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Chemosensitizing effect of *Alpinia officinarum* rhizome extract in cisplatin-treated rats with hepatocellular carcinoma

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ABSTRACT

This study was conducted to estimate the preventing and sensitizing efficiency of *Alpinia officinarum* rhizome extract (AORE) in an experimental model of hepatocellular carcinoma (HCC) +/− cisplatin. HCC was induced by a single intraperitoneal (i.p) dose of diethylnitrosamine (DENA, 200mg/kg). After 14 days, phenobarbitone (PB, 0.05%) was added to drinking water for 14 weeks to promote hepatocarcinogenesis. Cisplatin (CP) was given in a dose of 1.5 mg/kg (i.p), twice a week, alone or with AORE (400 mg/kg daily, orally) for 21 days. AORE was tried as a protective before the induction of HCC for three weeks as well. Results revealed that DENA/PB elevated hepatic indices as ALT and AST and total bilirubin with declining serum total protein. It increased oxidative stress, as hepatic malondialdehyde (MDA) with depressed hepatic reduced glutathione (GSH) contents, superoxide dismutase (SOD) and catalase activities. This was accompanied by an increase in hepatic expression of antioxidant genes (thioredoxin and glutaredoxin). Hepatocarcinogenesis was detected by histopathological changes in liver sections and the elevation of serum alpha-fetoprotein (AFP) level. Treatment with CP partially restored altered hepatic functions and oxidative stress markers. It also showed a partial decrease in the expression of antioxidant genes, improving histopathological changes in the liver and AFP level in serum. The treatment with AORE alone or AORE + CP enhanced hepatic function and oxidative stress markers. It also caused a decrease in the expression of antioxidant genes and improved histopathological changes in liver and serum AFP level. This effect is more potent than the treatment with CP alone. Our study suggested that AORE can be used as a promising natural chemoprevention or a chemosensitizing agent against hepatocarcinogenesis.

1. Introduction

Hepatocellular carcinoma (HCC) represents over 90% of primary liver cancers, being an offensive tumor with expected mean survival between 6 and 20 months [1]. It is considered the fifth most frequently diagnosed malignancy and the second major common cause of cancer mortality worldwide [2]. HCC is more prevalent among males than females. Its incidence increased in the middle and western Africa and eastern and southern Asia [3]. In Egypt, HCC is considered a major health problem and its incidence rate continues to rise in the past 10 years. Egypt has a rising rate of chronic hepatitis C virus infection, which is found to be the major risk factor for HCC in Egypt [4].

Diethylnitrosamine (DENA), recognized as N-nitrosodiethylamine, is generally used in experimental animal models for the induction of HCC [5]. DENA exists in cosmetics, tobacco smoke, agricultural chemicals, fried and cured meals, water and pharmaceutical agents [6]. DENA does not induce carcinogenicity by itself. It should be bioactivated via cytochrome P450 liver enzymes, forming DNA-adducts, which result from an alkylation mechanism [7]. Liver cell damage and oxidative stress produce reactive oxygen species (ROS), which may contribute to the pathogenesis of liver cancer induced by DENA [8].

Although phenobarbital (PB) is not genotoxic, it induces liver tumors in animals rapidly, when administered together with DENA [9].

Cisplatin (cis-diamminedichloroplatinum [II], CP) is one of the most broadly used and highly effective therapies that used in the management of numerous human cancers [10]. CP binds to DNA, resulting in

Abbreviations: ALT, alanine aminotransferase; AFP, alpha-fetoprotein; *AORE, Alpinia officinarum* rhizome extract; AST, aspartate aminotransferase; CMC, carboxy methylcellulose; CP, cisplatin; DENA, diethylnitrosamine; Grx, glutaredoxin; GSH, reduced glutathione; H&E, hematoxylin and eosin; HCC, hepatocellular carcinoma; i.p, intraperitoneal; MDA, malonedialdehyde; NF-κB, nuclear factor kB; PB, phenobarbital; PCR, polymerase chain reaction; ROS, reactive oxygen species; SOD, super oxide dismutase; Trx, thioredoxin

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inter- and intra-strand cross-links formation leading to defect in DNA templates and consequent inhibition of the replication and the synthesis of DNA. CP-DNA complex inhibits the replication of rapidly dividing cancer cells, and these cells are then damaged by the cross-links [10].

In spite of CP efficiency, its use in high-dose therapy has been demonstrated to be restricted by its acute and cumulative toxicity to kidney and heart [11]. Human liver cells take up CP in a significant amount and high doses, which lead to liver toxicity [12]. It has been recommended that numerous adverse effects are due to ROS production [13], as well, damage to mitochondria [14]. Therefore, a critical need for finding new therapeutic lines is always necessary to manage liver cancer with less toxic effects.

Alpinia officinarum is a perennial medicinal plant that is mostly spread in the tropical and subtropical regions of Southeast Asia. It is usually used as food additive, a sort of Chinese medicinal material. It has been recorded as Affinal Drug and Diet by National Health and Family Planning Commission of the People's Republic of China because it is highly safe. Several reports stated that *Alpinia officinarum* has antihyperlipidemic [15], anticancer [16], antibacterial [17] and anti-inflammatory properties [18]. The bioactive compounds of *Alpinia officinarum* extract have been identified by several previous studies. The rhizomes of *Alpinia officinarum* contain a higher percentage of compounds than that present in the aerial parts [19]. These compounds include diarylheptanoids (linear, cyclic, and dimeric), diterpenoids, phenylpropanoid, lignin, flavonoids and volatile oils [20]. The extract and its main components have an antitumor effect in many cancer cell lines, as lung, liver, neuroblastoma and breast [21–23].

