

Journal of Food and Dairy Sciences

Journal homepage: www.jfds.mans.edu.eg
Available online at: www.jfds.journals.ekb.eg

Alleviation of Tramadol-Induced Liver Toxicity in Experimental Rats by Using Kiwifruit, Turmeric Extract or Their Combination

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ABSTRACT

This work was designed to study the potential effect of kiwifruit, turmeric extract or their combination in alleviation of the liver toxicity induced by tramadol intake. Thirty rats were fed on a basal diet, six of them continued on the basal diet (negative control). The remaining rats were given tramadol daily and divided into four groups, one of them served as positive control, while the other three groups were treated daily with kiwifruit juice, turmeric water extract and their combination for four weeks. The results revealed that the positive control exhibited significant decreases in serum triglycerides, total cholesterol and HDL-c levels and a significant increase in serum LDL-c as compared to the negative control. In comparing with the positive control, the serum cholesterol, triglycerides, VLDL-c and HDL-c values increased while LDL-c value decreased significantly in the three treated groups which reached the normal values of the negative control. The findings revealed significant decreases in serum levels of ALT, AST, ALP, GGT and total bilirubin and significant increases in total protein and albumin of the treated groups in comparing with the positive control. An improvement of the antioxidant parameters was observed where the serum levels of tumor necrosis factor- α , acetylcholine esterase and total oxidative capacity decreased significantly while the levels of superoxide dismutase and total antioxidants capacity increased in all the treated groups in comparing with positive control group. It is recommended by using kiwifruit and turmeric extract in the diets of those who addicted to tramadol intake.

Keywords: Tramadol – Lipid profile – Liver functions – Antioxidant parameters - Rats



INTRODUCTION

Many people, especially those doing hard work, get used to take tramadol drug in their daily life to help them work for a long time and prevent their pain sensation. Others use it to relief the pain of their diseases while some persons use it thinking that it increases the period of intercourse, so unfortunately tramadol abuse spread rapidly among the young people

Tramadol is an artificial opioid painkiller as a rule for a mild to severe pain (Niesters *et al.*, 2013). Two hundred mg / day is the wanted dosage of tramadol whilst the extreme admissible daily gulp is 400 mg. Liver is the leading member of metabolism and disposal of toxic substances in the body, so liver damage is linked with degeneration of sundry metabolic functions. Taking tramadol will produce many harmful effects that can threaten the lives of the user (Pothiawala and Ponampalam, 2011). The liver and kidneys play a major role in dope metabolism, exposing them to toxic suffering. Inside the liver, tramadol is converted to O-dimethyl-tramadol by cytochrome P 450, that is an active item which is from 2 to 4 times stronger than tramadol. Furthermore, biotransformation produces passive products, that are eliminated by the kidneys (Dickman, 2007). Awadalla and Salah-Eldin (2015) revealed that tramadol abuse can stimulate hepatotoxicity and nephrotoxicity when acute or chronic in experimental rats, leading to liver and kidney damage. Tramadol leads to some changes in liver tissue, including the loss of normal pattern of liver tissues with the degeneration of some liver cells which may be

attributed to the increase in oxidative processes resulting from taking tramadol (Zagholol *et al.*, 2018). Using tramadol continuously may lead to the accumulation of toxic metabolites in the body, increasing the risk of the effects of its toxic movement and / or reducing the ability to dispose of it, increasing the likelihood of its toxicity (Shadnia *et al.*, 2008).

Kiwi fruit (*Actinidia deliciosa*) belongs to the family Actinidiaceae which is cultivated in mountainous areas of china, Italy, England, Japan, Greece, Chile and France. The fruit has small black seeds, green edible flesh and a brown hairy peel (Nishiyama, 2007). It contains a high level of vitamin C and numerous of important nutrients, especially dietary fiber, potassium, vitamin E and folate, as well as a wide range of antioxidants, phytonutrients and enzymes that provide functional and metabolic benefits (Richardson *et al.*, 2018). Kiwi's antioxidant characteristics protect the body from free radicals; flavonoids in kiwifruit protect cells from oxidative erosion and therefore have the ability to protect DNA from mutations and damage (Collins *et al.*, 2001).

