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Review Article

Experimental Hepatic Carcinogenesis: Oxidative Stress and Natural Antioxidants

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Abbreviations: HCC: Hepatocellular carcinoma; HC: Hepatic carcinogenesis; 4-HNE : 4-Hydroxynonenal; MDA: Malondialdehyde; 8-OHdG: 8-Oxo-7-hydroxydeoxyguanosine; DEN: Diethyl nitrosamine; 2-AAF: 2-Acetylaminofluorene; DNA: Deoxyribonucleic acid; SOD: Superoxide dismutase; CAT; Catalase; GSH-Px: Glutathione peroxidise; GSH:Glutathione; B.W: Body weight.

Abstract

Hepatocellular carcinoma is one of the most common cancers in the world, and it is influenced by agents such as DEN, 2-AAF, phenobarbital, alcohol, aflatoxin B1 metabolite or hepatitis viruses (B and C). Oxidative stress is becoming recognized as a key factor in the progression of hepatocarcinogenesis. Reactive oxygen species can play a leading role in initiation and promotion of hepatic carcinogenesis. The metabolites of DEN Diethylnitrosamine (DEN) mediate the binding of tumour promoters by covalently binding to the DNA with one or two oxidation-providing electrons. 2-AAF is the inducer of DEN, and it is involved in tumour formation in the bladder and liver. Reactive Oxygen species (ROS); carbohydrates, lipids, DNA and enzymes, such as affect all important structures. Additionally, an excessive amount of ROS is highly toxic to cells. Antioxidants are protects against ROS, toxic substances, carcinogens. This review focuses on the literature on studies of Hepatic Carcinogenesis, oxidative stress and antioxidant therapy.

Introduction

Hepatic carcinogenesis is the fifth most common cancer which third most common cause of cancer-related death globally and it is influenced by agents such as DEN, 2-AAF, phenobarbital (PB), alcohol, aflatoxin B1 metabolite or hepatitis viruses (B and C) [1-2].

Animal models are viewed as crucial tools in the study of hepatic carcinogenesis. Because of the physiologic and genetic similarities between rodents and humans, the short lifespan, the breeding capacity and the variety of manipulating methods, animal models are often used for cancer research [3]. Studies on induction of liver cancer in rats use chemical agents such as DEN, 2-AAF, PB and aflatoxin B1 [4].

2-AAF exhibits its carcinogenic effect through the formation of DNA adducts, over production of reactive oxygen species (ROS) and oxidative DNA damage [5]. Nitrosamines are widely recognized as carcinogenic compounds, but they require metabolic activation to exert their cytotoxic and carcinogenic activity. DEN is a nitrosamine compound that induces the formation of hepatic carcinoma. They showed that DEN increased lipid peroxidation in studies performed. This may increase the tumour [6-7].

Our aim in this study is to reveal the relationship between antioxidants and oxidative stress in experimental hepatic carcinogenesis studies. And to report chemopreventive natural antioxidants used as inhibitors.

Reactive oxygen species (ROS)

Reactive oxygen radicals; ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\cdot}$), which are present in small quantities during normal oxygen metabolism. Molecular oxygen (O_2) has two unpaired (unpaired) electrons with parallel spin states. An atom, group of atoms or molecules containing an unpaired electron, are defined as free radicals. Transition metals such as Fe^{3+}, Cu^{2+}, Mn^{2+} and Mo^{5+}, however, are not considered free radicals even if they have unpaired electrons. But they play an important role in the formation of free radicals [8]. They are lipids that are most affected by reactive oxygen species. Since cell membranes are rich in polyunsaturated fatty acids (PUFAs) and cholesterol, they are easily affected by oxidant radicals. Lipid peroxidation, where the unsaturated lipids are present, is a complex process that takes place with reactions involving molecular oxygen and is formed by lipid hydroperoxides. Lipid peroxidation is rather harmful as it is an autocatalytic and irreversible reaction [9-10]. Lipid peroxidation produces a wide variety of oxidation products, such as malondialdehyde (MDA), propanal, hexanal, and 4-hydroxy nonanal (4-HNE). MDA appears to be the most mutagenic product of lipid peroxidation, but 4-HNE is most toxic. MDA is one of the most popular and reliable markers that determine oxidative stress in research [11]. Proteins are less sensitive to the effects of radicals than lipids. Protein oxidation results in the covalent modification of peptide bonds or amino acid side chains with ROS or oxidative stress products. In particular, the interaction of free radicals with unsaturated bonds and sulphide inclusion molecules is excessive. ROS may have direct or indirect effects on proteins. Amino acids such as peptide bonds, proline and lysine are quite easily affected by free radicals [12].

