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Original Research Article

Pathological and Biochemical Evaluation of Methanolic *Lycium shawii* Extract in Reducing Amikacin Hepatotoxicity in Albino Male Mice

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Abstract: Plants extracts were used in herbal medicine since ancient times owing to their therapeutic effectiveness, availability and accessibility in an experimental study. In the current study we used methanolic *Lycium shawii* extract (MLSE) investigate biological and medical active compounds by gas chromatography spectrometry (GC-MS) and evaluate its therapeutic ability against amikacin induced liver toxicity. 32 experimental male mice were divided into 4 groups; GI (negative control) was given Dimethyl sulfoxide (DMSO), GII was given amikacin (100mg/kg), group GIII was received (MLSE) alone, while group GIV was received both 100mg/kg of amikacin and 200 mg/kg of MLSE. GC-MS result showed 20 medicinally active compounds as shown in table 1. Most of these compounds reported as anti-inflammatory, antioxidant, anti-apoptotic and even anti-cancer. The biochemical tests revealed significant $P \leq 0.05$ therapeutic potential of MLSE in GIV to normalize the disturbance in the liver enzymes values (ALT, AST and ALP) that induced by amikacin in GII compared with GI. Additionally, histopathological study was illustrated that MLSE exhibit potent role in GIV in reduction amikacin-induced hepatotoxicity in GII compared with normal control GI. Collectively the MLSE play an important role in overcoming and suppression of amikacin hepatotoxicity. According to above results we recommended that *Lycium shawii* extract can use in medical and pharmaceutical field after further clinical and genetic evaluation for its safety and activity.

Keywords: Plant extract, methanolic extract, liver, toxicity, GC-MS, inflammatory.

INTRODUCTION

Amikacin has a further activity among aminoglycosides where it is resist the enzymatic inactivation; therefore it is widely used in the presence of gentamycin resistance (Hudson, 2020). It has particular effects on certain organs in the body such as liver, kidney and ear (Salgado *et al*., 2007). The liver is a main organ for multiple physiologic and metabolic processes in the body including food metabolism, cholesterol and fats regulation and metabolism and excretion of numerous drugs and xenobiotics (particularly by Cytochrome P450), there for it become target for toxic effects of these substances (Trefts *et al*., 2017; Kulkeaw & Pengsart, 2021). The net balance between generation of toxic metabolic compounds and their detoxification determine the severity of hepatotoxicity. Drug-induced liver deterioration still develops gradually, and then natural products should be examined to diminish side effects of widely used hepatotoxic drugs (Piñeiro-Carrero & Piñeiro, 2004; Saran *et al*., 2022). The pathogenesis of liver toxicity by amikacin is mediated by formation of oxygen free radicals and induction of apoptosis resulting in mitochondrial membrane dysfunction and accumulation of phospholipid amorphous densities and eventually leading to micro hepatic jaundice, in addition to elevation of blood urea nitrogen (BUN) (Martines *et al*., 1998; Asci *et al*., 2015; Azırak & Özgöçmen, 2023). Plant extracts had been considered as promising source for generation various medication owing to their availability, safety, and they are accessible and give dramatic therapeutic reflexes, in addition to their evidenced antioxidant, anti-tumor and anti-inflammatory effects (Abdallah *et al*., 2023). Herbal extracts were presented that they had hepatoprotective potential against wide range of hepatotoxic remedies (Rashid, *et*

al., 2024); medical plant extract may act an important role in synthesis of promising remedies that can reduce several disorders (Hassan *et al*., 2019). The phenolic compounds, alkaloids and flavonoids presented in these plant extracts are the most important herbal chemicals that can used in hepatoprotection against different harmful therapeutics (Rao *et al*., 2023; Nwozo *et al*., 2023); therefore this study aim to investigate the activity of methanolic *Lycium shawii* extract **(**MLSE) in conserve or resolute the damaged liver organ in laboratory animals (male mice) against any injurious stimuli.

