Hepatoprotective and antioxidant effects of Azadirachta indica aqueous extract powder on liver toxicity in animal as a model

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Abstract

Antioxidative, hepatoprotective, anti-inflammatory, hypoglycemic, anti-gastric ulcer, antibacterial, and antitumor properties have been identified in numerous investigations on Azadirachta indica. This study assesses how Azadirachta indica aqueous extract powder affects the lipid profile, antioxidant enzymes, and liver enzymes in albino rats with liver damage. Twenty-four (24) rats, each weighing 150±10 g, were divided into four groups. As a control negative group (1), the negative group (-Ve) is given merely a baseline diet As a control positive group, group (2) positive group (+Ve) was given a baseline diet following a CCl_4 injection. Groups treated with CCl4 for liver problems were further separated into: group (3) was given a basal diet in addition to 5% powdered aqueous extract. Group (4) was given a 10% aqueous extract powder in addition to their basic diet. The results indicated that, Glutathione peroxidase (GPX) was significantly ($P < 0.05$) reduced, and AST, ALT, ALP, total bilirubin, and MDA were significantly ($P<0.05$) raised by CCl_4 injection (positive control group) in comparison to the negative control group. Additionally, it showed that adding aqueous extract to the meal reduced these negative effects and significantly improved the biochemical changes brought on by the injection of CCl4.

Key words: hepatoxicity, blood lipids , malondialdehyde , liver enzymes, Neem .

1. Introduction

For more than 200 years, India and its surrounding nations have acknowledged Azadirachta Indica, or neem, as a multipurpose medicinal plant with a broad range of biological attributes **(Kausik et al., 2002)**. It is extensively cultivated in Africa **(David et al., 2010)**. It is recognized to have anti-inflammatory, antipyretic, antimicrobial, and diabetes-relieving properties because of its phytochemical composition **(El-Hawary et al., 2013; Prashanth and Krishnaiah, 2014).** Hepatic injury is linked to the disruption of several metabolic activities. Liver injury is linked to cellular necrosis, elevated tissue lipid peroxidation, and lower levels of glutathione. Additionally, blood levels of various biochemical markers, including transaminases, alkaline phosphatase, bilirubin, triglycerides, and cholesterol, are elevated in hepatic disease **(Subramaniam et al., 2015)**.The values of AST and ALT have traditionally been utilized to evaluate liver function. Tissue toxicity has been linked to elevated ALT and AST plasma values **(Adeyemi and Akanji, 2011)**. An elevated serum concentration of these enzymes indicates hepatic intoxication **(Kpemissi, 2015)**. Nimbin, 6-desacetylnimbinene, ascorbic acid, nimbolide, nimbandiol, amino acids, 7-sdesacetyl-7-benzoylgedunin, 17-hydroxy azadiradione, 7-sdesacetyl-7-benzoylazadiradione, n-hexacosanol, and nimbiol are among the chemical components found in A. indica (neem) leaves **(Kokate et al., 2010; Hossain et al., 2013).** In the setting of paracetamol-induced hepatotoxicity in rats, **Nwobodo et al. (2018)** evaluated the effects of an aqueous extract from Neem leaves at two different dosages (0.5 and 1 g/kg body weight) on antioxidant enzymes. The findings indicated that plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) significantly decreased after receiving a high dose of neem (1000 mg/kg body weight), whereas levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), and malondialdehyde (MDA) increased.. MDA, a byproduct of polyunsaturated fatty acid peroxidation, is generated in response to elevated free radical activity. As a marker of oxidative stress within cells. and tissues, lipid peroxidation is recognized as a major contributor to cellular damage **(Ehiaghe, 2015)**.According to **Niedworok and Bielaszka (2007)**, the concentration of MDA acts as a strength indicator for the oxidation of polyunsaturated fatty acids (PUFAs) included in food. It is recognized that malondialdehyde levels serve as markers for antioxidant status and oxidative stress **(Fakher et al., 2007).**

2. Materials and methods

Materials:

Azadirachta indica specimens were acquired from the Agricultural Research Center in Cairo, Egypt. The kits were provided by Bio Diagnostics Company, located in Cairo, Egypt. Chemicals, including casein, cellulose, D-L methionine, choline chloride, mineral components, and vitamins, were procured from El-Gomhoriya Pharmaceutical in Cairo, Egypt. This study involved twenty-four (24) male albino rats, each weighing 150±10 g, obtained from the Institute of Ophthalmology, Giza, Egypt.