Turmeric (*Curcuma longa L.*) is one of the family Zingiberaceae, where its rhizomes represents the important part which is used frequently in foods and folklore medicine. It is a perennial herb cultivated in tropical and sub-tropical regions of the east of Asia such as India, Pakistan, Bangladesh and Sri Lanka. (Nasri *et al.*, 2014). It is vastly utilized in elaboration of food, where the powdered form of its rhizomes contain curcumin which has been shown to have anti-inflammatory activity and has

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DOI: 10.21608/jfds.2019.61874

the ability to inhibit proinflammatory transcription factors such as Tumor Necrosis Factor and Interleukin (IL-6) (Maheshwari *et al.*, 2006 and Gupta *et al.*, 2008). Turmeric has been revealed to be a potent antioxidant which inhibits creation of reactive oxygen species (ROS) in vitro and in vivo together (Joe and Lokesh, 1994).

Some patients may be forced to take tramadol pills to relieve pain, but this may lead to many damages affecting the liver and other organs of the body. So, this study was conducted to confirm the potential impact of kiwi fruit and turmeric or their combination against the toxicity caused by tramadol intake in experimental rats.

MATERIALS AND METHODS

Materials:

Plants: Fresh kiwifruit (*Actinidia deliciosa*) and turmeric (*Curcuma longa*) were obtained from the market in Mit Ghamr city, El-Mansoura, Egypt.

Chemicals: The utilized kits in biochemical analysis were gotten from Gama trade Company, Cairo, Egypt. Tramadol hydrochloride was obtained in the form of commercially packed tablets (Tamol-X) from the Pharmacy.

Animals: Thirty normal male albino rats of Sprague Dawley strain, with a weight ranged from 200 to 210 g were obtained from the experimental animal house in Food Technology Research Institute, Agric. Res. Center, Giza, Egypt. (Guidelines for ethical conduct in the care and use of animals in research obtained from the concerned department in Mansoura University).

Methods:

Preparation of kiwifruits juice and turmeric extract:

Kiwifruits were washed with distilled water, peeled and homogenized by electric blender. This homogenization was given daily in a dose of 4ml / rat by using a stomach tube.

Curcuma longa rhizomes were washed with distilled water then cut into small pieces and dried in a hot air oven at 40°C. The dried material was ground by using a grinder, and then stored in a drying cabinet at 4°C until use. Turmeric extract was prepared separately by soaking 100 g of turmeric powder in distilled water (1000 ml) at 37 °C for 48 hours, this mixture was filtered and stored in refrigerator till usage to be given to the rats in a dose of 200mg/kg b.w. as mentioned by Olatunde *et al.* (2014).

Gross chemical analysis:

Chemical constituents of kiwi fruit and turmeric powder: moisture, protein, crude fibers, fat content and ash contents were determined according to the methods described in the AOAC (2005). Total carbohydrates were calculated by difference.

Total phenolic contents:

The total phenolic content was analyzed with the Folin-Ciocalteu method modified from Cliffe *et al.* (1994). 0.1 ml of the extract was mixed with 2.8 ml of distilled water, 0.1 ml of 50% Folin-Ciocalteu reagent, and 2 ml of Na₂ CO₃ (2 g/100ml). The mixture was incubated at room temperature for 30 minutes. The mixture absorbance was measured spectrophotometrically at 750 nm. The total phenolic content was expressed as gallic acid equivalents (GAE) in milligrams per gram dry material.

Determination of vitamin C:

Vitamin C was determined by a spectrometric method as described by Rahman *et al.* (2006)

DPPH assay

One-gram sample was added to 10 mL of methanol then homogenized. The crude extract sample was mixed with 3.9 ml of methanol and 1 ml of a DPPH solution (1mM in methanol) and incubated for 30 minutes and the absorbance was measured at 517nm after incubation. (Coklar and Akbulut, 2017).

