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Protective Effects of *Actinidia deliciosa* Extract and Silymarin on CCl_4-Induced Hepatotoxicity and Behavioral Alterations in Male Albino Rats

Efectos Protectores del Extracto de *Actinidia deliciosa* y la Silimarina sobre la Hepatotoxicidad Inducida por CCl_4 y las Alteraciones Conductuales en Ratas Albinas Macho

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SUMMARY: This study aimed to evaluate the potential antioxidant, anti-inflammatory, antidepressant, and anxiolytic effects of *Actinidia deliciosa* extract (*ADE*) in comparison to silymarin (SILY) in mitigating carbon tetrachloride (CCl_4)-induced hepatotoxicity and behavioral changes in male albino rats. A total of forty-two male albino rats were randomly divided into seven groups: control, *ADE* 0.5 g/kg, *ADE* 1.0 g/kg, CCl_4 only, SILY + CCl_4, *ADE* 0.5 + CCl_4, and *ADE* 1.0 + CCl_4. The administration of *ADE* significantly reduced serum liver enzyme levels, improved antioxidant markers, and alleviated behavioral abnormalities. *ADE* also downregulated the hepatic expression of CYP2E1 and Type I collagen, suggesting its potential hepatoprotective and neuroprotective properties. These findings indicate that *ADE* may serve as a promising alternative to silymarin in protecting against chemical-induced liver damage.

KEY WORDS: *Actinidia deliciosa*; Antioxidant; Hepatotoxicity; CYP2E1; Anxiolytic; Depression; Liver injury.

INTRODUCTION

The liver is essential for controlling several physiological and biochemical processes in the body. It participates in many crucial processes, such as metabolizing nutrients, detoxifying drugs and toxic substances, bile production, and nutrition metabolism (AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a). Consequently, liver disorders will significantly impair health. Most hepatotoxic chemicals primarily harm hepatocytes by causing oxidative stress in the liver. Most biomolecules are easily reacted with and oxidized by reactive oxygen species (ROS) (Abdelghffar *et al*., 2022b). Hepatotoxicity is a very common ailment that results in fatal consequences such as severe metabolic problems (AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a). Numerous organs and systems throughout the body can be adversely impacted by liver impairment. A well-known side effect of both acute and/or chronic liver disorders, hyperammonemia is essential to the development of hepatic encephalopathy. Also, depression, psychomotor, and anxiety have been closely linked to liver problems (Ahmad *et al*., 2018). Consequently, maintaining a functioning liver is essential for general health and well-being.

The lipophilic carbon tetrachloride (CCl4) may easily move throughout the body's lipid compartments and be processed in the liver. Although it has narcotic and anesthetic properties (Abdelghffar *et al*., 2022a). It is a highly hepatotoxic agent, and the most well-known substance to cause liver damage in laboratory experiments by producing ROS and elevating proinflammatory cytokines. Proinflammatory cytokines that are overexpressed cause symptoms such as loss of interest in social activities, as well as a decrease locomotor activity, exploration, and body weight (Ahmad *et al*., 2018). A bio-activation process mediated by cytochrome P450 (CYP450) is necessary for the CCL4 mechanism of toxicity to produce the reactive metabolic trichloromethyl radical and the proxy trichloromethyl radical (CCL3 & CCL3O2, respectively) that generate free radicals (AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a). CYP2E1 has a crucial role in the hepatotoxicity of CCI4 (Ahmed *et al*., 2011). The free radicals of CCL4 can form alkoxy and peroxy radicals when they combine with polyunsaturated fatty acids. These radicals can cause lipid peroxidation (LPO), harm organelle/liver cell membranes, swell and hepatocyte necrosis, as well as the release of cytosolic enzymes like alanine/ aspartate aminotransferases (ALT, & AST) into the bloodstream (Amer *et al*., 2014; Abdelghffar *et al*., 2022a).

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The CCl4 has been widely used by researchers to cause liver cirrhosis in test animals (Amer *et al*., 2014; AbdElfatah *et al*., 2021). Liver cirrhosis is a serious issue for global public health. Currently, the primary and most important focus of hepatology therapy is the prevention of liver cirrhosis and fibrosis (AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a).

At present, despite the tremendous advances in modern medicine to protect the liver from damage. There is no reliable medication that promotes liver function, provides the liver with protection against harm, or aids in the regeneration of hepatic cells. Therefore, a critical need exists for safe, affordable, and effective medications to swap out and add to those now being used for the treatment of liver disorders. It is well-recognized that herbal remedies, which are secure and affordable, are crucial in the management of hepatopathy (Abdelghffar *et al*., 2022a). The most important herbal medicinal components are alkaloids, tannins, flavonoids, and phenolic compounds (Abdelghffar *et al*., 2022b).

Actinidia deliciosa family Actinidiaceae, commonly known as kiwi fruit, is a highly valued plant worldwide for its medicinal value and characteristic aroma. It is an edible fruit and is cultivated in many countries. It has a lot of vitamin C (more than oranges), vitamin E, potassium (almost as much as bananas), and beta-carotene (Essawy *et al*., 2010). It is superior to other fruits in terms of antioxidant properties (Beauchamp & Fridovich, 1971; Batool *et al*., 2023). Antioxidants in kiwi fruit are absorbed by the body faster than those in other fruits with high antioxidant content (Beauchamp & Fridovich, 1971). It has been found to possess biological and pharmacological activities as an antioxidant, free radical scavenging of free radicals, cytoprotective, anti-diabetic, anti-hyperlipidemic, hepatoprotective activity, anti-cancer, anti-inflammatory, neuroprotective, and cardioprotective qualities (Beaucham & Fridovich, 1971; Brand-Williams *et al*., 1995; Bulley *et al*., 2009; Carr *et al*., 2013; Batool *et al*., 2023). Further research is required to fully understand the defenses that kiwi fruit provides against hepatotoxicity. The most well-known hepatoprotective medication, silymarin (SILY), was shown to have a strong protective effect against liver dam-age caused by CCL4. It is also used as a reference standard. Therefore, the objective of this investigation was to evaluate the antioxidant, anxiolytic, antidepressant, and immunomodulatory efficacies of kiwi fruit (*Actinidia deliciosa*) in alleviating the oxidative stress and other side effects of CCl4-induced hepatotoxicity in rats.

MATERIAL AND METHOD

Chemicals. Carbon tetrachloride (CCl_4) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Fresh Hayward kiwi fruits (*Actinidia deliciosa*) were sourced from local markets in Al-Madinah Al-Munawwarah, Saudi Arabia. All analytical-grade reagents were obtained from Sigma-Aldrich Chemicals Co. (St. Louis, Missouri, USA).

