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Prospective Protective effect of Shilajit Aqueous Extract on Nephrotoxicity Induced by Cypermethrin in Albino Rats.

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Abstract

Cypermethrin (CYP) is a widely used pyrethroid insecticide in agriculture as a foliar application on food and feed crops, and in controlling insect pests in different sites. Shilajit has extensive medicinal value and is commonly utilized in the treatment of various diseases across the globe. Numerous studies have demonstrated that Shilajit exhibits some bioactive effects including antiviral, anti-inflammatory, immunomodulatory, antioxidant effects. This work examined the potential protective properties of Shilajit aqueous extract against nephrotoxicity caused by CYP in albino rats. The study involved 24 male albino rats, which were distributed into four individual groups randomly as follows: normal control (standard diet), cypermethrin, low-dose Shilajit (CYP + 200 mg/kg Shilajit), and high-dosage Shilajit (CYP + 400 mg/kg Shilajit). The phenolic compounds of Shilajit aqueous extract were estimated. The serum concentrations of hepatic enzymes, albumin, total protein, kidney function, electrolytes (Na+ and K+), tumor necrosis factor-α, lipid profile, kidney superoxide dismutase (SOD) activity, catalase (CAT), nitric oxide (NO) and malondialdehyde (MDA) levels, organ weight, body weight, and histopathological examination outcomes were measured after 28 days. Results showed that treatment with Shilajit significantly dropped the values of liver enzymes, kidney function, TNF-α, K+ TG, TC, LDL-c, MDA, NO, and organ weight, while increased body weight, albumin, total protein, Na+, HDL-c, SOD and CAT compared with the cypermethrin group ($p < 0.05$). Further, Shilajit treatment improved of cypermethrin- induced histopathological changes in the kidney. The best results recorded for high-dose of Shilajit. These findings suggest that there is potential applicability of Shilajit as a potent protective agent for nephrotoxicity.

Key words: Cypermethrin, Shilajit,Nephrotoxicity, Kidney Function, and Antioxidant Enzymes.

Introduction

Globally, pesticide use has become common, and its adverse effects pose a severe public health concern. One of these cypermethrin (CYP) is an important type two of pyrethroid pesticides used widely to protect crops against insect infestations and is efficient in controlling multiple insect populations. However, its toxicity is a risk to the surrounding environment and human health ***(Alalwani, 2020).*** Its residues are often noticed in the food, breast milk, and environment ***(Yuan et al., 2014; Saillenfait et al., 2015).*** Cypermethrin is a highly toxic chemical that can be inhaled, ingested, and dermally, it has been indicated that it tends to accumulate in in various tissues, including the skin, body fat, kidneys, liver, ovaries, adrenal glands, and brain. The muscular and nervous systems reported that the main body parts were affected ***(Sharma et al., 2018).*** CYP is considered toxic and has previously been associated with testicular cancer, impaired motor function, hepato-renal dysfunctions, and

neurotoxic effects, attributed to its capacity to cross the blood-brain barrier ***(Afolabi et al., 2019; Ali et al., 2020).***

The kidney is a vital organ within the human body, it produces some hormones, purifies the blood, and maintains electrolyte balance, homeostasis, and blood pressure. When toxins cause damage to the kidneys, nephrotoxicity occurs, and the kidneys can excrete nitrogenous waste from the body ***(Pandit et al., 2018).*** Nephrotoxicity is described by an imbalance and fast decrease in kidney function; it is often induced by exposure to medications and environmental contaminants ***(Gupta and Trivedi, 2018).*** Renal function decline has a main influence on metabolism and nutritional status. It has been revealed that numerous plants have antioxidant effects and can defend against kidney toxicity. Shilajit is one of the major herbomineral drugs and has antioxidant properties, which may exhibit nephroprotective effects ***(Mohana and Reddy, 2012).*** In India, Shilajit has been extensively utilized in traditional medicine for treating chronic illnesses and several ailments due to its medicinal properties (Jafari *et al.,* 2019). Shilajit is a natural herbomineral medicine, characterized by its blackish-brown hue, obtained from the high-altitude rocks of the Himalayan region in the Indian subcontinent ***(Ojha et al., 2021).*** It contains a range of valuable components. These include humic acid, fulvic acid, and dibenzopyrones, which have health benefits and antioxidant properties. It also comprises tannins, phytosterols, terpenoids, amino acids, and more than 40 trace minerals ***(Keller et al., 2019).*** A scientific study revealed that Shilajit exhibits a range of therapeutic advantages, for example rejuvenation, anti-aging, and anti-diabetic properties, anti-inflammatory, and antioxidant capabilities ***(Cengiz et al., 2020).***

The objective of this research was to evaluate the nephroprotective capabilities of Shilajit in mitigating nephrotoxicity caused by cypermethrin in male albino rats

Materials and Methods

Materials:

Shilajit was acquired from Natural Spirit Trading, Egypt. Cypermethrin was obtained as a cyperkill product from Egypt Gold for Agricultural Fertilizer Company, Egypt.Starch and corn oil were provided from the neighborhood market, while cellulose, casein, minerals, vitamins, L-cysteine, dextrin, and choline chloride were procured from chemicals trading company in Cairo, Egypt. Rats (twenty-four normal male albino; strain *Sprague Dawley*, its average weight = 180 ± 10 g), was purchased from the laboratory animal colony, at the Ministry of Health and Population, Helwan, Cairo, Egypt.

