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Free Radicals and Gastric Cancer

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1. Introduction

The inflammation is linked to tumorigenesis by a variety of molecules. The prostaglandins, cytokines, nuclear factor-kappa B (NF-kappa B), chemokines, angiogenic growth factors, and free radicals, are key factors involved in that process. Reactive oxygen and nitrogen species play a crucial role in the progression from normal gastric mucosa to cancer. Oxidative stress is associated with gastric disorders such as chronic gastritis, peptic ulcers, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. During malignant transformation, the increased oxygen radicals generation initiates lipid peroxidation and DNA and proteins oxidation processes causing DNA and proteins structural and functional damages that lead finally to the loss of cell integrity. The major interest in elucidating the role of oxidative stress in a range of diseases has focused attention on drugs that can prevent the generation of reactive oxygen species or enhance their metabolism. The response to such interventions can give insight into the underlying role of reactive oxygen species in the pathophysiology and may point to future therapeutic targets. In this chapter, we present the most updated knowledge on free radicals and antioxidants in gastric cancer.

2. Free radicals

Free radicals are molecules containing unpaired electrons such as O_2•, •OH, ROO•, and RO• (Figure 1). They are unstable and highly reactive components. Proteins, lipids, and nucleic acids are subject to oxidation by reactive oxygen species (ROS) generated during normal metabolism and even more so under conditions of oxidative stress. The intracellular levels of oxidized proteins have been shown to increase during aging and in the development of many age-related diseases, including Alzheimer's disease, rheumatoid arthritis, atherosclerosis, and Parkinson's disease (Khan et al, 2004) (Table 1). Moreover, an increase in intracellular ROS leads to initiation of various types of cell death (Yuyama et al., 2003).

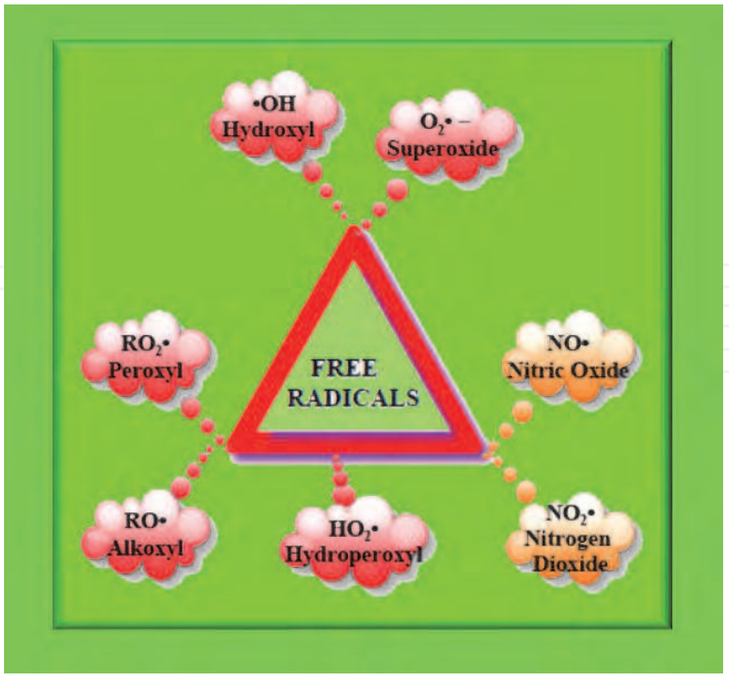

Fig. 1. Reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Generation of oxygen as superoxide, hydrogen peroxide and hydroxyl radicals are involved in killing microorganisms by leukocytes. However, these same reactive oxygen species may damage cells (Babior et al, 1973). To counteract these oxidants, cells have several antioxidant enzymes including superoxide dismutase (SOD; EC 1.15.1.I), glutathione peroxidase (GSH-PX) and catalase. Eukaryotic cells have two forms of SOD; one found in the mitochondrial matrix, the manganese SOD (Mn-SOD), and another found predominantly in the cytosol, the copper-zinc SOD (Cu/Zn-SOD). Prokaryotes have another, iron SOD (Marklund, 1984). These enzymes dismutate superoxide to H_2O_2, which is then converted to water by either catalase or GHX-PX. The GSH-PX uses the reduced glutathione to convert H_2O_2 to water as well as to convert lipid peroxide to lipid metabolites and eicosenoids. A delicate balance exists between expression of each SOD and GHX-PX to provide cellular resistance to oxidative stress (Kelner & Bagnell, 1990). It has been shown that in some cancers, reduced expression of Mn-SOD is due to mutations in the promoter of the gene, while in other types of cancer, reduced levels of Mn-SOD are due to abnormal methylation, loss of heterozygosity or mutation in the coding sequence (Hernandez-Saavedra & McCord, 2003). These different mechanisms cause the chaotic results about SOD in malignant tumors including gastric cancer, colorectal cancer and other gastrointestinal tumors (Hwang et al, 2007; Skrzydlewska et al, 2003; Tandon et al, 2004).

Proteins are ubiquitous in all cells and tissues, constituting more than 50% of the dry weight of cells, and are susceptible to oxidative/nitrosative modifications. When reactive oxygen species (ROS) and reactive nitrogen species (RNS) levels exceed the cellular antioxidant capacity, a deleterious condition known as oxidative/nitrosative stress occurs (Figures 2 & 3). It describes a status in which cellular antioxidant defenses are insufficient to keep the levels of ROS/RNS below a toxic threshold. This may be either due to excessive production of ROS/RNS, loss of antioxidant defenses or both. Unchecked, excessive ROS/RNS generation can lead to the destruction of cellular components including proteins, and ultimately cell death via apoptosis or necrosis (Giustarini et al, 2004).

Condition	Reference
Cancer	Hofseth, (2008).
Cigarette Smoking	Pasupathi et al, (2009) & El-Zayadi, (2006).
Aging	Adiga & Adiga, (2009).
Atherosclerosis	Shaikh & Suryakar, (2009) & Sumathi et al, (2010).
Rheumatoid Arthritis	Shinde et al, (2010) & Ahmed, (2005).
Diabetes	Kundu et al, (2011).
Infertility	Duru et al, (2001).
Asthma	Fabian et al, (2011).
COPD	Hakhamaneshi et al, (2007).
Neurodegeneration	Abraham et al, (2005).
Acute Ischaemic Stroke	Aygul et al, (2006).
Epilepsy	Hamed & Abdellah, (2004).
Skin disease	Aly & Shahin (2010).
Schistosomiasis Infection	Rizk et al, (2006).
Alcoholic Liver Disease	Maithreyi et al, (2010).
Esophagitis	Jiménez et al, (2005).

Table 1. Some clinical situations that are associated with altered oxidative/antioxidative balance as evidenced in the mentioned studies.

Fig. 2. The balance between free radicals levels and antioxidant defense system is favoring the health. On the contrary, the imbalance between them is leading to the oxidative stress and hence to the damage of cellular compartments and consequently to the disease.

3. Cancer and free radicals

Malignancy comprises a diverse set of diseases that not only originate from almost every tissue but also display remarkable heterogeneity in presentation and prognosis. Despite this immense range of clinical characteristics, all human tumors share a limited set of behaviors that define the malignant state (Hanahan &Weinberg, 2000). Among these hallmarks, unlimited replicative potential and widespread genomic disarray are among the most common characteristics exhibited by human cancer cells. Although numerous distinct molecular pathways regulate specific aspects of each of these phenotypes, emerging evidence now implicates that the oxidative stress and the programmed cell death are essential determinant s of the cell life span.

A role of free radicals has been proposed in the pathogenesis of numerous diseases as indicating above including cancer of different organs such as breast, gastric, colon, multiple myeloma, ovarian, renal, skin, leukemia, biliary, thyroid, and lung cancer (Table 2 & Figure 3).