Preparation of Kiwi Fruit Extract. The preparation of kiwi fruit extract followed a modified method based on previous studies (Beauchamp & Fridovich, 1971; Batool *et al*., 2023). Briefly, fresh Hayward green kiwi fruits were cleaned, peeled, weighed, and chopped. The fruit pulp was homogenized for 30 seconds and centrifuged at 3000 rpm for 10 minutes. The resulting supernatant was filtered using Whatman No. 1 filter paper. A 70 % ethanol solution (1:1 w/v) was used for extraction. The filtrate was concentrated using a rotary vacuum evaporator and lyophilized to yield a dry extract (110 g per 1 kg of fresh fruit). The extract was stored at –80 °C until use.

In vitro Study

Phytochemical Screening. Preliminary qualitative phytochemical screening of the *ADE* was performed using standard protocols to identify secondary metabolites, including flavonoids, steroids, terpenoids, and glycosides (Cassano *et al*., 2006; Chang & Liu, 2009; Carr & Vissers, 2012; Ciacci *et al*., 2014; Dai *et al*., 2014).

Antioxidant Activity Assays. DPPH Radical Scavenging: Assessed as per Dhiman *et al*. (2020). Superoxide Anion Scavenging (SAS): Performed following Dias *et al*. (2020). Ferric Reducing Antioxidant Power (FRAP): Conducted using the protocol by Abdelghffar *et al*. (2022a).

In vivo Study

Acute Oral Toxicity Test (AOTT). An acute oral toxicity test was performed according to OECD guideline No. 420. Forty Wistar albino rats (male and female) were divided into four groups (n=10/group). Groups I and II received vehicle only, while Groups III and IV received *ADE* at 5000 mg/kg (single oral dose). Observations were m*ADE* over 14 days for mortality and signs of toxicity. The *ADE* was deemed safe, and doses of 0.5 and 1.0 g/kg were selected for further studies (El Azab, 2021).

Animals. Adult male albino rats (*Rattus norvegicus*; 120–130 g) were obtained from the laboratory animal house, College of Pharmacy, Taibah University, KSA. The animals were housed under standard laboratory conditions (12-hour light/dark cycle, 26-28 °C) with access to food and water ad libitum. All experimental procedures were approved by the Taibah University Research Ethics Committee (COPTU-REC-60-20230401).

Experimental Design. Forty-two rats were randomly divided into seven groups (n=6 per group):

1. Control group (normal saline)
2. *ADE* 0.5 g/kg (oral, 10 weeks)
3. *ADE* 1.0 g/kg (oral, 10 weeks)
4. CCl_4-only (1.0 mL/kg in olive oil, 3×/week for 10 weeks)
5. SILY + CCl_4 (silymarin 100 mg/kg + CCl_4)
6. *ADE* 0.5 g/kg + CCl_4
7. *ADE* 1.0 g/kg + CCl_4

Treatment continued for 10 weeks. Body weights were recorded at baseline and end of the experiment.

Behavioral Assessments. Behavioral changes were assessed using the following tests:

Open Field Test (OFT). Motor activity was assessed using an arena (100 × 100 × 47 cm, divided into 16 equal squares). The number of line crossings, latency, rearing, grooming, and freezing time were recorded over a 3-minute period.

Elevated Plus Maze Test (EPMT). Anxiety-like behavior was evaluated by placing rats at the center of the elevated plus maze and observing the time spent and number of entries into open and closed arms for 3 minutes.

Forced Swim Test (FST). Rats were placed in a cylindrical tank (60 cm height, 80 cm width) filled to 40 cm depth with room temperature water. Immobility and swimming times were recorded during a 3-minute session. All apparatuses were cleaned with 10 % ethanol between trials (Fletcher *et al*., 2024).

Sampling and Tissue Processing. At the end of the study, rats were anesthetized with ketamine (10 mg/kg, i.m.), and blood samples were collected. Serum was separated by centrifugation (3000 rpm, 30 min, 4 °C) and stored at-80 °C. Livers were excised, weighed, and homogenized in phosphate buffer (pH 7.4). Homogenates were centrifuged (4000 rpm, 15 min, 4 °C) and supernatants stored at -80°C for further analysis.

Biochemical Analyses

Liver Enzymes. Serum levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using UDI kits (Dammam, KSA).

Lipid Profile. Total cholesterol, triglycerides, HDL cholesterol were measured using commercial kits; LDL and VLDL levels were calculated.

Protein Profile and Ammonia. Serum total proteins and albumin were measured; globulin was calculated. Ammonia levels were assessed using MyBioSource kits (USA).

Antioxidant and LPO Biomarkers. Levels of total antioxidant capacity (TAC), reduced glutathione (GSH), superoxide dismutase (SOD), ascorbic acid (Vitamin C), and malondialdehyde (MDA) were quantified using MyBioSource kits.

Cytokine Assays. Serum tumor necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) were measured using ELISA kits from MyBioSource (USA).

Gene Expression by qRT-PCR. Frozen hepatic tissues were pulverized in liquid nitrogen, and total RNA was extracted using the RNeasy Mini Kit (Qiagen, Germany). One-step RT-PCR was performed using the AffinityScript RT-PCR kit (Agilent, USA).

Primer sequences:

CYP2E1:

Forward: 5'-CTCCTCGTCATATCCATCTG-3'
Reverse: 5'-GCAGCCAATCAGAAATGTGG-3'

Type I Collagen:

Forward: 5'-TCCTAGTCTCAATACGCAG-3'
Reverse: 5'-CGCTCTATCACTGGGCATTGG-3'

PCR conditions: 25°C (5 min), 42°C (30 min), 85 °C (5 min). Relative expression was calculated using the DDCt method.

Statistical Analysis. Data were expressed as mean ± standard error (SE). One-way ANOVA followed by Tukey's post hoc test was used for statistical analysis. Differences were considered statistically significant at $P < 0.05$.

