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COMPARATIVE STUDY OF HEPATOPROTECTIVE EFFECT PRODUCED BY *CUMINUM CYMINUM*, FRUITS OF *PHYLLANTHUS EMBLICUS* AND SILYMARIN AGAINST CISPLATIN-INDUCED HEPATOTOXICITY

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ABSTRACT: Cisplatin is a cytotoxic drug which induced the hepatotoxicity in the albino mice when intra-peritoneally administered at the dose of 10mg/kg. Administration of cisplatin raised the level of LFT's enzymes and also reduced the level of antioxidant enzymes in the liver of the mice. Administration of *Cuminum cyminum*, *Phyllanthus emblicus* extract and silymarin remarkably showed the hepatoprotective effect in the albino mice. Administration of *C. cyminum, P. emblica* and silymarin decreased the level of ALT, AST, and ALP along with increasing the level of Total protein content. It also increased the level of antioxidant enzymes in the liver of mice showing its hepatoprotective activity. We found *C. cyminum* has a better hepatoprotective effect than *P. emblica*.

INTRODUCTION: *Phyllanthus emblica*, also known as emblic, emblic myrobalan, myrobalan, Indian gooseberry, Malacca tree, or amla from Sanskrit amalika is a deciduous tree of the family Phyllanthaceae [1]. It is known for its edible fruit of the same name. Indian gooseberry has undergone preliminary research, demonstrating *in vitro* anti-viral and anti-microbial properties [2]. There is preliminary evidence *in vitro* that its extracts induce apoptosis and modify gene expression in osteoclasts involved in rheumatoid arthritis and osteoporosis [3]. It may prove to have potential activity against some cancers [4].

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One recent animal study found treatment with *E. officinalis* reduced severity of acute pancreatitis (induced by L-arginine in rats). It also promoted the spontaneous repair and regeneration process of the rat pancreas occurring after an acute attack [5]. Experimental preparations of leaves, bark or fruit have shown potential efficacy against laboratory model of disease, such as for inflammation, cancer, age-related renal disease, and diabetes [6-8]. *Emblica officinalis* tea may ameliorate diabetic neuropathy due to aldose reductase inhibition [9-11].

In rats it significantly reduced blood glucose, food intake, water intake and urine output in diabetic rats compared with the non- diabetic control group [12]. Another recent study with alloxan-induced diabetic rats given an aqueous amla fruit extract has shown significant decrease of the blood glucose, as well as triglyceridemic levels and an improvement of the liver function caused by a normalization of the liver-specific enzyme alanine transaminase

activity [13]. It has a hepatoprotective and antioxidant effect [14-15].

The active chemical constituents of *Phyllanthus emblicus* are proteins, carbohydrates, calcium, phosphorus, vitamin c nicotinic acid, carotene, D-glucose, trigallayl glucose, D-fructose, riboflavin, myoinositol, darabinosyl, lrhamnosyl, G-glycosyl, D-xylosyl, dmanosyl, D-galactosyl, mucic, Phyllambic acid, phellembin, punigluconin, embicol, emblicanin-A, emblicanin-B, fatty acid, procyanidin, 3-Ogallated prodelphindin, leucodelphinidine, ellagic acid, gallic acid, 3 ethylgallic acid, methyl gallate, 1-O-galloyl-beta-D-glucose, 3,6-di-O-galloyl-Dglucose, chebulagic acid, chebulinic acid tannins, oleanolic acid, lupeol and pectin [16].

Cumin (*Cuminum cyminum* L.*)* with local name of green *cumin* and white *cumin* are the closest relative members in this family. The *Cumin* seeds possess aromatic properties so they are widely used in a variety of cultural foods, condiments, pickles and other baking products as a conventional flavouring agent [17]. The *C. cyminum* seeds contain carbohydrates, proteins, calcium and phosphorus along with vitamin-A, Vitamin-C and different fractions of various volatile oils [18]. *C. cyminum* have both anti-oxidant and free radical scavenging activities due to the presence of plenty of essential oil [19]. Cuminoside A and B (sesquiterpenoid glucosides), two alkyl glycosides as well as five additional well-known constituents are found in *C. cyminum* [20].