Cancer	Reference
Prostate Cancer	Pace et al, (2010).
Renal Cell Carcinoma	Soini et al, (2006).
Breast Cancer	Yeon et al, (2011).
Biliary Epithelial Cancer	Elsing et al, (2011).
Colon Cancer	Sangeetha et al, (2010).
Gastric Carcinoma	Tandon et al, (2004).
Hepatocellular Carcinoma	Gayathri et al, (2009).
Esophageal Carcinoma	Lee et al, (2001).
Thyroid Cancer	Koduru et al, (2010).
Lung Cancer	Gupta et al, (2010).
Cervical Cancer	Beevi et al, (2007).
Head and Neck Squamous Cell Carcinoma	Bentz, (2007).
Skin Cancer	Cooke et al, (2007).
Laryngeal Carcinoma	Dwivedi et al, (2008).
Leukemia	Kato et al, (2003).

Table 2. Oxidative stress as a result of altered oxidative/antioxidative balance is proposed as key factor in the pathogenesis of different tumors as shown above.

4. Gastric cancer

4.1 Epidemiology

Gastric carcinoma was the major cancer burden worldwide in the twentieth century. Its etiology and pathogenesis were obscure. Several events have changed that outlook, and currently, it ranks in the second place of mortality from cancer, after lung cancer. In the United States, the number of cases has remained around 20,000 for several years. The geographic distribution of gastric cancer is spotty. Areas of highest risk have traditionally been Japan, Korea, China, Eastern Europe, and the Andean regions of the Americas. In contrast, Australia, Africa, the coastal regions of the Americas, and Southern Asia have

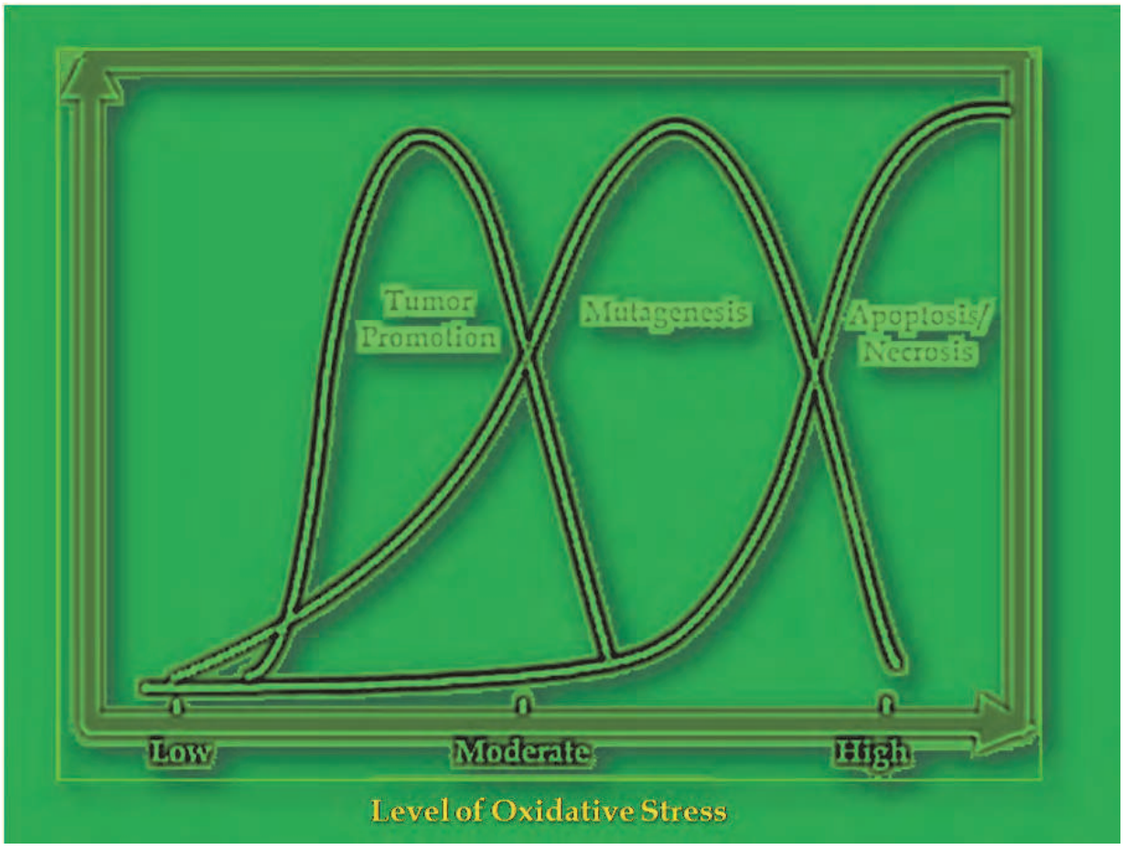

Fig. 3. The link between the dose of oxidative stress and the dependant effect on tumor promotion, mutagenesis and the apoptosis/necrosis (modified from Valko et al, 2007).

traditionally been areas of low risk. Western Europe and North America, with considerably higher risk several decades ago, have experienced a marked decrease since then, and at the present time are considered areas of low risk (reviewed in Correa et al, (2009).

4.2 Risk and protective factors

As reported earlier (Karagianni & Triantafillidis, 2010), the available evidence is indicating a probable protective role of vegetables, especially allium vegetables, fish, and fruit consumption against gastric cancer risk. It also seems probable that high salt intake increases gastric cancer risk. Furthermore, the available evidence is suggestive of a protective role of pulses and foods containing selenium. Limited, but still suggestive evidence exists concerning an inverse association between chilli, processed meat, smoked foods and grilled or barbecued animal foods with gastric cancer risk. Moreover, it has also been proposed that reducing the prevalence of smoking, obesity and gastroesophageal reflux could decrease the incidence of gastric cancer (Engel et al, 2003). Recently, it was reported that the salt intake is an important dietary risk factor for gastric cancer regardless of *H. pylori* infection and virulence, smoking, tumor site and histological type (Peleteiro et al, 2011).

Meta-analysis is a statistical methodology that can combine the results from multiple studies that investigating the same rationale. The utility of the meta-analysis is to conclude a clear

statement from these conflicting studies. Meta-analysis consists of three basic steps. The first step is the systematic search of the literature to identify the studies according to certain criteria. The second one to extract the numerical data from each study for the experimental versus control subjects in randomized clinical trials, on various outcomes and their difference. Finally, the third step is carried out to calculate the parameters and reflect their statistical confidence. Recently, numerous meta-analysis studies were publicized concerning with gastric cancer investigation. A recent meta-analysis showed that a high intake of pickled vegetables may increase gastric cancer risk and their data suggested that a high consumption of fresh vegetables is important to reduce gastric cancer risk (Kim et al, 2010). It was evidenced recently in this type of studies that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin is associated with a decrease in the development of gastric cancer. The associations were more obvious after they adjusted for several risk factors that are known to contribute to the development of gastric cancer (Tian et al, 2010). Reduced risk of noncardia gastric cancer is associated with the regular use of aspirin especially among Caucasians (Yang et al., 2010). Dairy product consumption (Huang et al, 2009), and *Helicobacter pylori* eradication treatment (Fuccio et al, 2009), might decrease the risk of gastric cancer.