DPPH radical scavenging activity was calculated as follows:

DPPH scavenging activity = {1 – (A sample/ A Blank)} x 100.

Animals and experimental design:

Rats were acclimatized in crates under sanitary status and fed on a basal diet, which has been formed as described by NRC (1995), for 5 days for adaptability. Thereafter 6 rats remained on the basal diet feeding during the experiment period as a negative control (G1). The other rats were fed on basal diet and received tramadol hydrochloride daily in a dose of 25mg/kg body weight dissolved in 0.4 ml distilled water by a stomach tube. They were divided into four groups (6 rats each) as follows; Group 2 (positive control) which remained on tramadol and the basic diet only while Group 3 treated daily with homogenized kiwi fruit (4ml / rat) by using a stomach tube, Group 4 received turmeric water extract (0.4ml / 200g b.w.) by using a stomach tube whereas Group 4 received a combination of homogenized kiwi fruit (2ml/rat) and turmeric water extract (0.2ml/rat) every day for 30 day . The Daily feed intake and body weight gains were recorded every week. Feed efficiency ratio (FER) was determined according to Chapman *et al.* (1959).

At the end of the experiment, the rats were fasted overnight and then weighed, after that they were sacrificed, and their blood samples were collected immediately from the portal vein. The obtained blood samples were centrifuged to separate serum which was stored at -20°C until further biochemical analysis.

Biochemical analysis:

Examination of Total cholesterol, Triglycerides and High-density lipoprotein cholesterol (HDL-c), (TG), were estimated by enzymatic colorimetric methods as described by Abell *et al.* (1952); Bucolo and David (1973) and Kostner (1976), respectively. On the other hand, very low-density lipoprotein cholesterol (VLDL-c) and low-density lipoprotein cholesterol (LDL-c) were calculated mathematically as follows;

$$\text{VLDL-c} = \text{TG}/5$$

While $\text{LDL-c} = \text{Total cholesterol} - (\text{HDL-c} + \text{VLDL-c})$ (Fruchart, 1982).

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) were estimated according to Reitman and Frankel (1957) while alkaline phosphatase (ALP) was assayed by the method of Kind and King (1954)

Total serum protein was determined as described by Henry (1964), while total albumin was assessed according to Bartholomewet and Delaney (1966) and total bilirubin was estimated by the method of Bruckner (1961).

Superoxide dismutase (SOD) activity was estimated by the method of Nishikimi *et al.* (1972)

Total antioxidants capacity (TAC), Total oxidative capacity (TOC), Tumor necrosis factor-alpha (TNF- α) were determined according to Koracevic *et al.* (2001); Flohe and Gunzler (1984) and Beutler *et al.* (1985) respectively. Acetylcholinesterase (AChE) activity was determined by the method of Ellmann *et al.* (1961)

Statistical analysis

The obtained values from this study had been submitted for statistical analysis by SPSS computer software by analyzed divergence ANOVA and follow up test LSD by SPSS ver.11. According to the method qualified by Abo-Allam (2003).

RESULTS AND DISCUSSION

Gross chemical composition of kiwifruits and turmeric:

The proximate composition of kiwifruit juice and turmeric powder were estimated and recorded in Table (1).

Table 1. Gross chemical composition of kiwifruit and turmeric powder (g/100g)*

Component	kiwifruit	Turmeric
Moisture	85.33	11.43
Protein	1.25	6.71
Fat	0.58	5.26
Ash	2.98	3.34
Fiber	3.12	3.11
Carbohydrate	6.74	70.15

*On wet weight basis

The results show that moisture, fiber, ash, fat, protein, and carbohydrates contents were 85.33, 3.12, 2.98, 0.58, 1.25 and 6.74 g/100g, respectively in fresh kiwi fruit, while their values in turmeric powder were 11.43, 3.11, 3.34, 5.26, 6.71 and 70.15, respectively. These results are nearly in same line with Halaby *et al.* (2013).