Methods:

Preparation of Shilajit aqueous extract

Shilajit washed carefully with running tap water and was then chopped into small segments. Then, the sample, weighing 70 grams, was dissolved in 1 liter of distilled water and agitated on a shaker for 10 hrs at ambient temperature. The mixture was filtered by Whatman paper (No. 41), and freeze-dried as described by ***(Ghasemkhani et al., 2021).*** The final extract was stored at −20°C until it was needed.

Chemical analysis:

HPLC was used to analyze phenolic compounds in Shilajit aqueous extract as reported by ***(Eldin et al., 2018).***

Experimental design:

Rats with the above-mentioned properties were selected and housed, and maintain cleanliness and adequate air flow in the cages and provided with a basal diet as recommended by ***(Reeves et al., 1993)*** for a week as an adaptation phase. Then, the rats were categorized into four groups, each containing six rats as follows: Group (1): normal healthy control; these rats were served as the negative (-) control group. Group (2): cypermethrin as cyperkill (CYP) was dissolved in corn oil and given via oral route at dose 25mg/kgbody weight orally for 28 consecutive days (served as toxic control group) (Puttanna *et al.,* 2016). Group (3 and 4): was administrated CYP 25 mg/kg.bw plus Shilajit aqueous extract (200 and 400 mg/kg bw) respectively by oral route ***(Vivek et al., 2011)*** every day for 28 days.

Biological evaluation:

Following the 28-day experimental period, measurements for feed intake (FI), body weight gain percentage (BWG%), feed efficiency ratio (FER), and the relative weights of organs were assessed, in accordance with the procedures described by Chapman et al. in 1959.

Biochemical analysis of serum:

Upon completing the experimental timeframe, the rats were subjected to fast during the night before sacrificing. Blood samples were taken and centrifuged to isolate the serum from each individual rat.The following markers were measured: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were evaluated by the method of ***Bergmeyer et al. (1978).***Alkaline phosphatase (ALP) was assessed as described by ***Roy (1970).***Albumin, total protein, and globulin were evaluated by ***(Drupt, 1974, Sonnenwirth and Jaret, 1980, and Busher, 1990*** respectively). Nitrogen, creatinine, uric acid, and urea were determined as in Patton & ***Crouch (1977), Bartels et al., (1972), and Fossati et al., (1980),*** respectively. Tumor necrosis factor-α (TNF-α) was evaluated as biomarker of inflammation ***(Luo et al., 2005).*** Serum Sodium (Na^+) and potassium (K^+) were measured as in ***(Berndt and Jackwerth, 1979).*** Total cholesterol (TC) was measured as described in ***(Richmond's, 1973),*** triglycerides (TG) was measured by the method of ***(Trinder and Ann's, 1969).*** A diagnostic kit for measuring high-density lipoprotein cholesterol (HDL-c) using spectrophotometry was evaluated ***(Richmond, 1973).*** Thus, VLDL-c and LDL-c concentrations were assessed ***(Friedewald et al., 1972).***

Antioxidant /oxidant biomarker in kidney tissue:

Kidneys were removed from each rat after being sacrificed and divided into two parts; one portion of each sample was homogenized and subjected to centrifugation at 10,000 rpm at -20°C for 20 min. The resulting supernatant was utilized to assess various oxidant and antioxidant levels through the ELISA calorimetric method, employing a spectrophotometer (microplate reader Ryto2100 C) at wave lengths of 520 and 535 nm. Lipid peroxidation, measured as malondialdehyde (MDA), was assessed using the thiobarbituric acid-reactive substances (TBARS) method as described by ***(Uchiyama and Mihara, 1978).*** Superoxide dismutase (SOD) levels were determined as in ***(Nishikimi et al., 1972),*** while catalase (CAT) activity was assessed through a colorimetric assay based on ***Sinha's protocol (1972).*** Nitric oxide (NO) concentration was measured according to the procedure outlined by ***(Bryan and Grisham, 2007).***

Histopathological Examination:

Second part of kidney samples were executed, instantly after removing from the body, put in a fixative (10% formalin neutral buffered solution) and enclosed in a 5 m thick sectioned paraffin. Subsequently, the pieces were treated with Mayers' hematoxylin and eosin for microscopic examination according to ***(Drury and Wallighton, 1980).***

Statistical analysis:

Results are presented as mean ± standard deviation (SD). The significant differences among means across diverse groups was assessed by a one-way analysis of variance (ANOVA) and Duncan's test. A P value of 0.05 or lower was concerned significant ***(Snedecor and Cochran, 1989),*** utilizing SPSS (version 20).

Results and Discussion

Phenolic compounds:

For Shilajit aqueous extract, phenolic compounds had been analyzed and shown in Table (1). The findings revealed that.Shilajit aqueous extract recorded a highest content of gallic acid (187.17), followed by gentisic, acids such as (p-hydroxybenzoic, protocatechuic, cateachin, syringic, ferulic, quecetin, caffeic , chrysin, sinapic , and cinnamic) (14.82, 8.17, 7.23, 6.20, 2.96, 2.06, 1.54, 1.47, 1.28, 1.08, and 0.47 (µg/g), respectively.