The modern life style and environmental pollution have been the causes of increased cancer burdens in the world. Chemotherapy is one of the most important methods used in cancer therapy. Cisplatin (CP) is a well-known anticancer drug. It is primarily used as a drug in the treatment of solid tumors. Use of CP in the treatment of tumors is restricted due to its toxic effect on kidney and liver, which can be seen after a single dose of CP in approximately 28% to 36% of cancer patients [21]. CP is a small molecule which can easily cross the plasma membrane and then to nucleus. In the nucleus, CP causes changes in the structure of the DNA molecule. These changes result from the formation of inter- and intra-chain adducts between CP and the nitrogen bases of the DNA [22].

Oxidative stress plays the key role in the CP induced hepatotoxicity. Previous studies showed that, the earliest signs of CP induced hepatotoxicity are the fall in the hepatic reduced glutathione (GSH) levels and an increase in the hepatic malondialdehyde (MDA) levels [23]. These signs indicate the acceleration of the peroxidative processes in the hepatic cell [24]. The oxidative stress and production of reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anions, and hydrogen peroxide are normally generated in liver. A detoxification mechanism working in the liver detoxifies the ROS by endogenous antioxidants such as GSH, SOD, and catalase. The accumulation of intracellular ROS leads to an increase in both DNA damage and peroxidation of membrane lipids [25].

Aims and Objectives: Objective of this study is to evaluate the hepatoprotective effect of *C. cyminum*, *P. Emblica* and Silymarin against the toxic effects of cisplatin on albino mice liver.

MATERIALS AND METHODS:

Chemicals: Cisplatin, 50mg/100ml, was provided from the Research Centre of College of Pharmacy. Al Qassim University.

Preparation of Extracts:

Preparation of crude extract of *Cuminum cyminum*: Dried *C. cyminum* seeds were purchased from a local herb store with a fair degree of quality assurance. Completely dried material was then ground to coarse powder by using electric grinder. 1000 g of ground powder was macerated in 2 L of 70% aqueous ethanol for five days. Soaked material was thoroughly stirred thrice daily. At the end of 5th day of maceration, it was filtered through muslin cloth and then through Whatman filters paper No. 1. Residue was again macerated to obtain more filtrate. This was repeated thrice and filtrate obtained after three soakings was evaporated by using rotary evaporator at 30-40˚C. In the end, thick, viscous, semisolid paste of golden brown color was obtained. The paste obtained was weighed out to find percentage yield. The extract obtained was 108 g and percentage yield calculated was 10.8%. The extract was packed in air tight container and labeled as *Cc*. E. It was then put in the refrigerator for future use [26].

Preparation of extractof *P. emblica*: Fresh fruits of *P. emblica* were purchased from the market. *P. emblica* fruits were shade dried and then powdered mechanically, passing through sieves. The grinded powder was soaked into 70% methanol for three days. After three days the material was filtered through the muslin cloth and then Whatman No.1 filter paper. The procedure was repeated three times. The whole filtrate was pooled and evaporated in the rotary evaporator until it became thick blackish paste. The extract was collected and stored. Dilutions were made in distilled water for the purpose of experimentation. The standardized silymarin extract was purchased from Sigma Aldrich Corporation. Dimethyl sulphoxide was used as solvent for *P. emblica* and ethanol was used for silymarin. All the samples were given by oral route.

Animals and Experimental: Albino mice of either sex weighing 30-35 gm were used in the experiment. All of the animals were kept in animal house of university at 25^{o}C with 12 hours light-dark cycle. Animals were divided into 5 groups with 6 mice in each group at Al-Qassim University, Kingdom of Saudi Arabia after IRB approval. Chow and water were provided. Group I served as negative control and were administered vehicle only. Group II received single dose of cisplatin 10mg/kg intraperitoneally and Group V tagged as positive control. Group III was administered extract of *C. cyminum* 150mg/kg orally for 14 days. Group IV was administered 70 % methanolic extract of *P. emblica* 150mg/kg orally for 14 days. Group V is silymarin 150mg/kg orally for 14 days. On 15th day, cisplatin, 10 mg/kg, was injected i.p in group III, IV and V.