It is obvious that both the kiwifruit juice and turmeric powder contain moderate levels of fiber which is very important for hyperlipidemic and hyperglycemia patients where the dietary fiber combine with cholesterol and bile acids and hence prevent cholesterol absorption. Dietary fibers also slow the absorption of glucose in the gut which is good for diabetic patients. Turmeric has a high content of protein and total fats which increases its nutritional value as a herb.

Total phenolic compounds, vitamin C and antioxidant activity of kiwifruit juice and turmeric powder:

Data in Table (2) pointed out that vitamin C content in kiwi fruit was 98.17 mg/100g while it was 47.13 mg/100g in turmeric. Regarding total phenolic compounds, the results showed that their concentrations were 9.6 and 118 mg GAE/g in kiwifruit and turmeric, respectively.

Table 2. Vitamin C, phenolic compounds and antioxidant activity of kiwifruit and turmeric powder

Sample	Vitamin C (mg/100g)	Total phenolic (mg/GAE/g)	DPPH %
Kiwifruit	98.17	9.6	47.5
Turmeric	47.13	118	81.7

The antioxidant activity which represented as DPPH scavenging activity was 47.5% for kiwifruit while it reached 81.7% for turmeric. These findings agreed to some extent with those of Tuba and Iihami (2008). Vitamin C and phenolic compounds are well known by their

antioxidant activity which reflected in their DPPH scavenging activity.

Effect of kiwifruit, turmeric extract or their combination on Weight gain (g), Feed intake (g/d) and Feed efficiency ratio (FER) of the rats.

As shown in Table (3), body weight gain ,Feed intake and feed efficiency ratio (FER) were reduced significantly in positive control group to 27.43±3.02g , 14.50±0.51g and 0.063±0.007 consecutively, in comparing with the normal control group (53.53±3.24g , 19.18±0.75 and 0.093±0.004), consecutively. The obtained results show that there were significant increases in weight gain, feed intake and feed efficiency ratio in all the treated groups as compared to positive control. The decreases occurred in the positive control group are attributed to tramadol abuse which led to some intestinal disturbances such vomiting, nausea and constipation with changing in appetite (Grond and Sablotzki, 2004). On the other hand, all the rats given kiwifruit and turmeric water extract, or their combination showed improvement in feed efficiency ratio which reached that of the normal control rats which confirmed the ability of the examined samples to alleviate the toxicity of tramadol. Group 5 which received the combination of kiwifruit juice and turmeric extract exhibited the best results in increasing the weight gain, feed intake and FER followed by turmeric extract. Consumption of kiwi fruit improves utilization of the meal by more effective digestion of dietary protein, increased fecal excretion and softness, better lubrication which helps in pushing the wastes along the colon (Kaur *et al.*, 2010).

Table 3. Effect of kiwifruit, turmeric extract or their combination on feeding and growth parameters of experimental rats.

Treatments	WG(g)	FI(g/d)	FER
G1 (-ve control)	53.53±3.24 ^a	19.18±0.75 ^a	0.093±0.004 ^a
G2 (+ve control)	27.43±3.02 ^c	14.50±0.51 ^d	0.063±0.007 ^b
G3 (Kiwi Fruit)	41.62±2.45 ^b	16.10±1.01 ^c	0.087±0.010 ^a
G4 (Turmeric)	45.40±3.36 ^b	16.92±1.17 ^{bc}	0.089±0.002 ^a
G5 (Combination)	49.72±3.32 ^a	17.98±0.52 ^b	0.092±0.006 ^a

Means ± SD. * Values with the same letters in each column are not significant at P < 0.05 .

