Grape Seed Oil plus DMBA Has a Hepatorenal Protective Effect against Damage Induced By DMBA in Rats

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ABSTRACT

7,12-dimethylbenz(a) anthracene (DMBA)has an oxidative damaging effects and grape seed oil (GSO), among its protective mechanisms is the antioxidant properties. ***Objective:*** *to investigate the hepatorenal protective effects of dietary GSO against liver and renal cytotoxicity induced by DMBA in the rats.* ***Materials and methods:*** *The experimental animals were divided into four groups, the first group was untreated and used as control, the second was treated for 2 weeks with DMBA alone, the third was treated with DMBA plus GSO for 2 weeks, and the fourth group was treated with GSO after DMBA for 2 weeks. Serum liver enzymes, lactate dehydrogenase (LDH), glutamic pyruvic acid transaminase (GPT), glutamic oxaloacetic acid transaminase (GOT), and total plasma proteins (TP_S), albumin and globulins were chosen to assess liver function. Urea and creatinine are measured as some of renal function tests.* ***Results:*** *In comparison with control group, DMBA alone significantly increased the serum level of liver GOT,GPT and LDH enzymes and urea and creatinine levels, while total proteins, albumin and globulin was decreased. GSO plus DMBA had decreased significantly, GOT, GPT and LDH and urea while, creatinine was insignificantly changed, also, it had increased total proteins, albumin and globulin when compared with rats subjected to DMBA alone. Administration of GSO weather plus or after DMBA had increased albumin, but, it is significantly lower than in control rats.* ***Conclusion****: Treatment with GSO plus DMBA significantly decreases the changes in some hepatic and renal functions induced by DMBA in rats.*
Key words*:7,12-dimethylbenz(a)anthracene, grape seed oil, liver enzymes, renal function.*

INTRODUCTION

Grape seed oil (GSO) is obtained from grape seeds after the wine pressing in Italy and France. The GSO contains 75% linoleic acid, 15% oleic acid, 6% palmitic acid, 3% stearic acid, and 1% linolenic acid [(1)]. Studies revealed the beneficial high density lipoprotein (HDL) effect of GSO and researches showed that in subjects who were instructed to use up to 45 ml of GSO in their daily diet as a substitute for their usual oil and within 2 weeks, there was 13–14% increase in HDL level[(2)]. The GSO has a very high level of antioxidant vitamin E (60–120 mg/100 g), which makes the oil very stable. The GSO has antioxidant properties[(2,3)]. The

antioxidant property is claimed to be the mechanism of hepatoprotective activity[3]. The GSO exhibits a variety of interesting properties such as reducing platelet aggregation, prevents hypertension caused by sodium excess, normalize lesions occurring from obesity and diabetes[4]. Polycyclic aromatic hydrocarbons (PAH) are a class of organic pollutants that are released into the environment in large quantities, mainly due to human activities. PAH are components of crude and refined petroleum, and coal. Many PAH are quite persistent and some are potent carcinogenic agents. Most PAH in the environment are found during incomplete combustion of organic matter at high temperatures. In addition, many domestic and industrial activities involve pyrosynthesis of PAH. The resulting PAH may be released to the environment in airborne particulates, or in solid or liquid by-products of the pyrolytic process.7,12-dimethylbenz (a) anthracene (DMBA) is one of polycyclic aromatic hydrocarbons chemical group. DMBA is well known as cytotoxic, carcinogenic, mutagenic and immunosuppressive agent[5]. **Al-Attar**[6] reported that several hematological and hematochemical parameters were changed in the toad *Bufore gularis*treated with DMBA and found that DMBA induced hepatocellular carcinoma.

Liver is the central organ of metabolism and act as an organ of storage. Many potentially toxic substances are metabolized by cells, especially the hepatic parenchyma cells. Metabolic action by the hepatic parenchyma cells has been regarded as an important defense system against toxicants and the transformations involved have been referred to as detoxification. The great susceptibility of liver to damage by chemical agent is presumably a consequence of its primary role in metabolism of foreign substances. The role of liver in metabolic conversion is due to its susceptibility to chemical injury [7]. Epidemiological studies show that dietary factors are the most important environmental risk determinants for human cancers [8]. **Goldman and Shields** [9] reported that several lines of evidence indicate that diet and dietary behaviors can contribute to human cancer risk. Many natural food components such as fat, protein, fiber and some minerals and vitamins may influence the incidence of cancer [10-13]. Numerous experimental studies have provided evidence that consuming fat diets have an important role in decreasing or increasing tissue carcinogenesis induced by carcinogenic agents [14]. Many investigators have been focused their attention on the effect of dietary fat on chronic exposure to carcinogens, tissue tumourigenesis and tumor induction. There have been few reports on the effect of grape seed oil on tumor DMBA inductionor cytotoxic and carcinogenic agent's action[14]. At present, however, the influence of short-term exposure of DMBA has not yet been fully evaluated. Also, the effect of grape seed oil on DMBA poisoning has not been fully established. In the present study, we have investigated the protective effect of grape seed oil against DMBA-induced changes in