Experimental section (Materials and methods):

Plant harvesting and extraction:

The leaves of plant (*Lycium shawii*) were gained and collected in clean containers from agricultural lands in Misan province in Iraq. The crop was well cleaned and rinsed by clean water and then dried by air at room temperature for 2 weeks and after that shredded and grind in to fine powder to be ready to extraction (Kaur *et al*., 2024).

Extraction

The extraction was achieved using 20mg of plant powder in each 100ml of 7% methanolic solution with well mixing on magnetic stirrer at 37℃ for 48 hours. The mixture of solution was filtrate by clean sieve and then by filter paper type Whatman no.1. The filtrate leaved at room temperature to evaporate the (70%methanolic solution) then separate and collect the extracted compounds. The extract was put at 4℃ till the using in experiment (Al-Husseini, 2020).

1. Gas Chromatography Spectrometry (GC-MS)

The methanolic extract of *H. indicum* was analyzed using gas chromatography–mass spectrometry (GC-MS), performed on an Agilent GC-7890B system coupled with a 5977A mass selective detector. Separation was achieved on an HP-5MS capillary column (30 m × 0.25 mm × 0.25 µm; 5% phenyl methyl siloxane). Helium was employed as the carrier gas at a constant flow rate of 1.0 mL/min. A 1 µL sample was injected with the injector maintained at 250 °C. The oven temperature program began at 40 °C (held for 2 minutes), then ramped up at 5 °C/min to 270 °C, where it was held for 15 minutes. Mass spectrometric detection was carried out in electron ionization mode at 70 eV, scanning across a mass range of 40–700 m/z. Identification of the extract's constituents was accomplished by matching acquired spectra against entries in the NIST Library (Version 2011) (Afroz Shoily *et al*., 2025).

Herbal Extract Preparation and Administration

Methanolic *Lycium shawii* extract (MLSE), part used, extraction method, solvent, Dimethyl sulfoxide (DMSO), and dissolved 200mg in 10 ml of DMSO. The herbal extract was freshly prepared and administered orally via gavage at a dose of 200 mg/kg body weight daily for 21 days.

Experimental study

Laboratory animals

A total of 32 healthy adult male mice, weighing between 26–32 grams, were used in this study. The animals were housed under standard laboratory conditions (12-hour light/dark cycle, temperature 22 ± 2°C, and humidity 55 ± 5%) with free access to standard rodent chow and water ad libitum. The study was conducted in accordance with institutional guidelines for the care and use of laboratory animals (Europe council No. 123, Strasbourg, 1985).

Experimental Design

The animals were randomly divided into four groups, each consisting of six mice (n=8), as follows:

1. Group I (GI), Control group: Received Dimethyl sulfoxide (DMSO) intraperitoneally.
2. Group II (GII), Amikacin treated group: Received Amikacin at a dose of 100 mg/kg, intraperitoneally to induce hepatotoxicity.
3. Group III (GIII), Herbal treated group: Received only the Herbal extract (200 mg/kg, orally).
4. Group IV (GIV), Amikacin + Herbal treated group: Received Amikacin (100 mg/kg, i.p.) and herbal extract at a dose of 200 mg/kg body weight, administered orally.

All treatments were administered once daily for 21 consecutive days.

2. Blood Collection and Biochemical Analysis

At the end of the treatment period (on day 21), blood samples were collected from the retro-orbital plexus under light anesthesia. The samples were allowed to clot, and then centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum was used for the biochemical assessment of liver Function Enzymes: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP). The serum biochemical parameters were measured using commercially available diagnostic kits according to the manufacturers' instructions.

2. Histopathology

The target organ (liver) was excised and put in 10% of neutral buffer formalin at specimen- fixative ratio 1:9 for 48 hours. Then, the specimens were processed by a graded series alcohols (50%-100%), cleared in xylene for 2 hours and infiltrated with molten paraffin. The specimens were then embedded in paraffin blocks. The blocks were sectioned by microtome at 5 µm in thickness, floated in water bath at 50 ℃, mounted onto glass slides, hot plate-dried and subsequently stained with hematoxylin and eosin (H&E). The stained slides were coverslipped and read under light microscope (Isaac *et al*., 2023).