4.3 Oxidative stress

Reactive oxygen species are closely associated with the intracellular signal cascade, thus strongly implicating involvement in tumor progression. The antioxidant enzymes activities such as GSH-PX, SOD, G6PD (glucose-6-phosphate dehydrogenase), MDA and GR were found to be related with malignant phenotype in gastric cancer and colorectal cancer (Kekec et al, 2009). The increase in oxidative stress in gastric carcinoma was evidenced by significant rise in plasma lipid peroxidation marker MDA measured as TBARS. There was a significant fall in serum albumin level in patients due to its protective effect against deleterious oxidative damage (Reddy et al, 2009). The source of cellular ROS production includes activated phagocytes for examples neutrophils and macrophages. The level of myeloperoxidase (MPO) (enzyme of granulocyte) and TAS (total antioxidant status) was evaluated in the plasma of gastric carcinoma patients. MPO is a measurement of neutrophils activation and synthesis of ROS. In gastric carcinoma patients before and after operation (1 and 10 day) MPO concentration was 3 times higher in comparison to the control group, but TAS level was decreased. These results suggest the presence of prolonged oxidative stress in malignant disease but it requires long time observation after surgery (Czygier et al, 2010). It was indicated that gastric cancer patients were characterized by increased the advanced oxidation protein products (AOPP) levels (Noyan et al, 2009).

Increased level of lipid peroxidation and significant differences in glutathione level and glutathione peroxidase, glutathione -S-transferase and glutathione reductase activities were observed in serum taken before and after surgery from patients with gastrointestinal tract tumors compared to those in control serum of healthy blood donors. Increase of lipid peroxidation and changes in GSH level and related enzyme activities, suggest oxidative stress in patients with gastrointestinal tract tumors. These alterations reflect the presence of functional defense mechanism against oxidative stress related firmly to the glutathione metabolism. The impaired antioxidant system may favor accumulation of free radicals (Ścibior et al, 2008). It has been found that low levels of essential antioxidants in the circulation are associated with an increased risk of cancer (Diplock, 1991). Persistent generation of reactive oxygen species such as superoxide, H_2O_2, and hydroxyl radicals is an

inevitable consequence of mitochondrial respiration in aerobic organisms, whose ATP requirements are correlated with the level of metabolic activity. Several potential mechanisms are thought to contribute to the increased ROS in cancer cells. First, oncogenic signals have been shown to cause increased ROS generation. The oncogene c-myc, for example, increases ROS generation, induces DNA damage, and mitigates p53 function.
Another possible mechanism by which cancer cells generate increased amounts of ROS may involve malfunction of the mitochondrial respiratory chain. Since the mitochondrial DNA (mtDNA) codes for 13 components of the respiration complexes and contains no introns, mutations of mtDNA are likely to affect the function of its encoded proteins and lead to malfunction of the mitochondrial respiratory chain. It is also known that mtDNA is more vulnerable to damage than nuclear DNA, and mtDNA mutations are frequently detected in cancer cells (reviewed in Pelicano et al, 2004).

4.3.1 Helicobacter pylori

Helicobacter pylori (H. pylori) infection (Figures 4 & 5), the main cause of chronic gastritis, increases gastric cancer risk. It was reported that *H. pylori* is implicated in many diseases in addition to the gastric cancer (Abdel-Hady et al, 2007; El-Masry et al, 2010; El-Shahat et al, 2005).The infection causes inflammatory cells to produce reactive oxygen metabolites that may damage DNA and promote carcinogenesis. It was showed that *H. pylori* water extract induces tumor formation via reactive oxygen species production (Ishikawa et al, 2006). Successful eradication treatment of *H. pylori* prevents the production of reactive oxygen metabolites (Farkas et al, 2005; Mashimo et al, 2006). In a recent study, a close relationship was demonstrated between the plasma malondialdehyde and nitric oxide levels, gastric histopathology and genotypes of *H. pylori* (Tiwari et al, 2010). In patients with *H. pylori* infection, NO metabolites concentration was increase demonstrating a positive correlation with grade of inflammatory lesions in gastric mucosa. The effective antibacterial therapy causes the decrease of NO metabolites concentration in gastric juice, especially in patients with chronic active gastritis. Eradication decreases the grade of lesions in gastric mucosa just in 12 months after effective antibacterial therapy (Walecka-Kapica et al, 2008).
8-Hydroxy-2'-deoxyguanosine (8-oxo-dG) levels in the gastric mucosa were increased in carriers of *H. pylori*, and were further increased in subjects infected with strains positive for the cagA gene, encoding the cytotoxin-associated protein, cagA. Oxidative DNA damage was more pronounced in males, in older subjects, and in *H. pylori*-positive subjects suffering from gastric dysplasia. Moreover, 8-oxo-dG levels were significantly higher in a small subset of subjects having a homozygous variant allele of the 8-oxoguanosine-glycosylase 1 (OGG1) gene, encoding the enzyme removing 8-oxo-dG from DNA. Conversely, they were not significantly elevated in glutathione S-transferase M1 (GSTM1)-null subjects. Thus, both bacterial and host gene polymorphisms affect oxidative stress and DNA damage, which is believed to represent a key mechanism in the pathogenesis of gastric cancer. The interplay between bacterial and host gene polymorphisms may explain why gastric cancer only occurs in a small fraction of *H. pylori*-infected individuals (Izzotti et al, 2007).
The mRNA of inflammatory markers and oxidant and antioxidant enzymes was investigated in gastritis, gastric ulcer and gastric cancer in gastric biopsy of patients infected with *H. pylori* and the results showed that the oxidant status in gastritis is different in the three lesions slightly. In gastritis, a significant expression of TNF-α (tumor necrosis factor-α), IL-8 (interleukin-8), IL-12, Nox1 (NADH oxidase 1) and iNOS (pathogen-inducible nitric oxide synthase) was detected. In gastric ulcer, a significant expression for TNF-α, IL-8, IL-12

and Nox1 was observed, while in gastric cancer a significant expression for TNF-α, IL-8, IL-1β, IL-10, IL-12, iNOS and Nox1 was evidenced. The oxidant status in gastritis was the only condition where TNF-α and IL-8 expression was associated to *H. pylori* virulence suggesting that they are the main oxidant stress markers responsible to trigger an increase in ROS levels that contributes to decrease the expression of the MnSOD and GSH-PX in gastritis (Augusto et al, 2007)(see Figure 6).

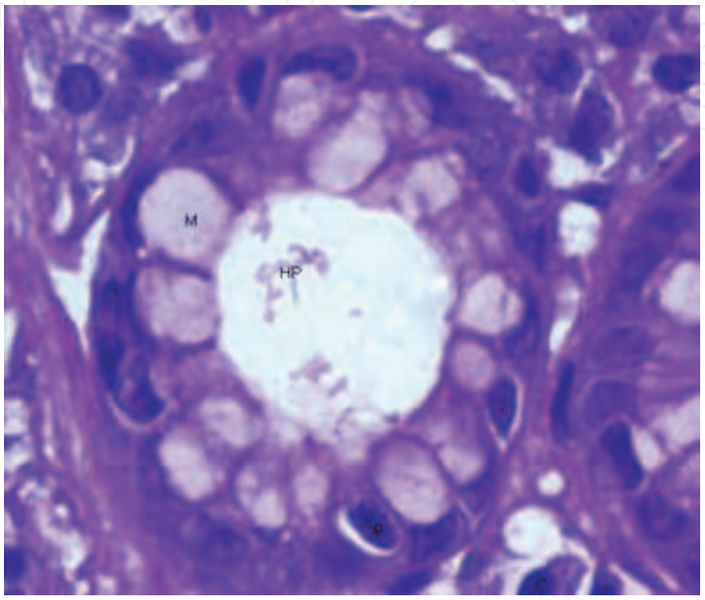

Fig. 4. Presence of *H. pylori* in corpus section stained with hematoxylin and eosin. M; Mucus secreting cells & HP; *H. pylori* (from Abusini et al, 2009).