Effect of kiwifruit, turmeric extract or their combination on serum lipid profile in experimental rats:

The data in Table (4) revealed that the rats of the positive group (G2) exhibited significant decrease in serum levels of the total cholesterol (TC), triglyceride (TG), VLDL_c and HDL_c, while a significant increase in LDL_c was observed in comparing with normal control (negative control).These results mean that tramadol administration caused disturbances in lipid metabolism which may be attributed to its hepatotoxicity effect which represented in elevation of LDL_c and decreasing the HDL_c levels. Regarding the treated groups either by kiwi fruit (G3) , or turmeric water extract (G4) or their combination (G5), the obtained results showed significant increases in serum TC, TG, VLDL_c and HDL_c levels in all the treated groups as compared to the positive control (G2).The increases in the mentioned values were within the normal values .The findings also pointed out that the serum LDL_c levels of the three treated groups had decreased significantly as compared to positive control and their levels were nearly similar to that of the negative

control. The improvement occurred in lipid profile of the treated groups especially groups 4 and 5 reached the normal values of lipid profile parameters of the normal control group. The actual amelioration is referred to the significant decreases in LDL_c and increasing in serum HDL_c as achieved in group 4 which treated by turmeric water extract and group 5 which treated by a mixture of kiwi fruit and turmeric extract. The increases percentage of HDL_c reached about 53% in group 4 followed by 50% in group 5 and finally 35% in group 3 in comparing with positive control (G2). On the other hand, the decreases percentage of LDL_c reached 36% in group (5), 34% in group (4) and 21% in group (3) as compared to positive control. These results agreed with that of Tomita *et al.* (2006) who stated that turmeric has a protective effect on the cardiovascular system as a result of its lowering effect on serum

cholesterol and triglycerides levels, decreasing the oxidation of LDL-c and inhibiting platelet aggregation. From these results, it is obvious that tramadol administration caused dyslipidemia in the experimental rats due to its toxicity of liver and kidney which impaired their functions. The treatments of the injured rats by the examined plants caused remarkable improvements in the rats' lipid profile which means that these plants contained antioxidants ingredients which protect the cells of the liver from damage or they may antagonist the action of tramadol. The decrease in total cholesterol and triglyceride in rats given tramadol has been achieved by El-Gaafarawi (2006) who noticed significant reduction in total cholesterol and triglyceride after giving opioid and non-opioid analgesics to rats.

Table 4. Effect of kiwifruit, turmeric extract or their combination on serum lipid profile of the experimental rats.

Treatments	TC	TG	HDL-c	LDL-c	VLDL-c
	mg/dl				
G1 (-ve control)	86.64±2.48 ^a	73.83±3.11 ^a	45.99±1.29 ^a	25.88 ±3.58 ^c	14.77±0.62 ^a
G2 (+ve control)	78.24±1.80 ^c	46.07±2.49 ^d	30.42±0.86 ^c	38.61±1.60 ^a	9.21±0.50 ^d
G3 (Kiwi Fruit)	83.05±1.69 ^b	56.18±2.69 ^c	41.23±1.10 ^b	30.58±2.77 ^b	11.24±0.54 ^c
G4 (Turmeric)	85.72±1.46 ^a	68.46±1.83 ^b	46.56±0.73 ^a	25.46±1.65 ^c	13.69±0.37 ^b
G5 (Combination)	84.35±1.29 ^{ab}	72.53±1.20 ^a	45.23±2.37 ^a	24.61±2.21 ^c	14.51±0.24 ^a

Means ± SD. * Values with the same letters in each column are not significant at P < 0.05 .

Effect of kiwifruit juice, turmeric extract or their combination on liver functions of the experimental rats

The data in Table (5) revealed that the positive group rats which received tramadol only exhibited high significant values of serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) , gamma glutamyl transferase (GGT) and total bilirubin (TB), while the serum albumin and total protein (TP) values reduced significantly in comparing with their values in the normal rats (negative control). This may be attributed to destruction in the cell membranes of the liver cells which led to releasing the liver enzymes such as ALT, AST, ALP and GGT. The observed increase in total bilirubin (TB) and decrease in total protein and albumin in rats of the positive control may be due to the decrease in the efficiency of liver as a result of tramadol administration .The results also showed that the groups which received tramadol and treated by either kiwifruit juice or turmeric water extract or a combination of them revealed significant amelioration in all the mentioned parameters (Table 5). Significant decreases in serum levels of ALT, AST, ALP, GGT and total bilirubin were recorded while significant increases in