Long-standing oxidative stress contributes to the pathogenesis of cirrhosis and hepatocarcinogenesis [24]. Redox systems play a vital role in oxidative stress reduction, apoptosis contribution, control of growth, cancer cells resistance to drug and angiogenesis [25]. Thioredoxins (Trx) and glutaredoxins (Grx) are redox proteins. They are part of thioredoxin superfamily and they are ubiquitously expressed [26]. They provide reducing equivalents to the cell and they can reduce protein disulfides. They contribute to apoptosis, synthesis of DNA, control of thiol redox within the cell and defense against oxidative stress. This is done by the control of the receptors and enzyme activity and transcription factors like p53, nuclear factor kappa (NF-κB) and activator protein-1 [27]. Trx over-expression has been detected in numerous cancers and it has been exposed to be related to worse prognosis in non-small cell lung cancer [28], squamous cell carcinoma of the tongue [29], gallbladder malignancy [30], gastric cancer [31] and colorectal cancer [32].

In the present study, we investigated the possible hepatoprotective and curative effects of an acetone extract of AORE +/- CP on DENA/PB-induced HCC in rats. This study was also carried out to examine the potential antioxidant activity and the effect of the AORE on the expression of Trx and Grx genes in an experimental model of HCC.

2. Materials and methods

2.1. Preparation of AORE

AORE was obtained from the local market and identified by Prof. Abed El-Halim A. Mohamed (The agricultural museum, Dokki, Cairo). Three kg of dried rhizomes was extracted using 80% aqueous acetone three times at room temperature. The rhizome was macerated for two days and the extract was filtered. Then, the filtrate was concentrated using a rotary evaporator under vacuum at 40 °C and the obtained viscous mass was dried. A known weight of the dry material was suspended in 1% carboxymethylcellulose (CMC) to prepare a dose of 400 mg/kg and used to carry out the experimental trials.

2.2. Chemicals

DENA was obtained from Sigma Chemical Co. (St. Louis, MO, USA), PB was purchased from Alpha Chemika (Mumbai, Maharashtra, India), CMC and acetone were purchased from EL-Gomhoria Company (EL Amyria, Cairo, Egypt). CP was obtained from CP ampule (50 mg/50 ml), a product of EIMC United Pharmaceuticals (Badr City, Cairo, Egypt).

2.3. Induction of hepatocellular carcinoma

DENA was dissolved in 0.9% NaCl physiologic saline solution. Fifty rats of five groups were injected intraperitoneally (i.p) with 200 mg/kg body weight of DENA as a single dose. Fourteen days later, 0.05% PB was supplemented in drinking water for 14 successive weeks to induce the carcinogenic effect. Throughout the last four 4 days, drinking water was deprived of PB. After 16 weeks, histopathological examination was used to confirm the HCC diagnosis [33].

2.4. Animals and treatment

The experiment was done on ninety healthy adult male albino rats, weighing 150–170 g. Animals were obtained from "Egyptian Organization for Biological Products and Vaccines" (Agouza, Giza, Egypt), housed in metallic cages with thermally controlled temperature (22–25 °C), automatically illuminated room (12 h light: 12 h darkness). They were kept under good ventilation and permitted a suitable standard diet and water *ad libitum* during the experiment. All procedures of the experiment were approved by the Institutional Animal Ethics Committee guidelines for animal care and use at Mansoura University. After one week acclimatization period, rats were randomly classified into 9 groups (10/each) as follows:

1 Normal control group: rats orally received 1% CMC in saline.
2 AORE group: rats orally received 400 mg/kg of AORE every day for 21 days [34].
3 CP group: rats were injected i.p with 1.5 mg/kg body weight CP alone twice a week for 21 days [8].
4 AORE + CP group: animals received both materials in doses mentioned in groups 2 and 3, respectively.
5 Untreated HCC group: HCCs were induced as described previously.
6 HCC + AORE group: after induction of HCC as described previously, rats were given AORE orally for 21 days as stated in group 2.
7 HCC + CP group: after induction of HCC as described previously, animals were injected i.p with CP for 21 days as described in group 3.
8 HCC + AORE + CP group: after induction of HCC as described previously, rats were given AORE + CP for 21 days as stated in groups 2 and 3, respectively.
9 Preventive group: Animals were pre-treated with AORE (400 mg/kg) daily by oral gavage for 3 weeks before they were induced for HCC and continued AORE treatment to the end of 16 weeks.

2.5. Blood and liver sampling

By the end of the experiment, clean capillary tubes were used for collection of blood samples from retro-orbital puncture of the eyes of each rat under mild ether anesthesia. After coagulation and centrifugation at 3000 rpm for 15 min, sera were immediately kept frozen at −20 °C for biochemical analysis. After that, rats were sacrificed by cervical decapitation after being anesthetized using diethyl ether and then dissected and livers were excised, cleaned, dried, weighed, and divided into three parts: the first was immediately immersed in 10% buffered formalin for histopathological examination. The second aliquot was immediately dipped in liquid nitrogen, then frozen at-80 °C for polymerase chain reaction (PCR) analysis. The third portion was homogenized in buffered saline (10% w/v) and liver homogenates were frozen at − 20 °C for selected biochemical analysis.

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