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Evaluation the Effectiveness of Nephelium Lappaceum (Nl) Peel Aqueous Extract Against Kidney Dysfunction Induced by Thioacetamide (TAA) in Male Albino Rats

Zahraa Fadel Thabet[1*], Heba A. Abd-Alsalam Alsalame[1,2]

[1] Department of Biology, College of Education for Pure Science, University of Kerbala, Kerbala 56001, Iraq
[2] Department of Medical Lab Technology, Al-Zahrawi University College, Kerbala 56001, Iraq

Corresponding Author Email: zahraa.fadhel@s.uokerbala.edu.iq

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ABSTRACT

Antioxidant system is one of the most important defense mechanisms in the body to reduce the effect of oxidative stress and reactive oxygen species (ROS). Thioacetamide (TAA) is a toxic substance which involved in many toxic effects on different body cells. the current study aimed to know the protective role of Nephelium lappaceum (*NI*) peel aqueous extract against functional and histological renal injury which induced by TAA in male's albino rats. Forty adult males rats were used for this study and randomly divided into equal 4 groups (10 animals per group), First negative (G1) group was given distilled water, second positive group (G2) was IP injected with 200 mg/kg inter of TAA twice a week, while the third group (G3) was gavage 25 mg/kg *NI*, the last group (G4) taken 200 mg/kg of TAA and 25 mg/kg (*NI*), After 12 weeks, the following parameters were measure Malondialdehyde (MDA), Glutathione (GSH), the effectiveness of the enzyme Superoxide dismutase (SOD), urea and creatinine, in addition to study the histological changes to evaluation the effectiveness of Nephelium lappaceum (*NI*) peel aqueous extract. the result showed that treatment with *NI* enhance normal kidney function as well as show its effectiveness against renal damage and renal abnormalities.

1. INTRODUCTION

The kidneys are considered as an important and essential organ that the body needs to perform many important functions, including the secretion of toxic and unnecessary metabolites, the regulation of extracellular fluids, and the elimination of toxins, which contribute into achieving the homeostatic functions of the body [1]. Kidney disorders occur through exposure to many drugs and Toxic chemicals that cause damage or destruction of kidney function [2]. One of these substances is TAA. It contains an organic compound with yellow or white crystals, is soluble in water, and has a chemical molecular formula (CH_3CSNH_2) [3, 4]. It contains a sulfide ion, so it is used as an antifungal and antibacterial, as well as other uses in the field of chemical industries, laboratory and technical uses, in addition to its uses in the food and beverage industry, leather tanning, textile industry, and fuel engines [5, 6]. TAA is widely used in many experimental studies due to its high toxicity, which causes many cellular damages to various organs of the body, especially in causing kidney damage and fibrosis in laboratory rats [7]. The TAA compound also causes destructive effects on many other organs of the body, including the brain, leading to neurological deterioration as a result of high ammonia levels and inflammation of the cerebral nerves, in addition to its role in the occurrence of cerebral edema and causing a change in the permeability of the blood-brain barrier (BBB) [8], in addition to its role in causing kidney disorders and toxic effects on the spleen, lungs, and intestines [9]. And its effective role in causing liver damage, liver tumors, and cirrhosis in laboratory rats [10, 11]. Humans can be exposed to the thioacetamide compound through direct inhalation of toxic fumes or through skin contact [12]. When TAA is bioactivated by cytochrome P450 system, it produces thioacetamide S-oxide (TAASO) and thioacetamide S-2 oxide ($TAASO_2$), which are among the highly toxic compounds that stimulate oxidative stress and renal failure [13, 14]. The metabolic path of the reactive metabolite $TAASO_2$ is completed by converting it to Acetonitrile, which in turn is converted by the enzyme Nitrile hydratase to another compound called Acetamide, after which acetate is produced by the Acetamidase enzyme as a final step in the metabolism of the compound TAA (see Figure 1) [15]. The rambutan plant is one of the most important medicinal plants because its activity as anti-inflammatory, antimicrobial, and cholesterol-lowering, in addition to being anti-diabetic and anti-cancer [16]. The rambutan plant belongs to the Saponaceae family, and the Nephelium genus contains 22 species, 16 of which are in Indonesia, and 9 of which are the most cultivated and consumed as food: *N. lappaceum and M. cuspidatum var. N. junglandifolium, N. maingayi, N. meduseum, N. ramboutan-ake, N. melanomiscum, and N. Reticulatum and N. uncimatum* [17]. N. lappaceum is characterized by containing many active compounds such as phenols, flavonoids, ascorbic acid, geraniin, and others, which enable it to scavenge reactive oxygen species (ROS), In addition, to their therapeutic properties in treating many