total protein and albumin have been found in comparing with the positive control group. The results stated that the group 5 which treated by *combination* of turmeric water extract and kiwi fruit juice was the best among the three treated groups in amelioration of the liver biomarkers assessed in this work followed by group 4 which treated with turmeric water extract and finally group 3 which treated with kiwifruit juice. The improvement occurred in the tested liver biomarkers by turmeric extract or kiwifruit juice or their combination may be attributed to their ability in preventing and repairing the cell membranes of the hepatocytes injured by tramadol administration as they have a potency of antioxidants which prevent the lipid oxidation of the liver cell membranes. These results are confirmed by Sheweita *et al.* (2018) who found that giving curcumin prior to tramadol administration to rats alleviated the changes in the antioxidant capacity and the marker enzymes of liver and kidney because of tramadol intake. They attributed this protective effect to the ability of curcumin for scavenging of reactive oxygen species (ROS) and suppression of the oxidative stress.

Table 5. Effect of kiwifruit, turmeric extract or their combination on liver function tests of the experimental rats.

Treatments**	AST (IU/L)	ALT (IU/L)	ALP (U/L)	GGT(U/L)	TB (mg/dl)	Albumin (g/dl)	TP (g/dl)
G1	49.87±2.66 ^c	40.51±3.52 ^c	79.09±2.40 ^d	26.12±0.15 ^d	0.50±0.01 ^d	5.08±0.07 ^{ab}	7.65±0.15 ^a
G2	82.64±6.26 ^a	78.18±2.22 ^a	127.75±3.71 ^a	29.07±0.52 ^a	1.29±0.04 ^a	3.49±0.05 ^d	5.16±0.08 ^d
G3	58.40±3.52 ^b	60.78±3.27 ^b	93.71±2.35 ^b	27.79±0.32 ^b	0.77±0.05 ^b	4.57±0.34 ^c	7.16±0.06 ^{bc}
G4	57.62±3.54 ^b	56.17±2.50 ^c	84.67±2.73 ^c	27.07±0.10 ^c	0.75±0.01 ^b	4.79±0.27 ^{bc}	7.13±0.11 ^c
G5	51.96±3.26 ^c	45.66±2.17 ^d	81.07±1.38 ^d	26.35±0.20 ^d	0.64±0.02 ^c	5.44±0.48 ^a	7.28±0.07 ^b

Means ± SD. * Values with the same letters in each column are not significant at P < 0.05.

** G1 (-ve control), G2 (+ve control), G3 (Kiwi Fruit), G4 (Turmeric) and G5 (Combination of kiwi & turmeric)

Antioxidant activity of kiwifruit juice, turmeric extract or their combination in experimental rats:

The Data in Table (6) illustrated the potentiality of using kiwifruit juice and turmeric water extract or their combination as potent agents in preventing diseases and increasing the body immunity because of their antioxidant

activities. The findings revealed that the rats of the positive control group (G2) which received tramadol only have significant increased values of tumor necrosis factor- α (TNF- α) which reached 3.39pg/ml as compared to negative control group (1.47 pg/ml). On the other hand, the treated groups (G3, G4 and G5) exhibited low significant values of