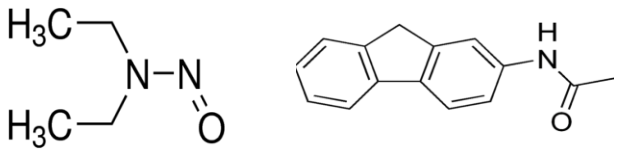
Protein oxidation occurs in the formation of carbonyl groups in amino acids such as histidine, tyrosine, phenylalanine. Products made by lipid peroxidation form covalent bonds with cysteine sulfhydryl groups or with lysine and histidines, leading to fragments and cross-linking of proteins. These events result in the deterioration of the structure and function of the proteins. Protein carbonyl levels area well-used marker for oxidative stress. [8-15].

DNA Damage and Free Radicals

The DNA molecule can undergo spontaneous chemical oxidative damage like carbohydrates and proteins.It has been suggested that every cell DNA of the human body is exposed to oxidative damage 10^3 times a day [8]. Due to the balance between DNA damage and repair, very low levels of damage are also found in healthy individuals. Oxidative base modification (8-OHdG) has been shown even in newborn rats [16]. All changes that occur due to the effects of endogenous or exogenous factors in molecular integration are called DNA damage. 8-OHdG indicates DNA damage [17-18]. In recent years, base damage has frequently been analysed as an indicator of oxidative DNA damage. Since Cu^{2+} ions are highly localized in the regions rich in G-C in DNA, the oxidative damage is the most exposed base guanine. 8-OHdG is a mutation that occurs in DNA, resulting from reactive oxygen species produced during normal oxidative metabolism [19]. All of the factors that lead to increased ROS production contribute to the formation of 8-OHdG, that is, oxidative DNA damage. The formation of 8-OHdG by substances such as cigarette smoke, x-rays, oxidized unsaturated fatty acids, gamma rays, polyphenols, paraquat, kainic acid, diethyl butyl sterol, benzene, fecapenene, furocoumarins hydroperoxide and heavy metals has been shown in vitro [20]. For example, Cigarette smoke contains carcinogenic substances such as nitrosamines and polycyclic aromatic hydrocarbons and causes the increased of 8-hydroxy-deoxyguanosine [19]. For this reason, the most commonly measured base damage is 8-OHdG. Therefore, 8-OHdG is considered as the "biological marker" of DNA damage [17]. Increased ROS production and oxidative DNA damage associated with hepato-carcinogenesis have been demonstrated in studies. Multivariate analysis found that levels of 8-OHdG and fibrosis were significant risk factor for hepatocellular carcinoma, especially in patients with hepatitis C virus infection [21]. The marker of oxidative stress, such as 8-OHdG is commonly elevated in the livers of patients with chronic viral hepatitis infection, which is known to be a risk factor for HC.

Experimental Hepatic Carcinogenesis

Hepatic carcinogenesis can be created experimentally in experimental animals by the application of various chemicals such as aromatic amines, nitrogen containing dyes, nitrosamines and aflatoxins [22]. Xenobiotics are carcinogenic to animals such as DEN, 2-AAF and phenobarbital, mouse, rat, hamster, rabbit, dog, pig and monkey. DEN and 2-AAF are the chemicals that cause tumours to form in the biological system. [23-24-25]. Co-administration of DEN and 2-AAF initiates hepatocarcinogenesis in rodents and causes preneoplastic initiation in hepatocytes. [26-27-28]. In a study with FB acting as a promoter, such as DEN and 2-AAF, it was reported that they caused a mutation in codon 61 of H-Ras [29].



1. DEN 2-AAF

Figure 1: DEN and 2-AAF of structure

Role of DEN in tumorigenesis

DEN is mostly used as tumour inducer in cancer researches [30-31]. In the structure of DEN; Amide, urease and carbon containing compounds are available [32]. It has been reported that DENs are composed of intoxicates, from agrochemicals and nitrattan, from those in cigarette smoke, as well as the formation of nutrients and nutrient nitrates [27-33]. DEN has a direct effect on cancer formation. This means that DEN spontaneously hydrolyzes, regardless of the enzymes. This biological activation of the active DEN by two hydroxylation reactions is catalysed by cytochrome p450. One strong mechanistic link between cancer is through the increased production of free radicals at the site of the resulting molecular changes, which include lipid peroxidation and oxidative DNA damage [34-35].

The role of 2-AAF in tumorigenesis.

2-AAF occurs as a result of the acetylation of the 2-amino floran in the synthetic arylamine structure. 2-AAF acts in the second phase of the detoxification reactions and after the first step of DEN, it binds to guanine base for the second time in DNA and creates a toxic effect This toxic effect occurs in the form of preneoplastic, neoplastic, benign neoplasm and malignant neoplasm, respectively, resulting in mutations [36-39]. If the levels of DEN and 2-AAF chemical tumour inducing agents increase in cells, the smooth endoplasmic reticulum enzymes are synthesized and detoxified [40-42].

