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Nephroprotective Effect of Ethanolic Extract of *Ficus vasta* Forssk. (Moraceae) Leaves on Acetaminophen-induced Acute Renal Failure in Guinea Pigs

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Abstract:

Nephrotoxicity is largely caused by metabolites of acetaminophen produced and causes damage to renal function. Medicinal plants have better activity and fewer side effects. This study was conducted to determine the protective effect of *Ficus vasta* Forssk. (Family Moraceae) ethanolic extracts protecting guinea pigs against acetaminophen-induced nephrotoxicity. The use of acetaminophen (PCM) suspension (2g/kg, p.o.) caused nephrotoxicity, and then treatment was done with ethanolic extract of *F. vasta* for 15 days. On day sixteen, all of the animals were given chloroform anesthesia, and kidney samples, and blood samples from each group were taken for biochemical and histological examination. In animals administrated PCM, showed a significant ($P < 0.05$) increase of serum blood urea nitrogen and creatinine, and a reduction of albumin and total proteins. Treatment with *F. vasta* (100 and 200 mg/kg) significantly ($P<0.05$) decreased serum blood urea nitrogen, and creatinine levels and caused increased total protein and albumin levels. Studies on histopathology also validate the extracts' protective properties. Restoration of serum blood urea nitrogen, creatinine, total protein, and albumin level was linked to the protective action of *F. vasta*. In guinea pigs exposed to acetaminophen-induced nephrotoxicity, ethanolic extracts of *F. vasta* demonstrated a strong nephroprotective effect.

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INTRODUCTION

Paracetamol (N-acetyl-p-aminophenol; APAP) is a common analgesic and antipyretic drug that is safe to use at therapeutic dosages for several conditions (Ayoub, 2021; Yapar *et al.*, 2007). Acute acetaminophen overdose has been shown to damage the kidneys and liver in both humans and laboratory animals (Ghosh and Sil, 2007; Yan *et al.*, 2018). Although hepatotoxicity is more common in cases of acetaminophen overdose than nephrotoxicity, both humans and experimental animals can die from acute renal failure and renal damage even in the absence of liver injury (Cekmen *et al.*, 2009). Nephrotoxicity is largely caused by metabolites of acetaminophen produced in the liver, especially glutathione conjugates. Acetaminophen damages renal function through the formation of the reactive intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI), which conjugates with glutathione sulfhydryl to be removed at therapeutic dosages. NAPQI can bind to cellular proteins, which can cause renal damage and start lipid peroxidation (Li *et al.*, 2003; Ozkan and Karabag, 2020).

Plant extracts have been used for a very long time in industrialised nations because they are natural and usually safe (Aernan *et al.*, 2023; Iqbal *et al.*, 2019). There are several medicinal plants that serve as biological habitats for pharmaceutical intermediates, nutritional supplements, and traditional and modern medicine (Al-Hakami *et al.*, 2022; Iqbal and Ashraf, 2018; Kalim *et al.*, 2016; Shahzad *et al.*, 2017). Phytochemicals are mainly responsible for the therapeutic qualities of plants (Aernan *et al.*, 2024).

The genus *Ficus* L., known as fig trees, belongs to the family Moraceae and includes about 800 species and 2000 varieties of woody trees, shrubs, and vines (Ahmed *et al.*, 2012; Rahman and Khanom, 2013). Several species in this genus are used worldwide in traditional medicine to treat a variety of conditions related to the reproductive, endocrine, gastrointestinal, and central nervous systems; they are also used to treat infectious diseases such as tuberculosis, respiratory, and skin disorders (Tkachenko *et al.*, 2016). *Ficus* L. genus in Yemen is represented by 11 species. *Ficus vasta* Forssk. (Local name Taluq) is a very large tree growing to 25 m tall, with grey bark, sometimes buttressed and sometimes sending down aerial roots. Branchlets are red-brown and pubescent. Leaves are alternate, smooth, bright green, entire, broadly ovate to suborbicular, 25-32 × 22-25 cm, base cordate, apex obtuse to rounded; glabrescent on the upper surface, pubescent below. Figs shortly pedunculate on the branchlets, globose, brown, and pubescent (Aqlan, 2008). This species is widespread in Tanzania, Sudan, Ethiopia, Yemen, Saudi Arabia, Uganda, and the arid regions of eastern and northern Africa.

