Possible Ameliorative Properties of *Tribulus terrestris* Extracts Against Liver and Kidney Toxicity Caused by Ivermectin in Rats

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Possible Ameliorative Properties of *Tribulus terrestris* Extracts Against Liver and Kidney Toxicity Caused by Ivermectin in Rats

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Abstract

The current study sought to determine whether *Tribulus terrestris* fruit extracts could protect rats from hepato-renal damage brought on by ivermectin.To assess the effectiveness of *Tribulus terrestris* extracts against liver and renal toxicity as well as related histopathological alterations ,vitamin "C" was employed as a comparison standard medication . Thirty rats were divided into two main groups; the first main group (6 rats) received a basal diet and used as the negative group.The second main group of 24 rats received ivermectin (IVM) (200 mg / kg of body weight) for 30 days in order to develop hepatic renal toxicity. Four separate groups were created from the second main group: Group 2 received a basal diet and used as the positive control group. Groups 3 and 4 consumed a basal diet in addition to oral *Tribulus terrestris* (TT) ethanolic and aqueous extracts (200 mg per kg of body weight) , respectively. Group (5) consumed a basal diet along with oral vitamin "C" (200 mg per kilogram of body weight) for 28 days. Phenolic compounds in TT extract were identified using a high-performance gas chromatograph. The outcomes proved that groups of rats administered for 28 days with *Tribulus terrestris* extracts as well as vitamin "C" at a dose of 200 mg/Kg body weight have shown improvement in feed efficiency ratio , body weight gain, feed intake , function of the kidneys and liver variables , serum and urinary electrolytes (sodium and potassium), some immunological profiles (interleukin 6 and interleukin 10) and antioxidant enzymes activity.The group given *Tribulus terrestris* ethanolic extract (200mg/Kg body weight) had the best outcomes .The biochemical evaluation was corroborated

by a histopathological investigation. According to the results of this investigation, *Tribulus terrestris* extracts could be utilized as a successful treatment to lessen the ivermectin - induced liver and kidney damage in rats because they contain many phenolic antioxidant compounds.
Key words : Ivermectin - *Tribulus terrestris* - Toxicity- vitamin "C"

Introduction

A family of insecticidal substances with acaricide and anthelmintic properties has been identified as avermectins, which have been identified from *Streptomyces avermititis* fermented products. Ivermectin (IVM), an avermectin derivative, demonstrates a wide range of efficacy against lung and gastrointestinal nematodes as well as clinically significant ectoparasites in domestic animals **(Suárez, *et al*., 2013)**. According to reports, IVM causes negative effects on the liver and kidneys, oxidative stress, and weight loss **(El-Far, 2013)**. Rat liver samples taken 24 hours after the previous IVM injection showed vacuolated hepatocyte cytoplasm along with congested hepatic blood arteries and blood sinusoids. In addition, endothelial cell growth in the capillaries' lining and congested intertubular capillaries and renal blood channels were also seen**(Rabab *et al*., 2015)**.

Antioxidants are a group of several chemical compounds that are unmistakably linked to significant health advantages and lower chances of numerous age-related disorders. Reactive oxygen species (ROS) are types of oxygen that have been slightly decreased or "energized"; some of those kinds are "free radicals" with an electron that is unpaired in an orbital structure, but others are "nonradical species" like peroxide made from hydrogen and singlet oxygen, whose responsiveness is even higher than that of oxygen molecules in their neutral state **(Lü *et al*., 2010; Benzie and Choi 2014 and Halliwell , 2022) .**

According to multiple studies **(Almeida *et al*., 1998) ,** antioxidant compounds protect cells from the negative effects

of a variety of environmental pollutants. In addition to maintaining transportation of ions and elasticity of membrane , vitamins' antioxidant properties can additionally inhibit the emission of Fe 2+ as well as Mg 2+ from their protein-binding structures, potentially slowing the pace of lipid peroxidation.

According to **Holford *et al*., (2020) ,** ascorbic acid (AA), sometimes known as "vitamin **"C"**, is a crucial supplementary treatment for respiratory infections. According to **Kojo, (2004) and El-Demerdash *et al*., (2005) ,** it has a high water solubility and works well as an agent for reduction. According to **Yavuz *et al*., (2004**), free radicals are trapped in the watery phase of outside fluids by vitamin C's hydrophilic nature, which makes it a significant free radical scavenger and preventing oxidative damage to biomembranes.Most primates, which includes people, certain birds, guinea pigs and fish cannot synthesis vitamin "C" and have to get it from their food. In contrast, the majority of mammals can synthesize vitamin "C" in their kidneys or liver. This is because of a genetic abnormality that prevented glucose from being transformed into AA **(Aversa *et al*., 2016).**

Tribulus terrestris (TT), sometimes referred to as goat head, devil's thorn, and puncture vine, is an annual plant. The genus *Tribulus* is classified as part of the *Zygophyllaceae* family. Both the mediterranean and subtropical desert regions contain it. Numerous ailments have been treated with TT due to its bioactive components, including alkaloids, tannins, saponins, vitamins, glutamic acid, and aspartic acid. Its ash is useful for external use in rheumatoid arthritis, and it is utilized to treat gonorrheal rheumatism with cystitis, gleet, and gout **(Al-Harrasi *et al*., 2023)**.