Table (1)
Phenolic compounds ofShilajit aqueous extract (µg/g)

Compound	Concentration (µg/g)
Gallic acid	187.17
Protocatechuic acid	7.23
Gentisic	14.82
p-hydroxybenzoic acid	8.14
Cateachin	6.20
Caffeic acid	1.47
Syringic acid	2.96
Ferulic acid	2.06
Sinapic acid	1.08
Cinnamic acid	0.47
Qurecetin	1.54
Chrysin	1.28

Some studies have shown that Shilajit contains some amount of triterpenes, fatty acids, ellagic acid, albumins, gums, and aromatic carboxylic acids ***(Mishra et al., 2019; Ezhilarasi et al., 2020).Kamgaret al. (2023)*** reported that Shilajit construction differs according to the regions that it

comes from. Shilajit is primarily made up of humic substances, which account for over 80% of its weight, including humins, fulvic acid, and humic acid. The remaining 20% comprises essential minerals such as calcium, magnesium, and potassium. Additionally, Shilajit contains fatty acids, proteins, glycine, and bioactive compounds like gallic acid and caffeic acid, along with trace elements including chromium, cobalt, and selenium.

Biological evaluation:

Table (2) indicates that the values of FI, BWG %, and FER in the (+ve) group were significantly lesser than their corresponding in the normal group. Conversely, the other groups exhibited a notable increment when compared to the (+ve) group. The group receiving extract of Shilajit at a dosage of 400 mg/kg demonstrated the most favorable outcomes for all three parameters, closely resembling their corresponding in the normal group.

Table (2)

Effect of Shilajit aqueous extract on feed intake (FI), body weight gain% (BWG) and feed efficiency ratio (FER) inrats with nephrotoxicity

Parameter / Groups	FI (g/28 day)	BWG (%)	FER
(- ve) control	695.62 ± 2.97^{a}	33.52 ± 2.16^{a}	0.087 ± 0.00^{a}
(+ ve) control	493.73 ± 3.02^{d}	-9.83 ± 2.47^{d}	-0.034 ± 0.01^{d}
Shilajit extract (200mg/kg bw)	597.80± 0.98^{c}	13.49 ± 1.98^{c}	0.026 ± 0.01^{c}
Shilajit extract (400 mg/kgbw)	628.60 ± 1.90^{b}	17.57 ± 0.39^{b}	0.042 ± 0.00^{b}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).
*(FI): feed intake. *(BWG %): body weight gain percent. *(FER): feed efficiency.

In the current study, the management of cypermethrin to rats reduced significantly ($P < 0.05$) the body weight in contrast to normal rats. This study is in accordance with ***Shuklan et al. (2023),*** who found that symptoms of cypermethrin intoxication are vomiting, decreased food consumption, loss of coordination, tremors, thick eye discharge, tilted neck, and convulsion episodes, which led to a significant decline in weight of the body. The observed decline might be linked to the impact of pesticides on the gastrointestinal system, leading to reduced appetite and nutrient absorption, or it may result from the direct cytotoxic impacts of pesticides on somatic cells. Additionally, these effects could occur indirectly via the central nervous system, which governs feed and water consumption as well as endocrine regulation ***(Hadi and Yassi, 2019).*** Furthermore, ***Elblehi et al. (2023)*** reported that cypermethrin adversely impacted on renal and hepatic tissues, significantly contributing to body weight loss.

These findings agree with ***Pandit et al.,(2018)*** who found a significant increment in rats' body weight administered Shilajit aqueous extract at two dose (200 & 400 mg/kg) plus cisplatin when compared with nephrotoxic rats induced by cisplatin. This improvement may be due to the high concentration of minerals and trace elements found in Shilajit ***(Musthafa et al., 2018).***The effect of Shilajit was assessed at two different doses, in combination with chemotherapy drugs, in relieving the harmful effects of metastasis of osteosarcoma in the kidney and liver tissues in rats. Results showed that osteosarcoma rats treated with Shilajit at two different doses, in combination with chemotherapy drugs, had a significant rise in the body weight ***(Jambi and Alshubaily, 2022).***

Relative organs weight:

Table (3) shows the variationin relative organ weight percent ages for control and treated groups. The data of relative (kidney, liver, and heart) weight demonstrated that Shilajit aqueous extract significantly decreased the averages of treated groups in contrast to (+ve) control group. Numerically, the groups that taken a high dose of Shilajit extract demonstrated superior results than the control group.

Table (3)

Effect of Shilajit aqueous extract on relative organ weights (kidney, liver and heart) in rats with nephrotoxicity

Parameter / Groups	Kidney	Liver	Heart
(- ve) control	0.54 ± 0.02^{d}	2.15 ± 0.02^{d}	0.20 ± 0.00^{d}
(+ ve) control	0.74 ± 0.01^{a}	3.01 ± 0.02^{a}	0.28 ± 0.01^{a}
Shilajit extract (200mg/kg bw)	0.65 ± 0.00^{b}	2.71 ± 0.05^{b}	0.25 ± 0.00^{b}
Shilajit extract (400 mg/kg bw)	0.61 ± 0.01^{c}	2.55 ± 0.01^{c}	0.23 ± 0.01^{c}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).

*Relative organs weight%.

Current data revealed that the administration of cypermethrin had increased all above organs weight in comparison with other treatments. This result disagrees with a study by ***Mansour et al., (2018); Seven et al., (2022)*** they found that the administration of cypermethrin to mice or rats at different doses led to declined weights of the kidney and liver compared to the control.