F. vasta leaves and bark poultice were utilized as an anti-tumor agent (Mosa *et al.*, 2014). Traditionally, the leaves were used to treat intestinal worms, rheumatism, and pain (Rashed *et al.*, 2015). Triterpenes, coumarins, flavonoids, carbohydrates, and tannins were found in the *F. vasta* leaves (Rashed *et al.*, 2015; Taviano *et al.*, 2018). Additionally, a variety of phytoconstituents, include ursolic acid, β-sitosterol, stigmasterol, and lupeol (Rashed and Ono, 2013).

In conventional systems, *F. vasta* is an interesting plant. Nevertheless, there have been no published scientific investigations on the nephroprotective benefits of *F. vasta*, and its chemical components might be helpful in the management of nephrotoxicity. The current study was conducted to investigate the nephroprotective effect of ethanolic extracts of the *F. vasta* leaf plant against nephrotoxicity induced by acetaminophen.

MATERIAL AND METHODS

Plant materials

Plant samples were collected from Wadi Al-Dor, Al-Udayn, Ibb, Yemen during the period 2-10/4/2023. The identification and authentication of plant specimens was done by Dr. Esam Aqlan, Biology Department, Faculty of Sciences, Ibb University. A voucher specimen was deposited at the Biology Herbarium, Faculty of Sciences, Ibb University under the code FV202303.

Preparation of ethanol extract of *Ficus vasta* leaves

Fresh leaves were cleaned with tap water to keep dust and other unwanted elements from building up on leaves in their natural habitat. The leaves were allowed to dry in an air-circulating oven at 40 °C in the biology laboratory. An electric blender was used to powder the dried leaves. Lastly, the powdered leaves were sieved through a kitchen strainer to extract a fine powder. Twenty grams of powder plant material was extracted individually by 200 ml of ethanol 70% was separately in a conical flask. Aluminium foil was used to cover the mouth of the conical flask and placed on a rotary shaker set at 150 revolutions per minute for a full day to ensure complete dissolution of the active ingredients in the appropriate solvent and thorough mixing. Next, Whatman No. 1 filter paper was used to filter the extract. At 40 °C, an oven was used to remove the extract's solvent. Ultimately, the leftover materials were collected and employed in the study (Aernan *et al.*, 2023).

Experimental animals

Thirty-five male guinea pigs that weigh between 450 and 600 grams were bought from the Ibb City, Yemen, local market. They did not appear to have any anomalies and were in good health. The animals were housed in a controlled environment with room temperature and a 12-hour light-dark cycle to accommodate free access to food and water *ad libitum*. The Institutional Animal Ethics Committee of Ibb University in Yemen approved the experiment protocol.

Experimental design

Seven groups, each consisting of five male guinea pigs, were randomly assigned. The following approach was used to group the animals following the previously described procedure (Palani *et al.*, 2010):

Group I was the control group; they were given distilled water orally for 15 days. Group II was administered oral PCM (2 g/kg) daily, suspended in olive oil. Group III gave oral PCM (2 g/kg), then given a silymarin treatment (100 mg/kg) while suspended in olive oil. Groups IV and V received daily oral ethanol extracts of *Ficus vasta* (100 mg/kg and 200 mg/kg, respectively) dissolved in distilled water. Group VI: was treated with ethanol extracts of *F. vasta* (100 mg/kg) diluted in distilled water after receiving PCM (2 g/kg) orally for one hour. Group VII: was treated with ethanol extracts of *F. vasta* (200 mg/kg) diluted in distilled water for 15 days after receiving PCM (2 g/kg) orally for one hour. On day sixteen, all of the animals were given chloroform anesthesia. Subsequently, blood and kidney samples were obtained for biochemical and histological investigation from each group.