Overall, Due to its numerous anti-inflammatory characteristics, TT has been utilized as a nutraceutical in the treatment of disorders caused by inflammation, including as obesity, diabetes, pancreatitis, tumors, inflammatory intestinal disease, liver and kidney damage, and arthritic

conditions **(Abbas *et al*., 2022 and Gunarathne *et a*l., 2022).** It has also been used as an adjuvant by modern herbalists .Therefore , the goal of the present research was to assess how *Tribulus terrestris* fruit extracts affected liver and kidney function markers in male rats that had received ivermectin injections.

Materials and methods

Chemicals and plants

The *Tribulus terrestris* fruits used in this study were provided by the Agricultural Seeds, Herbs, and Medicinal Plants Company in Cairo, Egypt. Starch and corn oil were purchased from the local marketplace in Cairo, Egypt .We bought dextrin, L-cysteine, casein, minerals, vitamins, and cellulose from the Cairo Corporation for Chemical Trade. The Ivermectin (IVM) was given by Sigma Chemical Company.

The process of making plant extracts

In accordance with **Kamboj *et al*., (2020)** method , the plant's fruit was weighed and submerged in two-fold distilled water (5% w/v) for an entire night at 4°C. The extract will be put through a muslin filter before being centrifuged for 10 minutes at 4^{o} C at 3,000 rpm. The supernatant that resulted was referred to as an aqueous extract.

The method used to prepare ethanolic extract was in accordance with the method used by **Lakshmi *et al*., (2012)** . In a separating funnel, one kg of the ground-up dried plant was thoroughly extracted using two liters of 70% ethanol. Under vacuum, the extract was vaporized to dryness using a rotatory evaporator at 25°C. To make the resulting crust acceptable for oral delivery, it was reconstituted in a solvent vehicle.

Plant phenolic compounds

In plant extract , polyphenolic components and phenolic and flavonoid compounds were separated and identified by HPLC **(Kim *et al*., 2006)**.

Experimental approach

Thirty mature male Sprague Dawley rats weighing roughly 150 ± 10g were acquired from the Laboratory of Animal Colony, Helwan , Egypt. They were kept in well - aerated cages under hygienic circumstances, fed on a basal diet, and had free access to water **(Reeves *et al*., 1993)**.The animals were acclimated for a week. Following this period, the rats were split into two major groups. The first major group, consisting of six rats, functioned as a negative control group and was fed a diet that is standard . Ivermectin (IVM) (200 mg / kg) was injected into the second main group of 24 rats for 30 days to cause hepato renal damage **(Ismaiel *et al*., 2017) .** The second main group was divided into four smaller groups . Group 2 , serving as the positive control , was provided with a basal diet for 28 days. Groups 3 and 4 were given a basal diet along with 200 mg of oral TT extracts per kg of body weight . Group (5) was provided with a base diet and 200 mg of oral vitamin "C" per kilogram of body weight.

After 28 days, rats were placed in cages for 24 hours, urine collected for creatinine clearance. The animals were weighed and fasted for one night before being exsanguinated .Each rat had blood extracted from its hepatic portal vein, which was then put in dry-clean centrifuge tubes.

Biological assessment

According to **Chapman *et al*., (1959) ,** feed efficiency ratio (FER) , body weight gain (BWG) and feed intake (FI) were calculated during the experiment.

Biochemical evaluation

Creatinine, urea nitrogen, and uric acid concentrations were determined using serum samples in accordance with **Bartels *et al*., (1972) ; Patton and Crouch, (1977) ; and Fossati *et al*., (1980)** , respectively. **Marshall and Robertson (1976**) method was used to determine the potassium and sodium levels in urine. Creatinine clearance (Cr Cl) was determined using 24-hour urine volumes, serum creatinine(SCr), and urine creatinine (UCr) levels. The

subsequent equation: Cr Cl is calculated as [(U Cr) mg/dL x (V) L/day] S Cr mg/dL by **Inker *et al*., (2019)**. Salt and potassium levels in the serum were measured by **Frazer *et al*., (1972)** Superoxide dismutase (SOD), among other antioxidant indicators of kidney tissue, was identified by **Nishikimi *et al*., (1972)**. The **Sinha (1972)** method was used to measure the catalase (CAT). The colorimetric assay, which was founded by **Buege and Aust, (1978),** was used to measure malondialdehyde (MDA).By using an ELISA assay, interleukin 6 and 10 levels in the serum were determined. According to **Henry, (1964)**, serum albumin (ALB) and serum total proteins (TP) were tested. BUN was estimated according to **Philip , (1994)**.

The **Reitman and Frankel (1957)** approach was used to determine ALP, AST, and ALT quantitatively.

Histopathological evaluation

After being removed, the kidney was washed in xylol, fixed in a 10% neutral formaldehyde buffering solution at a pH of 7.5, and then preserved in paraffin. Hematoxylin and eosin (H&E) was used to stain a portion that was between 4 and 5 mm thick for histological analysis **(Drury and Wallington, 1980)**.

Results and discussion

Table (1) :*Tribulus terrestris* ethanolic extract's phenolic components

Phenolic Compound	*Tribulus Terrestris* (µg / ml)
Gallic	**0.7**
Protocatechuic	**1.5**
p-hydroxybenzoic	**0.8**
Gentisic	**1.7**
Catechin	**5.3**
Chlorogenic	**0.5**
Syringic	**2**
Vanillic	**0.1**
Cinnamic	**0.22**

Data in Table (1) show the phenolic compounds in the ethanolic extract of *Tribulus terrestris* . From the previous

table, it is clear that TT contains many important compounds that are responsible for their effective role in treating many diseases. It contains catechin , gentisic and protocatechuic in a ratio of 5.3, 1.7 and 1.5 (µg / ml), respectively.