liver functions by determining the levels of total plasma proteins, albumin, globulin and serum levelsof lactate dehydrogenase (LDH), glutamic oxaloacetic acid transaminase (GOT) and glutamic pyruvic acid transaminase (GPT) and changes in renal functions by determining the levels of serum urea and creatinine,.

MATERIALS & METHODS

Experimental animals Male Wistar albino rats (150–250 g) were used. The animals were acclimatized to laboratory conditions for 5 days prior to the experiments and had access to food and water *ad libitum*. All animal procedures are in accordance with the recommendations for the proper care and use of Research Ethical Committee at Kasr Al-Ani Cairo.

Selection of dose of GSO: The human dose of GSO was converted into the animal dose using the standard dose-converting table [16]. Further, the dose for the hepatoprotective studies was adjusted based on the observation during the toxicity studies. The GSO at a dose of 3.7 g/kg (4 ml/kg) was administered orally to study the hepatoprotective activity [17].

Experimental animals: Rats were divided into four groups of 8 each and treated for 2 week as follows:

1. **Group 1**, were untreated and used as control which received 2%gum acacia orally for 2 weeks.
2. **Group 2**, were administered DMBA (Sigma Chemical Company, St. Louis, MO,USA) at a dose of0.5% DMBA solution (1 ml/rat) [18], twice weekly for2 weeks.
3. **Group3**, received GSO (3.7 g/kg, orally) daily for 2 weeks together with DMBA at the same level given in group 2.
4. **Group4**, were fed with GSO at a dose (3.7 g/kg, orally), daily for 2 weeks after 2 week of treatment with DMBA at the same level given in group 2.

An emulsion of GSO was prepared using 2% gum acacia by wet gum method. After 2 weeks, of treatment, the rats were kept overnight fasting. At the end of the treatment, blood samples were collected by direct cardiac puncture under ether anesthesia and the serum was used for the assay of marker enzymes viz., lactate dehydrogenase (LDH) estimated by kits obtained from Stanbio Laboratories (USA), glutamic pyruvic acid transaminase (GPT), glutamic oxaloacetic acid transaminase (GOT)using reagent kits purchased from Spinreact Company (Spain).Serum total protein and serum albumin levels were estimated using reagent kits purchased from Diamond Diagnostics Chemical Company, Egypt. Serum globulin level was calculated by subtracting albumin level form total protein concentration. to assess some of the liver functions and serum urea and creatinine concentrations were measured using reagent kits produced by Diamond Diagnostics (Egypt). to assess some of renal functions [19,20].

The results of serum liver enzymes were expressed as units/liter (U/l), total plasma proteins gm/dl, albumin gm/dl and globulins gm/dl, urea mg/dl and creatinine mg/dl.

Statistical analysis:

Analysis of data was done by IBM computer using Statistical Program for Social Science (SPSS) version 13.The data are parametric and normally distributed checked by Kolmogorov – Smirnov test..The data were analyzed using the one way analysis of variance (ANOVA) [21] followed by Post - hoc LSD analysis to compare various groups with each other. Results were expressed as mean ± standard deviation (SD). Values of $P>0.05$ were considered statistically non-significantly different, while values of $P<0.05$ were significantly different. F-probability expresses the general effect between groups.

RESULTS

In comparison with control group, the administration of DMBA alone significantly increased the serum level of liver GOT, GPT and LDH enzymes ($P<0.05$; LSD). Grape seed oil plus DMBA had decreased GOT, GPT and LDH levels significantly in comparison with the effect of DMBA alone ($P<0.05$; LSD) however, administration of grape seed oil after DMBA had significantly decreased the serum level of liver GPT and LDH only ($P<0.05$; LSD) . (Table 1).ANOVA results revealed that the effect between groups on GPT and LDH enzymes was significant ($P<0.05$; F-prob.) while the effect on GOT was in significant ($P>0.05$; F-prob.) (Table 2).. Regarding the level of plasma proteins, the administration of DMBA alone significantly decreased the serum level of total plasma proteins, albumin and globulin compared to the control group ($P<0.05$; LSD). Grape seed oil plus DMBA had increased all these parameters significantly compared to the effect of DMBA alone ($P<0.05$; LSD) while, administration of grape seed oil after DMBA had significantly increased the level of total plasma proteins and globulin only (table 3) ($P<0.05$; LSD). ANOVA results revealed that the effect between groups on level of total plasma proteins, albumin and globulin was significant ($P<0.05$; F-prob.) (Table 4).