Animals were sacrificed and liver was isolated after blood collection by cardiac puncture. Serum was separated after centrifugation at 3000 rpm for 10 min. Organs were preserved in the phosphate buffer saline and their homogenates were prepared which were further utilized for the assessment of biochemical markers and tests.

Preparation of Homogenates: Tissue homogenate were prepared in phosphate buffer saline (pH 7.4). After crushing, the mixture was centrifuged at 4000 rpm for 15 minutes. Supernatant was separated and stored at -20^{o}C till the for biochemical analysis.

BIOCHEMICAL ANALYSIS:

Estimation of Glutathione: Glutathione level was estimated using Moron *et al*. [27] method.

Chemicals used: 50% Trichloro acetic acid (TCA), 0.02 MEthylene diamine tetraacetic acid (EDTA), 0.15M Tris HCl, 6 mM Dithio-bis 2 nitrobenzoic acid)/ Ellman's reagent and distilled water were usedfor the GSH estimation.

Principle: Liver GSH was estimated according to the method of Moron *et al*.[27] GSH reacts with Ellman's reagent (5, 5-dithio bis Nitrobenzoic acid or DTNB) to produce a chromophore Thio Nitrobenzoic acid (TNB) that give maximal absorbance at 412 nm. Absorbance value can give the estimation of enzyme value.

Procedure: 0.1 ml of tissue homogenate was taken in test tube, 2.4 ml of 0.02M EDTA was added in each test tube and was kept in ice bath for 10 minutes. Then 2.0 ml of distilled water and 0.5 ml of TCA were added in each test tube and again kept in ice bath for 15 minutes. The mixture was centrifuged at 3000-3500 rpm for 10 minutes. The supernatant (1 ml) was separated and added 2 ml of 0.15 M Tris-HCl and 0.05 ml of DTNB and then mixed thoroughly on vortex. Absorbance was measured at 412 nm within 2-3 of the last step. Absorbance was taken against reagent blank, which was prepared in the same manner but without using tissue homogenates. And standard solution was prepared by using GSH in place of tissue homogenates. The standard curve of GSH was plotted for 40-200 µg concentration of standard. The absorbance was compared with standard curve generated by known GSH. Level of GSH in tissue homogenates was measured using linear regression equation. The conc. of GSH was measured in µg/g tissue.

Estimation of Catalase: Catalase activity was assayed using Aebi, 1974 method [28].

Chemicals: Phosphate buffer (pH 7), hydrogen peroxide (2 mmol/l).

Principle: Catalase enzyme degrades hydrogen peroxide (H_2O_2) into oxygen and water. Ultraviolet absorption of H_2O_2 can be measured at 240 nm. In the presence of catalase, absorption decreases due to degradation of H_2O_2.

Procedure: 0.1 ml of tissue homogenate, 1.0 ml freshly prepared hydrogen peroxide and 1.9 ml phosphate buffer were taken in cuvette. Standard and blank were similarly prepared using CAT in place of tissue homogenate and without tissue homogenate respectively. Absorption was measured at 240 nm against blank. Using different conc. of CAT, a standard curve was generated and absorption was compared with standard curve. Specific activity of CAT was expressed in unit/g of tissue. Tissue activity of CAT was measured using linear regression equation.

Estimation of Malondialdehyde (MDA): MDA was measured following Ohkawa *et al*. [29] method.

Chemicals: Thiobarbituric acid (TBA), Sodium dodecyl sulphate (SDS), n-butanil, acetic acid and distilled water were used in this assay.