According to **Mubarik *et al*., (2022) ,** flavonoids such as naringin, hesperidin , naringinin , quercetin , rutin , kaempferol , and salicylic acid are among the polyphenol components found in TT fruit by HPLC. Iso-ferulic acid , p-hydroxy benzoic acid, chlorogenic acid, gallic acid, catechol, ellagic acid, catechin, ferulic acid, coumaric acid, p-coumaric acid, resveratrol, cinnamic acid, vanillic acid, coumarin, and caffeic acid are examples of phenolic acids . According to **Oliveira *et al*., (2022)**, the ethyl acetate and butanol fractions from TT showed the greatest phenolic component and flavonoid recovery.

Mohamed *et al*., (2023) noted that phenolic chemicals in TT were investigated. Catechin, syringic, gentisic, and protocatechuic content was higher in TT ; however, Vanillic and Cinnamic levels were lower. The biological actions of TT, including saponins, were demonstrated by **Tian *et al*., (2023).**

Table (2): Effects of TT extracts and vitamin "C" on feed efficiency ratio (FER), feed intake (FI), and body weight gain (BWG) in rats with liver and kidney damage

Groups	FI (g/day) Mean ± SD	FER Mean ± SD	BWG (g /28 day) Mean ± SD
(G1):control negative (-ve)	23.2^{a}±2.02	0.111^{a}±0.006	72.46^{a}±2.37
(G2):control positive (+ve)	16.6^{c}±1.94	0.048^{c}±0.002	22.5^{e}±2.38
(G3): TTEE(200 mg / kg body weight , orally)	22.43^{ab}±2.34	0.107^{a}±0.009	67.16^{b}±2.02
(G4): TTAE(200 mg / kg body weight , orally)	17.93^{bc}±2.07	0.063^{b}±0.010	34.3^{d}±2.80
(G5): vitamin "C" (200 mg / kg body weight , orally)	19.3^{abc}±2.10	0.099^{a}±0.014	53.5^{c}±3.11
LSD	3.82	0.016	4.61

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05).TTEE: *Tribulus terrestris* ethanolic extract.**TTAE**: *Tribulus terrestris* aqueous extract

The information in table (2) show the effect of TT extracts and vitamin "C" on FER, FI, and BWG in rats suffering from liver and kidney toxicity. Compared to the positive group , the control negative group had the highest values of FI, FER, and BWG. Data confirmed that all rats treated with TT extracts and vitamin "C" demonstrated a substantial improvement in the previous indicators compared to the positive group. Rats treated with TTEE recorded the best results, while the TTAE group recorded the lowest results compared to the TTEE group and vitamin "C" group.

According to **Sutar and Kamble (2019) ,** TT includes flavonoids, which enhance health. TT aqueous extract increased the activity of metabolism.

In hyperoxaluria-induced rats, **Mohamed *et al.*, (2023)** found that TT aqueous extracts can increase FI , FER , and BWG. The group treated with 500 mg/kg BW of TT was the best group.

Table (3): Effect of TT extracts and vitamin "C" on the liver enzymes of rats with liver and kidney damage

Groups	ALP (U/L) Mean ± SD	AST (U/L) Mean ± SD	ALT (U/L) Mean ± SD
(G1):control negative (-ve)	53.23^{c}±1.9	15.2^{c}±0.75	39.86^{b}±1.33
(G2):control positive (+ve)	69.9^{a}±1.82	21.66^{a}±1.84	48.8^{a}±1.67
(G3): TTEE(200 mg/ kg body weight, orally)	55.1^{c}±1.95	16.13^{bc}±0.96	41.96^{b}±2. 0
(G4): TTAE(200 mg/ kg body weight, orally)	66.8^{a}±2.40	18.63^{b}±1.51	47.03^{a}±1.5
(G5): vitamin "C" (200 mg/ kg body weight , orally)	62.03^{b}±2.10	17.4^{bc} ±1.34	42.7^{b} ±2.12
LSD	3.72	2.44	3.18

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05).TTEE: *Tribulus terrestris* ethanolic extract.**TTAE**: *Tribulus terrestris* aqueous extract.

The previous table (Table 3) shows the impact of TT extracts as well as vitamin "C" on liver function in rats suffering from liver and kidney toxicity. It was clear from the presented outcomes that the level of liver enzymes increased in the infected group compared to the healthy group. The

groups treated with TT extracts showed a noticeable decline in the level of these indicators (ALP –AST and ALT) . Also, vitamin C helped to improve liver function significantly. However, the group treated with TTEE showed the best results compared to vitamin "C" and TTAE , where the mean value of decrease reached the normal level as in the healthy group for enzymes ALT and ALP , the mean values were 41.96±2. 0 and 55.1±1.95(U/L), respectively.

Table (4): Effect of TT extracts and Vitamin "C" on the urine albumin and serum total protein levels in rats with liver and kidney damage

Groups	Serum albumin (mg /dl) Mean ± SD	Total protein (mg /dl) Mean ± SD	Urine albumin (g /dl) Mean ± SD
(G1):control negative (-ve)	2.83^{a}±0.208	5.5^{a}±0.5	34.4^{d}±2.77
(G2):control positive (+ve)	1.06^{d}±0.152	2.33^{d}±0.35	86.23^{a}±2.02
(G3): TTE E (200 mg/ kg body weight , orally)	2.5^{a}±0.2	5.43^{a}±0. 45	30.86^{d}±2.27
(G4): TTAE (200 mg/ kg body weight , orally)	1.46^{c}±0.251	3.36^{c}±0.305	63.2^{b}±2.40
(G5): vitamin "C" (200 mg/ kg body weight , orally)	1.9^{b}±0.2	4.53^{b}±0.351	57.43^{c} ±1.90
LSD	0.372	0.724	4.17

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05).TTEE: *Tribulus terrestris* ethanolic extract.**TTAE**: *Tribulus terrestris* aqueous extract.