In table 5, the administration of DMBA alone significantly increased the serum level of urea and creatinine compared to control group ($P<0.05$; LSD), Grape seed oil plus DMBA had significantly decreased the level of urea only compared to the effect of DMBA alone while ($P<0.05$; LSD), administration of grape seed oil after DMBA had significantly decreased the level of both urea and creatinine . ANOVA results revealed that the effect between groups on level of urea was significant and while the effect on creatinine was in significant ($P>0.05$; F-prob.) (Table 6). There was no significant difference in any of all measured parameters between the group received grape seed oil plus DMBA and those received grape seed oil after DMBA

DISCUSSION

In the present study, Administration of DMBA resulted in elevation in the serum level of liver GOT, GPT and LDH enzymes. GSO plus DMBA resulted in decline in the level of these enzymes, that is consistent with the results of **Uma**

Maheswari M, et al. [17], who found ,in their study, that there was a significant ($P<0.05$)increase in the serum hepatic enzyme levels after carbon tetrachloride (CCL_4) treatment, which was prevented with GSO and that GSO when administered alone did not alter the enzyme levels. **Ozdemir,** et al. [22] reported that, DMBA administration also resulted in elevation of GOT,GPT and LDH activities. **Atef**. **Al-Attar** [23], found that, the administration of DMBA alone for 2 weeks significantly increased the activity of liver LDH, while the activities of GPT, GOT and alkaline phosphatase (ALP) were decreased in the frog, *Ranaridibunda*, Similar results were noted in frogs treated with DMBA plus grape seed oil. Also, it was found that the changes were more pronounced in frogs treated with DMBA plus grape seed oil than those subjected to DMBA[23]. The activities of liver enzymes (LDH, GPT, GOT and ALP) in frogs treated with grape seed oil or olive oil were not significantly different from those of controls. Also, in the present study, Administration of DMBA resulted in significant decline in the level of total proteins, albumin and globulin, which was prevented by the use of GSO plus DMBA. These results were in agreement with the results of **Uma Maheswari** et al.[17], where there was a significant decrease in TP level after CCL_4 treatment, which was prevented with GSO. **Ozdemir**, et al, [22] also, in their study, found that administration of DMBA caused decrease in levels of total plasma proteins, albumin and globulin. The decrease in their levels in plasma was reported in nephritic syndrome, inflammation, and chronic diseases [24,25] and ascribed to change in proteins synthesis and/or their metabolism. Thus, DMBA might have adversely affected the proteins synthesis and their metabolism. DMBA administration also resulted in elevation of GOT, GPT and LDH activities. Pathological changes in liver, kidney, heart and skeletal muscle and erythrocytes were found to increase these activities in plasma[26-28]. DMBA might have induced pathological alterations in these organs, particularly liver [29], resulting in elevation of these activities. DMBA is known to generate free radicals[22]. Liver damage by DMBA was evidenced by an elevation in the serum maker enzymes, namely GOT, GPT and LDH, and by the decrease in TP, albumin, and globulin. Treatment with GSO significantly prevented these changes. Further, GSO has increased the level of TPs, which indicates its hepatoprotective activity. Stimulation of protein synthesis accelerates the regeneration process and the production of liver cells [17]. The mechanism of hepatoprotection of GSO may be due to its antioxidant effect. Since GSO has significantly increased the glutathione, superoxide dismutase (SOD), catalase (CAT) contents of the liver, it may also be useful in hepatotoxicity induced by other agents[17]. In our study, administration of DMBA resulted in elevation of urea and creatinine levels, GSO caused a significant decrease in the level of urea not creatinine, which was in agreement with the results of **Ozdemir,** et al.[22], they found a significant increase in urea and

creatinine levels in rats subjected to DMBA. The elevation in their levels in DMBA-treated rats is considered as one of the markers of renal dysfunction. The GSO offers vast possibilities in the treatment of various liver disorders. This may be due to the high level of antioxidant vitamin E, which was claimed to be the mechanism of hepatoprotection. Further studies on any other models and extensive clinical trials are needed to confirm these results.