TNF- α in comparing with the positive control group. The best reduction was observed in the rats of group 5 which treated by the combination of both kiwifruit juice and turmeric water extract. Although the values decreased in the treated groups, they remained more than that of the normal (negative) control. This means that the examined materials antagonist the action of tramadol and hence improved the status of the rats. Concerning the acetylcholine esterase (AChE), the recorded values in Table (6) showed that the positive control group has high significant levels of serum AChE than that of the normal control group(G1). The increase percentage reached about 92%. On the other hand, all the three treated groups revealed significant decreases of AChE levels being 166.6, 166.8 and 151 U/L in G3, G4 and G5, respectively in comparing with the positive control (237.02 U/L) at $P < 0.05$. The superoxide dismutase (SOD) which consider one of the important antioxidant defenses in most of all living cells which catalyzes the dismutation of the superoxide radical (O_2^-) into O_2 or hydrogen peroxide (H_2O_2) was estimated and recorded in table (6). The value of SOD in the positive control group decreased significantly at $P < 0.05$ in comparing with normal control group (G1). The reduction percentage reached about 32%. However, all the treated groups (G3, G 4 and G5) showed significant increases in SOD levels as compared to positive control which reached the same level of SOD in the normal control group. From the same table, it was noticed that the total antioxidant capacity (TAC) of the normal control group (-ve control) was 1.92 mmol/L while it reduced significantly to 0.64 mmol/L in the positive control group (G2) which treated with tramadol only. This indicates that tramadol abuse may reduce the immunity of the body and makes it susceptible to diseases because of reducing the body antioxidants. The data showed that G3, G4 and G5 which

received tramadol and treated by either kiwi fruit, turmeric water extract or their combination had high values of total antioxidants capacity as being 1.75,1.77 and 1.87mmol/L, respectively in comparing with the value of the positive control group which was 0.64 mmol/L .However both of kiwi fruit and turmeric water extract exhibited the same effect while their combination was the best in this respect.

Regarding total oxidative capacity (TOC), the results in table (6) revealed that TOC of the rats in the normal group (G1) was 0.45mmol/L which had been raised to significant high value of 1.82 mmol/L by tramadol administration to the rats of the positive group (G2). However , The treated groups (G3, G4 and G5)which received tramadol in addition to kiwi fruit, turmeric water extract and their combination showed significant low values of total oxidative capacity that being 0.64, 0.57 and 0.45 mmol/L, respectively in comparing with the positive control group (1.82mmol/L). The lowest value of G5 was like to that of the normal control group. These results indicate that the examined plants have an antioxidant potency and their combination was the best among them where its reduction in TNF- α , AChE and TOC was remarkable. Also, the mixture of kiwifruit juice and turmeric water extract raised the values of SOD and TOC which reached the normal values of the negative control. These results indicate that the examined materials can be used safely in providing the human body with antioxidant defenses which protect it from weakness and fight diseases and dysfunction of the body organs. Govindarajan (1980) found that turmeric has a hepatoprotective effect in experimental animals injured either by carbon tetrachloride, galactosamine or acetaminophen. The hepatoprotective effect of turmeric was attributed to its ability to decrease the formation of pro-inflammatory cytokines.

Table 6. Antioxidant activity of kiwi fruit, turmeric extract or their combination in the experimental rats.

Treatments	TNF α pg/ml	(AChE) U/L	SOD U/ml	TAC mmol/L	TOC (mmol/L)
G1 (-ve control)	1.47±0.05 ^c	123.30±2.18 ^d	30.03±5.69 ^a	1.92±0.04 ^a	0.45±0.04 ^d
G2 (+ve control)	3.93±0.06 ^a	237.02±3.81 ^a	20.40±0.27 ^c	0.64±0.03 ^d	1.82±0.04 ^a
G3 (Kiwi Fruit)	2.29±0.04 ^b	166.60±4.56 ^b	25.35±1.98 ^b	1.75±0.03 ^c	0.64±0.05 ^b
G4 (Turmeric)	2.18±0.02 ^c	166.80±5.89 ^b	26.68±1.53 ^{ab}	1.77±0.04 ^c	0.57±0.03 ^c
G5 (Combination)	1.78±0.04 ^d	151.00±5.70 ^c	29.37±1.01 ^a	1.87±0.02 ^b	0.45±0.04 ^d

Means \pm SD. * Values with the same letters in each column are not significant at $P < 0.05$.