Statistics

The statistical analysis was achieved using statistical package SPSS 25.0, ver. 9. The data of groups was compared using T test and one way of variance (ANOVA test) after LSD values. The results were expressed as means± standard deviation. The significances were respected at value P≤ 0.05 regarding normal control values (Azırak & Özgöçmen, 2023).

RESULTS AND DISCUSSION

In summary, this study was involved methanolic plant extraction (MLSE), using of GC-MS examination, experimental study (using laboratory male mice) and including biochemical analysis and histopathological examination and eventually statistical analysis.

The previous study was presented that plant belong to *lycium* species extracts have diverse medical and biological active compounds for example alkaloids, terpenoids and flavonoids (Almoulah *et al*., 2017). *Lycium shawii* extract was used effectively in treatment or management of various diseases or disturbances in the body as in treatment of jaundice; mouth sore, stomachache and the whole plant was used in the treatment of liver diseases, constipation, cardiac episodes (Taghizadeh *et al*., 2021).

The results of current were as follow:

1. Gas chromatography spectrometry (GC-MS): GC-MS examination results revealed multiple medically and biologically active chemical ingredients as listed in the following table (1):

Table 1: shows active biological and medical chemical compounds resulted from GC-MS analysis

No	Ret. time. Min.	Peak Area %	Name of Compound	Chemical Nature	Medical & Biological activity
1	53.593	0.60	**Oxacyclododecan-2-one**	11-Undecanolactone is a macrolide.	Act as antitumor, antimicrobial, anti-inflammatory and antiplatelet.
2	42.203	2.83	Dodecanoic acid	A saturated medium-chain fatty acid	Has anticancer, and anti-inflammatory effects, anti-apoptotic, antioxidant and antibacterial activity.
3	46.129	0.15	Thiosulfuric acid	Oxoacid	Act as antioxidants, anti-inflammatory, exhibiting bacteriostatic effects. Act against acute cyanide poisoning & to reduce ototoxicity in pediatric patients undergoing cisplatin-based chemotherapy for certain cancers.
4	46.129	0.15	9-Octadecenoic acid (9Z)-	Fatty acid	Antioxidant, antiniflammatory, reduce blood pressure, anti-cancer, reduction of cardiovascular disease due to its potential to reduce LDL cholesterol, reduction rheumatoid arthritis and a variety of cancers. Anti-Gram-positive bacterial & neuroprotective.
5	46.129	0.15	Pentadecane	alkane hydrocarbon	Act as anti-inflammatory & antimicrobial activity particularly against *Leishmania* parasites.
6	49.678	7.59	Tetradecanoic acid	Fatty acid	Has antioxidant, anti-inflammatory, antifungi, antiviruses, anticancerous cells, and antiparasitic activity
7	50.404	0.13	Hexadecanoic acid	Fatty acid	Hepatoprotective, antioxidants, hypocholesterolemic, nematicide, and pesticide. inhibitors of phospholipase A(2) as anti-inflammatory agents & anticancer.
8	51.976	0.64	1-nonadecene	an unbranched alkene	Cytokine regulation, induce collagen synthesis, enhancing collagen synthesis, possesses antibacterial activity
9	63.063	0.66	Hexadecanamide	*fatty acid amide*	Anti-inflammatory, antioxidant, treatment of mastitis caused by *staphylococcus aureus*, & neuroprotective.

