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Protective Effect of Ethanolic Kumquat Fruit (Fortunella margarita) Extract Against Carbendazim Induced Hepatotoxicity in Rats

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Abstract

Carbendazim is extensively used to control various fungal pathogens. Carbendazim is a contaminant found in food, soil, and water, causing functional disorders and tissue changes. This study aimed to evaluate the impact of ethanolic kumquat fruit against carbendazim induced liver toxicity in rats. Thirty adult male albino rats were randomly divided into two main groups and fed on the standard diet. Group I: negative control (6 rats) and group II: carbendazim groups (24 rats). Carbendazim groups were treated with orally a daily dose of 250 mg/kg of body weight (B.W) carbendazim for 30 days after being divided into equal four subgroups (6 rats each), the first: positive control group, the second, the third, and the fourth groups gave a daily oral dose of ethanol extract of kumquat (100, 200 and 300 mg/kg) B.W, respectively. The rats were sacrificed at the end of the experiment (30 days). The serum was analyzed for liver enzymes, serum glucose, kidney functions, antioxidant tests and lipids profile. The results elucidated that the oral administration of carbendazim (250 mg/kg of B.W) significantly increased liver enzymes, kidney functions, and glucose and induced the antioxidant system suppression in the positive control group compared with the other groups. The oral administration with ethanol extract of kumquat reduced the level of liver enzymes, kidney functions, glucose, and the antioxidant system compared with the positive control group. The study concluded that the ethanol extract of the kumquat is more effective in reducing the toxic effect of carbendazim in experimental animals.

Keywords*: Carbendazim, Kumquat, Liver and kidney functions.*

Introduction

Carbendazim (CBZ), belongs to the benzimidazole class substituting for the primary amino group. CBZ is a widely used industrial fungicide with broad antifungal

characteristics that is used in cereal and fruit crops to treat fungal diseases (1). All these characteristics led to an overuse of carbendazim in fields, resulting in adverse effects on humans and wildlife. By ingesting infected food or inhaling fumes, carbendazim is absorbed by organisms. Deposition of the pesticide on a variety of mammalian tissues, including adipose tissue, skin, liver, and gonads, causes life-threatening illnesses in a variety of living species (2,3). Farag et al., (4) reported that after exposure mice to CBZ increased embryonic death and different malformations of the skeleton and internal organs were detected. Carbendazim is a known aneugen (5) and can be classified as a possible human carcinogen (6). In rats, carbendazim has been shown to have negative effects on biochemical, histological, and hematological markers in the liver, kidney, and endocrine glands, as well as their hormonal levels (7). Kumquat is a small, elliptical shaped fruit, closely related to citrus. The fruit can be consumed combined with the skin in the form of raw fruit or as juice and is distinguished by an acidic taste of flesh and a soft edible peel. It's also good for pickles and marmalades (8). They are used in traditional folk medicine to treat respiratory tract irritation (9). The health benefits of citrus are well-documented. Their bioactivity is attributed to the presence of flavonoid compounds (10). The antioxidant potential of kumquat fruit is due to its high phenolic and flavonoid contents with polyhydroxy groups (11). Kumquat fruit extract tends to prevent liver damage by maintaining the integrity of the plasma membrane, thereby suppressing the leakage of enzymes through membranes, exhibiting hepatoprotective activity (12). Therefore, this study aimed to evaluate the preventive effect of ethanol kumquat extract against carbendazim induced liver toxicity in rats.

Materials and Methods

Materials

Kumquat (Fortunella margarita) were purchased from a local market (Shebin El-Kom, El-Menofia, Egypt). All analysis kits were purchased from Bio diagnostic Co., Giza, Egypt. Carbendazim (purity > 98.0%) was provided by Weihai Pesticide Factory (Shandong, China). Kits were purchased from Bio diagnostic or Alkan Medical Company, St. El - Doky, Cairo, Egypt). Other chemicals used throughout the experiments were purchased from El-Nasr Pharmaceutical Chemicals, El-Ameriea, Cairo, Egypt. Thirty adult male rats Sprague Dawley weighting (200±5 g) were procured from the Vaccine and Immunity Organization, Ministry of Health, Helwan Farms, Cairo, Egypt.