Methods:

Preparing the extract:

Preparing the extract involved thoroughly washing the leaves and drying them for three hours at 45 to 50 degrees Celsius in a drying oven. After being ground into a powder and sieved through a 1 mm sieve, 200 g of the dried leaves were soaked in 1000 ml of water and left to stand for 48 h. According to **Nunomura et al., (2006),** the extract was filtered, and the filtrate was dried in a hot air oven set between 45 and 50 degrees Celsius.

Experimental Design:

Twenty-four (Sprague-Dawley) albino rats, each weighing 150±10 g, were placed in group cages with regulated temperatures (22-24°C) and lighting (12-h light cycle beginning at 6 AM) for at least six days before studies. Rats were split up into four major groups, each consisting of six rats: Group (1) negative or normal group (-Ve): given a baseline diet only according to **(Reeves et al., 1993)**. Group (2) injected with CCl4 then given a normal diet, as a positive control (+Ve). Liver disorders grouped by CCl_4; these groups were furtherly divided as follows: Group (3): fed on a basal diet plus 5% of aqueous extract powder. Group (4): fed on a basal diet plus 10% of aqueous extract powder.

Induction of disorders:

Carbon tetrachloride (CCl4)-induced acute hepatotoxicity in rats. Intraperitoneal injection of male albino rats with CCl_4 1 ml/kg (1:1) mixture with paraffin oil for 3 days increased serum alanine transaminase, aspartate transaminase, and alkaline phosphatase activities as well as total bilirubin, triglycerides and total cholesterol levels. (**Karthikeyan and Deepa., 2010).**

Chemical Analysis :

Polyhenolic compounds of Neem leaves were determined according to **(Agilent., 2014).**

Biological evaluation:

Body weight gain (BWG) and percentage of body weight gain (BWG %), feed efficiency ratio (FER) were estimated according to ***Chapman et al., (1959)*** ,using the following formulas:

BWG (g) = Final weight - Initial weight

$$\text{Body weight gain (BWG \%)} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

FER = Weight gain / Feed intake

Biochemical analysis:

Rats were starved overnight before the scarification at the end of the four-week experiment, and blood samples were taken from each rat. The serum was separated from each blood sample, for biochemical examination. The determination of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and total bilirubin was conducted following the method reported by **Young (2001)**. Alkaline phosphatase (ALP) activity in serum was measured using **Roy (1970)** methodology. The method described by **Richmond (1973)** was used to calculate total cholesterol (TC). while triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C) were calculated in mg/dL following **Fassati and Prencipe (1982)**. High-density lipoprotein cholesterol (HDL-C) was measured using **Lopez (1977)** methodology, and low-density lipoprotein cholesterol (LDL-C) was studied as described by **Fridewald et al. (1972)**. Malondialdehyde (MDA) levels were measured by **Draper and Hadley (1990**) methodology, and glutathione peroxidase (GPx) activity was assessed based on the method of **Hissin and Hilf (1976)**.

Statistical analysis:

The mean ± standard error (SE) was used to express the obtained data. To ascertain statistical significance between the groups, the Analysis of Variance (ANOVA) test was utilized, using the procedure outlined by **Armitage and Berry (1987).** Differences were considered statistically significant at P-values less than 0.05 ($P < 0.05$).

3. *Results and Discussion*

The data in table (1) indicated that Azadirachta Indica aqueous extract powder (AEP) had more powerful phenolic and flavonoid compounds. Results revealed that AE contained high amounts of ellagic acid and salicylic acid With a value of 699 and 630 mg, respectively . In addition, Neem leaves water extract contained myricetin with value 290.90 mg, these results were in agreement with **(Pandey et al., 2014).** The