RESULTS

In vitro Findings

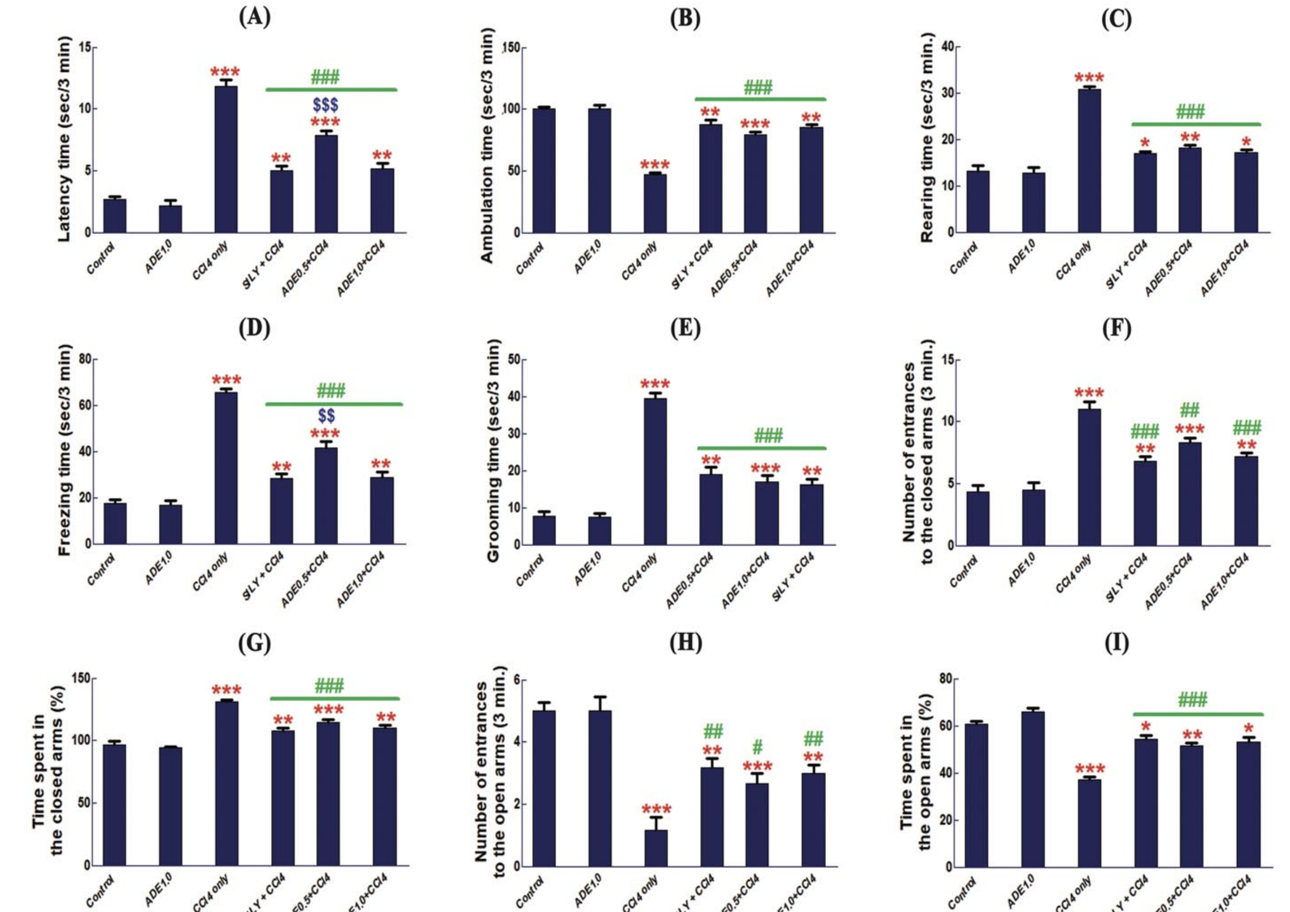
Phytochemical Screening. Preliminary qualitative phytochemical analysis of *Actinidia deliciosa* extract (*ADE*) revealed the presence of steroids, cardiac glycosides, terpenoids, flavonoids, and carbohydrates. In contrast, tests for alkaloids and tannins yielded negative results. The total phenolic content (TPC) was 31.24 ± 1.30 mg gallic acid equivalents (GAE)/g of dry extract, while the total flavonoid content (TFC) was 22.12 ± 1.86 mg quercetin equivalents (QE)/g of dry extract.

Antioxidant Activity. *ADE* exhibited strong antioxidant properties *in vitro*. The DPPH radical scavenging activity of *ADE* was recorded at 2.01 ± 0.35 mg/mL, which was significantly higher than that of the reference standard vitamin E (0.01 ± 0.001 mg/mL; $P < 0.001$). Similarly, superoxide anion scavenging activity was observed at 5.04 ± 0.07 mg/mL for *ADE*, compared to 0.21 ± 0.04 mg/mL for vitamin E ($P < 0.001$).

In vivo Findings

Acute Oral Toxicity. No mortality or observable adverse effects were reported in either male or female rats following oral administration of *ADE* at 5000 mg/kg over a 14-day observation period. Therefore, the acute lethal dose (LD_{50}) of *ADE* was estimated to be greater than 5000 mg/kg, indicating that *ADE* is safe for further pharmacological use.

Behavioral Assessments: Motor Activity and Anxiety-like Behavior. As shown in Figure 1, The results of the OFT illustrated increased latency, rearing, freezing, & grooming time and decreased ambulation time ($p<0.001$) in the CCl4-treated alone group in contrast to the healthy control animals. Furthermore, in the EPMT, the number & the time spent in the open arm significantly reduced and the number & the time spent in the closed arm significantly increased in the



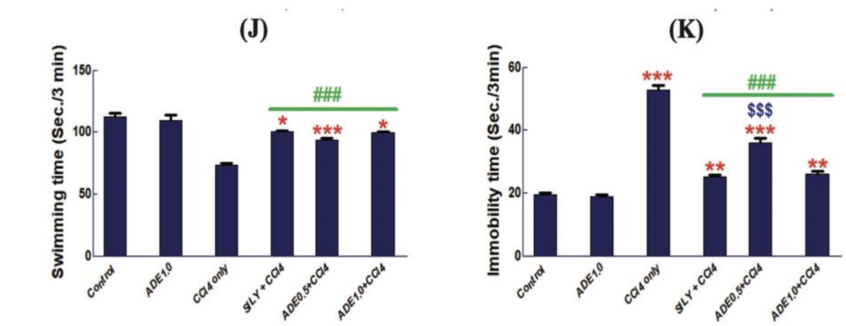


Fig. 1. The impact of *ADE* on the motor activity (A-E), anxiety like behavior (F-I) and depression like behavior (J-K) in the CCl4-induced liver injury. The symbol * denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0·05 in comparison to the CCL4 animals. $ symbol indicates a P-value < 0·05 in comparison to the SILY animals.

CCl4 group in contrast to the healthy control animals ($p<0.001$). Moreover, in MWMT, swimming time and immobility time significantly decreased and increased, respectively, ($p<0.001$) in the CCl_4 group in contrast to the healthy control animals. The above changes were partially regulated in a dose-dependent way in the pre-treatment rats that received either SILY or both doses of *ADE* (ranging from P<0.05-0.001 in contrast to the control animals; P<0.001: *vs* CCl_4-only animals). All these significant recordings are indicative of the anxiolytic and antidepressant effects of *ADE*. It is noted that the improving effect of SILY and *ADE* is similar (P>0.05) in most parameters, except the latency, freezing, and immobility significantly changed between SILY and a low dose of *ADE* (ranging from P<0.01-0.001 in contrast to the SILY animals).