Methods

Preparation of kumquat extract

Kumquat fruits were washed by tap water and cut to small slices, then dried using solar furnaces. The dried kumquat fruits (50 g) were extracted by shaking at 150 rpm with 500 ml of solvent (70% ethanol) for 6 h. Extracts were filtered using Whatman No. 1

filter paper and then concentrated under vacuum on a rotary evaporator at 40°C to constant dryness and stored at − 20 °C for further use as described by (13).

Chemical analysis

Total flavonoids, total phenols, and the DPPH radical (2,2–Diphenyl–1–Picrylhydrazyl)) scavenging activity of ethanol extract of kumquat were determined according to (14&15&11) respectively.

Experimental design

Thirty adult male rats Sprague Dawley weighting (200±5 g) were used in this study. They were housed at the animal house, Faculty of Home Economics, Menoufia University, Egypt. The animals were housed individually in well aerated cages under hygienic laboratory conditions and fed on the standard diet according to AIN-93 guidelines (16) for 7 days as an adaptation period. Rats were randomly divided into two main groups and fed on the standard diet. Group I: negative control (6 rats). Group II: carbendazim intoxication group (24 rats). Carbendazim groups were treated with orally a daily dose (250 mg/kg of B.W) of carbendazim for 30 days according to (17). The positive control group, the second, the third and the fourth groups were received a daily oral dose of ethanol extract of kumquat (100 ,200, and 300 mg/kg of B.W) respectively. At the end of the experimental period (30 days), rats were anesthetized with diethyl ether after fasting for 12h and the blood samples were collected and centrifuged to obtain serum and kept frozen until analysis.

Biochemical analysis:

Alanine transferase (ALT), aspartate amino transferase (AST), and total protien (TP) enzymes were measured according to the methods described by (18,19,20), respectively. Albumin and total bilirubin were estimated using the method of (20,21), respectively. Serum glucose was estimated according to (23). Urea and creatinine levels were determined in serum according to the method described by (24,25). Glutathione peroxidase (GSH), superoxide dismutase (SOD), lactate dehydrogenase (LDH), and total antioxidant capacity (TAC) were determined according to (26,27,28,29) respectively. Determination of serum total cholesterol, triglyceride, low density lipoprotein, and high density lipoprotein according to (30,31,32,33) respectively.

Histopathology examinations:

The liver organ was taken from each experimental group, fixed in neutral buffered formalin, dehydrated in ascending concentration of ethanol (70%), cleared in xylene, and embedded in paraffin. Histopathology examinations were described (34).

Statistical analysis:

Results were expressed as the mean ± SD. The experimental data were subjected to an analysis of variance (ANOVA) for a differences among means at the level of 5%.

Results and Discussion

As shown in table (1) total phenolic, total flavonoid contents, and DPPH radical scavenging potency of ethanol extract of kumquat (EEK). The results proved that the ethanolic extract of kumquat was higher in its content of total phenolic (331.25µg/ml) followed by total flavonoid (27.00µg/ml). These results agree with recent studies (36,37) who showed that kumquat fruit is a rich source of bioactive compounds with more effective antioxidants those citrus. Ethanol extract of kumquat had a capacity on DPPH radical by 14.51%. The high oxidation resistance of kumquat fruit extract may be attributed to the free radical scavenging activity (12). Kumquat could be considered as potential sources of flavonoids and phenolic compounds (38).

Table1(1): Total phenolic, total flavonoid contents, and DPPH radical scavenging potency of ethanol extract of kumquat.

Parameter	Ethanol extract of kumquat
Total flavonoid(µg/ml)	27.00±1.60
Total phenolic compounds (µg/ml)	331.25±24.3
DPPH(%)	14.51±1.50

Each value in the table is the mean ± standard deviation of three replicates.