phytoconstituents are likely primarily accountable for the many therapeutic qualities of Neem leaves. Ellagic acid is a potent antioxidant and polyphenol that reduces lipid peroxidation and serves as an effective free radical scavenger **(Devipriya et al., 2007).** The results in **Table (2)** indicated that feed intake was higher in the positive control group, with a mean value of 15.50 g/d, compared to the negative control group, which had a mean value of 14.60 g/d. The data also showed that the groups treated with 5% and 10% aqueous extract powder, with mean values of 13.92 and 14.70 g/d, respectively, exhibited feed intake levels similar to that of the negative control group.The positive control group's BWG% was substantially lower ($P<0.05$) than that of the negative control group (15.96 and 41.05, respectively). However, as compared to the positive control group, groups 3 and 4 displayed a substantial rise ($P<0.05$) in BWG%. Additionally, it was noted that the group who consumed 10% aqueous extract powder had the greatest BWG%. The results also revealed that the feed efficiency ratio (FER) in the positive control group was significantly lower ($P < 0.05$) compared to the negative control group.It was also shown that all treated groups were significantly increased ($P< 0.05$) for FER with the positive control group; also observed that there were no significant differences in FER for all treated groups compared to the negative control group, also Results in **Table 2** showed that CCl_4 administration significantly reduced the body weight of rats in the positive control group compared with the normal group. This finding is consistent with the results demonstrated by **Wang et al. (2018).**The substantial weight loss in the positive control group may be ascribed to the adverse biochemical impact caused by induced hepatotoxicity **(Nwobodo, 2017)**.The BWG% results aligned with the findings of **Nwobodo et al. (2016)**, which indicated that a high dosage of Neem leaves aqueous extract (1000 mg/kg body weight) resulted in increased body weight compared to the positive control group. This is also consistent with the results of **Nwobodo et al. (2018)**.Regarding results from **Table (3),** it showed that the positive control group's mean values for AST, ALT, ALP, and total bilirubin increased significantly ($P<0.05$). as compared with those of the negative control group , Furthermore, there were significantly ($P<0.05$) reduced serum values of AST, ALT , ALP and total bilirubin for all treated groups with aqueous extract powder of Neem compared to the positive control group. , respectively. The most significant improvements in liver function were observed in the group that was fed 10% aqueous extract powder of *Azadirachta indica*. The findings align with **Ezz-Din et al. (2011)**, who demonstrated that Azadirachta indica treatment significantly reduced elevated serum liver function parameters (ALT, AST, and ALP). This result was corroborated by **Devmurari and Jivani (2010**). **Bhanwra et al. (2000)** demonstrated that the aqueous extract of Azadirachta indica leaves significantly reduced serum AST and ALT levels. The observed results can be ascribed to the antioxidative properties of Azadirachta Indica leaves, aligning with existing literature on the hepatoprotective effects of Neem. **Ha et al. (2010)** This finding indicates that Azadirachta indica has good potential to act as hepatoprotective agent. **Kale et al., (2003),** found that Azadirachta Indica leaves aqueous extract significantly ($P<0.05$) prevented changes in the serum levels of