Biochemical analysis

Centrifugation was used to separate the serum for 15 minutes at 3000 rpm and 4°C. Serum samples were used to test the amounts of total proteins, albumin, blood urea nitrogen, and creatinine. For all estimations, a diagnostic kit (Span Diagnostics Ltd., India) was utilized following the manufacturer's instructions (Parameshappa *et al.*, 2012).

Histopathological examination

After the animals were sacrificed, kidney slices from each group were dried in graded (50–100%) alcohol, embedded in paraffin, and fixed in 10% neutral formalin for at least 24 hours. Haematoxylin-eosin dye was used to produce and stain kidney tissue cross-sections that were 5-7 µm thick. A microscopical inspection was used to assess the sections (Parameshappa *et al.*, 2012).

Statistical analysis

The data is presented in the form of mean ± standard deviation (SD). SPSS (version 21) and one-way analysis of variance (ANOVA) were utilized to look for statistical differences between the treatments and the controls. A variation in P<0.05 mean values was considered statistically significant.

RESULTS

Following acetaminophen-induced toxicity, serum levels of blood urea nitrogen, creatinine, total proteins, and albumin were measured to assess the protective effects of *Ficus vasta* extracts in guinea pigs. The kidney histopathology investigation was also conducted to evaluate the protective role of *F. vasta*.

Effect of treatment of ethanolic extract of *F. vasta* leaves on serum biochemical parameters

Acetaminophen administrated elevated the level of blood urea nitrogen and creatinine which was 25.25±0.50, 0.80±0.08 when compared with the control 19.88±0.62, 0.63±0.05. Treatments with silymarin (standard drug) and *F. vasta* ethanolic extracts 100 and 200 mg/kg significantly decreased (P<0.05) the blood urea nitrogen to 22.87±0.53, 22.65±0.42 and 21.33±0.47 mg/dL; creatinine to 0.70±0.14, 0.73±0.09 and 0.70±0.08 mg/dL, respectively**.**

The levels of total proteins and albumin were significantly reduced (P< 0.05) by paracetamol administration at 3.90±0.24 g/dL relative to the control group at 4.73±0.20 g/dL. However, treatment with silymarin (standard drug) and *F. vasta* ethanolic extracts 100 and 200 mg/kg increase the total protein level to 5.63±0.26, 5.75±0.17, 6.00±0.81 g/dL and albumin level to 4.67±0.16, 4.35±0.51 and 4.00±0.81 g/dL respectively.

Table 1. Effect of *Ficus vasta* extracts treatment on the biochemical processes involved in nephrotoxicity brought on by paracetamol.

Parameters	Urea (mg/dl)	Creatinine (mg/dl)	Total protein (g/dl)	Albumin (g/dl)
Control	19.88±0.62	0.63±0.05	6.40±0.50	4.73±0.20
PCM only	25.25±0.50#	0.80 ±0.08#	5.53±0.33#	3.90±0.24#
PCM+Silymarin (100 mg/kg)	22.87±0.53#*	0.70±0.14	5.63±0.26#	4.67±0.16*
Ficus vasta (100 mg/kg)	19.84±0.81*	0.65±0.05*	6.35±0.69*	4.70±0.46*
Ficus vasta (200 mg/kg)	20.00±0.44*	0.70±0.08	6.40±0.34*	4.73±0.35*
PCM+ *Ficus vasta* (100 mg/kg)	22.65±0.42#*	0.73±0.09	5.75±0.17#	4.35±0.51
PCM+*Ficus vasta* (200 mg/kg)	21.33±0.47*	0.70±0.08	6.00±0.81	4.00±0.81#

All value represents the mean± SD of 5 animals. # P < 0.05 compared with normal control value. * P < 0.05 compared with PCM alone values.

Histopathological observations

Histopathological analysis of the kidney sections from the PCM alone group of guinea pigs revealed altered renal morphology all around, including extensive tubular degeneration, damaged glomeruli, broad lumina, interstitial vascular congestion, and epithelial degeneration. Figure 1 depicts mild degenerative alterations in the glomeruli and tubules of kidneys from rats simultaneously treated with *F. vasta* 100 and 200 mg/kg.