Antioxidants compounds are very important in survival of the body cells where they can inhibit, prevent or delay oxidation process of lipids of cell membrane or any other oxidizable materials by reducing oxidative stress and scavenging free radicals. Increasing amounts of reactive oxygen or nitrogen species such as superoxide anion, hydroxyl radical, hydrogen peroxide and peroxynitrite lead to oxidative stress because these high amounts of oxidant materials overcome the endogenous anti-oxidant capacity, leading to oxidation of a varieties of biomacromolecules, such as enzymes, proteins, DNA and lipids. There is a strong relation between the oxidative stress and the development of chronic diseases such as cancer, coronary heart diseases and aging (Ames *et al.*, 1993). Rice-Evans *et al.* (1996) stated that phenolic compounds are considered powerful antioxidants in vitro and proved to be more potent antioxidants than Vitamin C and E and carotenoids. In one study, it was found an inverse relationship between consuming fruits and vegetables and the risk of oxidative

stress associated diseases because of their content of phenolic compounds (Scalbert *et al.*, 2005).

CONCLUSION

It could be concluded that consumption of kiwifruit juice or turmeric water extract or a combination of them is important for those who used to take tramadol in their daily life as an opioid or forced to take it to alleviate their pain because of some diseases. However, the combination of kiwi fruit juice and the aqueous extract of turmeric exhibited the best results, this may be attributed to their different functional components which synergized and revealed their significant effects.

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التخفيف من سمية الكبد الناتجة عن استخدام الترامادول في فئران التجارب باستخدام فاكهة الكيوي أو مستخلص الكركم أو مخلوط منهما

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تم تصميم هذا العمل لدراسة التأثير المحتمل لثمرة الكيوي أو مستخلص الكركم أو مزيجهما في التخفيف من سمية الكبد الناتجة عن تناول الترامادول. تم إطعام ثلاثين فأراً على نظام غذائي أساسي، ستة فئران منهم استمرت على النظام الغذائي الأساسي (الكنترول السالب). أما الفئران المتبقية فقد أعطيت جرعة ترامادول يومياً وتم تقسيمها إلى أربع مجموعات، بقيت إحداها ككنترول موجب ، بينما عولجت المجموعات الثلاث الأخرى يومياً بعصير ثمرة الكيوي ، أو المستخلص المائي للكركم أو مزيج منهما لمدة أربعة أسابيع. أظهرت النتائج انخفاضات كبيرة في الدهون الثلاثية ، والكوليسترول الكلي ومستويات HDL-C، VLDL-C مع زيادة معنوية في مستوى LDL-C في سيرم فئران مجموعة الكنتترول الموجب عند مقارنتها بالكنترول السالب. من ناحية أخرى ، ارتفعت مستويات السيرم من الكوليسترول الكلي ، الدهون الثلاثية ، و VLDL-C و HDL-C بينما انخفضت قيمة LDL-C بشكل كبير في المجموعات الثلاث المعالجة وذلك بمقارنتها بالكنترول الموجب التي وصلت تقريبا إلى قيم الكنتترول الطبيعي. كما كشفت النتائج عن انخفاضات كبيرة في مستويات السيرم من ALT ، AST ، ALP ، GGT والبيليبروبين الكلي وزيادة كبيرة في البروتين الكلي والألبومين في المجموعات المعالجة بالمقارنة مع الكنتترول الموجب. وقد لوحظ تحسن في مؤشرات مضادات الأكسدة حيث انخفضت مستويات السيرم من عامل نخر الورم α ، الأستينيل كولين استيراز وقدرة الأكسدة الكلية بشكل كبير بينما زادت مستويات انزيم سوبر اوكسيد ديسميوتاز والقدرة الكلية لمضادات الأكسدة في جميع المجموعات المعالجة عند المقارنة مع مجموعة الكنتترول الموجب. ولهذا توصى الدراسة باستخدام ثمرة الكيوي ومستخلص الكركم في الوجبات الغذائية لأولئك الذين يدمنون على تناول الترامادول.

الكلمات المفتاحية: ترامادول – ليبيدات الدم – وظائف الكبد – مضادات الأكسدة – الفئران