There are three possible mechanisms by which *H. pylori* infection leads to loss of genomic integrity and promote carcinogenesis (Figure 7). The first is the increase in DNA damage and decrease in repair activity. The second is the mutations in mtDNA. The last is the induction of a transient mutator phenotype resulting in mutations in the DNA upon infection with *H. pylori*. Due to *H. pylori* infection and to inflammatory response, increased amounts of ROS are generated in the gastric epithelial cells that induce oxidative damage in the DNA. *H. pylori* infection also leads to methylation of gene promoters, causing gene silencing and is associated with several other DNA alterations such as chromosomal instability, p53 mutations, influence on the expression of p53 and c-Myc, as well as MSI. At the same time, infection leads to a deficiency in the activity of major repair pathways. The increase in DNA damage coupled to the decrease in repair activity may be two of the key factors involved in the induction of a transient mutator phenotype that could contribute to nuclear and mtDNA mutations. The appearance of mtDNA mutations after *H. pylori* infection might be partly due the down-regulation of BER. BER is one of the best characterized DNA repair pathways in the mitochondria. Several proteins involved in BER have been described in mitochondria, such as DNA glycosylases, APE1, polymerase γ and DNA ligase III . It was observed that APE1 expression is down-regulated in gastric cells infected with *H. pylori*, suggesting an imbalance between generation and repair of AP sites. This could be one the mechanisms behind the induction of mtDNA mutations, which may lead to the impairment of oxidative phosphorylation, cell damage, and disease (reviewed in Machado et al, 2010).

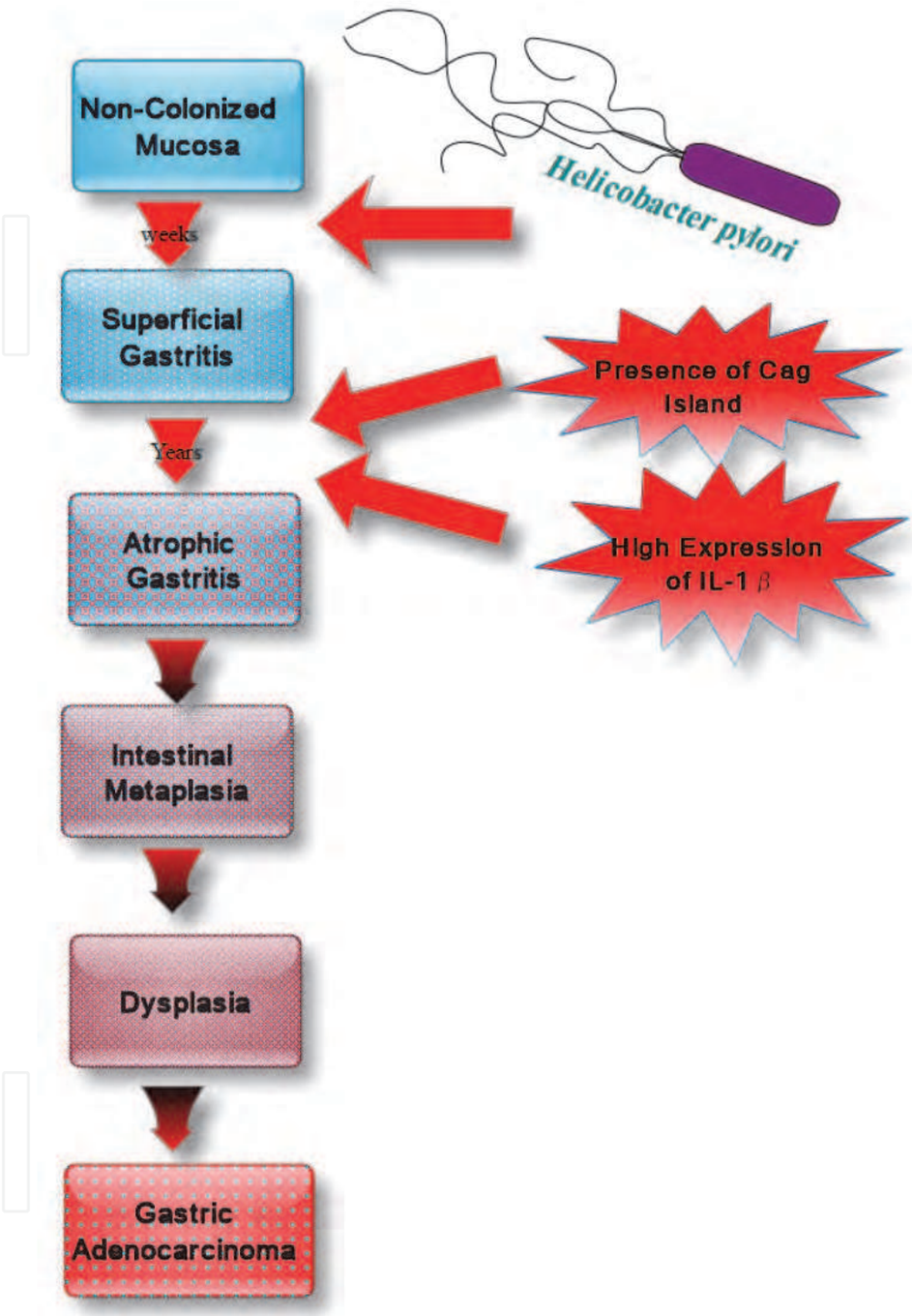

Fig. 5. Multi-step development of intestinal-type gastric adenocarcinoma. *Helicobacter pylori* cag pathogenicity island within *H. pylori* strains and host polymorphisms that promote high expression levels of the cytokine interleukin-lβ augment the risk for gastric adenocarcinoma (adapted from Israel & Peek, 2006). It is well known that gastric cancer is associated with alterations of oncogenes and tumor suppressor genes. Furthermore, prostaglandins, cytokines, nuclear factor-kappa B, chemokines, angiogenic growth factors, and free radicals are involved in GC pathogenesis.