DISCUSSION

The current study's findings show that ethanolic extracts of *Ficus vasta* can effectively protect guinea pigs from acetaminophen's nephrotoxic effects. Biochemically, this is demonstrated by a reduction in the elevated levels of acetaminophen on serum blood urea nitrogen, creatinine, total proteins, and albumin. Pathological confirmation of the extract's protective effect came from its amelioration of renal lesions caused by acetaminophen and proximal tubular cell necrosis, which included congestion and RBC infiltration.

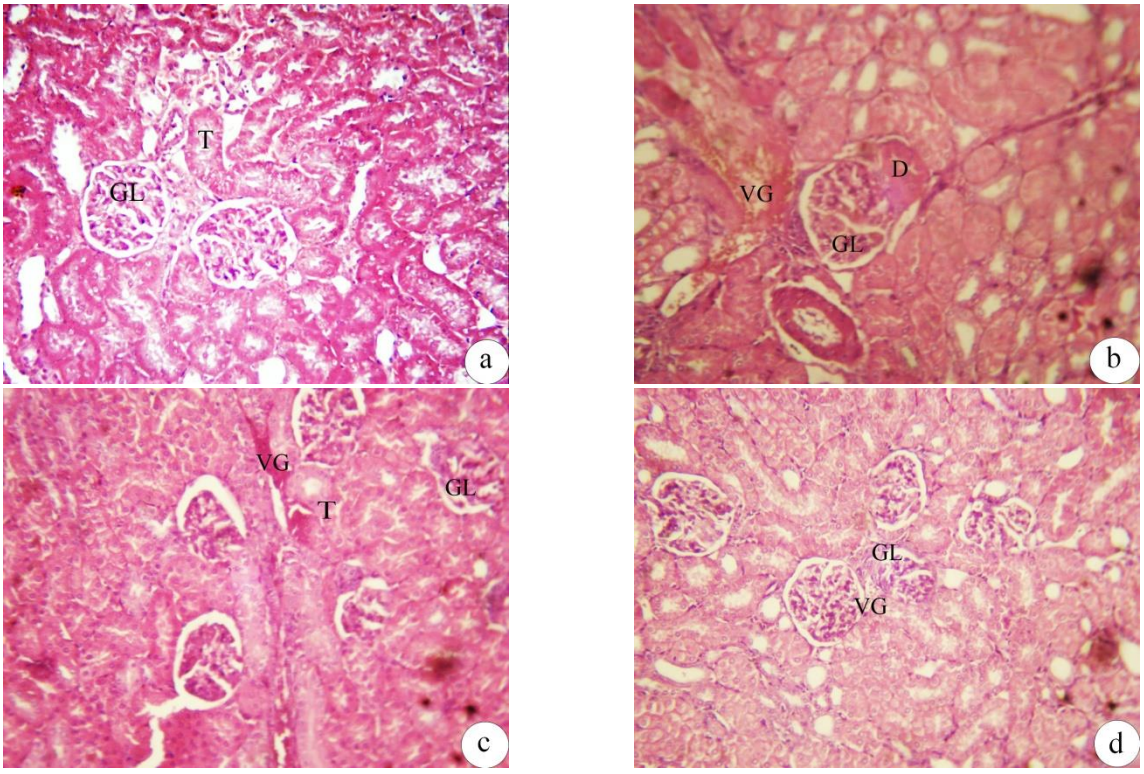

Fig. 1. Histopathology of kidney. (**a**) Section of kidney from guinea pigs in the control group demonstrating the typical morphology of the renal tubules (T) and glomerulus (GL); (**b**) sections of the guinea pigs administrated with PCM alone revealed severe tubular degeneration (D), damaged glomeruli (GL) and interstitial vascular congestion(VG); (**c**) sections of guinea pigs treated with *F. vasta* 100 mg/kg showed considerable nephroprotection along with slight interstitial vascular congestion (VG) and moderate degenerative alterations in the glomeruli (GL) and tubules (T); (**d**) sections of guinea pigs treated with *F. vasta* 200 mg/kg exhibited significant nephroprotection with little deteriorative modifications in the glomeruli (GL) and mild interstitial vascular congestion (VG) (H & E stain; 400x).