In this study; the change of relative organs weight is a sign of toxicity. Thus, cypermethrin must have considerable toxicity on these organs and the occurrence of inflammation.

Alternatively, another study found an insignificant decrease in kidney weight in rats administered Shilajit (200 mg/kg) plus cisplatin. And showed significant decreased in the kidney weight in the group treated with Shilajit (400 mg/kg) plus cisplatin when compared with nephrotoxic rats ***(Pandit et al., 2018). Ghezelbash et al., (2020)*** who examined the hepatoprotective effects of Shilajit on rat's non-alcoholic fatty liver illnesses, showed that Shilajit had significantly decreased the liver weights of treated rats in contrast to the (+ve) control.

Biochemical parameters of the biological experiment:

Liver enzyme:

Table (4) revealed that the average value of ALT, AST, and ALP in positive control was significantly increased compared to the (-ve) group, while other treatments significantly reduced than their corresponding in the (+ve) group, and the superior results were noticed in the group that had administered the highest dosage of Shilajit extract when compared to the normal group.

Table (4)

Effect of Shilajit aqueous extract on liver enzyme in rats with nephrotoxicity

Parameter / Groups	ALT (U/L)	AST (U/L)	ALP (U/L)
(- ve) control	28.33 ± 3.89[d]	77.66 ± 3.18[d]	220.00 ± 4.94[d]
(+ ve) control	74.00 ± 2.12[a]	188.5 ± 5.30[a]	330.50 ± 3.88[a]
Shilajit extract (200mg/kg bw)	54.50± 3.18[b]	129.10 ± 4.81[b]	289.00 ± 5.65[b]
Shilajit extract (400 mg/kg bw)	37.00 ± 3.93[c]	97.00 ± 5.65[c]	253.00 ± 4.94[c]

Different letters assigned to values in the same column reflect a significant difference among those values at (p<0.05).

(ALT): Alanine aminotransferase (AST): Aspartate aminotransferase

(ALP): Alkaline posphatase

Murat Kanbur et al., (2016) examined the effect of cypermethrin in male rats. Researchers analyzed liver enzymes (i.e. AST, ALT, and ALP. The results reported that CYP led to significant variations in these enzymes.***Adeniyi et al., (2024),*** studied the protective ability of ascorbate and alpha-tocopherol in contradiction of toxicity induced by cypermethrin. Results cleared that a raise in ALT and AST concentrations was noted in the test group (p<0.05). Oral exposure of rats to cypermethrin led to significantly elevated alkaline phosphatase and alanine transaminase activities ***(Rashid et al., 2023).***

These data are accorded with ***Ghezelbash et al., (2020),*** who studied the influence of Shilajit on non-alcoholic fatty liver disease in rats. 3. Findings revealed that rats exposed to Shilajit exhibited a marked decline in serum values of ALT, and AST compared with the positive ***control.Jambi and Alshubaily (2022)*** showed that osteosarcoma rats administrated with Shilajit at two different dosages, blended with chemotherapy drugs, notably decreased serum levels of hepatic enzymes ($p < 0.05$), including (AST, ALT, and ALP) Rats that received Shilajit 250 mg/kg oral led to a decrease of ALT and AST ***(Atashbar et al., 2018).***

Serum proteins:

The result in Table (5) revealed that the group administered CYP as (cyperkill) recorded a highly significant decrease in total protein (TP), albumin (Alb), and globulin (Glob) compared to the normal control. Whereas all treated rats that co-administrated Shilajit aqueous extract achieved the highest level of total protein and its fractions, albumin and globulin, of the (+ve) group. The group treated with Shilajit extract (400 mg/kg) was close to normal rats.

Table (5)

Effect of Shilajit aqueous extract on serum protein in rats with nephrotoxicity

Parameter / Groups	TP (mg/dl)	Alb (mg/dl)	Glob (mg/dl)
(- ve) control	6.88 ± 0.10[a]	4.60 ± 0.05[a]	2.28 ± 0.05[a]
(+ ve) control	4.05 ± 0.06[d]	3.19 ± 0.00[d]	0.86 ± 0.05[d]
Shilajit extract (200mg/kg bw)	5.11 ± 0.16[c]	3.72 ± 0.07[c]	1.39 ± 0.08[c]
Shilajit extract (400 mg/kg bw)	6.05 ± 0.30[b]	4.20 ± 0.18[b]	1.85 ± 0.12[b]

Different letters assigned to values in the same column reflect a significant difference among those values at (p<0.05).

*(TP): total protein. *(Alb): albumin. *(Glob): globulin.

The data obtained in this present work agreed with ***Murat Kanbur et al. (2016)*** who studied the influence of cypermethrin in male rats and found that cypermethrin significantly decreased the serum TP and Alb compared to normal rats.Also, ***Oladele et al., (2020)*** stated that exposure to cypermethrin promoted significant declines ($P < 0.05$) in TP, Glob, and Alb compared to other treated groups.

Sancak et al., (2023) who studied the Shilajit effects on kidney and liver in rats with experimental injury in spinal cord using two doses ofShilajit; they found thatTP and Alb levels were higher in groups treated with Shilajit in contrast to the control group.

Kidney function:

From Table (6), the significant differences in plasma uric acid, urea, and creatinine levels among the (+) control set and all groups were obvious. The (+ve) control displayed a significantly higher increament in uric acid, urea, and creatinine than the negative control. The most favorable outcomes were observed in the groups subjected to Shilajit extract (400 mg/kg), recording a decrease in urea, uric acid, and creatinine levels. The percentage of change was (28.43%, 46.31%, and 47.33%) respectively.