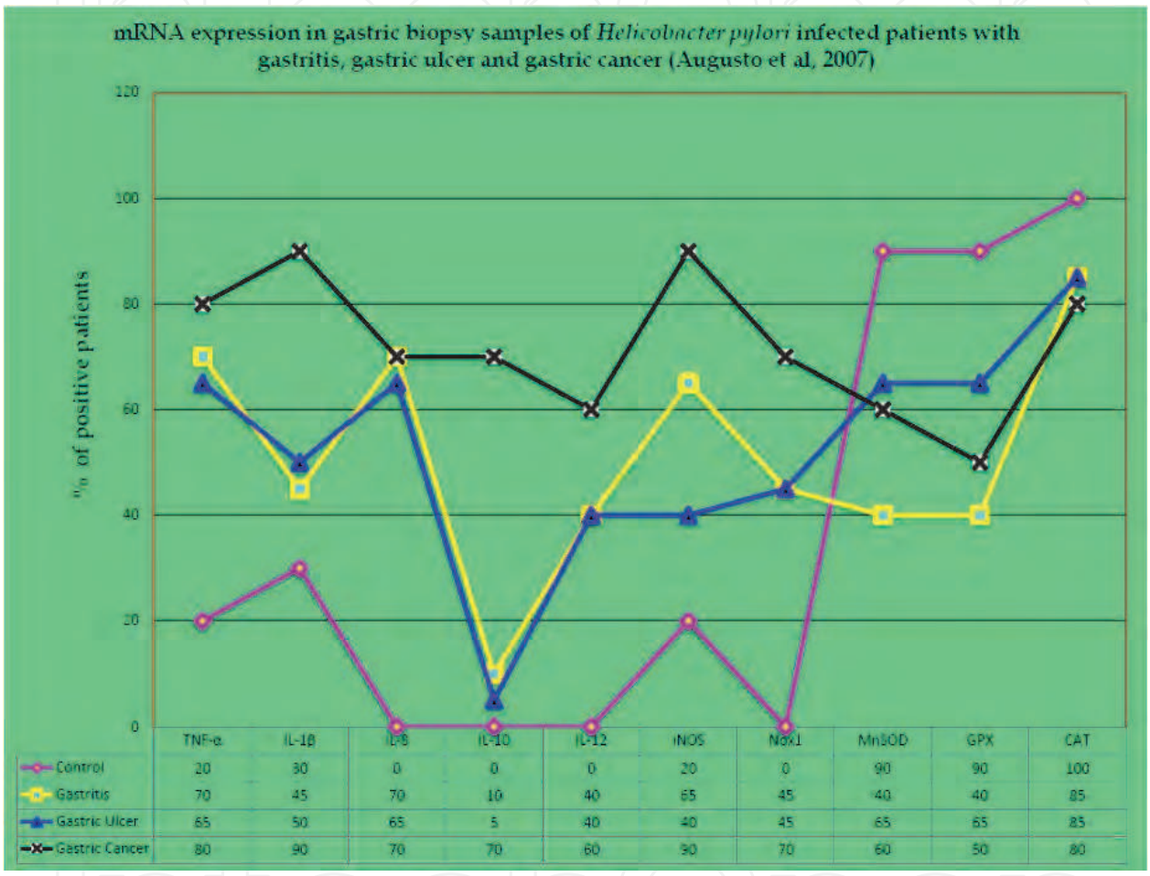

Fig. 6. mRNA expression of inflammatory markers and both oxidant and antioxidant enzymes in gastric biopsy samples of *Helicobacter pylori* infected patients with gastritis, gastric ulcer and gastric cancer. This figure was produced based on the data presented in table 2 of Augusto et al, (2007) publication with permission of Rightslink, Copyright Clearance Center (CCC), and Elsevier.

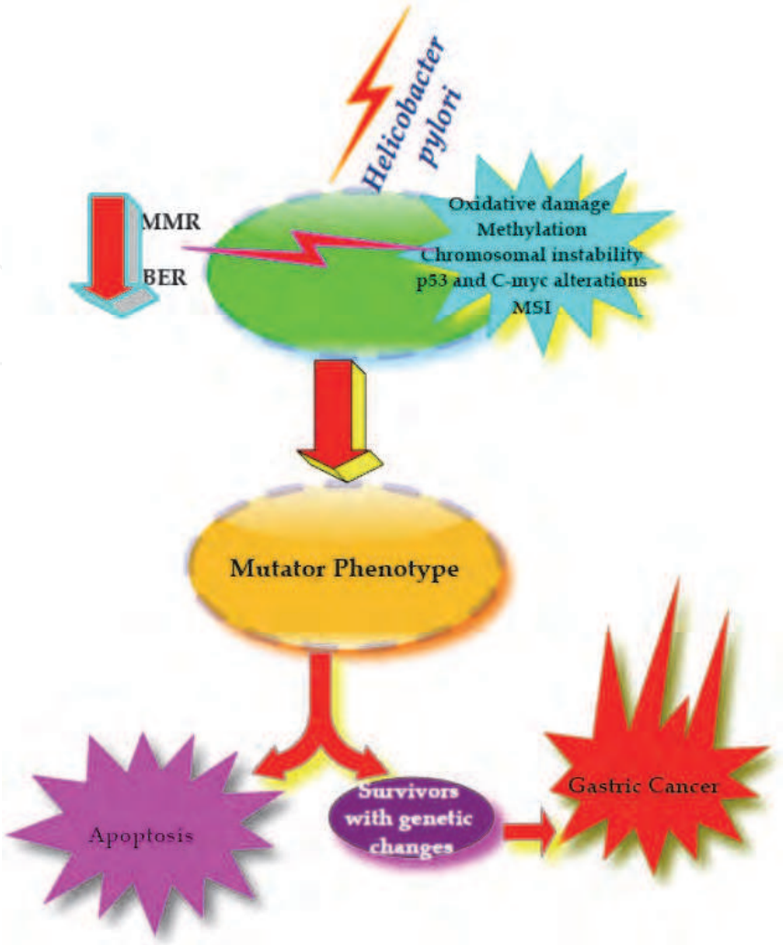

Fig. 7. Proposed model for the development of gastric cancer (adapted from Machado et al, 2010). Microsatellite instability (MSI) is simple repetitive sequences or microsatellites may undergo length alterations. MMR is the DNA mismatch repair pathway. MSI can lead to deficiency of MMR. *H. pylori* gastritis might lead to a deficiency of MMR in gastric epithelium that may increase the risk of mutation accumulation in the gastric mucosa cells during chronic *H. pylori* infection. Base excision repair (BER) is another major repair pathway critical for the maintenance of genome stability as it repairs a number of endogenously generated DNA lesions. Therefore, it is possible that this repair pathway plays an important role ensuring genetic stability in gastric cells. BER removes various forms of base damage such as oxidation, methylation, deamination, depurination and hydroxylation. BER is initiated by DNA glycosylases that recognize and cleave the damaged bases, creating abasic (AP) sites. The AP sites created are cytotoxic and mutagenic and are, therefore, further processed by DNA glycosylases with AP-lyase activity or by APE1. The single nucleotide gap is filled and the nick sealed to complete the repair reaction. It was suggested that increased levels of cellular damage and death due to reactive oxygen species would lead to increased inflammation and consequently to the production of more ROS and tumor-promoting cytokines. It also strongly indicates that one mechanism underlying genetic instability caused by *H. pylori* infection is deregulation of central DNA repair pathways (see Machado et al, 2010).

4.3.2 Smoking

Tobacco smoke contains many toxic, carcinogenic and mutagenic chemicals, as well as stable and unstable free radicals and reactive oxygen species (ROS) in the particulate and the gas phase with the potential for biological oxidative damage. Epidemiological evidence established that smoking is one of the most important extrinsic factor of premature morbidity and mortality (Valavanidis et al, 2009). It was estimated that the number of gastric cancer cases attributable to tobacco smoking occurring worldwide, in total, over 80,000 cases of gastric cancer (11% of all estimated cases) may be attributed to tobacco smoking each year. The majority of published studies reported a positive association between gastric cancer and cigarette smoking. Meta-analysis suggested a risk of stomach cancer among smokers of the order of 1.5–1.6 as compared to non-smokers (Trédaniel et al, 1997).

Thiobarbituric acid reactive substances (TBARS) level was found higher in smokers than non-smoking gastric cancer patients. The activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, reduced glutathione, and vitamins A, E and C were decreased in gastric cancer patients who were smokers as compared to other groups ($p < 0.001$). The lipid peroxidation and possible breakdown of antioxidant status in the cigarette smoking may increase the risk of gastric cancer. Thus, chronic smoking enhances erythrocyte lipid peroxidation in gastric carcinoma patients with concomitant failure of both plasma and erythrocyte antioxidant defense mechanisms. The low antioxidant status of healthy smokers may predispose them to oxidant-mediated tissue damage, which may increase the risk of gastric cancer (Pasupathi et al, (2009). It was concluded that the TNF-alpha-857 C/T polymorphism may play an independent role in gastric carcinogenesis and the risk for gastric cancer by TNF genetic effect is pronounced by cigarette smoking (Yang et al, 2009). Recently, it was detected that the cigarette smoking was associated with risk of oesophageal squamous cell carcinoma, oesophageal adenocarcinoma, gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma (Steevens et al, 2010). Plasma levels of MDA were significantly increased but melatonin content of the blood was significantly decreased in smokers as compared to nonsmokers. It seems that melatonin can reduce free radical damage to the respiratory system induced by cigarette smoke (Ozguner et al, 2005). A significant decrease in free malondialdehyde levels in light smokers after one month phytonutrient supplementation was achieved (Bamonti et al, 2006). The effect of the consumption of a pear, an apple and 200 ml orange juice, during 26 days, on total plasma antioxidant capacity and lipid profile of chronic smokers and non-smoking healthy adults was analyzed. Fruit consumption increased total plasma antioxidant capacity in non-smokers, but not in smokers. In non-smokers, total cholesterol, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol increased significantly; while in smokers, total cholesterol and low-density lipoprotein-cholesterol decreased (Alvarez-Parrilla et al, 2010). Antioxidant-rich food was found to modulate positively the cellular stress defense of smokers (Bohn et al, 2010).