The kidney is one of the body's most intricate organs, with distinct parts that work together in a highly synchronized manner. It has been demonstrated that several medications, chemicals, and heavy metals can damage the kidney by changing its composition and functionality (Alam *et al.*, 2016; Almansory *et al.*, 2021; Priyamvada *et al.*, 2010). Acetaminophen is a common, well-tolerated medication that is used as an antipyretic and an analgesic in place of aspirin (Alchin *et al.*, 2022; Ishitsuka *et al.*, 2020).

Potentially well-known side effects of paracetamol include nephrotoxicity and hepatotoxicity, which are brought on by the drug's initial biotransformation (Offor *et al.*, 2022). The water-soluble metabolites of paracetamol are eliminated by the kidney after being metabolized by glucuronidation and sulfation reactions, which predominantly take place in the liver (Cekmen *et al.*, 2009). NAPQI, a highly reactive intermediary product of paracetamol, has hazardous properties that cause nephrotoxicity. NAPQI produces acrylates

that cause the proteins in the S3 segment of the proximal tubule, specifically glutamine synthetase and selenium-binding protein, to begin dying (Adeneye and Benebo, 2008). Nephrotoxicity from paracetamol overdose is also thought to be largely caused by glutathione depletion and the lipid peroxidation that results from it. It is believed that in humans and animals, the selective accumulation of paracetamol in the kidneys sets off a series of biochemical events that can result in either chronic or acute nephropathies (Adeneye *et al.*, 2008). Nephrotoxicity caused by drugs is frequently linked to marked elevations in acute tubular necrosis, serum creatinine, and blood urea nitrogen. Thus, to study drug-induced nephrotoxicity in humans and animals, biochemical parameters like blood urea and serum creatinine are estimated (Adeneye and Benebo, 2008). The kidney is more vulnerable to damage because of greater perfusion and higher amounts of chemicals released by renal tubular cells (Radi, 2019). The principal nitrogenous byproduct of protein metabolism as well as the purine nucleotides adenosine and guanosine metabolism is urea (Renugadevi and Prabu, 2009). Blood urea nitrogen is present in the liver protein that is typically eliminated in the urine and is obtained from food or tissue sources. When urea accumulation occurs in the serum due to renal disorders, the rate of production of serum urea surpasses the renal clearance rate (Pradhan *et al.*, 2013). Uremia can result from a high-protein diet, malnutrition, steroid therapy, sepsis, tissue destruction, or increased catabolism. It can also result from bleeding in the gastrointestinal lumen and amino acid and peptide absorption from digested blood (Adeneye *et al.*, 2008; Palani *et al.*, 2010). Racial function is thought to be indicated by serum levels of creatinine and urea. Creatinine is produced by tissue creatinine breakdown from endogenous sources. Elevated blood or serum urea levels are associated with heightened protein catabolism, and in mammals, elevated arginase synthesis results in the transformation of ammonia into urea (Renugadevi and Prabu, 2009).

