List of Publications


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Caffeic acid attenuates 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced NF-κB and COX-2 expression in mouse skin: Abrogation of oxidative stress, inflammatory responses and proinflammatory cytokine production

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Abstract

Polyphenols are the abundant micronutrient in our diet and attention has been given to them for the prevention of degenerative diseases. Since over production of ROS and proinflammatory cytokine are often act as the triggers for the promotion stage of carcinogenesis by transcriptional up-regulation of nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2). We investigated the protective effects of caffeic acid (CA) on 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced oxidative and inflammatory responses, expression of NF-κB and COX-2 in mouse skin. Animals were given pre-treatment of CA at two different doses 10 μmol (D1) and 20 μmol (D2) (200 μL of acetone) prior to each TPA (10 nmol) (0.2 mL of acetone) application. Our results show that CA significantly inhibit the TPA induced lipid peroxidation (LPO), inflammatory response, tumor necrosis factor alpha (TNF-α) release and also found to up regulate GPx content and the activity of different antioxidant enzymes. Further, CA was found to inhibit the TPA induced expression of NF-κB and COX-2. Thus, our results suggest that CA attenuates TPA induced tumor promotion triggers partly by inhibition of oxidative and inflammatory responses thereby diminishing the expression of NF-κB and COX-2.

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1. Introduction

In the present era, attention has been given to the use of naturally occurring compounds and their formulations for the treatment of different degenerative diseases. These effects are attributed to their antioxidant as well as anti-inflammatory potential. Moreover most of the plant based products are considered to be safe.

Epidemiological findings also revealed that use of natural compounds is a well promising approach for the chemoprevention and management of human cancers (Nakachi et al., 1996). Chemoprevention is a strategy of cancer control by administration of one or more naturally occurring and/or synthetic compounds to block initiation or suppress or delay promotion/progression of carcinogenesis (Surh, 2003).

Polyphenols represents one of the most diverse and widely distributed plant secondary metabolites including acids, flavonoids, lignins etc. Caffeic acid (CA) (3,4-dihydroxybenzoic acid), is one of the important phenolic acid present in medicinal plants, vegetables, beverages like wine, tea, coffee and apple juice (Shahidi and Nasr, 1985). It is also an active constituent of bee propolis (Crutcher et al., 1988). CA has been known to exhibit wide spectrum of positive biological effects such as antioxidant, anti-inflammatory, immunomodulatory, anti-HIV (Johnson et al., 2000), anti-tumor and anti-metastatic effects (Chung et al., 2004; Oktar et al., 2005; Nardini et al., 1995; Yamada et al., 2006).

Now, it is well established that oxidative stress and inflammation are the two concurrent conditions critically associated with etiology and progression of a number of human diseases. Reactive oxygen species (ROS) production is part of the inflammatory processes as activated inflammatory cells produce these kinds of free radicals to kill the pathogens in general. ROS production by activated neutrophils and macrophages leads to cancer promotion in...
Perillyl alcohol protects against ethanol induced acute liver injury in Wistar rats by inhibiting oxidative stress, NFκ-B activation and proinflammatory cytokine production

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ABSTRACT

Oxidative stress and inflammation are two major etiological factors that are suggested to play key roles in the development of ethanol induced liver injury. Release of proinflammatory cytokine like tumor necrosis factor alpha (TNF-α) and activation of nuclear factor kappa-B (NFκ-B) may strongly intensify inflammation and cell damage. Additionally, reactive oxygen species (ROS) also exerts significant effect on this whole cell signaling machinery. The present study was designed to investigate the protective effects of perillyl alcohol (POH) on ethanol-induced acute liver injury in Wistar rats and its probable mechanism. We have successfully demonstrated that pre-treatment with POH, besides exerting antioxidant activity might be able to modulate TNF-α release and NFκ-B activation. Rats were divided into five groups and treated with ethanol or POH via an intragastric tube for one week. Control group was treated with vehicle, and ethanol treated group was given ethanol (5 g/kg body wt). Animal treatment groups were pretreated with POH (50 & 100 mg/kg body wt) and have been given ethanol. Serum aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase and hepatic malondialdehyde were increased significantly by ethanol treatment. Ethanol administration decreased hepatic reduced glutathione content and various antioxidant enzymes activity, TNF-α production and NFκ-B activation was also found to be increased after ethanol administration. POH pre-treatment significantly ameliorates ethanol induced acute liver injury possibly by inhibition of lipid peroxidation, replenishment of endogenous enzymatic and non-enzymatic defense system, downregulation of TNF-α as well as NFκ-B.