Principle: Malondialdehyde (MDA) is the end product of lipid peroxidation. They are produced as a result of breakdown of polyunsaturated fatty acids. This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells and form covalent protein adducts referred to as advanced lipoxidation end-products (ALE), in analogy to advanced glycation end-products (AGE). The production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism. Malondialdehyde reacts with deoxyadenosine and deoxyguanosine in DNA, forming DNA adducts. MDA reacts with TBA to produce pink colored end product having maximum absorption at 532nm.

Procedure: Lipid peroxidation was estimated calorimetrically by measuring Thiobarbituric acid reactive substances (TBARS). To 0.2 ml of tissue homogenate, 0.2 ml of 8.1% Sodium dodecyl sulfate (SDS), 1.5 ml of 20% acetic acid and 1.5ml thiobarbituric acid (0.8%) and 0.6 ml of distilled water were added and vortexed. The solution was incubated in water bath at 95°C for 1 hour. After that mixture was cooled and 5 ml of pyridine butanol mixture (1:15 v/v) and 1 ml distilled water were added and centrifuged for 10 minutes at 3000 rpm. The upper organic layer was taken and its optical density was measured at 532 nm against blank. The standard solution was prepared using 10-100 nmol concentration. Level of MDA in the reaction was calculated using linear regression equation. The levels of lipid peroxides were expressed as nmol of Thiobarbituric acid reactive substances (TBARS)/g protein.

Estimation of superoxide dismutase (SOD): SOD activity was determined using Kakkar *et al*. [30] method.

Chemicals: Phenazine methosulphate, Nitro blue tetrazolium (NBT), reduced (NADH), n-butanol, Trichloro acetic acid (TCA), sodium pyrophosphate buffer, glacial acetic acid.

Principle: This assay is based on the formation of formazan resulting from the reaction of NADH, Phenazine methosulphate and nitro blue tetrazolium. A blue colored formazan is developed by the reduction of NBT during this reaction. SOD inhibits the reduction of NBT. The color is extracted into butanol and measured at 560 nm.

Procedure: To 0.2 ml of tissue homogenate, 1.2 ml of sodium pyrophosphate buffer (pH 8.3, 0.025 M), 0.1 ml of Phenazine methosulphate (186 µmol/l), 0.3 ml of nitro blue tetrazolium (300 µmol/l) and 0.2 ml of NADH (750 µmol/l) were added. Reaction was started after of NADH. After incubation at 30°C for 90 sec, the reaction was stopped by the addition of 0.1 ml of glacial acetic acid. The reaction mixture was stirred vigorously with 4.0 ml of n-butanol. The mixture was allowed to stand for 10 min; centrifuged and n-butanol layer was separated. The color intensity of choromogen in butanol layer was measured at 560nm reagent blank. Standard curve was constructed for SOD using 10-100 µl concentration. Tissue activity if SOD was measured using linear regression equation. Concentration of SOD was expressed in unit/gram of liver tissue.

Estimation of LFT's: Liver function tests including AST, ALT, ALP and TP were estimated by using commercially available Bio Merux and Randox kits.

Statistical Analysis: Values were expressed as mean ± SD. When compared with toxicant control group. One way (ANOVA) analysis of variance was used followed by Dunnetts test to determine the difference between groups in terms of all studied parameters using SPSS computer program.

Differences were considered significant when value of *P* is less than 0.05.

RESULTS: To evaluate the liver function of mice before and after the treatment strategies alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and total protein (TP) tests were performed. As per **Table 1**, the level of liver enzymes was elevated and total protein (TP) was decreased after the administration of Cisplatin (10 mg /kg) in group II. The level of these enzymes was decreased and protein content was increased in group III, IV and V treated with *C. cyminum* (150 mg/kg) and *P. emblica* (150 mg/kg) *and* silymarin (150 mg/kg).

As per **Table 2**, level of antioxidant enzymes (GSH, CAT and SOD) was decreased after the administration of Cisplatin (10 mg/kg), while MDA level was increased due to the hepatotoxic effects of Cisplatin on liver. Level of antioxidant enzymes was significantly increased and MDA level was decreased in group III, IV and IV. Better antioxidant effect was observed in animal groups treated with *C. cyminum* (150 mg/kg) than *P. emblica* (150 mg/kg).