Acetaminophen administration to control guinea pigs resulted in nephrotoxicity, marked by a substantial decrease in albumin and total proteins and a substantial increase in serum urea nitrogen and creatinine. This suggests that acetaminophen can produce significant nephrotoxicity at a dosage of 2 g/kg body weight. According to the data from this study, acetaminophen interacts with the cell membrane, altering its permeability and causing the kidney to lose its functional integrity. This is evident in the elevated serum levels of kidney function indicators (creatinine, blood urea nitrogen) following acetaminophen administration. Conversely, guinea pigs given *F. vasta* had a substantial decrease in these markers, indicating the plant's capacity to protect against kidney injury brought on by paracetamol. Due to defective protein manufacture in the liver, total protein levels, including albumin levels, are decreased in hepatotoxic conditions (Khanam *et al.*, 2016; Kumar *et al.*, 2009). The chemical constituents of the *F. vasta* plant reported the incidence of diverse phytochemicals such as flavonoids, tannins, and triterpenes (Aati *et al.*, 2022; Rashed *et al.*, 2015). The saponins, triterpenoids, and alkaloids showed nephroprotective activity (Balakumar *et al.*, 2010; Bildziukevich *et al.*, 2023; Nerdy and Ritarwan, 2019). Thus further investigations are required to determine the bioactive chemicals responsible for its nephroprotective effect and to discover the mechanistic action of *F. vasta* extract as nephroprotective agents against acetaminophen.

CONCLUSION

In summary, guinea pig kidneys treated with acetaminophen showed histological alterations and decreased renal function indicators. All of these measures significantly decreased in guinea pigs given paracetamol after receiving extracts from *Ficus vasta*.

F. vasta may have these advantageous benefits because it improves kidney function indicators. According to our research, *F. vasta* may have a role in preventing nephrotoxicity brought on by acetaminophen.

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CONFLICT OF INTEREST

Authors hereby declare that they have no conflict of interest.

REFERENCES

Aati, H.Y., Anwar, M., Al-Qahtani, J., Al-Taweel, A., Khan, K.U., Aati, S., Usman, F., Ghalloo, B.A., Asif, H.M., Shirazi, J.H., Abbasi, A., 2022. Phytochemical Profiling, In Vitro Biological Activities, and In-Silico Studies of *Ficus vasta* Forssk.: An Unexplored Plant. Antibiot., (Basel, Switzerland), 11(9).

Adeneye, A., Olagunju, J., Benebo, A., Elias, S., Adisa, A., Idowu, B., Oyedeji, M., Isioye, E., Braimoh, O., Oladejo, O., 2008. Nephroprotective effects of the aqueous root extract of *Harungana madagascariensis* (L.) in acute and repeated dose acetaminophen renal injured rats. Int. J. Appl. Res. Nat. Prod., 1(1): 6-14.

Adeneye, A.A., Benebo, A.S., 2008. Protective effect of the aqueous leaf and seed extract of *Phyllanthus amarus* on gentamicin and acetaminophen-induced nephrotoxic rats. J. Ethnopharmacol., 118(2): 318-323.

Aernan, P.T., Odo, J.I., Ado, B.V., Mende, I.U., Yaji, E.M., Iqbal, M.N., 2024. Phytochemical and Antibacterial Assessment of *Ageratum conyzoides* Cultivated in Benue State, Nigeria. PSM Biol. Res., 9(1): 41-50.

Aernan, P.T., Odo, J.I., Omeji, J.M., Eunice, Y.M., Iqbal, M.N., 2023. Anti-bacterial Activity of *Moringa oleifera* Seeds against Selected Bacterial Pathogens. PSM Microbiol., 8(3): 82-90.

Ahmed, F., Ahmed, K.M., Abedin, M., Karim, A., 2012. Traditional uses and pharmacological potential of *Ficus exasperata* Vahl. Sys. Rev. Pharm., 3(1): 15.

Al-Hakami, I.A., El-Shaibany, A., Al-Mahbashi, H., Humaid, A., Raweh, S., Elaasser, M.M., 2022. Phytochemical Screening, Antimicrobial, Antioxidant and Anticancer Activities of Yemeni *Croton socatranus*. Int. J. Nanotechnol. Allied Sci., 6(1): 1-13.

Alam, S., Masood, S., Iqbal, M.N., Ashraf, A., Xiao, S., Ahsan, M., 2016. Effect of Sodium Selenite on Kidney Function Test of Rabbits. PSM Vet. Res., 1(1): 17-21.

Alchin, J., Dhar, A., Siddiqui, K., Christo, P.J., 2022. Why paracetamol (acetaminophen) is a suitable first choice for treating mild to moderate acute pain in adults with liver, kidney or cardiovascular disease, gastrointestinal disorders, asthma, or who are older. Curr. Med. Res. Opin., 38(5): 811-825.