Table (2) showed that exposure of rats to carbendazim resulted in a significant ($p < 0.05$) increase of ALT, AST, and TB in the positive control group compared with negative control and treated groups while, TP and AL had an opposite trend. The same results were obtained by other study (39) who postulated that the damaging effect of CBZ on the liver is manifested by increases in serum ALT, AST, ALP, and total bilirubin levels. Administration rats with different concentrations of ethanol extract of kumquat caused a decrease in serum levels of ALT, AST, and TB an increase in TP. These results are in agreement with other studies (12,40) who illustrated that the levels of liver enzymes (ALT, AST, and GGT) in rats treated with ethanol extract of kumquat was significantly reduced. No significant differences were observed ($p > 0.05$) in AST between rats were given EEK (300 mg/kg of B.W) and the negative group. Also, treated rats with 200 and 300 mg/kg (B.W) of EEK did not differ ($p > 0.05$) in their effect on TP. The highest reduction in AST (72.25%), ALT (59.68%), and TB (77.63%) were observed in rats administrated with 300 mg/kg (B.W) of EEK. Our results are compatible with other studies (37,41) who found that kumquat fruit extract has a protective effect on hepatocyte membranes because it contains antioxidants, particularly carotenoids, and anti-inflammatory compounds. Moreover, Kumquat enhances liver enzymes (AST, ALT, ALP) because it includes vitamin C and phenolic compounds (36).

Table 2: Effect of Ethanol extract of kumquat on the liver functions in control and carbendazim intoxicated groups.

Variable	Negative control	Carbendazim intoxicated groups			
		Positive control	Ethanol extract of kumquat (mg/kg of B.W)		
			100	200	300
AST(u/L)	90.41d±2.21	333.34a±14.51	251.97b±6.84	213.08c±4.95	92.48d±7.11
ALT(U/L)	41.31e±3.51	306.43a±6.19	249.16b±4.57	186.53c±4.05	123.54d±5.42
TP(U/L)	7.02a±0.14	4.33d±0.18	5.55c±0.24	6.20b±0.17	6.40b±0.39
TB(U/L)	0.13e±0.02	1.52a±0.13	0.99b±0.08	0.73c±0.58	0.34d±0.12
AL(U/L)	4.10a±0.17	2.34d±0.29	3.21c±0.10	3.21c±0.10	3.75b±0.35

Values are expressed as means ± SD; means in the same raw with the different letters are significantly different (P < 0.05). EEK: kumquat ethanol extract, ALT: alanine amino transferases, AST: aspartate aminotransferases, TP: total protein, TB: total bilirubin, AL: albumin

Table (3) shows the effect of ethanol extract of kumquat on lipids profile in control and carbendazim groups. There were significant ($p < 0.05$) increases in serum TC, TG, LDL, and VLDL in the positive control group compared with the negative control and the treated groups. while HDL had an opposite trend. These results were similar with one study (42) who showed that the treated mice with CBZ showed an increase in blood cholesterol and triglyceride levels. Administration rats with different concentrations of ethanol extract of kumquat resulted ($p < 0.05$) in a decrease in TC, TG, LDL, VLDL and an increase in HDL compared with the positive control. These changes were corrected to normalcy upon oral administration of ethanol extract of kumquat to carbendazim-intoxicated rats. These results are compatible with another study (38) who said that the findings imply the complete kumquat, as well as its peel and pulp, have anti-atherogenic properties. No significant differences were observed ($p > 0.05$) in HDL between rats given 200 and 300 mg/kg of B.W of EEK. The highest reduction in TC (53.23%), TG (63.45%), LDL (66.28%), and VLDL (63.45%) were observed in rats administration with 300 mg/kg of B.W of EEK while, HDL had an opposite trend (42.95%). This may be due to the high contents of total flavonoid, total phenolic compounds, and high radical scavenging activity in 300 EEK than other concentrations of kumquat extracts. The same trend was obtained by other study (43) which found that the whole kumquat was found to have hypocholesterolemic activity ,which could be mediated by flavonoids and phenolic substances. Also, the inclusion of polysaccharides, carotenoids, and sterol in the kumquat extract may be responsible for the improvement in lipids profile (44). Polysaccharides are the primary bioactive components in kumquat. Moreover, polysaccharides' hypolipidemic mechanism was achieved by increasing lipase activity, increasing antioxidant enzyme activity, and improving polysaccharides' ability to bind bile acid (45).

