of cancer and other degenerative diseases.

9. References

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