Conclusions: Administration of GSO either together with or after DMBA can protect the liver and kidneys from the damage induced by exposure to DMBA in rats and there were no significant differences between the effect of GSO either together with or after DMBA administration.

Table 1: Effects of DMBA, grape seed oil plus DMBA, grape seed oil after DMBA on the serum levels of liver enzymes

Parameter	Control	DMBA	GSO+ DMBA	GSO after	P_1	P_2	P_3	P_4	P_5	P_6
SGOT (U/l)	198.88± 34.35	243.75 ±39.77	201.13± 36.67	221.63± 46.21	.031	.910	.259	.040	.272	.308
SGPT (U/l)	55.88± 15.35	76.88 ±21.59	55.38 ±14.80	55.25± 11.03	.015	.951	.939	.013	.012	.988
LDH (U/l)	1238.88 ±35.90	1819± 332.76	1417.5 ±109.50	1505.63 ±430.34	.000	.209	.065	.007	.032	.531

Table 2 : ANOVA test comparing the serum liver enzymes in the 4 groups

Parameter	Group	N	Mean	Std. Deviation	ANOVA	P value
SGOT	Control	8	198.88	34.349	2.24	0.15
	DMBA alone	8	243.75	39.770		
	GSO+DMBA	8	201.13	36.674		
	GSO after DMBA	8	221.63	46.214		
	Total	32	216.34	41.822		
SGPT	Control	8	55.88	15.385	3.50	0.02
	DMBA alone	8	76.88	21.590		
	GSO+DMBA	8	55.38	14.803		
	GSO after DMBA	8	55.25	11.029		
	Total	32	60.84	18.004		
LDH	Control	8	1238.88	35.902	6.09	0.003
	DMBA alone	8	1819.00	332.756		
	GSO+DMBA	8	1417.50	109.477		
	GSO after DMBA	8	1505.63	430.337		
	Total	32	1495.25	339.729		

Table 3: Effects of DMBA, grape seed oil plus DMBA, grape seed oil after DMBA on the levels of plasma proteins

Parameter	Control	DMBA	GSO+ DMBA	GSO after DMBA	P_1	P_2	P_3	P_4	P_5	P_6
TPs g./dl	7.53± 0.09	6.54± 0.50	7.43± 0.37	7.15± 0.53	.000	.630	.078	.000	.006	.191
Albumin g./dl	4.30± 0.42	3.53± 0.30	4.01± 0.34	3.81± 0.25	.000	.097	.007	.007	.097	.242
Globulin g./dl	3.34± 0.17	2.83± 0.24	3.36± 0.33	3.2± 0.26	.000	.845	.288	.000	.007	.211

Table 4 : ANOVA test comparing the plasma proteins in the 4 groups

Parameter	Group	N	Mean	Std. Deviation	ANOVA	P value
TP	Control	8	7.525	.0886	9.37	0.000
	DMBA alone	8	6.538	.4955		
	GSO+DMBA	8	7.425	.3694		
	GSO after DMBA	8	7.150	.5318		
	Total	32	7.159	.5517		
ALBUMIN	Control	8	4.300	.4243	7.63	0.001
	DMBA alone	8	3.525	.3012		
	GSO+DMBA	8	4.013	.3399		
	GSO after DMBA	8	3.813	.2475		
	Total	32	3.913	.4286		
GLOBULIN	Control	8	3.338	.1685	7.37	0.001
	DMBA alone	8	2.834	.2354		
	GSO+DMBA	8	3.363	.3292		
	GSO after DMBA	8	3.200	.2563		
	Total	32	3.183	.3229		

Table 5: Effects of DMBA, grape seed oil plus DMBA, grape seed oil after DMBA on the serum levels of urea and creatinine

Parameter	Control	DMBA	GSO+ DMBA	GSO after DMBA	P_1	P_2	P_3	P_4	P_5	P
Urea mg/dl	20.38± 1.60	22.19± 1.13	20.58± 1.46	20.25± 0.89	.009	.760	.849	.019	.006	.621
Creatinine mg/dl	0.35± 0.04	0.39± 0.20	0.37± 0.26	0.36± 0.04	.013	.367	.621	.091	.039	.680