Table 3: Effect of Ethanol extract of kumquat on lipids profile in control and carbendazim intoxicated groups

Variable	Negative control	Carbendazim intoxicated groups			
		Positive control	Ethanol extract of kumquat (mg/kg of B.W)		
			100	200	300
TC (mg/dL)	100.94e±4.51	269.29a±17.8	174.33b±6.02	146.75c±4.81	125.91d±9.10
TG (mg/dL)	62.10e±5.41	226.05a±9.11	128.37b±3.39	116.84c±5.05	82.60d±9.31
HDL (mg/dL)	50.20a±1.48	31.00d±2.66	40.79c±1.87	43.40bc±2.3	44.32b±2.58
LDL (mg/dL)	38.33e±5.21	193.08a±18.26	107.86b±7.78	79.99c±6.40	65.09d±9.13
VLDL (mg/dL)	12.41e±1.09	45.21a±1.80	25.67b±0,67	23.36c±1.01	16.52d±1.22

Values are expressed as means ± SD; means in the same raw with the different letters are significantly different (P < 0.05). EEK: Ethanol extract of kumquat, T C; total cholesterol, T G; triglyceride; HDL; high density lipoprotein, LDL; low density lipoprotein, VLDL; very low-density lipoprotein.

Data in table (4) indicated that the effect of ethanol extract of kumquat on serum blood glucose and kidney functions in control group and carbendazim intoxicated groups. There was a significant ($p < 0.05$) increase in serum glucose, urea, and creatinine in the positive group compared with the negative and carbendazim intoxicated groups. These results are in agreement with another study (2) who found that the separated doses of CBZ resulted in a significant increase in plasma urea and creatinine. Also, rats treated with CBZ alone resulted in significant increases in serum glucose (64%), urea (99%), and creatinine (52%) levels compare with the negative group (46). Treatment rats with ethanol extract of kumquat led to dramatically lower blood glucose, urea, and creatinine levels in rats. These results had the same trend of one study (47) who showed that natural products such as kumquat have been shown to have a protective effect on blood sugar levels in diabetic rats. Researchers found that serum creatinine and urea were lowered in rats treated with kumquat crude ethanol extract by 33.3% and 13.35% respectively (48). Administration rats with 100 and 200 mg/kg of B.W of EEK did not differ ($p > 0.05$) in their effect on creatinine. The highest reduction of glucose level (56.28%), urea (69.33%), and creatinine (56.16%) was observed in rats given 300 mg/kg of B.W of EEK.

Table 4: Effect of ethanol extract of kumquat on serum blood glucose and kidney functions in control and carbendazim intoxicated groups

Variable	Negative control	Carbendazim intoxicated groups			
		Positive control	Ethanol extract of kumquat (mg/kg of B.W)		
			100	200	300
Glucose(mg/dl)	93.61e±10.97	266.35a±11.72	186.88b±7.41	157.96c±5.81	116.43d±7.72
Urea (mg/ dl)	16.24e±2.94	94.60a±1.77	70.74b±1.53	56.52c±3.01	29.016d±2.18
Creatinine(mg/dl)	0.33d±0.05	1.46a±0.21	0.91b±0.06	0.84b±0.02	0.64c±0.04

Values are expressed as means ± SD; means in the same raw with the different letters are significantly different (P < 0.05). EEK: Ethanol extract of kumquat.