5. Antioxidants

ROS are generated during normal aerobic metabolism and increased levels are present during oxidative stress. It has been proposed that ROS is necessary for life and essential for the regulation of essential physiologic functions. However, at high concentrations, ROS are cytotoxic. ROS are important in cell differentiation, apoptosis, and cell proliferation. These functions are regulated by redox-sensitive signal transduction pathways. The amount of antioxidants in the cells is high and so cells prevent or repair the damages caused by

Fig. 8. The antioxidant content is different from food to another. Dried fruits (dates, raisins, and prunes), vegetables (red cabbages, spinach, and garlic), fruits (red grape, different types of berries, red apple, and red plum) and juices such as orange juices are among the foods with highest antioxidant content. Furthermore, drinks such as espresso coffee and oils such as soybean and virgin olive oil are rich sources of antioxidants. On the other hand, the most powerful natural foods to scavenge the oxygen free radicals and to inhibit the lipid peroxidation are blackberry, orange, lemon, strawberry, kiwi, garlic, green pepper, and cabbages (Miller et al, 2000; Pellegrini et al, 2003).

ROS. ROS-induced damage can result in cell death, mutations, chromosomal aberrations and also carcinogenesis (Cerutti, 1985). The antioxidants are antioxidant enzymes and some vitamins (Figures 8-12). There are three major types of antioxidant enzymes in mammalian cells: superoxide dismutase, catalase, and peroxidase, of which glutathione peroxidase is the most important component of these (Hurt et al, 2007) (Figure 12). Both endogenous and exogenous antioxidants play an important and interdependent role in preventing cancer.

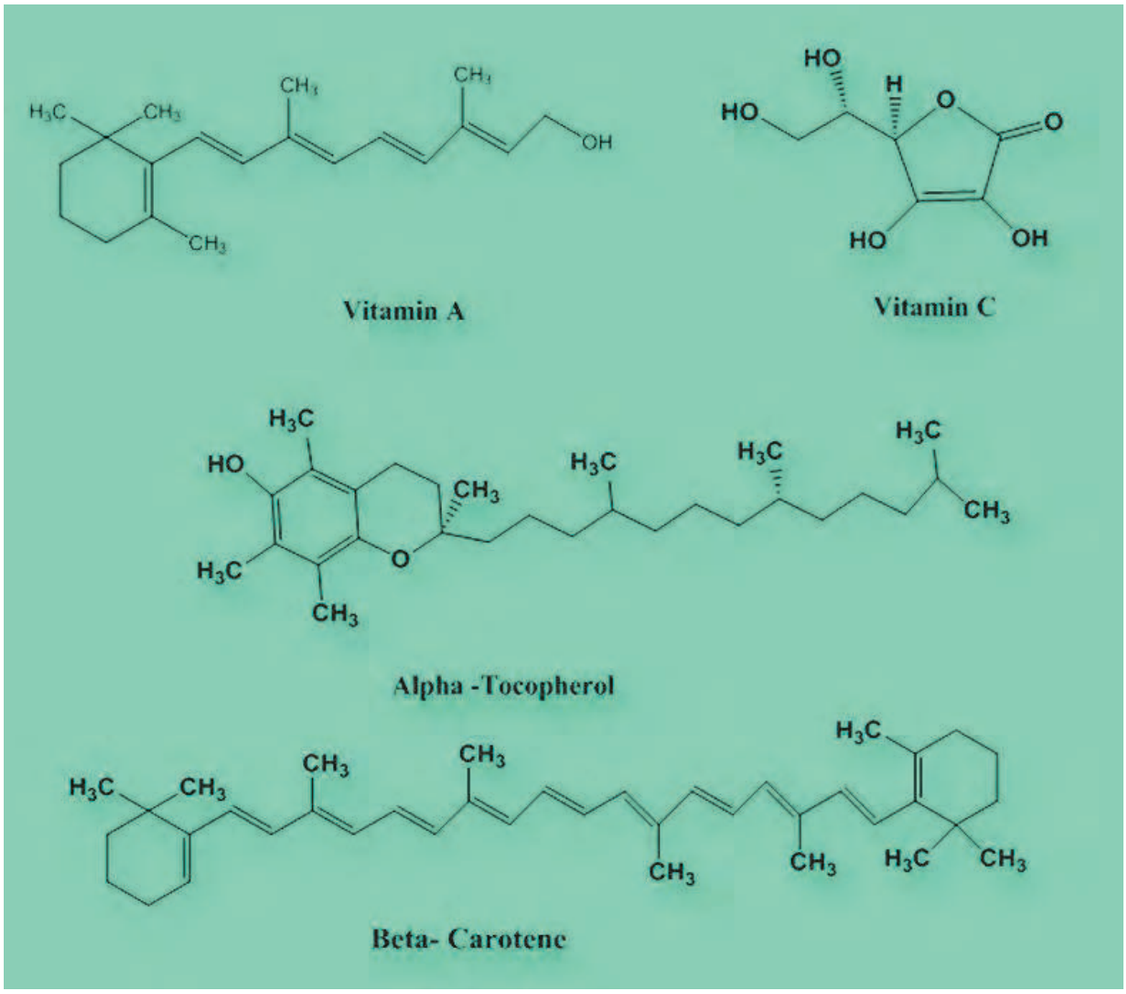

Fig. 9. Antioxidant vitamins include vitamin A, E, and C. The ascorbic acid is the only one feature of the ROS scavenging capacity of fresh fruit and vegetable juices. Other free radical scavengers present in fruits and vegetables are flavonoids, carotenoids, organic acids (cinnamic acid and gallic acid), vitamin E, and sulfhydryl compounds. A well balanced diet of fruit and vegetables may enhance the antioxidant defenses against ROS induced injuries to cells and tissues (Leonard et al, 2002).

It was evidenced that the MnSOD Val-9Ala polymorphism may contribute to cancer development through a disturbed antioxidant balance, where the decreased consumption level of dietary antioxidant s is an essential contributing factor (Li et al, 2005 & Wang et al, 2009). It was showed that ascorbic acid protects against gastric cancer by scavenging reactive radical species which would otherwise react with DNA, with resultant genetic damage (Drake et al, 1996). Vitamin C-releasing acetylsalicylic acid in comparison with plain acetylsalicylic acid induces less gastric mucosal damage and this protective effect is probably due to the attenuation of oxidative stress in gastric mucosa (Konturek et al, 2004). High dietary antioxidant quercetin intake is inversely related to the risk of noncardia gastric adenocarcinoma, and the protection appears to be particularly strong for women exposed to oxidative stress, such as tobacco smoking (Ekstrom et al, 2011). Treatment with Allopurinol

(inhibits the enzyme xanthine oxidase which is responsible for the formation of superoxide radicals and scavenges hydroxyl radicals) and dimethyl sulphoxide (DMSO; scavenges hydroxyl radicals) was found to provide gastric cancer patients with a survival advantage (Salim, 1992). In was observed upon following up 29,133 male smokers that the higher dietary intake of retinol was protective, but dietary intake of α-tocopherol and γ-tocopherol increased risk of gastric cardia cancer. Higher intakes of fruits, vitamin C, tocopherols, and lycopene were protective against gastric noncardia cancer (Nouraie et al, 2005).