Table (6)

Effect of Shilajit aqueous extract on kidney function in rats with nephrotoxicity

Parameter / Groups	Uric acid (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
(- ve) control	1.73 ± 0.09^{d}	27.00 ± 2.68^{d}	0.54 ± 0.03^{d}
(+ ve) control	2.99 ± 0.11^{a}	66.12 ± 4.47^{a}	1.31 ± 0.02^{a}
Shilajit extract (200mg/kg bw)	2.53 ± 0.14^{b}	50.86 ± 5.92^{b}	0.80 ± 0.05^{b}
Shilajit extract (400 mg/kg bw)	2.14 ± 0.14^{c}	35.50 ± 4.79^{c}	0.69 ± 0.04^{c}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).

In the current research, increased serum levels of creatinine and urea in the cypermethrin group are strongly linked to compromised renal function. The effects of cypermethrin were experimented in male rats by ***Murat Kanbur et al., (2016***), who found that CYP brought about a significant increment in serum blood urea nitrogen and creatinine than normal rats.In a similar study, ***Oladele et al., (2020)*** conducted that cypermethrin caused significant nephrotoxicity, where it induced a significant elevation in serum uric acid, urea, and creatinine values.Additionally, ***Adeniyi et al., (2024),*** who studied the protective potential of ascorbate and alpha-tocopherol against toxicity induced by cypermethrin. The test group revealed an increase in serum creatinine level compared to the other groups.

Pandit et al., (2018) revealed that there is no significant variation in urea, creatinine, and uric acid) in the serum of rats administered Shilajit 200mg/kg plus cisplatin. But, a significant decline was noticed in urea, uric acid, and creatinine in the serum of rats administered 400 mg/kg of Shilajit plus cisplatin compared to the rats that have nephrotoxicity induced by cisplatin). ***Jambi and Alshubaily (2022)*** showed that osteosarcoma rats treated with Shilajit at two different doses, in combination with chemotherapy drugs, significantly declined serum levels of kidney functional signs ($p < 0.05$), including urea, uric acid, and creatinine. Also, this agrees with ***Sancak et al., (2023)*** who found that urea, uric acid, and creatine values were lesser in groups subjected to Shilajit-treated groups compared to the (+ve) group.

Tumor necrosis factor and serum electrolyte sodium (Na+) and potassium (K+)

The influnce of Shilajit extract on the tumor necrosis factor-alpha (TNF-α), sodium (Na), and potassium (K) is shown in Table (7). It displays that administration of CYP led to a significant rise in TNF-α & serum electrolyte K of the positive control compared to the normal group. Shilajit aqueous extract had a significant decrease of TNF-α and K in all treated groups than the (+ve) group. The administration of cyperkill decreased Na in the (+ve) group than the normal and treated rats. The most favorable results were noticed in a group that was treated with Shilajit extract (400 mg/kg) achieving insignificant differences with normal rats.

Table (7)

Effect of Shilajit aqueous extract on serum in rats with nephrotoxicity

Parameter / Groups	TNF-α (pg/mL)	Na (mmol/L)	K (mmol/L)
(- ve) control	47.00 ± 1.10^{d}	146.10 ± 0.75^{a}	4.87 ± 0.03^{d}
(+ ve) control	107.50 ± 3.80^{a}	138.20 ± 1.37^{c}	6.04 ± 0.12^{a}
Shilajit extract (200mg/kg bw)	87.55 ± 4.95^{b}	141.96 ± 1.97^{b}	5.51 ± 0.10^{b}
Shilajit extract (400 mg/kg bw)	62.60 ± 4.06^{c}	143.73 ± 1.06^{ab}	5.26 ± 0.12^{c}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).

*(TNF-α): tumor necrosis factor alpha. *(Na): sodium. *(K): potassium.

Oladele et al., (2020) found that management of cypermethrin in rats caused an imbalance in electrolytes with significant rise in serum potassium ion and chloride ion and a significant drop in serum of bicarbonates and sodium ions. Cypermethrin has biological activity results from neuronal membrane depolarization, which allows a lot of sodium ions to pass through voltage-gated sodium channels (Yang *et al.,* 2020). Cypermethrin mostly acts through delaying the action of the sodium–potassium channels ***(Kasuba et al., 2022).*** The treated group with cypermethrin showed that alterations in the levels of serum electrolytes sodium (Na+) and potassium (K+) (***(Rashid et al., 2023). Elblehiet al., (2023)*** reported that rats that administrated CYP significantly increased TNF-α and pro-inflammatory cytokines (interleukin-1β (IL-1β) and IL-6).

The serum level of TNF-α significantly declined by injection of Shilajit in rats that have Non-alcoholic Fatty Liver Disease ***(Haddad et al., 2022).***Shilajit contains bioactive components such as humic acid and fulvic acid that possess anti-inflammatory, antioxidant, and immunomodulatory properties that may help preserve the blood cells from damage induced by free radicals and other bad agents ***(Arif et al., 2019).***

Lipid profile (TC, TG, HDL-c, LDL-c, and VLDL-c):

Cyperkill administration to rats led to significant elevation in some lipid fractions (TC, TG, LDL-C, and VLDL-C); at the same time, cyperkill led to a decline of HDL-C compared to the negative group. Other groups treated with Shilajit aqueous extract had improvement in mean values of all the above parameters that were assessed, whereas administration of Shilajit significantly decreased the mean values for TC, TG, LDL-C, and VLDL-C and increased the averages of HDL-C than the Cyperkill group. The best results were observed in the group that was adninstrated with the high dosage of Shilajit aqueous extract as show in table (8).