1. Introduction

Alcoholic liver disease (ALD) involves hepatocellular injury induced by consumption of ethanol. ALD is a major public health hazard in developed as well as in developing world. In spite of very good scientific efforts made to understand the pathogenesis of ALD, there remains no effective therapy for this disease. Most of the evidence shows that both oxidative stresses and abnormal cytokine production play an important etiological role in the pathogenesis of ALD. Therefore agents possessing antioxidant and anti-inflammatory properties are promising therapeutic interventions for ALD. A large number of research studies have suggested that oxidative stress plays an important role in the development of ALD. Ethanol intake causes accumulation of reactive oxygen species (ROS) like superoxide, hydroxyl radical, and hydrogen peroxide (Nordmann et al., 1992). These free radicals cause lipid peroxidation (LPO) of cellular membranes, oxidation of protein and DNA, ultimately leading to injury of hepatocytes (Kotase et al., 1997; Navazimuthu et al., 2000; Rouach et al., 1987).

Reduced glutathione (GSH) is one of the most prominent defense molecules in the liver and plays a pivotal role to maintain redox homeostasis (Dickinson and Forman, 2002). A number of research studies have shown evidence that acute ethanol administration decreases hepatic GSH content (Masini et al., 1994; Shaw et al., 1983; Song et al., 2003). Selective depletion of mitochondrial GSH was also reported in ethanol induced liver toxicity (Fernandez-Gracia et al., 1991). Additionally, administered ethanol induces the activation of NFκ-B, which accounts for an increased synthesis of the proinflammatory cytokine TNF-α. TNF-α plays an important role in the development of liver injury produced by ethanol in rat models (French, 2001;
Chrysins protects against cisplatin-induced colon toxicity via amelioration of oxidative stress and apoptosis: Probable role of p38MAPK and p53

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ABSTRACT

Cisplatin, a standard anticancer drug, is widely used as a foremost therapy against numerous forms of cancer but it has pronounced adverse effects viz., nephrotoxicity, neurotoxicity etc. Cisplatin-induced emesis and diarrhea are also normal toxicities that may be due to intestinal injury. Chrysins (3,5-dihydroxyflavone), a natural flavone commonly found in many plants possesses multiple biological activities, such as antioxidant, anti-inflammatory and anti-cancer effect. In the present study, we investigated the protective effect of chrysin against cisplatin induced colon toxicity. The plausible mechanism of cisplatin-induced colon toxicity and damage includes oxidative stress, activation of p38MAPK and p53, and colorectal epithelial cell apoptosis via upregulating the expression of Bak and cleaved caspase-3. Chrysins was administered to Wistar rats once daily for 14 consecutive days at the doses of 25 and 50 mg/kg body weight orally in corn oil. On day 14, a single intraperitoneal injection of cisplatin was given at the dose of 7.5 mg/kg body weight and animals were euthanized after 24 h of cisplatin injection. Chrysins ameliorated cisplatin-induced lipid peroxidation, nitrosative oxidative activity, glutathione depletion, decrease in antioxidant (catalase, glutathione reductase, glutathione peroxidase and phospho-6-phosphate dehydrogenase) and phase II detoxifying (glutathione S-transferase and quinone reductase) enzyme activities. Chrysins also attenuated gut epithelial cell disintegration, expression of phosphoprotein p38MAPK and p53, and apoptotic tissue damage which were induced by cisplatin. Histopathological findings further supported the protective effects of chrysin against cisplatin induced colon toxicity. The results of the present study suggest that the protective effect of chrysins against Cisplatin induced colon toxicity was related with attenuation of oxidative stress, activation of p38MAPK and apoptotic tissue damage.