Table (4) shows the effect of TT extracts and vitamin "C" on serum albumin ,total protein and urine albumin in rats suffering from liver and kidney toxicity. Regarding serum albumin and total protein, the results showed that there was an increase in the level of serum albumin and total protein in the negative group compared to the positive control group, in contrast to the results of urine albumin, which showed an increase in the value of albumin in the urine in the positive control group compared to the negative group. However, all the data agreed that TT extracts have a positive effect on the

status of serum and urine albumin as well as total protein. The third group (TTEE) showed the best results compared to the other treatments.

After IVM administration under the skin in this present study, biochemical examination revealed high increases in ALT, AST, and ALP concentrations. These findings, which show an harm influence of IVM on the liver cells, are consistent with findings made by other researchers **(Arise and Malomo, 2009 ; Shoeb, 2013 and Rabab *et al*., 2015) .**

The flavonoids in TT would increase the effectiveness and cellular leakage of transaminases (AST and ALT), and they might be in charge of defending the liver from oxidative stress and tissue-damaging enzymatic activities. However, we also need to take into account that the TT plant also includes steroidal saponins, steroidal glycosides, and alkaloids **(Stefănescu *et al*., 2020).**

Additionally, *Tribulus terrestris* and vitamin "C" were studied by **Kilany *et al*. (2020)** to see how well they protected albino rats' kidneys from GNT-induced renal damage. They demonstrated that TT substantially raised serum levels of albumin and total protein. According to **Al-Eisa *et al*., (2022),** TT extract can be used to treat diabetes and minimize the symptoms that are associated with the liver.

However, **Abdel-Kader *et al*., (2016)** found that the 400 mg/kg of TT ethanolic extract had only a negligible impact on serum and tissue liver markers. **Adimoelja and Ganeshan (1997) ,** on the other hand, found no appreciable variations in the liver indicator enzymes (ALT and AST) prior to and following TT administration.

He *et al*., (2021) demonstrated that supplementing with vitamin "C"; especially at 1,000 mg each day enhanced liver function and glucose metabolism in people with non - alcoholic fatty liver disease over the course of 12 weeks. According to **Garea *et al*., (2023),** the vitamin "C"- treated alcohol group had markedly lower levels of bilirubin, AST, ALT, and ALP, while significantly higher levels of albumin

as well as total protein were observed. This may be explained by the antioxidant properties of vitamin "C", which may have kept levels of free radicals in alcohol use disorder patients at lower levels. This may have decreased the oxidative stress that hepatic cell membranes (and possibly other cells) are exposed to, reducing liver cell damage **(Kukielka *et al.*, 1994).**

Table (5): Effect of TT extracts and vitamin "C" on serum and urine sodium levels as well as serum and urine potassium levels in rats with liver and kidney damage

Groups	Serum sodium (mmol/L) Mean ± SD	Urine sodium (mmol/L) Mean ± SD	Serum potassium (mmol/L) Mean ± SD	Urine potassium (mmol/L) Mean ± SD
(G1):control negative (-ve)	146^{d}±1.81	63.3^{a}±2.05	5.96^{a}±1.47	0.09^{c}±0.01
(G2):control negative (+ve)	167.86^{a}±2.41	32.56^{c}±1.32	2.63^{c}±1.26	0.5^{a}±0.105
(G3): TTEE (200 mg/ kg body weight , orally)	142^{d}±2.64	61.6^{a}±2. 02	5.46^{ab}±0.351	0.17^{bc}±0.02
(G4): TTEA (200 mg/ kg body weight , orally)	163.53^{b}±1.59	34.96^{c}±1.37	3.33^{bc}±0.862	0.43^{a}±0.152
(G5): vitamin "C" (200 mg/ kg body weight , orally)	151.13^{c}±2.50	47.93^{b}±1.95	2.63^{abc}±0.723	0.35^{ab}±0.141
LSD	4.06	3. 23	1.84	0.19

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05). TTEE : *Tribulus terrestris* ethanolic extract .**TTAE**: *Tribulus terrestris* aqueous extract

Data presented in Table (5) show the effect of TT extracts and vitamin "C" on serum and urine sodium levels as well as serum and urine potassium levels in rats suffering from liver and kidney toxicity. As for serum sodium, the findings revealed a considerable rise in its level in the positive control group compared to the negative group, when

treatment with TT extracts and vitamin "C" helped to effectively reduce this level. The same results were obtained for urine potassium . In contrast to these results, the urine sodium and serum potassium levels increased in the negative control group compared to positive control group. Treatment with vitamin "C" and TT extracts showed a significant improvement in the level of these salts compared to the positive control group, and the best outcomes were noted for the group treated with TTEE.

A study was created to find out how TT herbal extract affected rabbits' electrolytes and urine production. Over the course of the trial, a considerable rise in urine volume was seen. Additionally, it markedly reduced serum potassium and sodium levels over the course of the research **(Jabbar *et al*., 2012).**

In line with **Maharana and Dadhich's (2015)** research, our study found that after intervention with TT extract compared to positive rats, the electrolyte balance was potentially restored.