Almansory, A.H., Al-Shaibani, E.A., Shediwah, F.M., Ibrahim, H.M., 2021. The Effect of Cisplatin and 5-Fluorouracil versus *Aloe perryi* extracts on Rat Liver and Kidney Tissues. PSM Vet. Res., 6(3): 59-73.

Aqlan, E., 2008. Studies on the flora of Ibb governorate, Republic of Yemen. Unpublished Thesis, Sana'a University, Yemen.

Ayoub, S.S., 2021. Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action. Temperature, 8(4): 351-371.

Balakumar, P., Rohilla, A., Thangathirupathi, A., 2010. Gentamicin-induced nephrotoxicity: do we have a promising therapeutic approach to blunt it? Pharmacol. Res., 62(3): 179-186.

Bildziukevich, U., Wimmerová, M., Wimmer, Z., 2023. Saponins of Selected Triterpenoids as Potential Therapeutic Agents: A

Review. Pharm., (Basel, Switzerland), 16(3).

Cekmen, M., Ilbey, Y.O., Ozbek, E., Simsek, A., Somay, A., Ersoz, C., 2009. Curcumin prevents oxidative renal damage induced by acetaminophen in rats. Food Chem. Toxicol., 47(7): 1480-4.

Ghosh, A., Sil, P.C., 2007. Anti-oxidative effect of a protein from *Cajanus indicus* L against acetaminophen-induced hepato-nephro toxicity. BMB Rep., 40(6): 1039-1049.

Iqbal, I., Ashraf, A., Iqbal, A., 2019. Plant Essential Oils as Potential Antimicrobials: Present Status and Future Perspectives. PSM Microbiol., 4(3): 71-74.

Iqbal, M.N., Ashraf, A., 2018. Recombinant Protein Production in Plants: Biofactories for Therapeutics. Int. J. Molec. Microbiol., 1(1): 38-39.

Ishitsuka, Y., Kondo, Y., Kadowaki, D., 2020. Toxicological property of acetaminophen: the dark side of a safe antipyretic/analgesic drug? Biol. Pharm. Bull., 43(2): 195-206.

Kalim, M., Hussain, F., Ali, H., Ahmad, I., Iqbal, M.N., 2016. Antifungal activities of methanolic extracts of *Datura inoxia*. PSM Biol. Res., 1(2): 70-73.

Khanam, F., Iqbal, M.N., Ashraf, A., Alam, S., Muhammad, A., Xiao, S., Toor, S., Mumtaz, H., 2016. Evaluation of Changes in Liver Enzymes in Broiler Chicks (*Gallous domesticus*). PSM Vet. Res., 1(1): 26-31.

Kumar, S.S., Kumar, B.R., Mohan, G.K., 2009. Hepatoprotective effect of *Trichosanthes cucumerina* Var cucumerina L. on carbon tetrachloride induced liver damage in rats. J. Ethnopharmacol., 123(2): 347-350.

Li, C., Liu, J., Saavedra, J.E., Keefer, L.K., Waalkes, M.P., 2003. The nitric oxide donor, V-PYRRO/NO, protects against acetaminophen-induced nephrotoxicity in mice. Toxicol., 189(3): 173-80.

Mosa, E., Justin, D., Hamam, S., Mohamed, E., Saad, M., 2014. Evaluation of phytochemical and antimicrobial activities of some sudanese medicinal plants. World. J. Pharm. Pharm. Sci., 3(12): 1769-76.

Nerdy, N., Ritarwan, K., 2019. Hepatoprotective Activity and Nephroprotective Activity of Peel Extract from Three Varieties of the Passion Fruit (Passiflora Sp.) in the Albino Rat. Open access Maced. J. Med. Sci., 7(4): 536-542.

Offor, S.J., Amadi, C.N., Chijioke-Nwauche, I., Manautou, J.E., Orisakwe, O.E., 2022. Potential deleterious effects of paracetamol dose regime used in Nigeria versus that of the United States of America. Toxicol. Rep., 9: 1035-1044.