Introduction

Cisplatin [cis-diamminedichloroplatinum(II) (CDDP) or cisplatin] (Fig. 1) is a platinum (Pl) containing antineoplastic drug widely used as a foremost therapy against numerous forms of cancer including testicular cancer, ovarian germ cell tumor, epithelial ovarian cancer, head and neck cancer, advanced cervical cancer, colon cancer, bladder cancer, mesothelioma, enteral cancer, non-small cell lung cancer, malignant melanoma, carcinoid, penile cancer and adenocarcinotic carcinoma (Adenis et al., 2005; Lebowich and Garettta, 1998; Saad et al., 2004; Thigpen et al., 1994; Van Rassen et al., 1997; Wang et al., 2004a, 2004b). It is used as an adjuvant therapy following surgery or radiation and also used in combination with other antineoplastic agents (Nees and Krishnamurthy, 2010). The therapeutic efficacy of Cisplatin is enhanced by dose augmentation but its therapeutic intervention is due to its damaging effects on normal cells consequently causing pronounced adverse effects viz., nephrotoxicity, neurotoxicity, hepatotoxicity, nausea, emesis and 67% of patients experienced diarrhea (Bencatt et al., 1999; Kim et al., 2005; Kris et al., 1998; Langenau and Droesch, 2003; Ziece et al., 2004). The precise mechanism of CDDP toxicity is not fully understood but the plausible mechanism may be through the DNA adduct formation and the generation of paraxyl of reactive oxygen species (ROS) e.g., superoxide anion (O2−), hydrogen peroxide (H2O2), hydroxyl radical (OH•) etc. which may interact with DNA, lipids and proteins (Sun, 1990). CDDP can act on the sulfhydryl (-SH) groups of cellular proteins (Bau and Krishnamurthy, 2010) but DNA is the main cellular target of CDDP that may lead to DNA damage induced by ROS and PI-DNA adduct formation, thus hampers the cell division or DNA synthesis and its repair mechanism which leads to apoptotic cell death (Eiseman, 1985; Sherman et al., 1985).

Several lines of evidence exhibited that this chemotherapeutic drug is not specific in action against tumors but also cytotoxic to rapidly dividing normal cells viz., intestinal epithelial cells, through the production of ROS which provides a nidus for the development of...
Chrysin abrogates cisplatin-induced oxidative stress, p53 expression, goblet cell disintegration and apoptotic responses in the jejunum of Wistar rats

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Abstract

Cisplatin (cis-diaminedichloroplatinum II) (CDDP) is a commonly used chemotherapeutic drug for the treatment of numerous forms of cancer, but it has pronounced adverse effects, namely nephrotoxicity, ototoxicity, neurotoxicity, hepatotoxicity, diarrhea and nausea. CDDP-induced emesis and diarrhea are also reported toxicities that may be due to intestinal injury. Chrysin (5,7-dihydroxyflavone), a natural flavone commonly found in many plants, possesses multiple biological activities, such as antioxidant and anti-inflammatory properties.

In the present study, we investigated the protective effect of chrysin against CDDP-induced jejunal toxicity. The plausible mechanism of CDDP-induced jejunal toxicity includes oxidative stress, p53 and apoptosis via up-regulating the expression of caspase-6 and –3. Chrysin was administered to Wistar rats orally in maize oil. A single intraperitoneal injection of CDDP was given and the animals were killed after 24 h of CDDP injection. Chrysin attenuated CDDP-induced lipid peroxidation, increase in xanthine oxidase activity, glutathione depletion, decrease in antioxidant (catalase, glutathione reductase, glutathione peroxidase and glucose-6-phosphate dehydrogenase) and phase-II detoxifying (glutathione-S-transferase and quinone reductase) enzyme activities. Chrysin attenuated CDDP-induced goblet cell disintegration, enhanced expression of p53 and apoptotic tissue damage. Histological findings further substantiated the protective effect of chrysin against CDDP-induced damage in the jejunum. The results of the present study demonstrate that oxidative stress and apoptosis are closely associated with CDDP-induced toxicity and chrysin shows the protective efficacy against CDDP-induced jejunal toxicity possibly via attenuating the oxidative stress and apoptotic toxic damage.