Effect of *ADE* on the weights of the body & the liver, and the relative liver weights. In Table I, the CCl_4-treated alone group had a significant reduction ($p<0.001$) in body weight gain in contrast to the control animals. In contrast to the control group, rats given CCl4 alone had a considerable rise ($p<0.001$) in the weight of the liver as well as its relative weight. This marked loss of body weight and alterations in the relative liver weight were partially ameliorated by either SILY or low & high doses of *ADE* (ranging from P<0.05-0.001 in contrast to the control animals; P<0.05-0.001 vs the CCl_4-only animals). It is noted that the improving effect of SILY and *ADE* is similar (P>0.05) in most parameters, except the weight of the liver as well as its relative weight significantly changed between SILY and a low dose of *ADE* (P<0.001 in contrast to the SILY animals).

Effect of *ADE* on the serum hepatic toxicity

ALP, ALT, and AST, indicators for serum cellular toxicity, were substantially elevated ($p<0.001$) in the CCl_4-treated alone group in contrast to the healthy control animals, according to Figure 2. In the pre-treatment rats that received either SILY or both doses of *ADE*, all these alterations were only marginally regulated (ranging from a P-value <0.05-0.001 in contrast to the control animals; the P-value <0.001 vs the CCl_4-only animals). It is noted that the improving effect of SILY and *ADE* is similar (P>0.05) for ALP, ALT, and AST.

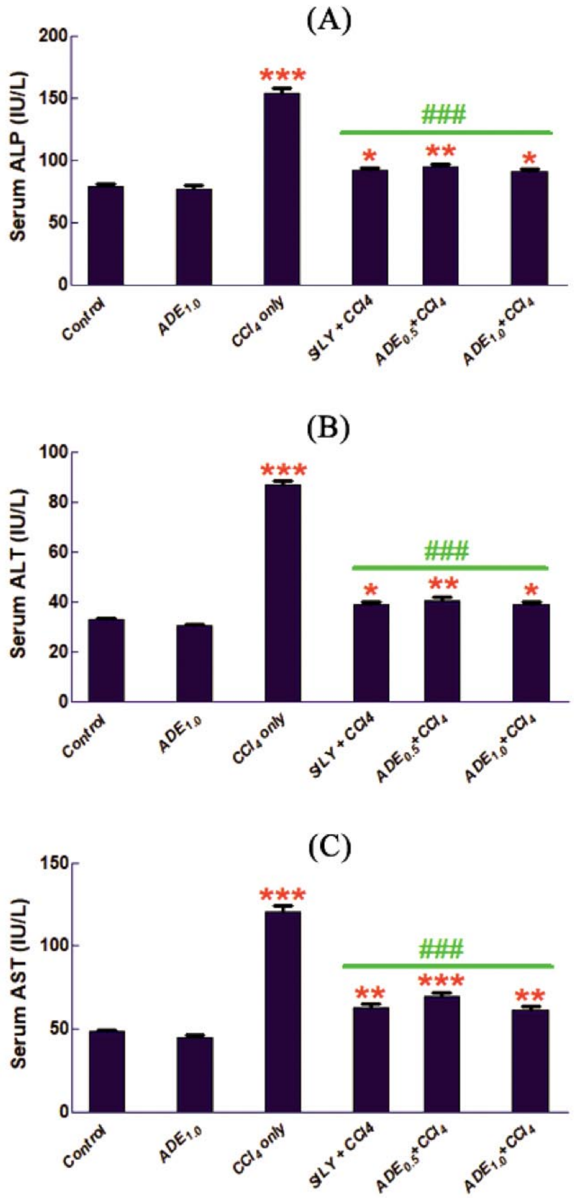
Effect of *ADE* on the serum lipids & proteins profile indices and ammonia. According to Table II, the CCl_4-treated alone group's blood levels of total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, total protein, and ammonia substantially increased ($p<0.001$) in comparison to the animals in the healthy control group. Moreover, HDL-chol. and albumin levels in serum significantly reduced ($p<0.001$) in the CCl_4 group in contrast to the healthy control animals. The above changes were partially regulated in a dose-dependent way in the pre-treatment rats that received either SILY or both doses of *ADE* (ranging from a P-value <0.05-0.001 in contrast to the control animals; P<0.001: vs CCl4-only animals). It is seen that the beneficial impact of *ADE* and SILY is comparable (P>0.05) in most parameters, except for triglycerides, HDL-chol, LDL-chol, and VLDL-chol, which altered considerably between *ADE* and a low dosage (P<0.001 compared to the SILY animals).

Effect of *ADE* on the weights of the antioxidants and lipid peroxidation. As shown in Figure 3, the hepatic MDA level significantly elevated (P<0.001) in CCl_4-alone animals in contrast to the healthy control animals. While the hepatic GSH, SOD, TAC, and ascorbic acid (Vit. C) significantly decreased (P<0.001) in the CCl_4-treated alone animals in comparison to the control animals. Oral administration of low or high doses of *ADE* caused partial alteration in the hepatic MDA (the P-value <0.05-0.001 *vs* the healthy animals; the P-value <0.001 vs CCl4 only animals), in dose-dependent manners. Also, changes of hepatic GSH, SOD, TAC, and ascorbic acid (Vit. C) were partially alleviated in the pre-treatment rats that taken a low dose of *ADE* (ranging from the P-value P<0.05-0.01: in contrast to the control animals; the P-value <0.001 vs CCl_4 only group). Otherwise, the hepatic GSH, SOD, TAC, and ascorbic acid (Vit. C) were returned to a state that was almost normal levels after treatment with a high dose of *ADE* (the P-value>0.05 in contrast to the control animals; P<0.001 in contrast to CCl_4 only group). It is shown that the positive effects of *ADE* and SILY are equal (P>0.05) in these antioxidant parameters.

Table I. The impact of *ADE* on weights of body & liver (g) and relative liver weight (g/100 g b.w) in the CCl4-induced liver injury.