Antioxidant Systems Against Reactive oxygen Species

İn the cells and extracellular fluid there are antioxidant defence mechanisms that try to bring the reactive oxygen radicals to a harmless state,

Antioxidant enzyme systems, which convert ROS into less toxic products: Superoxide dismutase (SOD), catalase (CAT) and glutathione redox cycle enzymes (such as glutathione peroxidase (GSH-Px), glutathione reductase, etc.). SOD enzymatically converts superoxide anion to hydrogen peroxide and molecular oxygen. Hydrogen peroxide is reduced by water and oxygen with two important intracellular enzymes, catalase and glutathione peroxidase [43-46].

Antioxidants that catch and neutralize the radicals: Alpha Tocopherol (E vitamin) and Ascorbic acid (C vitamin) function as antioxidants. Vitamin E prevents lipid peroxidation in the cell membrane. Ascorbic acid shows antioxidant activity in the cytoplasm and extracellular fluids and inhibits the inactivation of antiproteases with oxidants. Additionally, Glutathione is a multifunctional intracellular antioxidant, α-Lipoic acid (ALA), which is a sulfur-containing antioxidant with metal-chelating and antiglycation capabilities. N-acetyl-L-cysteine is a thiol containing an antioxidant that has been used to decrease conditions of oxidative stress. The most reported activity of flavonoids is protection against oxidative stress. Thus flavonoids can help scavenger ROS and are effective inhibitors of lipid peroxidation [47].

Systems that prevent the formation of ROS and prevent the formation of ROS

Structures such as ceruloplasmin, ferritin, transferrin, lactoferrin, zinc, selenium, cytochrome oxidase reduce ROS. For example; Zinc has been serving as a metal that prevents lipid peroxidation and DNA damage [48-49].

Experimental Investigations

Most of the factors that influence tumour formation cause radical production in the cell. These factors also induce tumour formation and development by affecting the initiation, development and progression stages of carcinogenesis. Various animal model studies have been done on this subject. As seen in Table 1, many natural antioxidants have been tried.

Models	Animals	Materials	Effect	Dose	References
DEN (90 mg/kg)	Mice	Lawsonia inermis extract	MDA ↓; GSH ↑	LIE group was given 200 mg/100 ml drinking water from the first day of DEN injection until the end of week	[50]
2-AAF (50 mg/kg)	Wistar albino Rats	Tannic acid	GSH↑,GSH-Px↑,SOD↑, MDA↓	125 and 250 mg/kg	[51]
DEN (200 mg/kg)	Wistar albino Rats	Caesalpinia bonducella leaves	SOD ↑ CAT↑ GSH ↑ ; MDA ↓	100 and 200 mg/kg body weight (b.w)	[52]
2-AAF (200 mg/kg)	Wistar albino rats	Garcinia kola Seed Extract	MDA ↓; GSH ↑	100 and 200 mg kolaviron/kg	[53]
DEN(200 mg/kg)+ 2-AAF (0,2 g/kg)	Rattus norwegicus rats	Tocotrienol	GSH ↑	30 mg/kg	[54]
DEN (200 mg/kg)	Rats	Vaccinium corymbosum Leaf (Blue berry)	PC↓ MDA ↓GSH ↑	5 and 10% BB-Chow,diet	[27]
2-AAF (0.02 %)	Wistar albino rats	Geraniol (GE)	SOD↑, CAT↑, GSH ↑; MDA ↓	100 and 200 mg/kg (b.w)	[33
DEN (200 mg/kg)	Wistar albino rats	Thymoquinone (Nigella sativa seeds)	CAT↑, GSH-Px, ↑GSH ↑; (MDA)TBARS ↓	The rats were given Thymoquinone (4 mg/kg) in drinking water.	[55]
0.01% DEN – Drinking water	Wistar strain albino rats	Carvacrol	SOD↑, CAT↑, GSH-Px, ↑GSH ↑; MDA ↓	15 mg/kg (b.w)-orally	[56]
DEN (200 mg/kg - i.p.)	Wistar albino rats	Cassia fistula Linn. leaf extract	SOD↑, CAT↑; MDA ↓	500 mg/kg (b.w.)	[57]
2-AAF (0.02%) in diet + DEN 200 mg/kg (i.p)	Wistar rats	Aegle marmelos	GSH-Px↑	(50 mg/kg and 25mg/kg)	[58]
DEN (20 mg/kg – i.p)	Mice and IL-17A knockout mice	-	8-OHdG ↑	-	[59]
DEN (200 mg/kg-i.p),	Sprague-Dawley rats	Nano curcumin	SOD↑, CAT↑, GSH ↑ ; MDA ↓	20 mg/kg (b.w)	[60]

In conclusion, the relationship between HC and oxidative stress is a research area. ROS contributes to the initiation and progression of HC. In current clinical trials, the mechanisms of HC treatment of drugs or compounds may be partly due to anti-oxidative ability, especially the effect originating from ROS. Therefore, antioxidant therapeutics play an important role in the treatment of HC. Time, effective doses and reliable doses require further investigation of antioxidant absorption and bioavailability.

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