Key words: Cisplatin, Jejunum toxicity; Oxidative stress; p53; Caspases; Goblet cells

Cisplatin (cis-diaminedichloroplatinum II) (CDDP), Fig. 1 is a commonly used chemotherapeutic drug for the treatment of various forms of cancer1–3. The chemotherapeutic efficacy of CDDP is increased by increasing the dose, but it is usually accompanied by severe adverse effects including nephrotoxicity, ototoxicity, neurotoxicity, hepatotoxicity, nausea and emesis, with 67% of patients experiencing diarrhea4–6. The cytotoxic effects of anti-neoplastic drugs are not specific in action against tumour cells but also damage normal rapidly proliferating cells, namely intestinal epithelial cells7. The exact mechanism of CDDP toxicity is not fully understood, but the plausible mechanism may involve oxidative stress8–10 which is due to the degrading production of reactive oxygen species (ROS), e.g. the superoxide anion \( \text{O}_2^- \), \( \text{H}_2\text{O}_2 \), hydroxyl radical \( \text{OH}^- \), etc. by CDDP11, and consequently these ROS may further interact with DNA, lipids and proteins12. CDDP can act on the sulphhydryl (–SH) groups of cellular proteins13, but DNA is the main cellular target of CDDP that may lead to DNA damage induced by ROS and platinum–DNA (Pt–DNA) adduct formation, thus hampering the cell division or DNA synthesis and its repair mechanism which leads to apoptotic cell death14,15.

Increasing amounts of evidence suggest that the natural compounds with antioxidant properties substitute CDDP toxicity16–20. Therefore, chemotherapy treatment with compounds having antioxidant properties may augment the efficiency of anti-neoplastic drugs and also may decrease the systemic toxicity induced by chemotherapy20. There is
Benzo(a)pyrene-Induced Pulmonary Inflammation, Edema, Surfactant Dysfunction, and Injuries in RATS: Alleviation by Farnesol

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ABSTRACT

Benzo(a)pyrene (BaP) is a well-known environmental contaminant and carcinogen. Its sources include tobacco smoke, automobile exhaust, forest fires, and other combustion processes. Farnesol, an active principle of Vachellia farnesiana and other aromatic plants, possesses preventive properties against various toxicities. Present study was designed to estimate chemoprotective effects of farnesol against BaP-induced pulmonary injuries. To determine the protective effects of farnesol, it was administered orally at 2 doses (100 and 200 mg/kg body weight [b.w.]) once daily for 14 days. Rats were exposed intratracheally to BaP, 5 mg/kg b.w. on days 12 and 14, thereafter assessed for pulmonary toxicities 24 hours post last dose of BaP. BaP-induced edema, inflammation, oxidative stress, and consequential damages in lungs were assessed in terms of total protein, total cell count, nitric oxide (NO), lactate dehydrogenase (LDH), alkaline phosphatase, and lipid peroxidation in bronchoalveolar lavage fluid (BALF). It also reduced the levels of phospholipids (lung surfactants) in BALF. However, pretreatment with farnesol at both the doses significantly reduced the lung injuries and inflammatory responses. Farnesol also protected the levels of phospholipids to normal when compared with control. It also modified the activities of BaP metabolizing enzymes NADPH-cytochrome P450 reductase, microsomal epoxide hydrolase (mEH), and glutathione S-transferase (GST) in lung tissue of rats. Present findings suggest a prominent role of farnesol against BaP-induced lung inflammation, edema, surfactant dysfunction, and epithelial damages in Wistar rats. In conclusion, farnesol shows lung protection against BaP toxicities in Wistar rats.

KEYWORDS bronchoalveolar lavage fluid (BALF), environmental contaminant, intratracheal, NADPH-cytochrome P450 reductase, neutrophil elastase, toxicity

Lung is one of the most susceptible organs to injuries; being an interface between organism and ambient environment, it directly interacts with inhalant toxicants. Large surface area and massive vasculature further increases the susceptibility of the lungs. Benzo(a)pyrene (BaP), a polynuclear aromatic hydrocarbon (PAH) family member, present in environment and tobacco smoke [1], is known to play a role in airway inflammation and injuries [2, 3]. Most of the lethal lung conditions are associated with chronic inflammation and consequent injuries. Smokers are exposed to such compounds categorized as PAH, including BaP, primarily through inhalation of tobacco smoke, automobile exhaust, and through diet [4]. In short-term exposure, BaP is reported to alter cellular antioxidant levels [5], an initial role in oxidative imbalance of the cell, besides its known carcinogenic activities. Such kind of exposures can play an instrumental role in alterations of lung architecture and physiology that may lead to development of various lung disorders, including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, emphysema, and lung cancer. BaP has been proven as a model toxicant to study adverse effects on pulmonary system in rodents [6, 7]. In the present study, BaP