bilirubin that caused by hepatotoxicity agent. Also**, (Dkhil et al., 2013)** and (**Choudhary et al., 2014),** confirmed that Azadirachta Indica treatment reduced significantly in serum total bilirubin. The enhancement of results on liver functions may be due to the fact that Azadirachta Indica contains antioxidants, alkaloids, flavonoids, phenolic compounds, carotenoids and steroids **(Tibebu et al., 2018).** The data presented in Table (4) demonstrate a significant reduction ($P < 0.05$) in serum GPX activity, along with a notable increase ($P < 0.05$) in serum MDA levels in the positive control group compared to the negative control group. In contrast, the treated groups exhibited a significant ($P < 0.05$) decrease in serum MDA levels and a significant ($P < 0.05$) increase in serum GPX activity when compared to the positive control group. The group that received 10% (AEP) treatment was the most effective in lowering blood MDA levels and raising serum GPX activity. This table's findings are consistent with those given by **Dkhil et al. (2013)** and **Nwobodo et al. (2018)**, who indicated that Neem therapy significantly elevated GPX activity in comparison to the positive control group. Furthermore, **Maruthappan and Shree (2009)** discovered that blood GPx levels were significantly increased following the administration of Neem leaves powder in comparison to the hepatotoxic group. **Mahmoodzadeh et al. (2017)** and **Goodla et al. (2019)** reported a significant elevation in MDA levels following CCl4-induced oxidative stress compared to the control group, corroborating the findings of the current study. The findings of MDA corroborated those of **Nwobodo et al. (2017)**, who reported a notable decrease in MDA levels in the treated cohorts with *Azadirachta Indica* relative to the positive control group. Additionally, **Yanpallewar et al. (2003)** confirmed these findings. Rats fed a meal containing 5% and 10% aqueous extract powder demonstrated a substantial ($p<0.05$) decrease in T.C., TG, LDL-C, and VLDL-C when compared to the positive control group according to the findings in **Table (5)**. The results indicated that the blood HDL-C levels in the positive control group were considerably ($P<0.05$) lower than those in the negative control group. Additionally, compared to the positive control group, the treated groups showed a substantial increase ($P < 0.05$). The most significant enhancement in lipid profile was noted in the group that consumed 10% aqueous extract. The results align with **Nwobodo (2017)**, who noted a substantial rise in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c), alongside a decrease in high-density lipoprotein cholesterol (HDL-c) in hepatotoxic rats (+ve control) relative to (-ve control). This study corroborates the established lipid profile associated with hepatocellular damage. On the other hand, rats given different concentrations of Neem aqueous leaf extract showed a substantial decrease in TC, TG, and LDL-c in comparison to the positive control group. Flavonoids and polyphenols can reduce intracellular lipids, hence mitigating the risks of hyperlipidemia and atherosclerosis **(Du et al., 2015)**. **Alshammari et al. (2017)** Nimbolide, a bioactive substance obtained from neem, can lower intracellular triglycerides, free fatty acids, and cholesterol while simultaneously boosting antioxidant systems to stop secondary damages.

4. *Conclusion*

The ingestion of powdered Azadirachta Indica aqueous extract may improve liver enzymes and enzymatic antioxidants, which would have hepatoprotective effects. It is advised that more research be done to clarify the fundamental role that this extract plays in bringing about this improvement.

Ethical Approval

All experiments of the study were ethically approved by the Scientific Research Ethics Committee from the University of Alexandria, Animal Ethics Committee, Faculty of Medicine (Approval no. 05- 01-2024, SREC0307076).

Table 1: Polyphenolic Compounds Concentration of aqueous extract powder

Polyphenolic Compounds	Concentration of Polyphenolic Compounds (mg/kg)
Gallic acid	46.40
p- Hydroxy benzoic acid	103.54
Catchin	28.58
Chlorgenic	54.08
Vanillic acid	156.21
Caffeic acid	11.43
Syringic acid	43.28
p- Coumaric acid	11.91
Ferulic acid	27.46
Ellagic	699.10
o- Coumaric acid	98.49
Salicylic acid	630.13
Cinnamic acid	17.13
Rosemarinic	194.76
Myricetin	290.90
Kampherol	113.92
Total	2527.89

Table 2: Effect of AEP on Feed Intake (FI), Body Weight Gain (BWG%) and Feed Efficiency Ratio (FER)

Parameters / Groups	FI (g/d)	BWG%	FER
G1: -ve control	**14.60**	**41.05±1.43** ^{a}	**0.14±0.017** ^{ab}
G2: +ve control	**15.50**	**15.96±1.50** ^{c}	**0.04±0.003** ^{c}
G3: 5% AEP	**13.92**	**30.01±1.12** ^{ab}	**0.11±0.009** ^{b}
G4: 10% AEP	**14.70**	**38.11±1.44** ^{a}	**0.14±0.005** ^{a}

*Mean values are expressed as means ± SE.
** Differences are significant at ($P < 0.05$).
*AEP= aqueous extract Powder.

Table (3): Effect of Two levels of aqueous extract powder (AEP) on liver Enzymes

Parameters / Groups	AST	ALT	ALP	Total Bilirubin
	U/L			mg/dl
G1: -ve control	89.91±0.79[c]	30.44±0.60[d]	83.84±0.38[d]	0.34±0.017[d]
G2: +ve control	140.32±1.04[a]	51.01±0.98[a]	147.66±0.30[a]	0.93±0.003[a]
G3: 5% AEP	107.23±1.87[b]	43.00±0.81[b]	109.28±0.48[b]	0.50±0.005[b]
G4: 10% AEP	101.77±2.08[b]	37.04±1.01[c]	95.09±1.18[c]	0.41±0.007[c]

*Mean values are expressed as means ± SE.
* Differences are significant at (P < 0.05).
* AEP= aqueous extract Powder.