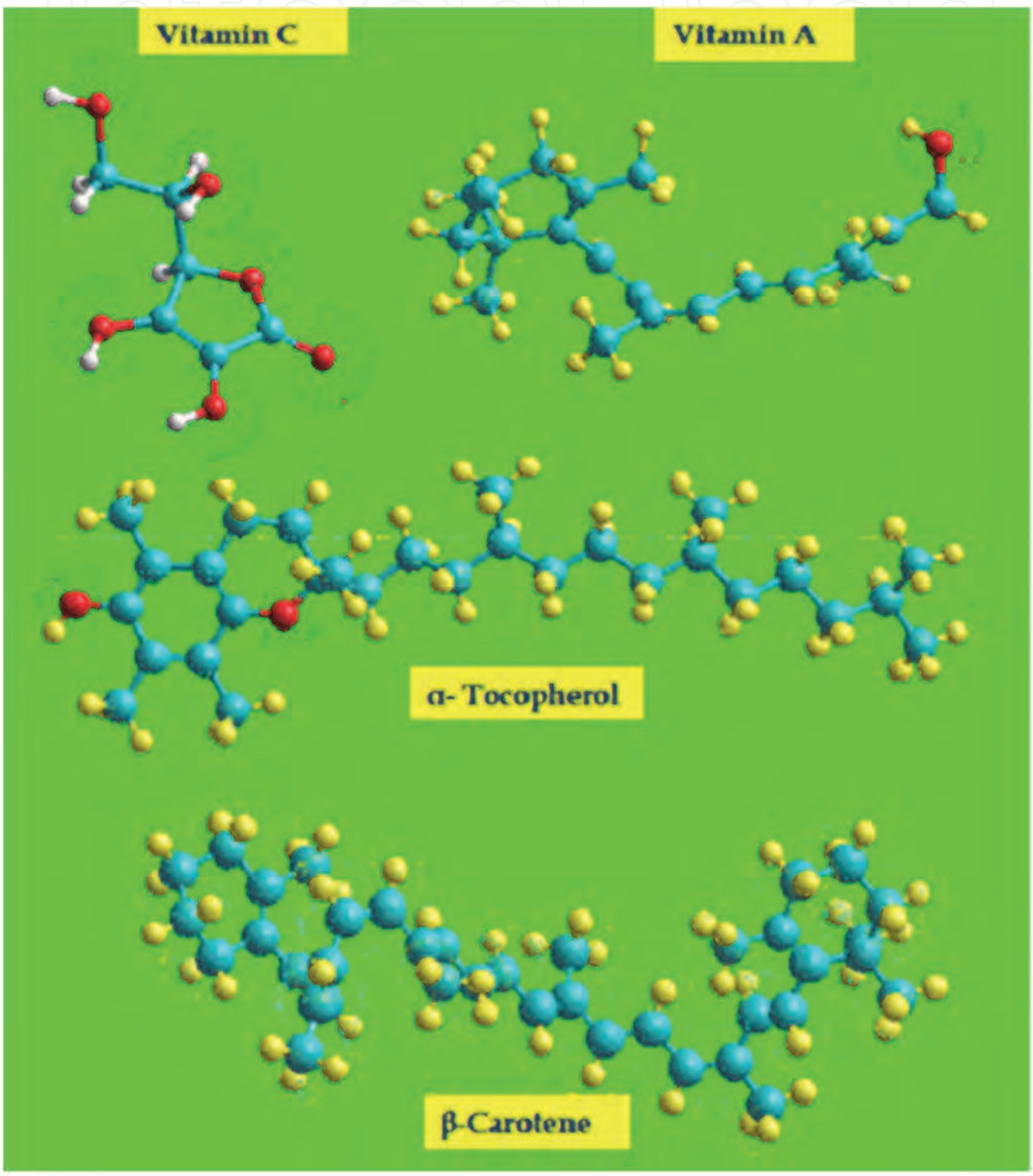

Fig. 10. Vitamins with antioxidant activity in three dimensional structures.

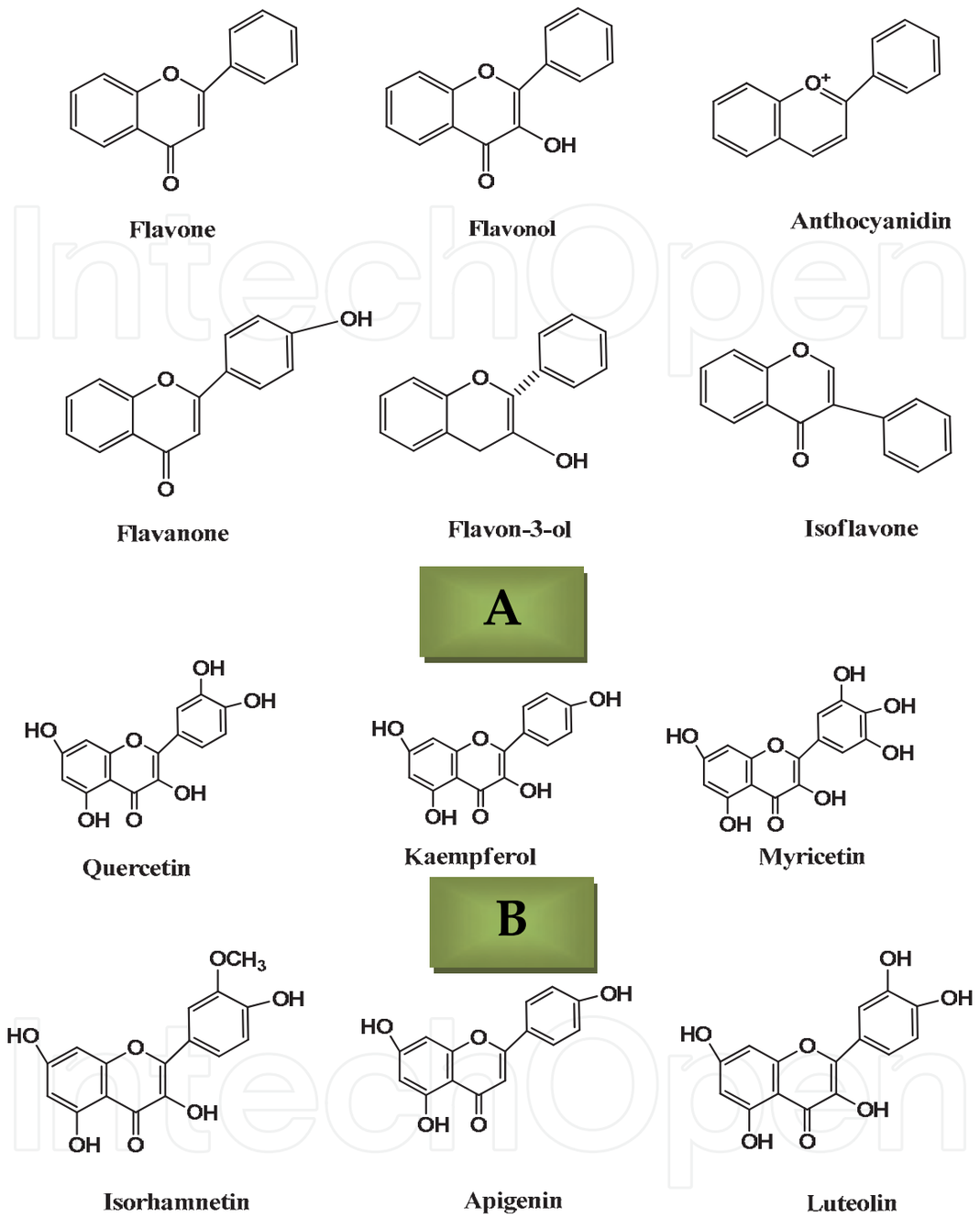

Fig. 11. Fruits and vegetables are sources of polyphenolic compounds called flavonoids. The flavonoid family is flavonols, flavones, flavan-3-ols, isoflavones, flavanones and anthocyanidins (A). Flavonols and flavones are synthesized in plant tissues and it comprises quercetin, myricetin, kaempferol and isorhamnetin, while a more limited number of fruits and vegetables contain the structurally-related flavones, apigenin and luteolin (B). Flavonoids are known to have antioxidant activity and various foods are containing such components as blueberry, onion, lettuce, tomato, and tea (Crozier et al, 2000). Tea is a good scavenger of free radicals as indicated previously (El-Sayed et al, 2006; Oyama et al, 2010).