The reduction in urea and creatinine levels caused by the *T. terrestris* extract was dose-dependent and extremely significant. Increases in calcium, sodium, and potassium levels were also noted **(Abdel-Kader *et al*., 2016)**

Kamboj *et al*., (2020) showed that treatment with an aqueous extract of TT reduced urine excretion of oxalate, calcium, and phosphate by a significant amount when contrasted with the positive control group. According to **Gupta and Dubey (2020)** , rodents treated with an aqueous extract of TT had lower calcium levels than rats with hyperoxaluria. Additionally, the aqueous extract raised magnesium levels while decreasing phosphorous levels. Magnesium is able to break down a stable oxalate molecule, which reduces the amount of calcium oxalate present and preventscalciu oxalate stones from forming in the renal tubules.

Table (6) : Effect of TT extracts and vitamin "C" on serum creatinine , urine creatinine and creatinine clearance in rats with liver and kidney damage

Groups	Serum creatinine (mg /dl) Mean ± SD	Urine creatinine (mg /dl) Mean ± SD	Creatinine clearance (ml /hour) Mean ± SD
(G1):control negative	0.5^{c}±0.1	0.53^{a}±0.095	0.55^{a}±0.055
(G2):control positive	2.46^{a}±0.351	0.25^{d}±0.066	0.21^{b}±0.095
(G3): TTEE (200 mg/ kg body weight , orally)	0.7^{c}±0.2	0.513^{a}±0. 11	0.54^{a}±0.075
(G4): TTAE (200 mg/ kg body weight , orally)	1.63^{b}±0.305	0.37^{ab}±0.157	0.34^{ab}±0.141
(G5): vitamin "C" (200 mg/ kg body weight , orally)	0.96^{c}±0.208	0.44^{ab}±0.047	0.48^{a} ±0.146
LSD	0.452	0.18	0.198

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05). **TTEE** : *Tribulus terrestris* ethanolic extract .**TTAE**: *Tribulus terrestris* aqueous extract.

Table (6) shows the effect of TT extracts and vitamin C on serum creatinine, urine creatinine and creatinine clearance in rats suffering from liver and kidney toxicity . Regarding these indicators, all the results of the research indicated that TT extracts and vitamin "C" have a clear role in improving these indicators, but the TTAE showed the least improvement results compared to other treatments, unlike the TTEE, which showed the most effective results, where the mice treated with it reached the normal level, followed by rats that were treated with vitamin "C".

Table (7): Effect of TT extracts and vitamin "C"on urea, uric acid and BUN in rats suffering from liver and kidney toxicity

Groups	Urea (mg /dl) Mean ± SD	Uric acid (mg /dl) Mean ± SD	BUN (mg /dl) Mean ± SD
(G1):control negative	38.63^{d}±1.58	1.76^{b}±0.251	17.92^{c}±0.739
(G2):control positive	60.4^{a}±1.47	4.13^{a}±0.321	28.22^{a}±0.690
(G3): TTEE (200 mg/ kg body weight , orally)	40.26^{d}±1.90	1.9^{b}±0. 2	18.81^{bc}±0.891
(G4): TTAE extract (200 mg/ kg body weight , orally)	56.4^{b}±2.17	3.76^{a}±0.251	26.48^{a}±1.012
(G5): vitamin "C"(200 mg/ kg body weight , orally)	44.03^{c}±2.51	2.13^{b}±0.251	20.42^{b} ±1.423
LSD	3.57	0.469	1.79

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05) . TTEE: *Tribulus terrestris* ethanolic extract .**TTAE**: *Tribulus terrestris* aqueous extract**.**

The influence of TT extracts and vitamin "C" on urea, uric acid and BUN in rats suffering from liver and kidney toxicity is reported in Table (7). Data showed that ivermectin elevated serum urea, uric acid and BUN but treatment with TTE E , TTAE and vitamin "C" reduced this elevation.

Arise and Malomo (2009), reported comparable mild elevations in urea and creatinine levels after IVM injection. These increases could be the result of IVM or its metabolites having an immediate impact on renal tissue. The rise in the levels of urea and creatinine concentrations in IVM-treated mice could be attributed to a decrease in kidney malfunction or failure of the renal tubules**.** IVM was discovered to dramatically lower the body's overall capacity for antioxidants and to produce more nitric oxide **(Atakisi *et al*., 2009)**. NO can damage kidney tissue and result in kidney dysfunction. The retention of chemicals including uric acid, urea, and creatinine due to glomerular filtration dysfunction may be the cause of their high serum levels **(Selvakumar *et al*., 2013).**

Our findings support those of **Kaushik *et al*., (2019) ,** who discovered that TT treatment can lower uric acid levels.

Also, the promising preventive impact of TT on renal functions (urea and creatinine) was reported by **Abdel-Kader *et al*., (2016).** TT contains diuretic ingredients such as saponins ; it is a well-known immune-modulating, diuretic, and anti-urolithic agent**(Chhatre *et al*., 2014).**

In mice treated with cisplatin , **Sharma *et al*., (2019)** described the contents of the hydroalcoholic portion of (TT) . Comparatively to the cisplatin group, blood creatinine levels in the treated TT with induced nephrotoxicity were lower.

According to **Sudheendran *et al*. (2021),** treatment with TT increased diuresis, which resulted in the treated group producing more urine than the infected group. This decreased ion saturation in the urine sped up the process of dissolving the stones.