Data in table (5) indicated that the effect of ethanol extract of kumquat on antioxidant status in control and carbendazim intoxicated groups. The levels of superoxide dismutase (SOD), total antioxidant capacity (TAC), and glutathione peroxidase (GSH) in positive control were significantly decreased after oral administration of carbendazim ($p<0.05$), while lactate dehydrogenase (LDH) had an opposite trend. Youssef (49) found that the repeated administration of carbendazim in rats resulted in an increase in MDA content and a decrease in both glutathione transferase and catalase activity compared with the negative group. The decrease in the levels of SOD, TAC , GSH, and an increase in LDH may be due to the cause of the oxidative stress resulting from exposure to carbendazim. Exposure rats to the High doses of carbendazim may cause severe oxidative stress, which disrupts the cell homeostasis and promotes apoptosis (50). The levels of SOD, TAC, and GSH were significantly increased ($p<0.05$) of rats treated with ethanol extract of kumquat. Our results are in agreement with a recent study (51) who showed that Kumquat's antioxidant and anti-inflammatory properties may also be attributed to its d-limonene concentration. No significant differences were observed ($p > 0.05$) in LDH between rats, which were given 300 mg/kg B.W of EEK and the negative group. Given rats 300 mg/kg of B.W of EEK caused an increase levels of SOD, TAC, and GSH 1069.12,1001.57, and 1144.83%, respectively and reduction the .LDH level by 75.34%. Our results had the same trend as that of two studies (12,52) who reported that kumquat has a high antioxidant capacity, which is related to the high flavonoid content, as flavonoids are widely regarded as the basis of antioxidant capacity. Also, flavonoids have been shown to significantly reduce lipid peroxidation and boost the body's own antioxidant defense system (46).

Table 5: Effect of Ethanol extract of kumquat on antioxidant status in control and carbendazim intoxicated groups.

Variable	Negative control	Carbendazim intoxicated groups			
		Positive Control	Ethanol extract of kumquat (mg/kg of B.W)		
			100	200	300
LDH(U/L)	302.16d±31.55	1347.03a±79.77	836.85b±62.11	491.92c±70.02	332.16d±26.55
SOD(U/L)	60.33a±7.06	2.98e±1.17	11.26d±1.75	26.47c±2.55	34.84b±1.49
GSH(U/L)	183.00a±2.36	13.83e±2.13	107.76d±2.58	144.16c±2.63	172.16b±2.31
TAC(U/L)	17.75a±1.78	1.27e±0.39	5.12d±0.63	10.88c±1.62	13.99b±1.08

Values are expressed as means ± SD; means in the same raw with the different letters are significantly different ($P < 0.05$). EEK: Ethanol extract of kumquat, LDH: Lactate dehydrogenase, SOD: Superoxide Dismutase: Total antioxidant capacity, GSH: glutathione.

Histopathologic results

Fig. (1) showed the effect of ethanol extract of kumquat on histological examination of liver tissues of rats exposed to carbendazim and negative control rats. Negative control rats' liver sections exhibited normal histological structure, whereas positive control rats' liver sections demonstrated congestion of hepatic blood arteries and significant dilatation of the hepatic sinusoids. Also, the hepatocytes showed variable degrees of necrobiotic changes as granular and vacuolar degeneration with widespread necrosis. On the other hand, the findings revealed that giving rats an ethanol extract of kumquat reduced carbendazim-induced degenerative alterations and preserved the normal histological architecture of the liver tissue, with minimal lipid droplets and isolated necrotic regions. In addition, it was observed that rats treated with 300mg/kg BW of ethanol extract of Kumquat provided significant protection against carbendazim-induced changes, and the hepatocyte pattern resembled that of a normal hepatocyte. These results agree with those reported by (53) who showed that the methanol extract of kumquat reduced increased liver enzymes to normal levels, indicating the preservation of hepatocytic cell membrane structural integrity or the regeneration of damaged liver cells.

Conclusion

From the above results, it can be concluded that ethanolic Kumquat extract can be used as a powerful preventative treatment for liver damage, possibly due to its antioxidant and anti-inflammatory properties. So, we recommend ingesting more kumquat fruits for workers such as farmers who are exposed to pesticides, especially containing Carbendazim to protect the liver from poisoning.