Table (4): Effect of Two levels of aqueous extract powder (AEP) on Glutathione Peroxidase (GPX) and Malondialdehyide (MDA)

Parameters / Groups	GPX (U/mg)	MDA (µmol/dL)
G1: -ve control	**61.43±0.45** [a]	**10.44±0.27** [d]
G2: +ve control	**32.30±0.62** [d]	**22.11±0.51** [a]
G3: 5% AEP	**50.35±0.29** [c]	**18.24±0.35** [b]
G4: 10% AEP	**53.22±0.72** [b]	**16.28±0.20** [c]

*Mean values are expressed as means ± SE.
* Differences are significant at (P < 0.05).
* AEP= aqueous extract Powder.

Table (5) Effect of Two levels of aqueous extract powder (AEP) on lipids profile.

Parameters / Groups	TC	TG	HDL-C	LDL-C	VLDL-C
	mg/dl				
G1: -ve control	**88.19±0.38** [d]	**47.59±0.44** [c]	**50.93±0.55** a	**30.54±0.90** d	**8.92±0.08** [d]
G2: +ve control	**145.64±0.65** a	**102.61±0.76** a	**25.13±0.33** c	**103.59±0.64** a	**21.12±0.15** a
G3: 5% AEP	**134.46±0.29** b	**74.78±0.49** [b]	**37.54±0.36** b	**89.20±0.46** b	**15.05±0.09** b
G4: 10% AEP	**121.31±0.79** c	**75.13±0.51** [b]	**38.14±0.28** b	**67.73±0.74** c	**15.14±0.10** b

*Mean values are expressed as means ± SE.
* Differences are significant at (P < 0.05).
* AEP= aqueous extract Powder.

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التأثيرات الوقائية للكبد ومضادات الأكسدة لمسحوق المستخلص المائي لنبات النيم على سمية الكبد في الحيوانات كنموذج

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أفادت العديد من الدراسات بأن نبات النيم له خصائص مضادة للأكسدة، وواقية للكبد، ومضادة للالتهابات، وخافضة للسكر، ومضادة لقرحة المعدة، ومضادة للبكتيريا، ومضادة للأورام. وتقيم هذه الدراسة تأثير مسحوق المستخلص المائي لأوراق النيم على إنزيمات الكبد، والأنزيمات المضادة للأكسدة ومستوى الدهون على سمية الكبد في جرزان الألبينو. أربعة وعشرون (٢٤) فمن الجرزان مقسمه في أربع مجموعات، تحتوي كل منها على ستة جرزان ، يزن كل منها ١٥٠ ± ١٠ جم :المجموعة (١) المجموعة الطبيعية :(Ve−) تتغذى على نظام غذائي عادي فقط كمجموعة ضابطه سلبية. المجموعة (٢) المجموعة الإيجابية :(Ve+) تتغذى على نظام غذائي أساسي بعد الحقن بـCCl4 ، كمجموعة ضابطه إيجابية. المجموعات المعالجة: مجموعة اضطرابات الكبد بواسطةCCl4 ، تم تقسيم هذه المجموعات إلى: المجموعة (٣): تتغذى على نظام غذائي أساسي بالإضافة إلى ٥٪ من مسحوق المستخلص المائي للنيم . المجموعة (٤): تم تغذيتها على غذاء أساسي مضافاً إليه ١٠٪ من مسحوق المستخلص المائي للنيم . و أشارت النتائج أن AST و ASTو ALPوالبيليروبين الكلي و MDA ارتفعت بشكل ملحوظ ($P<0.05$) بإعطاء CCl4 (المجموعة الضابطه الإيجابية) مقارنة بالمجموعة السلبية، كما انخفضت بشكل ملحوظ ($P<0.05$) في الجلوتاثيون بيروكسيديز .(GPX) كما أشارت إلى أن الغذاء المدعم بالمستخلص المائي للنيم خفف من هذه التأثيرات السلبية وخفف بشكل ملحوظ التغيرات الكيميائية الحيوية التي تسببها إعطاء.CCl4

الكلمات المفتاحية: النيم ، سمية الكبد، دهون الدم، مالونديالدهيد، إنزيمات الكبد.