According to **Hussein *et al*., (2022) ,** therapy with TT lowers levels of uric acid, creatinine, and blood urea nitrogen in the treated groups than ethylene glycol does. Our research confirmed the antilithic efficacy by observing a decrease in uric acid concentration following treatment with the aqueous and ethanolic extract of TT. **Adimoelja and Ganeshan (1997),** in contrast, found little change in the levels of the renal biomarker enzymes creatinine and urea prior to and after TT treatment.

Even after cisplatin induction in cancer patients, vitamin E, C, and riboflavin significantly lowered serum urea and elevated levels of antioxidant enzymes in the kidney. These natural items can be used without risk as a supplement or as part of a combination therapy to treat cisplatin-induced nephrotoxicity since they have powerful anti-inflammatory and antioxidant therapeutic qualities **(Ridzuan *et al*., 2019)**.

According to **Chahrazed *et al*., (2021) ,** vitamin "C" co-treatment may reduce the nephrotoxic and neurotoxic effects of IVM. Also. Also, **Mehany *et al*., (2023)** reported that vitamin C improves kidney functioning by lowering levels of urea, creatinine, and malondialdehyde.

Table (8): Effect of TT extracts and vitamin" C" on immunological profile in rats suffering from liver and kidney toxicity

Groups	IL-6 (Pg / ml) Mean ± SD	IL-10 (Pg / ml) Mean ± SD
(G1):control negative	8.86^{d}±0.321	33.3^{e}±2.07
(G2):control positive	20.6^{a}±1.41	89.46^{a}±2.26
(G3): TTEE(200 mg/ kg body weight , orally)	10.4^{d}±0.624	43.36^{d}±2. 93
(G4): TTAE (200 mg/ kg body weight , orally)	17.03^{b}±1.15	67.3^{b}±2.57
(G5): vitamin "C" (200 mg/ kg body weight , orally)	13.13^{c}±1.02	52.4^{c}±2.20
LSD	1.80	4.402

Values are expressed as means ± SD ; means in the same column with different letter are significantly different (p≤ 0.05). TTEE : *Tribulus terrestris* ethanolic extract .**TTAE**: *Tribulus terrestris* aqueous extract.

Table (8) indicates the effect of TT extracts and vitamin C on some indicators of immunity in rats infected with liver and kidney toxicity by ivermectin. It is clear from the data that there is a significant increase in the value of IL-10 and IL-6 in the positive group compared to the negative group. It was found that treatment with TT extracts and vitamin "C" led to a decrease in this value. The TTEE recorded the best results compared to vitamin "C" and the TTAE.

In vitro experiments on macrophage activity and stimulation of non-specific immunity in animal models, steroidal saponins found in TT have shown immunostimulant action **(Tilwari *et al*., 2011).** Additionally, TT demonstrated an improvement in B cell function with appreciable rises in serum antibody titers, which may be effectors of the immune system's reaction **(Tilwari *et al*., 2013).** These results go counter to those reported by **Milasius *et al*., (2009),** who claimed that there was a detrimental impact on the body's immune system. According to the same authors, 20 days of taking 1875 mg of TT causes granulocytes to transition into leukograms in endurance athletes, with a significant drop in

lymphocytes and an increase in basophils, neutrophils and eosinophils. In this sense, the immunosuppression that may resemble that caused by corticosteroids may be caused by the dosage and/or the high proportion of saponins in TT **(Fernández-Lázaro *et al*., 2021).**

In both in vitro and in vivo tests, TT extracts have been shown to exhibit anti-inflammatory properties **(Stefănescu *et al*., 2020) .** Down-regulation of the enzymes necessary for the generation of cytokines and inflammatory mediators is another one of TT's features **(Coutinho *et al*., 2011).** These results were consistent with the single study that examined the anti-inflammatory effects of TT, which found that supplementing with 500 mg of TT daily for two weeks was enough to cause a modest but statistically significant drop in IL-6 **(Talemi *et al*., 2021).**

According to **Ranjithkumar *et al*., (2019),** a potential explanation for how TT works is that it suppresses the NF-B signaling pathways. Activation, leukocyte infiltration and maturation as well as the generation of pro- inflammatory mediators TNF–α and IL-4, can all be suppressed by TT via down-regulating NF-B and inhibiting COX-2 **(Oh *et al*., 2012 and Ranjithkumar *et al*., 2019).** A variety of inflammatory events that impact the organism's homeostasis could be reduced with IL-6 level regulation. These qualities are shared by other dietary supplements such as glycophosphopeptical AM3 **(Fernández-Lázaro *et al*., 2021),** which have similar features. ESR is a measure of the body's indirect level of inflammation **(Lombardo *et al*., 2019). Milasius *et al*., (2009)** found that the ESR in the TT group increased only slightly. Perhaps this is due to the fact that many TT active components are needed for the anti-inflammatory effect, and saponins alone are insufficient.

Vitamin "C" was found to reduce IL-10 and IL-6 according to **Kilany *et al*., (2020) and Mehany *et al*., (2023) .**Vitamin "C" can enhance immune system cell processes, enhancing immunity. It enhances the function of the cell

barrier against harmful substances and encourages oxidative scavenger activity by guarding against oxidative stress.