Groups / Parameters	Control	$ADE_{1.0}$	CCl_4 only	SILY+CCl_4	$ADE_{0.5}$+CCl_4	$ADE_{1.0}$+CCl_4
Body weight before (g)	124.30±1.39	123.50±1.15	125.70±1.00	126.90±0.81	125.30±0.96	127.30±0.76
Body weight after (g)	253.40±1.56	258.30±2.12	234.10±1.58	245.70±1.36###	240.00±1.99 #	243.60±1.36###
Body weight gain (g)	129.10±2.43	134.80±2.03	108.50±1.92	118.80±1.14##	114.70± 1.67#	116.30± 1.34#
Liver weight (g)	5.45±0.05	5.34±0.17	7.85±0.05	5.82±0.05###	6.63±0.06###$$$	5.99±0.06###
Relative liver weight	2.15±0.03	2.07±0.08	3.35±0.04	2.37±0.03###	2.76±0.03###$$$	2.46±0.02###

ADE: *Actinidia deliciosa* extract. CCL4: carbon tetrachloride. The symbol denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0·05 in comparison to the CCL4 animals. $ symbol indicates a P-value < 0·05 in comparison to the SILY animals.



Effect of *ADE* on the weights of the serum cytokines levels. Figure 4 revealed that the markers for serum pro-inflammatory markers including TNF-α as well as IL-6 cytokines significantly elevated ($p<0.001$) in CCl_4- only animals in comparison to the healthy control animals. The rats who received either SILY or both *ADE* dosages had some degree of partial modulation of all these alterations (ranging from P<0.05-0.001 in contrast to the control animals; P<0.001 vs the CCl_4 animals) in a dose-dependent way. Also, it is seen that the positive effects of *ADE* and SILY are equal (P>0.05) in these pro-inflammatory markers.

Effect of *ADE* on the CYP2E1 and type I collagen gene expressions. Figure 5 showed that the expression level of CYP2E1 and type I collagen significantly elevated ($p<0.001$) in CCl_4- only animals in comparison to the healthy control animals. In a dose-dependent manner, oral administration of either SILY or low and high dosages of *ADE* partially altered the expression level of hepatic CYP2E1 and type I collagen (P<0.05-0.001 in contrast to the control animals; P<0.001 vs CCl_4 only animals). It is shown that the beneficial impact of *ADE* and SILY is equivalent (P>0.05) on CYP2E1 gene expression, except for type I collagen gene expression, which changed considerably between *ADE* and a low dosage (P<0.001 compared to the SILY animals).

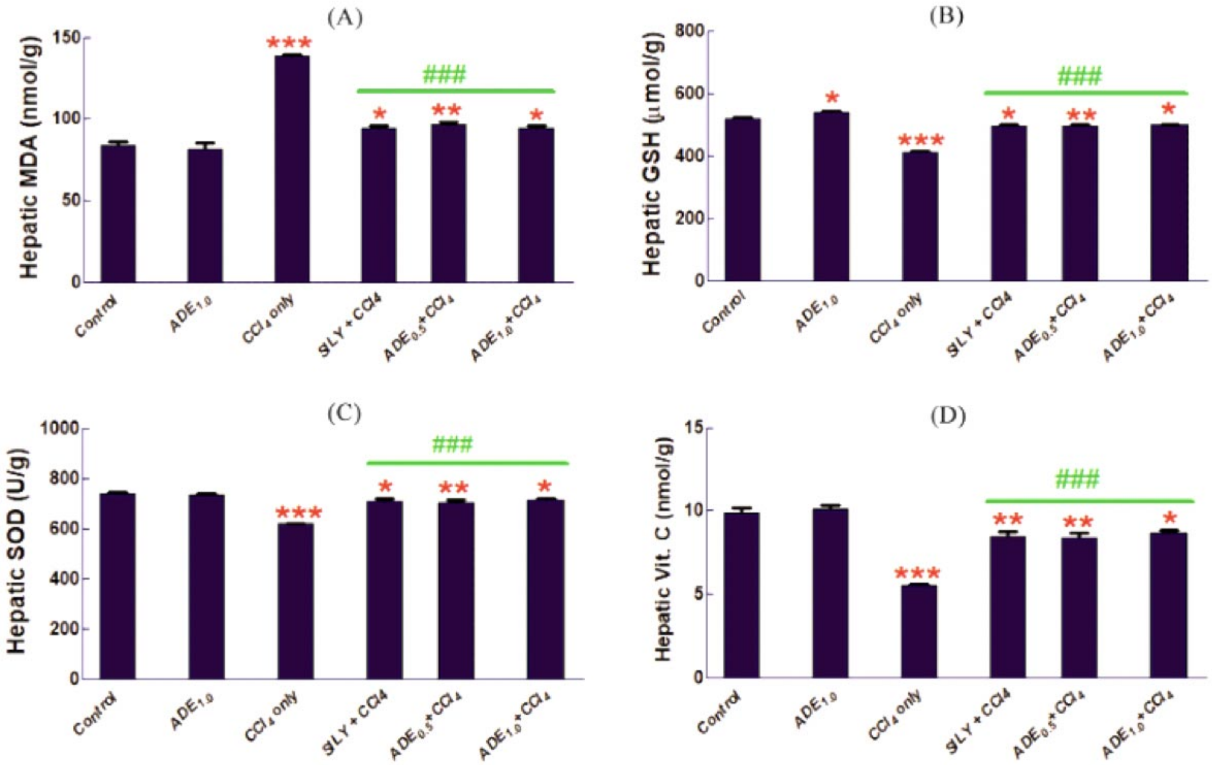
The healthy rats' response to *ADE*. Additionally, our study found no statistically significant difference (p > 0.05) in any of the measures between the healthy *ADE*-treated group (especially low dose; the data not shown) and the control group (Tables I and II; Figs. 1 to 5), except only the high dose of *ADE* had significant rise (p<0.05) in serum TAC & hepatic GSH levels in contrast to the control animals, as shown in Figure 3.

Fig. 2. The impact of *ADE* on serum alkaline phosphatase, ALP (A), alanine/aspartate transaminases, ALT & AST (B&C) in the CCl_4-induced liver injury. The symbol * denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0·05 in comparison to the CCL_4 animals.

Table II. The impact of *ADE* on serum lipids & proteins profile and ammonia in the CCl4-induced liver injury.