Table (8)

Effect of Shilajit aqueous extract on lipid profile in rats with nephrotoxicity

Parameter / Groups	T.C (mg/dl)	T.G (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
(- ve) control	82.50 ± 2.41^{d}	76.50 ± 1.76^{d}	56.00 ± 1.41^{a}	11.20 ± 0.03^{d}	15.30 ± 0.35^{d}
(+ ve) control	125.40 ± 1.93^{a}	142.00 ± 5.78^{a}	43.00 ± 1.41^{d}	54.00 ± 0.70^{a}	28.40 ± 1.15^{a}
Shilajit extract (200mg/kg bw)	98.40 ± 1.54^{b}	111.50 ± 1.98^{b}	48.60 ± 0.22^{c}	27.50 ± 1.76^{b}	22.30 ± 0.91^{b}
Shilajit extract (400 mg/kg bw)	87.12 ± 2.82^{c}	96.50 ± 0.39^{c}	51.50 ± 0.35^{b}	16.32 ± 2.94^{c}	19.30 ± 0.35^{c}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).

*(TC): cholesterol *(TG): triglycerides *(HDL-c): high-density lipoprotein *(LDL-c): low-density lipoprotein *(VLDL-c): very low-density lipoprotein

The effects of cypermethrin were investigated in male rats. Results reported that CYP significantly elevated the serum TG, TC, and LDL-c and declined HDL-c compared to normal rats ***(Murat Kanbur et al., 2016).***Cypermethrin negativly impacted on kidney and liver tissues via a significant increase in livers enzymes, renal function markers, and cholesterol ***(Elblehiet al., 2023).***

Saqib et al., (2016) stated that Shilajit raises metabolism, and has an antioxidant effect on fat oxidation in several ways and can drop cholesterol levels in the blood. Rats that had diabetes induced by streptozotocin when treated with 200 mg/kg of Shilajit orally had significantly elevated high-density lipoprotein while significantly decreasing TG, LDL-, and VLDL-c***(Vemuri et al., 2018).*** These findings agree with ***Ghezelbash et al., (2020)*** who revealed that rats treated with Shilajit recorded a significant decline in the values of TC, low-density lipoprotein, and TG but had an increment in high-density lipoprotein than (+ve) when evaluating the impacts of Shilajit on rats that have non-alcoholic fatty liver disease.

Antioxidant enzymes and oxidant indicators in tissues:

The activities of antioxidant enzymes in the kidney (i.e. SOD and CAT) and oxidant parameters (i.e. MDA and NO) are shown in Table (9). Compared to the negative control, cyperkill administration decreased SOD and CAT and rosed MDA and NO. Groups treated with Shilajit aqueous extract induced an elevation in antioxidant enzymes (SOD & CAT). The best result was recorded with 400 mg/kg of Shilajit aqueous extract.While oxidant parameters were decreased by co-administration rats Shilajit extract. MDA & NO concentrations of the group treated with 400 mg/kg of Shilajit aqueous extract were close to those of the normal group, which were reduced by about 47.26 and 45.83%, respectively.

Table (9)

Effect of Shilajit aqueous extract on the activity of antioxidant enzymes and oxidant parameters in kidney tissue of rats with nephrotoxicity

Parameter / Groups	SOD (U/g)	CAT (U/g)	MDA (nmol/g)	NO (µmol /g)
(- ve) control	166.79 ± 1.25^{a}	80.59 ± 2.07^{a}	8.66 ± 1.25^{d}	3.02 ± 0.86^{c}
(+ ve) control	67.69 ± 1.24^{d}	39.61 ± 2.46^{d}	29.88 ± 1.24^{a}	8.29 ± 1.44^{a}
Shilajit extract (200mg/kg bw)	91.23 ± 1.78^{c}	50.16 ± 4.59^{c}	20.79 ± 1.78^{b}	5.74 ± 1.54^{b}
Shilajit extract (400 mg/kg bw)	144.81 ± 1.06^{b}	65.92 ± 5.57^{b}	15.76 ± 1.06^{c}	4.49 ± 0.70^{bc}

Different letters assigned to values in the same column reflect a significant difference among those values at ($p<0.05$).

*(SOD): superoxide dismutase. *(CAT): catalase. *(MDA): malondialdehyde.

*(NO): nitric oxide.