Table (9): Effect of TT extracts and vitamin "C" on CAT, SOD and MDA in rats suffering from liver and kidney toxicity

Groups	CAT Mean ± SD (U/g.t)	SOD Mean ± SD (U/g.t)	MDA Mean ± SD (nmol/g.t)
(G1):control negative	2.43^{a}±1.33	5.13^{a}±1.28	0.19^{d}±0.072
(G2):control positive	0.516^{b}±0.205	2.3^{b}±0.5	0.893^{a}±0.066
(G3): TTEE (200 mg/ kg body weight , orally)	1.3^{ab}±0.556	4.43^{ab}±0.503	0.276^{cd}± 0.117
(G4): TTAE (200 mg/ kg body weight , orally)	0.64^{b}±0.104	2.4^{b}±0.888	0.516^{b}±0.100
(G5): vitamin "C" (200 mg/ kg body weight, orally)	0.97^{ab}±0.304	3.46^{ab}±0.907	0.416^{bc}±0.105
LSD	1.21	1.58	0.171

Values are expressed as means ± SD; means in the same column with different letter are significantly different (p≤ 0.05). TTEE: *Tribulus terrestris* ethanolic extract.**TTAE**: *Tribulus terrestris* aqueous extract

The effect of TT extracts and vitamin C on CAT, SOD and MDA in rats suffering from liver and kidney toxicity is shown in Table (9). A significant elevation in MDA was reported in the ivermectin - intoxicated group compared to the negative group. On the other hand, levels of SOD and CAT were low in positive control group. Treatment with TTEE and vitamin C led to increase levels of SOD and CAT but decrease levels of MDA. As for CAT, SOD and MDA, there was no significant difference between the group treated with TTA E and the positive group. The group "3" result was most impressive followed by group "5" which was treated with vitamin "C".

The findings of the present investigation are consistent with those of **Kamboj *et al.*, (2020) ,** who demonstrated that TT decreased the amounts of free radicals that lead to lipid

peroxidation and decreased malondialdehyde. Alo, **Kilany *et al.*, (2020) ,** who showed that the extract of TT stopped the creation of NO phenolic amides in TT fruits and suppressed NO in the treated groups compared to the positive control groups.

T. terrestris herbal medicine extracts that have been supplemented with saponins have antiglycation, antioxidant, and antiproliferative effects on tumor cell lines in humans. The extract with more saponins demonstrated stronger antiglycation and antioxidant action. In addition , *T. terrestris* showed promising antioxidant capabilities. Additionally, it has anti-aging and anti-diabetic properties **(Figueiredo *et al.*, 2021).** In comparison to aqueous extract, methanolic extract of *Tribulus terrestri* fruits has stronger antioxidant, antibacterial, and phytochemical activity **(Abdulqawi and Quadri, 2021)**

These results are in line with those of **Hussein *et al.*, (2022),** who found that mice fed TT Aqueous extract showed higher SOD concentrations and lower levels of malondialdehyde in their kidneys. The free radical scavenging and antioxidant abilities of TT, which contain phenolic components, were credited with these findings. Also, **Mohamed *et al.*, (2023**) showed that TT can increase the activity of antioxidant enzymes in rats.

According to **Garea *et al.*, (2023**), giving vitamin C to alcohol users led to an increase in amount of GSH and CAT than the control group.The interacting effects of vitamin "C" can lessen the cellular harm brought on by ROS. Additionally, it is applied to people with alcohol use disorders to counteract oxidative damage. Free radicals are removed, and oxidative stress is countered.

Kidney histopathological analysis

The normal histological architecture of the renal parenchyma was seen in the rat kidneys from group "1" under a microscope **(photo 1).** On the other hand, group (2) rats' kidneys displayed cytoplasmic vacuolization of the

epithelial lining of the renal tubules,perivascular inflammatory cells infiltration **(photo 2).** However, a small amount of cytoplasmic vacuolization of the epithelial lining of certain renal tubules was visible in some group 3 analyzed sections **(photo3).** Meanwhile, rats in group four, kidneys revealed cytoplasmic vacuolization of epithelial lining renal tubules and few intertubular inflammatory cells infiltration **(photo4).** On the other hand, rats in group 5 showed renal tissue that seemed to be normal **(photo5).**

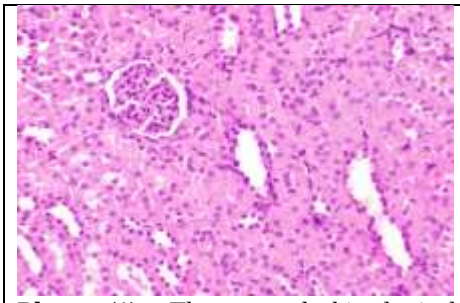

Photo (1): The normal histological architecture of the renal parenchyma is visible in the photomicrograph of a rat kidney from group 1 (which fed on basal diet as a control (-) group) (H & E X 400).

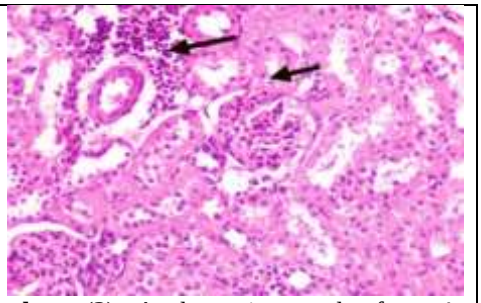

photo (2): A photomicrograph of a rat's kidney from group 2 (which functioned as the positive control) demonstrates the infiltration of perivascular inflammatory cells and the cytoplasmic vacuolization of the epithelial lining of the renal tubules.

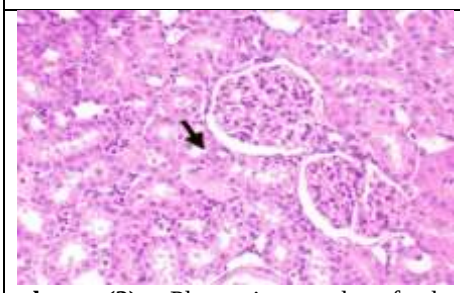

photo (3): Photomicrograph of the kidney of a group 3 (hepato and renal toxicity rats fed on basal diet and TTE extract 200 mg/ kg body weight, orally) rat demonstrating mild cytoplasmic vacuolization of some renal tubules (H & E X 400).