Groups / Parameters	Control	*ADE*$_{1.0}$	CCl_4 only	SILY+CCl_4	*ADE*$_{0.5}$+CCl_4	*ADE*$_{1.0}$+CCl_4
Total cholesterol (mg/dl)	133.40±1.86	129.3±1.29	181.50±1.15	139.80±1.49 ###	142.5±1.53 ###	140.40±1.10 ###
Triglycerides (mg/dl)	100.5±1.36	100.7±1.20	192.0±2.01	110.40±1.03 ###	132.70±3.60###$$$	114.00±2.43###
HDL- Chol. (mg/dl)	22.57±0.63	24.79±0.88	7.33±0.27	19.50±0.43 ###	13.10±0.73###$$$	19.06±0.37 ###
LDL- chol. (mg/dl)	90.75±1.86	84.36±2.13	135.80±1.04	98.10±1.59 ###	111.40±1.54###$$$	100.50±0.60 ###
VLDL- chol. (mg/dl)	20.09±0.27	20.14±0.24	38.40±0.40	22.09±0.21 ###	26.53±0.72###$$$	22.79±0.47 ###
T. protein (mg/dl)	6.58±0.26	6.85±0.28	5.21±0.100.26	5.68±0.10 #	5.28±0.08	5.51±0.15
Albumin (mg/dl)	3.52±0.12	3.86±0.09	2.40±0.05	3.13±0.85 ###	2.94±0.07 ###	3.03±0.08 ###
Globulin (mg/dl)	3.07±0.30	2.99±0.27	2.82±0.10	2.55±0.14	2.34±0.15	2.49±0.19
Ammonia (_mol/L)	34.72±1.35	34.89±1.14	93.71±1.27	42.87±1.10 ###	74.11±2.27 ###	43.87±1.28 ###

ADE: *Actinidia deliciosa* extract. CCL4: carbon tetrachloride; HDL high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol. The symbol denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0·05 in comparison to the CCL4 animals. $ symbol indicates a P-value < 0·05 in comparison to the SILY animals.



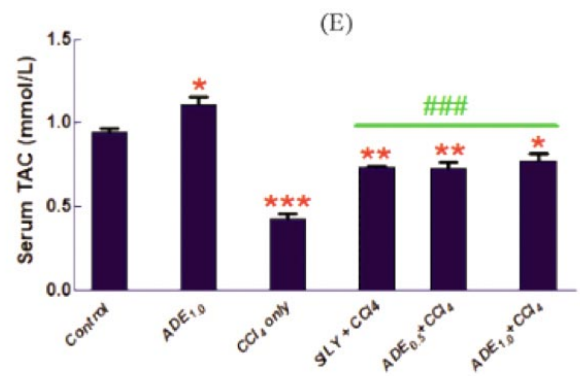


Fig. 3. The impact of *ADE* on hepatic malondialdehyde (A), reduced glutathione (B), superoxide dismutase (C), vitamin C (D), and total antioxidant capacity (E) in the CCl_4-induced liver injury: *ADE*: *Actinidia deliciosa* extract. CCL_4: carbon tetrachloride; SOD: superoxide dismutase; MDA: malondialdehyde; TAO: total antioxidant; GSH: glutathione reduced, Vit. C: vitamin C. The symbol * denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0.05 in comparison to the CCL_4 animals.

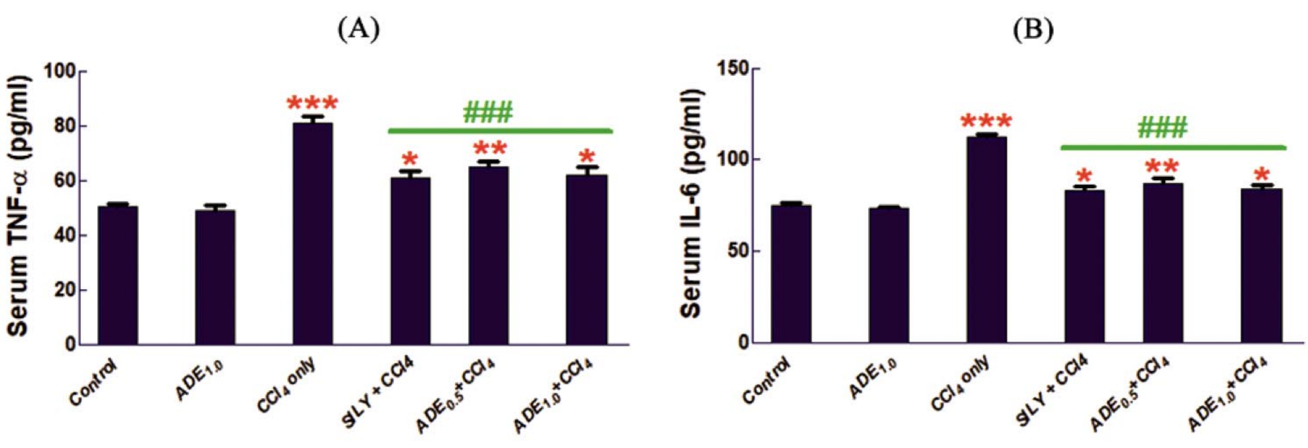


Fig. 4. The impact of *ADE* on serum TNF (A) and IL-6 (B) in the CCl4-induced liver injury. *ADE*: *Actinidia deliciosa* extract. CCL4: carbon tetrachloride; IL-6: interleukin-6; TNF: tumor necrosis factor. The symbol * denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0·05 in comparison to the CCL4 animals.