The effect of cypermethrin was experimented in male rats by ***Murat Kanbur et al., (2016).*** The result proved that CYP significantly changes the oxidative stress of malondialdehyde, nitric oxide, catalase, and superoxide dismutase in the blood for tissues (liver and kidney) compared to normal rats. ***Adeniyi et al., (2024),*** showed elevated levels of malondialdehyde and a decrease in superoxide dismutase, catalase, and glutathione peroxidase effects were noted in the group treated with CYP as than the normal group. Also, rats that were administrated cypermethrin had a clear elevation in malondialdehyde levels with a significant decrease in total superoxide dismutase and catalase activities in kidney tissues ***(Elblehiet al., 2023).***

Atashbar et al., (2018) reported that rats that received Shilajit 250 mg/kg orally, leading to a decrease of nitric oxide and oxidative stress, and it significantly increased glutathione peroxidase.administered Shilajit at a dosage of 800 mg/kg in rats for two weeks significantly rose glutathione, glutathione peroxidase, catalase, and superoxide dismutase, while significantly declining oxidative stress (MDA***) (Derhami et al., 2022).***

Histological examination:

Fig. 1 showsmicroscopic pictures of HE-stained renal cortical sections showing normal structure of glomeruli and tubules without evidence of inflammation or fibrosis in the negative control group (A). However, renal sections from the positive control group (B) displayed shrunken glomerular tuft with widened Bowman's space (arrowhead), tubular dilation (thin black arrow), marked tubular epithelial degeneration(*), and tubular epithelial necrosis (thin blue arrows). While moderately dilated Bowman's space (arrowhead), deceased tubular dilation (thin black arrow), and some tubular cast formation (red arrows) were observed in renal sections from the treated group (C) that received Shilajit aqueous extract 200 mg/kg body weight. Renal sections from the treated group (D), which was administered Shilajit aqueous extract 400 mg/kg body weight, indicated mildly dilated of Bowman's space (arrowhead), deceased tubular dilation (thin black arrow), and few tubular cast formations (red arrows).

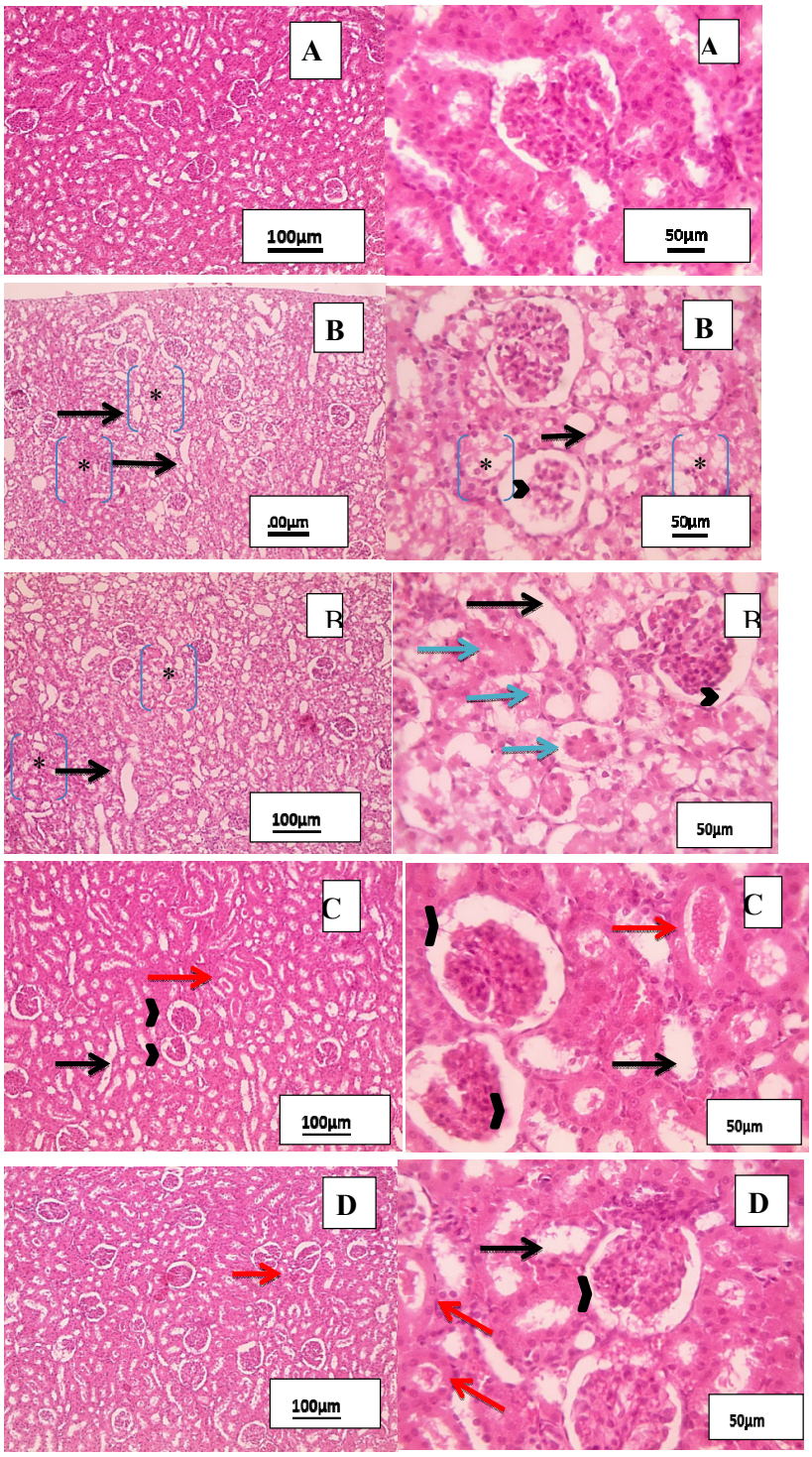

Fig. 1
Histological examination of kidney tissue

These findings agree with ***(Mamun et al., 2014)*** who evaluated the extent of damage caused by cypermethrin on the mice's kidney tissue. Observations revealed necrosis of the kidney tubules, depletion of blood vessels, glomerular atrophy, and pronounced congestion of the kidney glomerulus, as well as hemorrhage in kidney tissues compared to the control. Microscopic findings confirmed that cypermethrin induced glomerular shrinkage, necrosis in both the glomeruli and kidney tubules, blood cell congestion, and hemorrhagic alterations in the kidney tissue ***(Shuklan et al., 2023).***Rats that were administered cypermethrin had periglomerular inflammation with degenerated renal tubules as well as congested and inflamed interstitial space ***(Adeniyi et al., 2024). Oladele et al., (2020)*** revealed that cypermethrin administration induced distortion in the histoarchitecture of the kidney characterized by damaged Bowman's capsule, lesions of the glomerulus, degenerated and vacuolated kidney tubules.