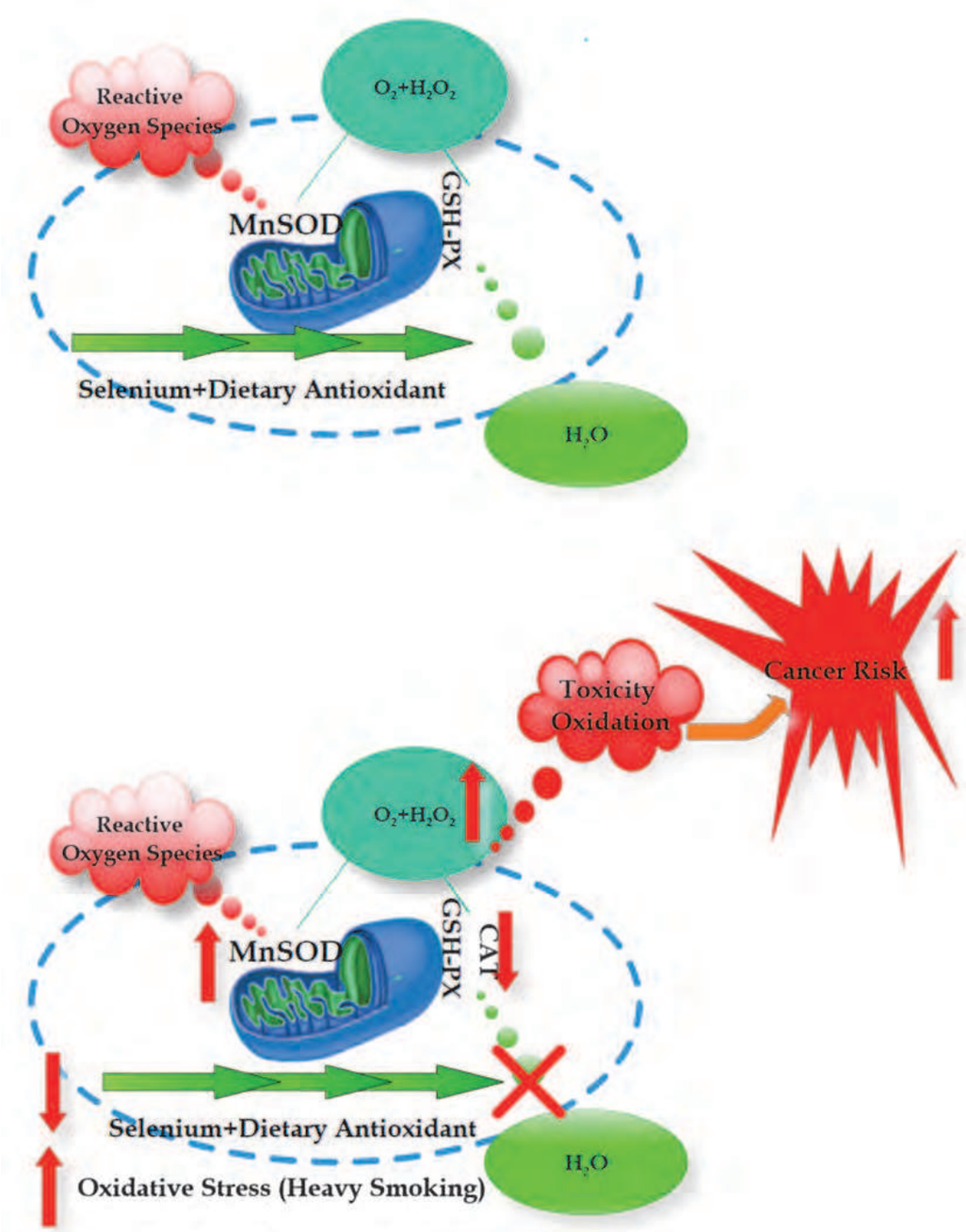

Fig. 12. Potential mechanism for the interaction between MnSOD and antioxidant status in cancer development (modified from Li et al, 2005 & Wang et al, 2009). In mitochondria, the ROS is dismutated by MnSOD into oxygen and hydrogen peroxide (H_2O_2), which is further detoxified to water (H_2O) by mitochondrial glutathione peroxidase (GSH-PX) (an enzyme requiring selenium) and catalase (CAT). High levels of MnSOD expression may lead to increased O_2 and H_2O_2, and induce toxicity if glutathione peroxidase activity is low due to inadequate selenium or dietary antioxidant intake. The normal pathway is shown above and the altered one is shown below.

6. Conclusions

Gastric cancer ranks the second leading cause of cancer-specific mortality worldwide. It has a poor prognosis; 5-year survival rate of gastric cancer is less than 20%-25% in the USA, Europe, and China (Hartgrink et al, 2009). Cells in tissues and organs are continuously subjected to oxidative stress and free radicals on a daily basis. This free radical attack has exogenous or endogenous (intracellular) origin. The cells withstand and counteract this occurrence by the use of several and different defense mechanisms ranging from free radical scavengers like glutathione (GSH), vitamins C and E and antioxidant enzymes like catalase, superoxide dismutase and various peroxidases to sophisticated and elaborate DNA repair mechanisms (Kryston et al, 2011). Reactive oxygen species along with reactive nitrogen species are well recognized for playing a dual role as both deleterious and beneficial species. The "two-faced" character of ROS is substantiated by growing body of evidence that ROS within cells act as secondary messengers in intracellular signalling cascades, which induce and maintain the oncogenic phenotype of cancer cells, however, ROS can also induce cellular senescence and apoptosis and can therefore function as anti-tumourigenic species. The cumulative production is common for many types of cancer cell that are linked with altered redox regulation of cellular signalling pathways. Oxidative stress induces a cellular redox imbalance which has been found to be present in various cancer cells compared with normal cells; the redox imbalance thus may be related to oncogenic stimulation. DNA mutation is a critical step in carcinogenesis and elevated levels of oxidative DNA lesions (8-OH-G) have been noted in various tumors, strongly implicating such damage in the etiology of cancer (Valko et al, 2006). Finally, the eradication treatment for *H. pylori*, smoking quitting, eating of fresh and dried fruits with high antioxidant content such as dates, raisins, and prunes, and avoiding the salts and pickled vegetables, all are seemingly justifiable means for reduction the gastric cancer prevalence and for general health. Further studies are warranted to explore the effect of different combinations of antioxidants on the healthy heavy smokers to find out if these compounds can protect them or lessen both the gastric cancer incidence and the other debilitating diseases associated with smoking.

7. References

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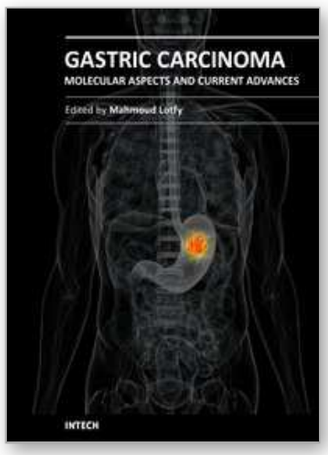

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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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