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Alleviation of lung injury by glycyrrhizic acid in benzo(a)pyrene exposed rats: Probable role of soluble epoxide hydrolase and thioredoxin reductase

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ABSTRACT

Benzo[a]pyrene (BaP) is known to alter lung physiology by interfering in various intracellular pathways, including alterations in NF-κB activities, cytokine release and cell survival. NF-κB suppression/activation plays a major role in cell survival status. Present investigation deals with such kind of effects of BaP on lungs in relation with soluble epoxide hydrolase (sEH) and thioredoxin reductase (TrxR) activities. Glycyrrhizic acid (GA), an active principle of Glycyrrhiza glabra (Licorice), is known to modulate various molecular processes. In the present study, we investigated the protective effects of GA against BaP induced edibility in lungs of Wistar rats. Intratracheal instillation of BaP significantly suppressed NF-κB translocation, sEH, TrxR and caspase activities in lung tissue. A marked induction of H2O2 levels along with caspases activation (caspase-2, -3, -6, -8, and -9) in lung tissue after BaP exposure was observed. Lung injury was assessed by measuring lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total cell count, total protein, neutrophil elastase activity in bronchoalveolar lavage fluid (BALF). Reduction in phospholipid content further potentiated these parameters. GA oral administration (50 and 100 mg/kg b.w.) significantly showed protection of lung epithelium by suppression of caspases activities in lung tissue and reduction of total protein, total cells, elastase activity, LDH and ALP activities along with normalization of phospholipids in BALF. Histological observations also confirm the findings in above mentioned parameters. Results indicate a strong correlation between amelioration of sEH and TrxR activities, and NF-κB activation. The present investigation gives an insight into probable mechanisms of lung injuries induced by short term exposures of BaP and prevention by glycyrrhizic acid.

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1. Introduction

Benzo[a]pyrene (BaP), a prototype of polynuclear aromatic hydrocarbons (PAHs) family, is formed during the process of incomplete combustion of organic matter such as fossil fuel, garbage and plant parts. It is also present in tobacco smoke (Picciotto et al., 2010). BaP is an environmental contaminant and known to cause various toxicities including airway inflammation and injuries (Podchard et al., 2008). In acute exposures BaP is reported to alter cellular antioxidant levels (Luo and Yang, 2007). BaP exposure can play an instrumental part in modifications in lung structural design and physiology that may lead to development of various chronic lung disorders. In various studies BaP has been used to find our adverse effects on pulmonary system (Garry et al., 2003; Woltersbeek et al., 1995). In the present study BaP was used to study the alterations in NF-κB, a transcription factor that controls expression of numerous genes involved in immunological processes and cell survival, in relation with activities of soluble epoxide hydrolase (sEH) and thioredoxin reductase (TrxR) in lungs of Wistar rats. sEH is known to play a major role in cardiovascular diseases and possess proinflammatory properties. sEH is responsible for metabolizing epoxyeicosatrienoic acids (EETs) to dihydroxyeicosatrienoic acids (DHETs). Inhibition of sEH is reported to reduce inflammation due to elevated levels of EETs (Schmeizer et al., 2005). These activities could be due to NF-κB inhibition properties of EETs (Nade et al., 1999). TrxR is a selenocysteine containing flavoprotein and has an ability to maintain thioredoxin (Trx) in reduced state, which regulates the activity of NF-κB. Thus TrxR plays a role in downregulation of NF-κB (Hayashi et al., 1993; Sakurai et al., 2004). Interference with activities of sEH and TrxR by BaP can affect NF-κB activities and dependent immunological alterations and cell survival. Glycyrrhizic acid, a triterpenoid saponin glycoside, is an active principle of Glycyrrhiza glabra (Licorice). It is widely applied as a sweetener in food and tobacco products (Ploeger et al., 2001). In
Cyclophosphamide-induced nephrotoxicity, genotoxicity, and damage in kidney genomic DNA of Swiss albino mice: the protective effect of Ellagic acid