Ozkan, E., Karabag, F., 2020. Investigation of boron effect on trace elements and antioxidant capacity in paracetamol-induced nephrotoxicity model. Veteriner. Hekimler. Derneği. Dergisi., 91(1): 25-35.

Palani, S., Raja, S., Kumar, R.P., Parameswaran, P., Kumar, B.S., 2010. Therapeutic efficacy of *Acorus calamus* on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats. Acta Pharm. Sci., 52(1).

Parameshappa, B., Ali Basha, M.S., Sen, S., Chakraborty, R., Kumar, G.V., Sagar, G.V., Sowmya, L., Raju, K.K., Sesh Kumar, P.K.R., Lakshmi, A.V.S.M., 2012. Acetaminophen-induced nephrotoxicity in rats: Protective role of *Cardiospermum halicacabum*. Pharm. Biol., 50(2): 247-253.

Pradhan, S., Mandal, S., Roy, S., Mandal, A., Das, K., Nandi, D.K., 2013. Attenuation of uremia by orally feeding alpha-lipoic acid on acetaminophen induced uremic rats. Saudi Pharm. J., 21(2): 187-92.

Priyamvada, S., Khan, S.A., Khan, M.W., Khan, S., Farooq, N., Khan, F., Yusufi, A., 2010. Studies on the protective effect of dietary fish oil on uranyl-nitrate-induced nephrotoxicity and oxidative damage in rat kidney. Prostaglandins, Leukot. Essent. Fat. Acids., 82(1): 35-44.

Radi, Z.A., 2019. Kidney pathophysiology, toxicology, and drug-induced injury in drug development. Int. J. Toxicol., 38(3): 215-227.

Rahman, A., Khanom, A., 2013. Taxonomic and ethno-medicinal study of species from Moraceae (Mulberry) Family in Bangladesh Flora. Res. Plant Sci., 1(3): 53-57.

Rashed, K., Anthonissen, R., Cappoen, D., Verschaeve, L., 2015. Phytochemical Composition and Potential Genotoxic effects of Important Egyptian Medicinal Plants. Phcog. Commn., 5(3).

Rashed, K., Ono, L., 2013. Evaluation of cytotoxicity, anti-herpes simplex virus type 1 (HSV-1) and antibacterial activities of *Ficus vasta* and phytoconstituents. Int. Cur. Pharm. J., 3(1): 211-218.

Renugadevi, J., Prabu, S.M., 2009. Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. Toxicol., 256(1-2): 128-134.

Shahzad, M.I., Ashraf, H., Iqbal, M.N., Khanum, A., 2017. Medicinal Evaluation of Common Plants against Mouth Microflora. PSM Microbiol., 2(2): 34-40.

Taviano, M.F., Rashed, K., Filocamo, A., Cacciola, F., Dugo, P., Mondello, L., Bisignano, C., Acquaviva, R., D'Arrigo, M., Miceli, N., 2018. Phenolic profile and biological properties of the leaves of *Ficus vasta* Forssk. (Moraceae) growing in Egypt. BMC Complement. Altern. Med., 18(1): 161.

Tkachenko, H., Buyun, L., Terech-Majewska, E., Osadowski, Z., 2016. In vitro antimicrobial activity of ethanolic extracts obtained from Ficus spp. leaves against the fish pathogen *Aeromonas hydrophila*. Fish. Aquat. Life., 24(4): 219-230.

Yan, M., Huo, Y., Yin, S., Hu, H., 2018. Mechanisms of acetaminophen-induced liver injury and its implications for therapeutic interventions. Redox Biol., 17: 274-283.

Yapar, K., Kart, A., Karapehlivan, M., Atakisi, O., Tunca, R., Erginsoy, S., Citil, M., 2007. Hepatoprotective effect of L-carnitine against acute acetaminophen toxicity in mice. Exp. Toxicol. Pathol., 59(2): 121-128.