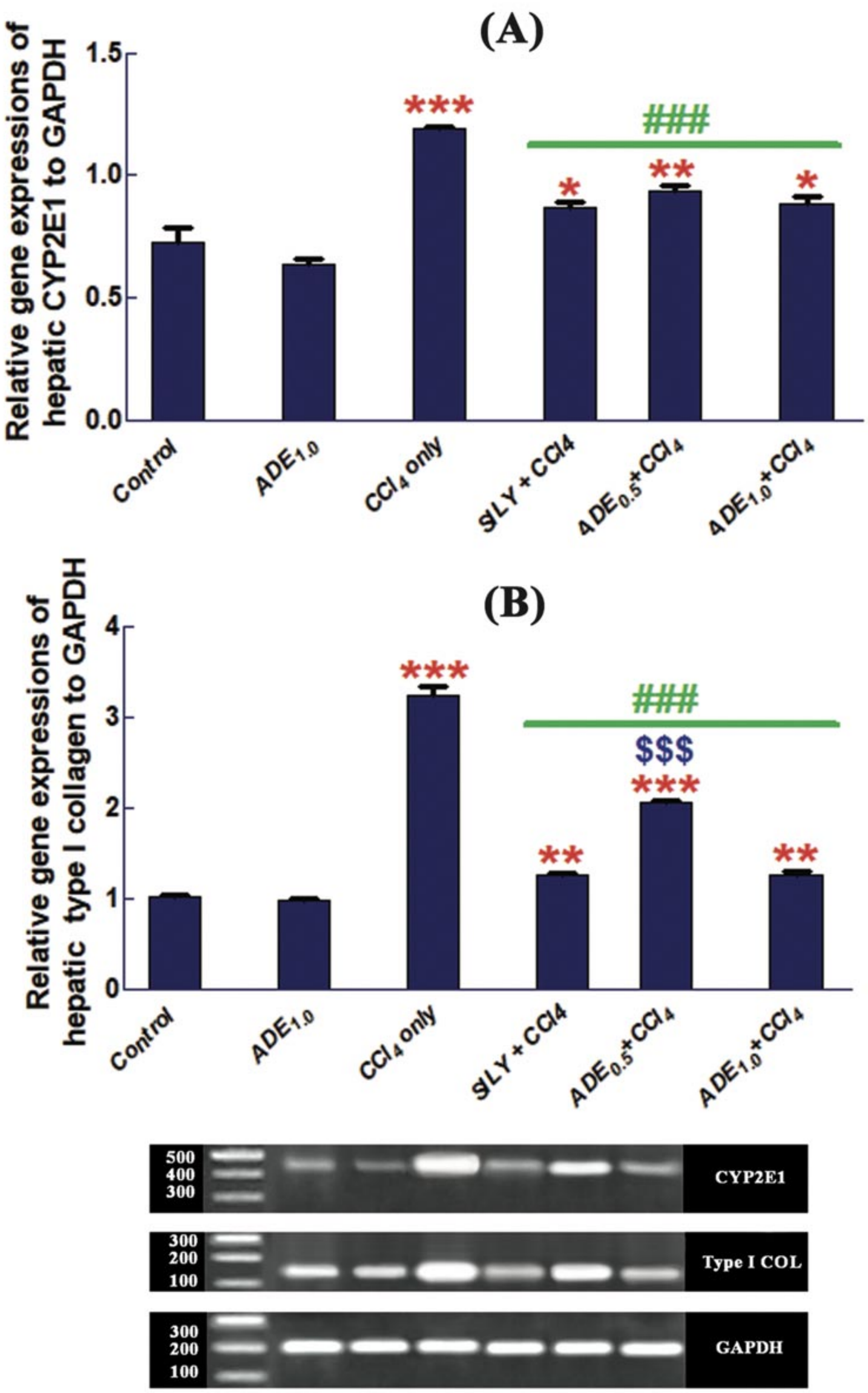


Fig. 5. The impact of *ADE* on the relative gene expression of CYP2E1 (A) and type I collagen (B) in the CCl_4-induced liver injury. *ADE*: *Actinidia deliciosa* extract. CCL_4: carbon tetrachloride; CYP2E1, Cytochrome (CYP) P450 family (2) subfamily (E) member (1). The symbol * denotes a P-value < 0.05 relative to the control group of animals. # symbol indicates a P-value < 0.05 in comparison to the CCL4 animals. $ symbol indicates a P-value < 0.05 in comparison to the SILY animals.

DISCUSSION

Numerous studies have shown that mental illnesses like anxiety and despair were present in many individuals with liver diseases including cirrhosis and hepatitis (Harborne, 1998; He *et al*., 2006; Ahmad *et al*., 2018). Several investigations have shown that liver damage or failure can result in hyperammonemia, which can cause oxidative stress and neuroinflammation as well as several neurological problems (Hunter *et al*., 2012; Huang *et al*., 2017; Ahmad *et al*., 2018; Fletcher *et al*., 2024). The toxic lipophilic CCl4-induced liver injury is a frequent model for testing the anti-hepatotoxic, antidepressant, and anxiolytic activities of pharmaceutical products (AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a, 2022b). According to previous research, kiwifruit has been associated with enhancing memory deficits, and mood disturbance via inhibiting neuroinflammation and oxidative stress (Iwasawa *et al*., 2010, 2011; Carr *et al*., 2013). Considering this data, the current investigation reported *ADE* has possible anxiolytic and antidepressant-like effects concerning CCl4-induced liver damage.

Moreover, the structural integrity of the liver may be harmed by the elevation of lipid peroxidation and oxidative stress leading to an increase in ALP, ALT, and AST levels, which are discharged into the blood. The CCl4 metabolism is initiated with the formation of highly active toxic metabolites of CCl4 that combine with biomolecules (Kang *et al*., 2012; Amer *et al*., 2014; AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a). An imbalance between intracellular free radical generation and cellular defense systems causes increased oxidative stress. Numerous investigations have shown that CCl4 lowers GSH, reduces the antioxidant enzymes activities like SOD & Vit. C, and raises hepatic MDA levels (Kang *et al*., 2012; Amer *et al*., 2014; AbdElfatah *et al*., 2021; Abdelghffar *et al*., 2022a). However, it was suggested that liver injury may also be due to the elevation of oxidative stress, LPO, and inflammatory mediators that are released from the activated stellate macrophage (Kupffer cells) (Carr *et al*., 2013; Abdelghffar *et al*., 2022a). The upregulation of cytochrome P450 2E1 is the primary cause of the traditional route of ROS production in hepatocytes. So, the downregulation of this gene can result in a decrease in reactive metabolites, and CYP2E1 knock mice were resistant to CCl4-induced liver damage (Kassab & Elwan, 2020). Also, LPO is one of the most significant indicators of oxidative stress. Our research showed that CCl4 elevated CYP2E1, which accounted for the elevated LPO and decreased GSH levels in the CCl4 group (Ahmed *et al*., 2011; Khan *et al*., 2019). In addition, the elevation of oxidative and nitrosative stresses are caused by overexpression of CYP2E1. Hepatic injury, which often progresses to fibrosis, results in hepatic stellate cells (HSCs) activation and synthesis of procollagen-I which is the main source of collagen I, and other fibrosis-deposited matrix proteins. CCl4 is upregulated the type-I collagen in hepatic tissue (Lee *et al*., 2011).