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Abstract Cyclophosphamide (CPM), an alkylating agent is used as an immunosuppressant in rheumatoid arthritis and in the treatment of several cancers as well. In this study, Ellagic acid (EA), a naturally occurring plant polyphenol, was evaluated for its antigenotoxicity and antioxidant efficacy against the CPM-induced renal oxidative stress and genotoxicity in Swiss albino mice. The mice were given a prophylactic treatment of EA orally at a dose of 50 and 100 mg/kg body weight (b.wt) for seven consecutive days before the administration of a single intraperitoneal (i.p.) injection of CPM at 50 mg/kg b.wt. The modulatory effects of EA on CPM-induced nephrotoxicity and genotoxicity were investigated by assaying oxidative stress biomarkers, serum kidney toxicity markers, DNA fragmentation, alkaline unwinding assay, micronuclei (MN) assay, and by histopathological examination of kidney tissue. A single intraperitoneal administration of CPM in mice increased malondialdehyde level with depletion in glutathione content, antioxidant enzymes activities, viz., glutathione peroxidase, glutathione reductase, catalase, quinone reductase, induced DNA strand breaks, and MN induction. EA oral administration at both doses caused significant reduction in their levels, restoration in the activities of antioxidant enzymes, reduction in MN formation, and DNA fragmentation. Serum toxicity marker enzymes like BUN, creatinine, and LDH were also increased after CPM treatment which was significantly decreased in EA pretreated groups. Present findings suggest a prominent role of EA against CPM-induced renal injury, DNA damage, and genotoxicity.

Keywords Cyclophosphamide · DNA damage · Ellagic acid · Genotoxicity · Nephrotoxicity

Abbreviations
EA Ellagic acid
CPM Cyclophosphamide
GSH Reduced glutathione
GPx Glutathione peroxidase
GR Glutathione reductase
XO Xanthine oxidase
MDA Malondialdehyde
BUN Blood urea nitrogen
LDH Lactate dehydrogenase

Introduction
Natural products have been shown to be an excellent and reliable source for the development of new drugs [1]. Epidemiologic studies have showed that there is an association between the intake of phenolic foods and the protection from various diseases [2]. These phenolic compounds have tremendous antioxidant and chemoprotective properties in vivo [3]. Phenolic compounds are the most promising anticarcinogenic agents in plants [4]. Ellagic acid (EA) has been reported to inhibit peroxynitrite-induced oxidation and nitration reactions [5]. EA is a potent dietary antioxidant found in variety of fruits, nuts, and many other food sources. EA is reported to exhibit antioxidant, antiproliferative, radical scavenging, antiapoptotic, antinocicogenic,
Topically applied vitamin E prevents massive cutaneous inflammatory and oxidative stress responses induced by double application of 12-O-tetradecanoylphorbol-13-acetate (TPA) in mice


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Abstract

Vitamin E (α-tocopherol) is a promising chemopreventive and pharmacologically safe agent, which can be exploited or tested against skin cancer. It is an established antioxidant with an ability to ameliorate the UV-induced skin damage and chemically induced inflammation in lungs. However, there are some conflicting reports about its role as a modulator of chemically induced promotion. We evaluated its efficacy in preventing the inflammatory and oxidative stress responses in a double 12-O-tetradecanoylphorbol-13-acetate (TPA) application tumor skin promotion protocol. Double application of TPA was undertaken to produce massive inflammatory and oxidative stress responses. Topical TPA treatment adversely altered many of the marker responses of stage I skin tumor promotion. Vitamin E application 50 min prior to TPA treatment (10 nmol) inhibited induction of hydrogen peroxide, myeloperoxidase (MPO) activity, xanthine oxidase (XO) activity and lipid peroxidation (LPO). Vitamin E also positively modulated altered antioxidants of mouse skin. Histological examination also revealed marked improvement. These results confirm the efficacy of vitamin E against early inflammatory and oxidative stress responses, which are hallmark of tumor promotion and provide rational basis for chemopreventive action of vitamin E in skin cancer.

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Keywords: Skin tumor promotion; 12-O-tetradecanoylphorb | stress; Inflammatory response; Vitamin E; Chemoprevention

1. Introduction

The promotion is the most important stage in the multistage skin carcinogenesis [1]. It is a two-stage lengthy process that involves clonal expansion of initiated cells giving rise to a pre-malignant lesion, essentially by alterations in the signal transduction pathway. The molecular