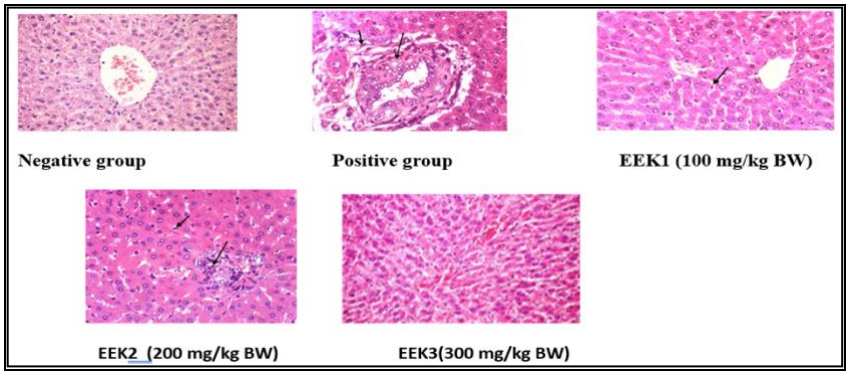

Fig (1): Effect of ethanol extract of kumquat on histological examination of liver tissue of rats' exposure to carbendazim

EEK: Ethanol extract of kumquat

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التأثير الوقائي لمستخلص فاكهة الكمكوات الإيثانولي ضد تسمم الكبد الناتج عن الكاربيندازيم في الفئران

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لملخص العربي

يستخدم الكاربندزيم على نطاق واسع للتحكم في مسببات الأمراض الفطرية المختلفة. ويعتبر الكاربندزيم مادة ملوثة توجد في الطعام والتربة والماء ويسبب تغيرات وظيفية وتغيرات في الأنسجة. لذلك هدفت هذه الدراسة إلى تقييم التأثير الوقائي لمستخلص فاكهة الكمكوات الإيثانولي ضد تسمم الكبد الناتج عن الكاربيندازيم في الفئران. تم تقسيم ثلاثين من ذكور الفئران بشكل عشوائي إلى مجموعتين رئيسيتين وتغذيت على نظام غذائي قياسي. المجموعة الأولى: الضابطة السالبة (6 فئران) والمجموعة الثانية: (24 فار) تم إعطائها الكاربندزيم بجرعة يومية مقدارها 250 مجم / كجم من وزن الجسم (BW) لمدة 30 يومًا بعد تقسيمها إلى أربع مجموعات فرعية متساوية (6 فئران لكل منهما)، المجموعة الأولى: المجموعة الضابطة الموجبة ، الثانية ، الثالثة و الرابعة أعطت جرعة يومية من مستخلص الإيثانول من الكمكوات (100 ، 200 ، و 300 مجم / كجم) من وزن الجسم على التوالي. في نهاية التجربة (30 يومًا)، تم تخدير الفئران وتجميع عينات الدم من اجل تحليل وظائف الكبد والكلي وسكر الدم ودهون الدم ومضادات اللأكسدة. أوضحت النتائج ان تناول 250 ملجم / كجم من وزن الجسم من الكاربيندازيم عن طريق الفم أدى إلى زيادة مستويات وظائف الكبد والكلى وسكر الدم ومضادات الأكسدة في المجموعة الضابطة الموجبة. كما أدى تناول مستخلصات الكيموكوات الإيثانولي عن طريق الفم إلى خفض مستويات الجلوكوز و (LDH)ووظائف الكبد والكلى مقارنة بالمجموعة الضابطة الموجبة. ولذلك خلصت الدراسة إلى أن مستخلص الإيثانول من الكمكوات أكثر فاعلية في تقليل التأثير السام لمادة الكاربيندازيم في حيوانات التجارب.

الكلمات المفتاحية: الكاربندازيم، الكيموكوات، وظائف الكبد، الكلي.