TABLE 1: EFFECT OF CISPLATIN, *CUMIN P. EMBLICA* AND SILYMARIN ON LIVER FUNCTION TESTS (N=6)

	Group I	Group II	Group III	Group IV	Group V
ALT, IU/L	27.5±1.3	118.9±7.1	55±1.0	63±5	46±1.1
			P=0.006	*P*=0.012	*P*=0.005
AST, IU/L	29.8 ± 2.9	104 ± 2.9	49.4 ± 0.9	54.4± 3.01	38.5±0.5
			P=0.002	*P*=0.004	*P*=0.001
ALP, IU/L	83 ± 7.8	136 ± 1.2	108 ± 7.0	113 ± 5.9	106.5±5
			P=0.031	*P*=0.033	*P*=0.015
T. protein, mg/dl	6.3±0.5	2.8 ± 0.7	5.5 ± 0.5	6.2± 0.5	5.1±0.02
			P=0.047	*P*=0.031	*P*=0.043

TABLE 2: EFFECT OF CISPLATIN, *CUMIN P. EMBLICA* AND SILYMARIN ON OXIDATIVE STRESS MARKER IN LIVER

	Group I	Group II	Group III	Group IV	Group V
GSH, mg/dl	6.9 ± 0.03	3 ± 0.06	5.5 ± 0.04	4.3 ± 0.1	5.8±0.7
			P=0.001	*P*=0.004	*P*=0.03
CAT, mg/dl	29.3 ±0.5	15.8 ± 0.5	20.4 ± 0.35	18.0 ± 0.2	21.3±0.6
			P=0.009	*P*=0.029	*P*=0.01
SOD, mg/dl	26.6± 1.4	19.3 ± 1.1	22.2 ± 0.6	20.6 ± 0.5	21±1.3
			P=0.082	*P*=0.26	*P*=0.2
MDA, mg/dl	34.3 ± 2.7	94.0 ± 2.4	53.1 ± 1.7	76.2 ± 3.9	44.1±1.3
			P=0.003	*P*=0.032	*P*=0.001

DISCUSSION: Cisplatin is a cytotoxic drug used against various types of cancers. This drug may also cause much toxicity inside the different organs of body including heart, kidneys and liver [30, 31]. In the present study application of cisplatin at 10 mg/kg induced the hepatotoxicity in the mice which was supported by biochemical findings i.e. increase in the ALT, AST, ALP and total protein contents (TP) and decrease in the antioxidant enzymes (SOD, Catalase, GSH and MDA). Various studies have also supported that treatment of rats with cisplatin induced changes in the ALT and AST by damaging hepatocytes. Cisplatin induced oxidative stress also contribute to damage the liver cells. Some studies have shown that repeated administration of cisplatin at high dose reduces the level of antioxidant enzymes. Cisplatin administration also elevated the level of MDA, which caused the hepatic cell damage. In the present study treatment of mice with *C. cyminum* extract and *P. emblica* prevented the hepatic cell damage by increasing the liver function test parameters and by also remarkably decreasing the MDA level and increasing the level of antioxidant enzymes i.e. catalase, superoxide dismutase and glutathione. The healing of hepatic cells is due to the tissue regeneration property present in both *C. cyminum* and *P. emblica*

CONCLUSION: The given data suggests that cisplatin which is cytotoxic drug causes the hepatotoxicity and as well weakens and decreases the level of antioxidant enzymes in the liver of mice and hence increases the oxidative stress. From the present study it was also concluded that administration of *P. emblica* extract, *C. cyminum*

and silymarin individually after the administration of cisplatin remarkably reduced the level of ROS by increasing the level of oxidative enzymes inside the liver of the mice. *P. emblica* and *C. cyminum* also improved the liver function tests showing hepatoprotective effect. Hence it is concluded that *C. cyminum* has better hepatoprotective and antioxidant effect than *P. emblica.*

CONFLICT OF INTEREST: No conflict of interest.

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