Table 6 : ANOVA test comparing the urea and creatinine in the 4 groups

Parameter	Group	N	Mean	Std. Deviation	ANOVA	P value
Urea	Control	8	20.38	1.598	3.87	0.02
	DMBA alone	8	22.19	1.132		
	GSO+DMBA	8	20.58	1.460		
	GSO after DMBA	8	20.25	.886		
	Total	32	20.85	1.469		
Creatinine	Control	8	.3538	.03583	2.68	0.06
	DMBA alone	8	.3938	.01847		
	GSO+DMBA	8	.3675	.02550		
	GSO after DMBA	8	.3613	.03643		
	Total	32	.3691	.03236		

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زيت بذور العنب بالإضافة الى مادة ٧،١٢ – ثنائي ميثيل (أ) أنثراسين له تأثير وقائى ضد التلف الناتج عن مادة ٧،١٢ – ثنائي ميثيل (أ) أنثراسين فى الكلى والكبد في الفئران

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المقدمة: ان من بين الآليات المختلفة المعنية في التأثير السام للكبد من مادة ٧،١٢ - ثنائي ميثيل (أ) أنثراسين واحد منها هو الضرر التأكسدي وتعتبر مضادات الأكسدة واحدة من آليات تأثير العقاقير الواقية للكبد. وان زيت بذور العنب له خصائص مضادة للأكسدة. ومن هنا، كان الهدف من هذه الدراسة تقييم تأثير زيت بذور العنب على السمية الكبدية و الكلوية الناتجة عن مادة ٧،١٢ - ثنائي ميثيل (أ) أنثراسين.
الهدف من البحث : كان الهدف من الدراسة الحالية هوتحديد ما إذا كانت التغذية بزيت بذور العنب تثبط السمية الناجمة فى الكبد والكلى عن ٧،١٢ – ثنائيميثيل (أ) أنثراسين (المادة المسرطنة) في الفئران.
طرق البحث: قسمت حيوانات التجارب إلى أربع مجموعات، المجموعة الأولى وكانت هى المجموعة غيرالمعالجة وتم استخدامها كمجموعة ضابطة .المجموعة الثانية عولجت بمادة ٧،١٢ - ثنائي ميثيل (أ) أنثراسين لمدة اسبوعين . المجموعة الثالثة عولجت بمادة ٧،١٢ - ثنائي ميثيل (أ) أنثراسين بالاضافة الى زيت بذور العنب لمدة اسبوعين ، واما المجموعة الرابعة فقد عولجت بزيت بذور العنب بعد مادة ٧،١٢ - ثنائي ميثيل (أ) أنثراسين لمدة اسبوعين. وقد تم اختيار انزيمات الكبد في الدم ، نازعة اللاكتات ، حمض الجلوتاميك البيروفيك ناقلة الامين ، حمض الجلوتاميك الاوكسالو اسيتيك ناقلة الامين ، وبروتينات البلازما الكليه ، والزلال والجلوبيولين لتقييم وظيفة الكبد. وتم قياس البولينا والكرياتينين كبعض من اختبارات وظائف الكلى.
النتائج: بالمقارنة مع المجموعة الضابطة ، اظهرت المادة المسرطنة وحدها زيادة كبيرة في مستوى نازعة الهيدروجين من اللاكتات ، حمض الغلوتاميك البيروفيك ناقلة الأمين ، حمض الغلوتاميك أكسالوأسيتك ناقلة الأمين و مستويات البولينا ، والكرياتينين ، في حين أن وبروتينات البلازما الكليه والألبومين والجلوبيولين قد انخفضت.بينما تسبب اعطاء زيت بذور العنب بالإضافة إلى المادة المسرطنة فى انخفاض مستونازعة الهيدروجين من اللاكتات ، حمض الغلوتاميك البيروفيك ناقلة الأمين ، حمض الغلوتاميك أكسالوأسيتك ناقلة الأمين بشكل ملحوظ، وقد انخفض ايضا مستوى البولينا ، وعلى الرغم من وجود تغير طفيف فى مستوى البولينا والكرياتينين ، أيضا، فقد ارتفعت بروتينات البلازما الكليه ، والزلال والجلوبيولين بالمقارنة مع الفئران التي تعرضت إلى المادة المسرطنة وحدها. وعلى الرغم من ان اعطاء بذور العنب مع أو بعد المادة المسرطنة زاد من مستوى الزلال، فهو أدنى بكثير منه فى الفئران في المجموعة الضابطة.

الخلاصة : **العلاج** بزيت بذور العنب بالإضافة إلى المادة المسرطنة ادى الى تحسن ملحوظ في بعض التغييرات فى وظائف الكلى والكبد الناجمة عن المادة المسرطنة في الفئران.