10	62.069	4.99	Oleic Acid	*Fatty acid*	Anti-inflammatory, anti-endometrial cancer cells, antibacterial activity particularly Gram positive bacterial species. Improve heart conditions by decreasing blood pressure, lowering cholesterol and reducing inflammation.
11	60.177	2.01	Glycidyl Palmitate	a synthetic fatty acid ester	Antioxidant, anti- *Cryptococcus neoformanc*, Inhibit apoptosis.
12	60.177	2.01	Diethylmalonic acid		Used as sedatives and anesthetics. Potential in anticancer application. promise in inhibiting inflammation, specifically histamine-induced paw edema & anxiolytic (anxiety-reducing) and antidepressant effects
13	59.674	0.27	hexacosanal	fatty aldehyde	Has anti-inflammatory, antioxidant & antimicrobial activities.
14	58.800	0.79	2- Chloropropionic acid, octadecyl ester	Organic acid	Anti-inflammatory, antioxidant, antimicrobial activity.
15	57.337	0.34	l-(+)-Ascorbic acid 2,6-dihexade		Possess antioxidant, antibacterial, antitumor, and wound healing properties.
16	55.679	1.77	Palmitoleic acid	Omega-7 fatty acid	Suppresses hepatic steatosis and improves insulin sensitivity in the whole body, wound healing, bactericide against *S. aureus* and Propionibacterium acnes, which cause rough skin and acne.
17	55.079	0.44	Pentadecanoic acid	long-chain fatty acids	Anti-inflammatory, anticancer, antifibrotic, support heart health, antibacterial and antifungal activity.
18	54.119	1.23	9-Hexadecenoic acid, methyl ester, (Z)-	A fatty acid methyl este	Has antioxidants, hypocholesterolemic, nematicide, and antibacterial properties.
19	53.593	0.60	Cyclooctane acetic acid, 2-oxo-		Has antimicrobial, anti-inflammatory effects, antioxidant activity by scavenging free radicals, potential for wound healing, & promoting tissue regeneration.
20	34.584	0.43	DL-Proline, 5-oxo-, methyl ester	Flavonoid	Has anti-inflammatory & antioxidant

Biological and medical activities were depend on Database for phytochemicals and Enthobotanica of Dr. Duke

The results of GC-MS were showed 20 medical and biological compounds as shown in the table 1, including flavonoid, vitamin c, and healthy fatty acids, Omega fatty acids, macrolide and alkanes and others. This results were in consistent with result of (Jabur and Fajer, 2023; El-Amier *et al*., 2024).

2. Biochemical analysis

Biochemical analysis for liver enzymes showed significant increases ($P \leq 0.05$) in ALT values in GII compared with GI while no significant increases ($P > 0.05$) in ALT values in group IV compared with GI. In addition, there were significant decreases ($P \leq 0.05$) in ALP values in GII compared with GI, while it showed no significant decrease ($P > 0.05$) in GIV compared with GI. On the other hand, there were no significant increases or decreases ($P > 0.05$) in values of AST in all groups compared with GI as shown in table 2 & figure1:

Table 2: Shows the values of liver enzymes for each animal groups

Group	ALT	AST	ALP
GI	39.75± 38.73	173.0± 52.35	251.8± 122.6
GII	42.00± 36.40	226.3± 81.65	244.3± 85.85
GIII	39.75± 29.39	128.0± 21.60	243.0± 111.5
GIV	33.25± 23.64	212.3± 39.36	242.0± 68.60

The values were expressed as means± standard deviations and significant differences were respected at P≤ 0.05