The histopathological analysis of rats renal that have nephrotoxic induced by cisplatin which administered Shilajit aqueous extract at two dose (200& 400 mg/kg) showed nephroprotective potential of aqueous extract of Shilajit***(Pandit et al., 2018).***This agrees withthe research conducted by **Sancak *et al.,* (2023)** who examined the effects of Shilajit on the rats' kidney and liver suffering from an experimental injury in the spinal cord. The study demonstrated that administering higher dosages of Shilajit resulted in a higher noticeable protective effect on the tissues of the kidney and liver's tissues, whereas lower dosages exhibited only a limited protective effect, as indicated by their histopathological evaluations.

Conclusion

The present study demonstrated that rat's exposure to cypermethrin induced renal dysfunction. It has been conducted that biochemically and histopathologically treatment with Shilajit significantly inhibited the lesions forming in kidney associated with its anti-inflammatory characteristics.The antioxidants properties for Shilajit are due to active ingredients such as fulvic acid and humic acid and may be also to other components.

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التأثير الوقائي المحتمل لمستخلص الشيلاجيت المائي على السمية الكلوية المحدثة بالسيبرميثرين في الجرذان البيضاء

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الملخص العربي

السيبرميثرين (CYP) هومبيد حشري من مجموعة البيرثرويدات يستخدم على نطاق واسع في الزراعة لوقاية المحاصيل الغذائية والأعلاف،كما يستخدم في مكافحة الآفات الحشرية في المواقع المختلفة. الشيلاجيت له قيمة طبية واسعة ويستخدم على نطاق واسع لعلاج العديد من الأمراض في جميع أنحاء العالم. أظهرت العديد من الدراسات أن الشيلاجيت له نشاط حيوي لاحتوائه على مركبات تعمل كمضادات للأكسدة ،الالتهابات والفيروسات كما أن له خصائص مناعية. تم إجراء العمل الحالي لدراسة الخصائص الوقائية المحتملة لمستخلص الشيلاجيت المائي على السمية الكلوية في الفئران البيضاء. تم تقسيم أربعة وعشرين من ذكور الفئران البيضاء بشكل عشوائي إلى أربع مجموعات على النحو التالي: الضابطة السليمة (الغذاءالقياسي)، السايبرميثرين ،الشيلاجيت بجرعة منخفضة (سيبرميثرين + ٢٠٠ملجم من مستخلص الشيلاجيت / كجم من وزن الجسم)،والشيلاجيت بجرعة عالية (سيبرميثرين +٤٠٠ملجممن مستخلص / كجم من وزن الجسم).تم تقدير المحتوى الفينولي للمستخلص المائي للشيلاجيت. كما تم قياس مستويات إنزيمات الكبد والألبومينو البروتين الكليو وظائف الكلى والإلكتروليتات (الصوديوموالبوتاسيوم) وعامل النخر ألف اوالدهون الكلية فى السيرم وأيضا تم قياس نشاط كلا من إنزيم السوبر أكسيد ديسميوتيز وإنزيم الكتاليز ومستوى المالون ثنائى الدهيد وأكسيد النيتريك في نسيج الكلى .تم تسجيل وزن الأعضاء والجسم كما تم إجراء الفحص لنسيج الكلى بعد ٢٨ يومًا. أظهرت النتائج أن العلاج بالمستخلص المائي للشيلاجيت أدى إلى انخفاض كبيرفي مستوى إنزيمات الكبد ووظائف الكلى وعامل النخر ألفا والبوتاسيوم والدهون الثلاثية والكوليسترول الكلى والكوليسترول المرتبط باللليبوبروتينات منخفضة الكثافة و المالون ثنائى الدهيد وأكسيد النيتريكو وزن الأعضاء،بينم ازاد وزن الجسم والألبومينوالبروتين الكليو الصوديوم و الكوليسترول المرتبط باللليبوبروتينات مرتفعة الكثافة وانزيم السوبر أكسيد ديسميوتيز والكتاليزمقارنة بمجموعة السايبرميثرين .($p < 0.05$) علاوةعلى ذلك ،أدى العلاج بالشيلاجيت إلى تحسين الآثارالضارة للتغيرات النسيجية المرضية التي سببها السيبرميثرين في الكلى. سجلت الجرعة العالية من الشيلاجيت أفضل النتائج لكل البارامتر المختبرة. تشير هذه النتائج إلى إمكانية استخدام الشيلاجيت كعامل وقائي ضد السمية الكلوية.

الكلمات المفتاحية: السيبرميثرين ,الشيلاجيت،السمية الكلوية ،وظائف الكلى،الإنزيمات المضادة للأكسدة.