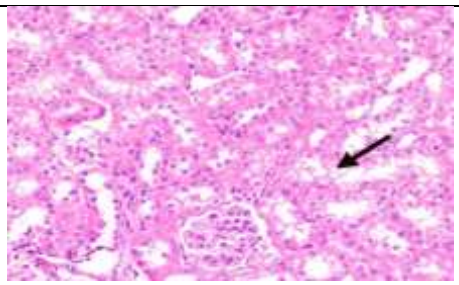

photo (4): The epithelial lining of the renal tubules can be seen in cytoplasmic vacuolization in the photomicrograph of a rat kidney from group 4 (hepato and renal toxicity rats fed on basal diet and TTA extract 200 mg/ kg body weight, orally) (H & E X 400).

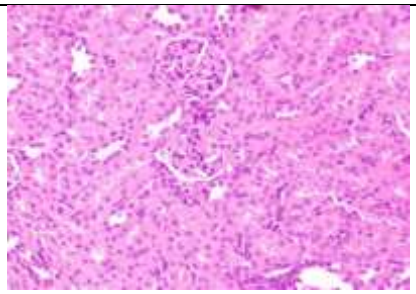

photo (5): An apparent normal histological structure may be seen in the photomicrograph of a rat kidney from group 5 (hepato and renal toxicity rats fed on basal diet and vitamin "C"(200 mg/ kg body weight , orally) (H & E X 400)

Conclution

In the present study, it is clear that ivermectin causes liver and kidney toxicity in rats. In summary, the results obtained demonstrated that both ethanolic and aqueous extracts of *Tribulus terrestris* as well as vitamin C had strong antioxidant effects,which helped improve ivermectin-induced hepato- renal toxicity , in addition to that ethanolic extract of *TT* showed more antioxidant effects than vitamin C and aqueous extract. Therefore, this study may provide supportive evidence that TT has a role in treating hepato-renal toxicity, as well as its distinctive role in stimulating sexual arousal.

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الخصائص التحسينية المحتملة لمستخلصات الحسك ضد سمية الكبد والكلى المحدثة بالإيفرمكتين في الفئران

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سعت الدراسة الحالية إلى تحديد ما إذا كانت مستخلصات ثمار الحسك يمكن أن تحمي الفئران من التلف الكبدى الكلوي الناجم عن الإيفرمكتين .ولتقييم فاعلية مستخلصات الحسك ضد سمية الكبد والكلى وكذلك التغيرات الهستوباثولوجية المرضية ذات الصلة ، تم استخدام فيتامين "ج" كدواء قياسي للمقارنة. تم تقسيم ثلاثين فأرًا إلى مجموعتين رئيسيتين؛ المجموعة الرئيسية الأولى (ست فئران) ، حصلت على الوجبة الأساسية واستخدمت كمجموعة ضابطة سالبة . تلقت المجموعة الرئيسية الثانية والمكونة من أربعة وعشرون فأرًا الإيفرمكتين بجرعة 200 ملجم لكل كجم من وزن الجسم لمدة ثلاثون يومًا وذلك من أجل الإصابة بتسمم كلوي كبدي . تم إنشاء أربع مجموعات منفصلة من المجموعة الرئيسية الثانية : المجموعة الثانية (حصلت على الوجبة الأساسية واستخدمت كمجموعة ضابطة موجبة). بينما استهلكت المجموعتان الثالثة والرابعة نظامًا غذائيًا أساسيًا بالإضافة إلى المستخلصات الإيثانولية والمائية لثمار الحسك عن طريق الفم بجرعة (200 مجم لكل كجم من وزن الجسم)، على التوالي . وتناولت المجموعة الخامسة نظاماً غذائياً أساسياً مع فيتامين "ج" عن طريق الفم بجرعة (200 ملجم لكل كجم من وزن الجسم) وذلك لمدة 28 يوماً. تم التعرف على المركبات الفينولية في مستخلص الحسك باستخدام كروماتوجرافيا الغاز عالى الاداء .أثبتت النتائج أن مجموعات الفئران التي تم إعطاؤها مستخلصات ثمار الحسك و كذلك فيتامين "ج" بجرعة (200 ملغم/كغم من وزن الجسم) لمدة 28 يوماً قد أظهرت تحسن فى معدل الاستفادة من الغذاء ، وزن الجسم المكتسب، المأخوذ الغذائى ، مؤشرات وظائف الكلى والكبد، اليكتروليتات السيرم والبول (الصوديوم والبوتاسيوم)، وبعض المؤشرات المناعية (الإنترلوكين 6 والإنترلوكين 10) وكذلك نشاط الإنزيمات المضادة للأكسدة. وقد حصلت المجموعة التي أعطيت مستخلص الحسك الإيثانولي (200 ملجم/كجم من وزن الجسم) على أفضل النتائج. وقد تم دعم التقييم البيوكيميائي من خلال الفحص النسيجي المرضي . ووفقا لنتائج هذا البحث، يمكن استخدام مستخلصات الحسك كعلاج ناجح لتقليل تلف الكبد والكلى الناجم عن الإيفرمكتين في الفئران .

الكلمات المفتاحية: ايفرمكتين - الحسك - السمية - فيتامين "ج"