Our findings of the present investigation showed kiwi fruit exerts antidepressant, anxiolytic, and hepatoprotective effects through ameliorating depressive/anxiety-like behaviors, the body weight, lipid profile, and liver enzymes as well as increasing the total enzymatic and non-enzymatic antioxidant capacity as well as decreasing LPO indicator (MDA) & inflammatory cytokines (Beauchamp & Fridovich, 1971; Bulley *et al*., 2009; Lin *et al*., 2011; Mahesh *et al*., 2013; Yang *et al*., 2015) as well as down-regulation of CYP2E1& type-I collagen in liver (Khan *et al*., 2019). This might be explained by a combination of antioxidant, anti-inflammatory, membrane-stabilizing, and detoxification mechanisms of kiwi fruit, making it a valuable protective agent for liver diseases and disorders. Silymarin (SILY) is a flavonoid complex, widely known for its hepatoprotective properties. It was clear from the previous results that the improving effect of kiwi against liver toxicity is similar in most indications compared to SILY. The kiwi fruit's capacity to protect the liver is enhanced by many mechanisms: (I) Antioxidant Activity: Kiwi fruit is rich in flavonoids (quercetin, kaempferol, and catechins), carotenoids (beta-carotene and lutein), polyphenolic compounds (chlorogenic acid and caffeic acid), vitamins (A, B2, B9, C, E, K), minerals (Ca, Cu, Mg, & P), and other compounds. Flavonoids also have the potential to be antioxidants and may have additional health benefits (Maillar, 1998; Mitra *et al*., 2001; Motohashi *et al*., 2002; OECD, 2002; Essawy *et al*., 2010; Milaneschi *et al*., 2012; Navinés *et al*., 2012; Moreira *et al*., 2014; Mazzarella *et al*., 2019). As a strong antioxidant, kiwi helps to prevent liver damage and the advancement of fibrosis by scavenging free radicals and ROS that can harm liver cells. It raises the body's natural antioxidant levels, including GSH, which aids in detoxification and oxidative stress resistance. Kiwi fruit phytochemicals neutralize free radicals and stop LPO, which also blocks the initial and following (initiation & propagation) steps of oxidative chain reactions (Owen *et al*., 2005; Huang *et al*., 2017). Furthermore, kiwifruit can prevent HFD from raising LPO, oxidative stress, and plasma lipid profiles (Park *et al*., 2010). We discovered that this kiwi treatment inhibited all the downstream effects, including oxidative stress and LPO, indicating that kiwi may block the initial stage of the signaling pathway. This is because CYP2E1 catalyzes the production of free radicals during the metabolism of CCl4, which leads to liver dysfunction. Therefore, we hypothesized that proanthocyanidins might lessen the increased expression of CYP2E1 after CCl4 treatment (Khan *et al*., 2019). Moreover, MDA and free radicals can activate HSCs and promote collagen production such as Type I collagen (Park *et al*., 2006). The antioxidant or radical scavenging properties of kiwi may contribute to its anti-fibrotic effects. (II) Anti-inflammatory effects: Kiwi shows anti-inflammatory abilities by preventing the generation of pro-inflammatory cytokines and their mediators (Beauchamp & Fridovich, 1971; Maillar, 1998; Mitra *et al*., 2001; Motohashi *et al*., 2002; OECD, 2002; Bulley *et al*., 2009; Essawy *et al*., 2010; Lin *et al*., 2011; Milaneschi *et al*., 2012; Navinés *et al*., 2012; Mahesh *et al*., 2013; Shi *et al*., 2013; Moreira *et al*., 2014; Yang *et al*., 2015; Richardson *et al*., 2018; Batool *et al*., 2023; Ugwah, 2023). (III) Membrane Stabilization & Inhibition of Fibrosis: Kiwi protects hepatocyte membranes from oxidative stress caused by CCl4, and supports liver function by preserving the integrity of cell membranes (Bulley *et al*., 2009), and prevents the activation of hepatic stellate cells, which play a key role in the progression of liver fibrosis because they produce collagen and other ECM components (Dai *et al*., 2014). Several researchers who have studied the effects of chlorogenic acid, which is often present in kiwi fruit, on liver fibrosis in rats (Shi *et al*., 2013, Carr *et al*., 2013; Richardson *et al*., 2018). According to their studies, kiwi fruit extract reduced liver fibrosis by inhibiting the activation of hepatic stellate cells and suppressing the expression of genes involved in fibrosis progression. (IV) Antidepressant and anxiolytic effect: It has been demonstrated that low levels of vitamins C & E, and carotenoids are associated with higher depression & cognitive impairment (Wong *et al*., 1998; Wang *et al*., 2000, 2007; Wu *et al*., 2023). Kiwi fruit is particularly rich in these micronutrients (Xue *et al*., 2017; Yadav *et al*., 2017), which may contribute to improved mood as well as vitality disorders (Yamamoto, 1990; Iwasawa *et al*., 2010). Furthermore, according to Richardson *et al*. (2018), it is an excellent source of folate, (or vitamin B9), necessary to produce neurotransmitters like serotonin, essential for controlling mood and anxiety (Zhu *et al*., 2021). Kiwi fruit also has a lot of potassium, which is important for maintaining nerve function and muscle control. Potassium levels may indirectly affect mood and anxiety levels (Richardson *et al*., 2018). Some research suggests that certain compounds in kiwi fruit may act as precursors to serotonin (Zhu *et al*., 2021), which associated with mood regulation.

CONCLUSION

As an edible medicinal plant, kiwifruit (*Actinidia deliciosa*) effectively reduces the oxidative stress caused by CCl4 in the liver of rats by enhancing the body's natural antioxidant defenses, decreasing oxidative stress, regulating LPO, and alleviating depressive and anxious symptoms. The kiwifruit's phenolic-flavonoid concentration might be the cause of this effect. The kiwifruit has potential antioxidant capabilities that support its use for treating liver ailments or preventing illnesses caused by oxidative stress. It's important to note that while these findings are promising, more research is needed to fully understand the mechanisms underlying the protective effects of kiwi fruit on mental and liver health.

Ethical approval. The National Institutes of Health Publications' Guidelines for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1985) governed all animal activities. The design of this research was authorized by the College of Pharmacy, Taibah University-Research Ethics Committee (COPTU-REC-60-20230401).

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MOHAMMEDSALEH, Z. M. Efectos protectores del extracto de *Actinidia deliciosa* y la silimarina sobre la hepatotoxicidad inducida por CCl_4 y las alteraciones conductuales en ratas albinas macho. *Int. J. Morphol., 43(5)*:1714-1725, 2025.

RESUMEN: Este estudio tuvo como objetivo evaluar los posibles efectos antioxidantes, antiinflamatorios, antidepresivos y ansiolíticos del extracto de *Actinidia deliciosa* (*ADE*) en comparación con la silimarina (SILY) para mitigar la hepatotoxicidad inducida por tetracloruro de carbono (CCl_4) y las alteraciones conductuales en ratas albinas macho. Un total de cuarenta y dos ratas albinas macho se dividieron aleatoriamente en siete grupos: control, *ADE* 0,5 g/kg, *ADE* 1,0 g/kg, solo CCl_4, SILY + CCl_4, *ADE* 0,5 + CCl_4 y *ADE* 1,0 + CCl_4. La administración de *ADE* redujo significativamente los niveles séricos de enzimas hepáticas, mejoró los marcadores antioxidantes y alivió las anomalías conductuales. *ADE* también disminuyó la expresión hepática de CYP2E1 y colágeno tipo I, lo que sugiere sus posibles propiedades hepatoprotectoras y neuroprotectoras. Estos hallazgos indican que *ADE* podría servir como una alternativa prometedora a la silimarina en la protección contra el daño hepático inducido por sustancias químicas.

PALABRAS CLAVE: *Actinidia deliciosa*; Antioxidante; Hepatotoxicidad; CYP2E1; Ansiolítico; Depresión; Lesión hepática.

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