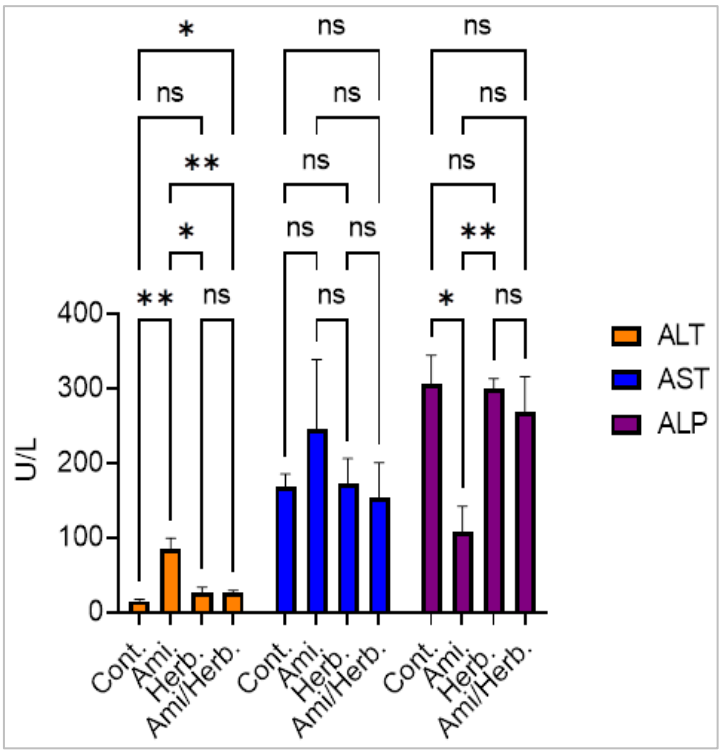

Figure 1: Shows significant and non-significant differences between all animal groups of study:

The biochemical disturbance in the liver enzymes by increased (ALT) or decreased (ALP) than normal control values in GII may due to acute injury of hepatic parenchyma in animals of this group as shown in figure 2, and this in agreement with (Mehboob *et al*., 2021). On the other hand, the normalization and restoration of these enzymes levels to the normal physiological limits in animal of GIV is attributable to hepatoprotective activity of MLSE against amikacin toxicity by reduction of oxidative stress (Gaweesh *et al*., 2015; Mehboob *et al*., 2021; Azırak & Özgöçmen, 2023), where all aminoglycosides caused elaboration of wide range of reactive species of oxygen (ROS) causing hepatic apoptosis (Tabuchi *et al*., 2011).

3. Histopathology

The histopathological results illustrate prominent hepatic changes in the GII (amikacin treated) compared with normal control group, while there was dramatic protection and normalization of liver histology in GIV (amikacin+ MLSE treated) suggesting protective activity of MLSE against amikacin hepatic toxicity as shown in figure 2:

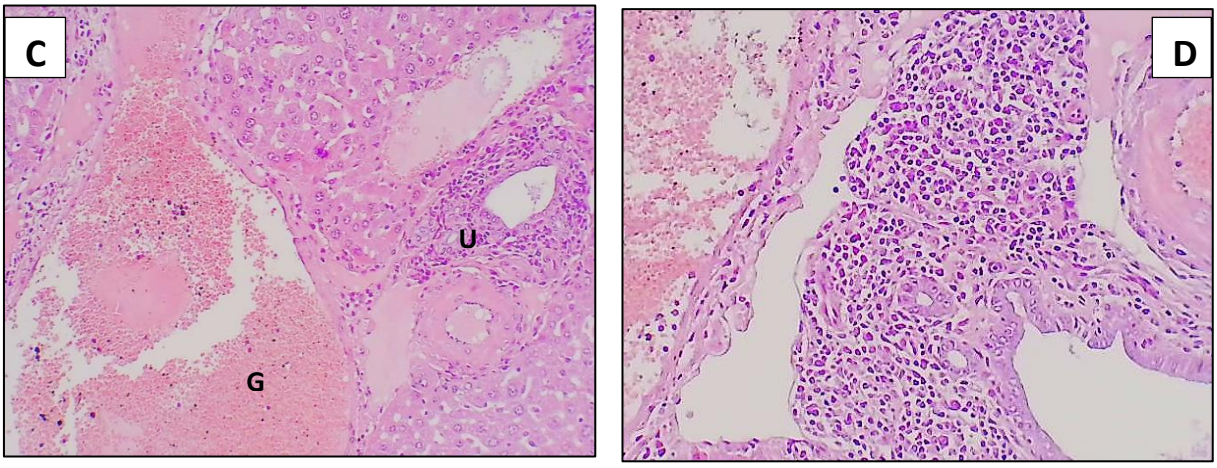

Figure (2): A. Belong to GI (DMSO treated) Represent the normal histological architecture of mice live appear with normal hepatic cord (arrow heads), normal sinusoids (S) and normal hepatic lobules and central and portal vessels (V). B. Belong to GII (amikacin treated) there is prominent portal perivenular inflammation characterized by lymphocytic and macrophagic aggregation with some neutrophilic infiltrations (asterisks), also there is clear hepatic cord and sinusoidal disruption (H) with severe acute cellular degeneration (R) and focal necrosis (N). Also the injured hepatocytes appear with pyknotic nuclei and prominent nucleoli suggesting severe apoptosis or early stage of necrosis. C. Belong to GII large central vein appear with severe congestion (G), and periductal inflammatory cell infiltration (U). D. Other hepatic field for GII, the field shows severe biliary inflammation (L) appear with predominant lymphocytic macrophagic infiltrations (asterisks) and vascular congestion (G). E. Venular congestion (G) with prominent neutrophilic aggregation (T) with necrosis of some hepatocytes (N). F. Liver section

Amikacin was induced acute liver tissue damage in animals of GII. The molecular investigation of was showed that this damage in hepatic tissue attributable to over production of ROS, induction of apoptosis and function loss of mitochondria (Li et *al*., 2021), where the generated ROS in mitochondria and smooth endoplasmic reticulum via CYP450, mainly disrupt the cellular structural compartments as cytoskeletal proteins, lipid, and nuclear and mitochondrial DNA (Cichoż-Lach & Michalak, 2014). Azırak & Özgöçmen (2023) was confirm that amikacin stimulate caspase-3 (a protease) has important role in inflammatory and apoptotic processes (Van Opdenbosch & Lamkanfi, 2019). Recently (Yousef *et al*., 2024) presented that aminoglycosides in particular amikacin caused liver enzymes disturbances alongside with overproduction of reactive oxygen species resulting in severe hepatic tissue damage and inflammation. These findings were in compatible with previous study (Valko *et al*., 2007).

In the current study, the histopathological changes induced by amikacin toxicity in GII, such as vascular congestion, degeneration, necrosis, mononuclear or polymorph nuclear cell infiltrations and focal perivascular and biliary inflammations previously illustrated in the figure 2, were in consistent with result of (Mehboob *et al*., 2023; Azırak & Özgöçmen (2023); Yousef *et al*., 2024).

In this experimental study, methanolic *Lycium shawii* extract (MLSE) that used to reduce amikacin liver toxicity in GIV revealed remarkable protection against amikacin hepatotoxicity indicating by restoration of normal values of all liver enzymes (ALT, ALP & AST) and normal liver histology. This improvement or protection was mainly due to antioxidant activity of MLSE which can clear amikacin induced-reactive free radical reducing their toxic effect on hepatocytes and this activity was evidenced by (El-Amier *et al*., 2024) in vitro against DEHP (Di (2-ethylhexyl) phthalate). In addition, the presence of flavonoid, healthy fatty acids, ascorbic acids and others compounds that considered effective antioxidants (Petrovic *et al*., 2020) and then prevented or decreased the oxidative stress that can cause mitochondrial impairment, cellular damage and interfere with cellular metabolism leading to cell death. Sher *et al*. (2011) also were presented similar experimental findings using *Lycium shawii* extracts for maintenance of liver parenchyma and an insults, where suggested the anti-inflammatory effects of this plant extract. The hepatoprotection may due to presence of flavonoids which considered potent antioxidant, anti-inflammatory and even anticancer agents in *L. shawii* extract (Ullah *et al*., 2020). Xie *et al*. (2021) were experimentally evidenced that an plant belong to *Lycium* species play an effective anti-inflammatory, antioxidant and anti-apoptotic role leading to prominent suppression of cell death in other organ. Furthermore, Kamil (2023) was recorded inhibition of CCl4-hepatotoxicity using *Lycium shawii* extract that prevent liver damage and maintain the liver enzymes within physiological ranges. Recently, Hussain *et al*. (2025) were found that *L. shawii* extracts had have the optimum antioxidants and flavonoids content among other plant extracts that they used in their study.

CONCLUSION

In the current study we found that methanolic *Lycium shawii* extract exhibit prominent hepatoprotective ability against amikacin hepatotoxicity that evidenced by both biochemical and histopathological parameters. Then, further experimental and clinical studies are recommended for this plant extract, in addition to genetic correlation.

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