diseases, including kidney disorders [18]. Many studies indicate the protective role of the peels of rambutan fruits in protecting the body's cells from the influence of free radicals and activating the biosynthesis of internal antioxidants, as well as repairing oxidative damage and reducing the damage resulting from harmful substances such as TAA, in addition to the positive effect of these fruits in regulating kidney functions. and various vital processes carried out by renal cells [19-21]. Our study aims to clarify the potential role of rambutan peel extract on kidney activities and levels of endogenous antioxidants to alleviate TAA-induced renal injury in the rat model. It is expected that rambutan peels have protective properties for the kidneys by enhancing internal antioxidants and reducing the toxic effects of thioacetamide.

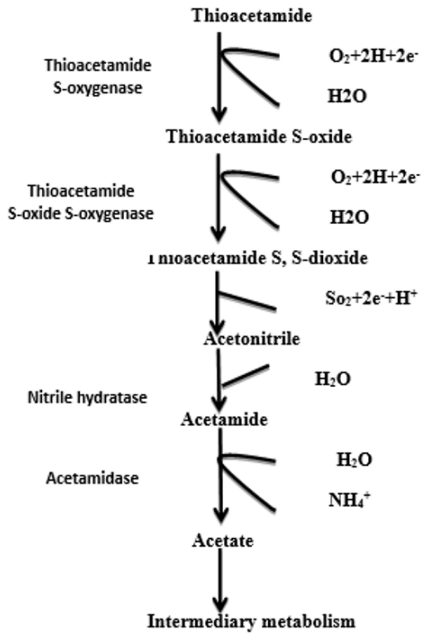

Figure 1. Model of metabolism of TAA

2. MATERIALS AND METHODS

2.1 Chemicals

TAA was obtained from Sigma-Aldrich (St. Louis, MO, USA), kidney injury was induced by TAA (200 mg/kg) dissolved in 5ml of distilled water, intraperitoneally tow times a week during a 12-week period [22].

2.2 Animals

40 male albino white rats (age: 10-12 weeks, average weight: 200-250 grams) were obtained from animal houses in Karbala, Iraq. They were placed in special plastic cages, and their floors were spread with fine sawdust. The animals were kept under standard laboratory conditions at a temperature 25℃ with controlled humidity and 12/12 light-dark cycle, with the lights turned on at 8:00 A.M. Rats were monitored daily, with a standard diet including concentrate pullet and tap water.

2.3 Experience design

Forty adult males randomly divided equally into four groups (10 animals per group).

-G1 was given distilled water.

-G2 was injected sub peritoneal injections with TAA at a concentration of 200 mg/kg twice a week.

-G3 was administered 25 mg/kg of *NI* peels aqueous extract.

-G4 was administered 25 mg/kg of *NI* peels aqueous extract with Sub peritoneal injections 200 mg/kg of TAA.

After 90 days, all the animals were anesthetized after given a piece of cotton and placed in a closed transparent box. The animals were dissected, and the kidney organ was removed and cut into small pieces longitudinally and transversely. They were preserved in 10% formalin at 48h. Later the specimens processed during stander procedure by use histological techniques [23].

2.4 Aqueous extract preparation

Rambutan fruits were purchased from Malaysia. The fruits were cleaned of dust and impurities, washed with water and dried well. Then the peels were removed from the pulp, cut into small slices. They were exposed to sunlight for 7-15 days to dry completely (Figure 2). After that, it was ground by using electric blender to obtain fine powder of the peels. 20g of dry powder of rambutan peels add with 300 ml of DW. The mixture was left for 24h at room temperature. And mixture was filtered by using medical gauze, then centrifuged for 10 minutes at 3000 rpm, then extract was cleared by using Whatman No. 0.1. To obtain a clear solution and dried at room temperature for 12 hours, then keep in glass bottles in the refrigerator until use [24].

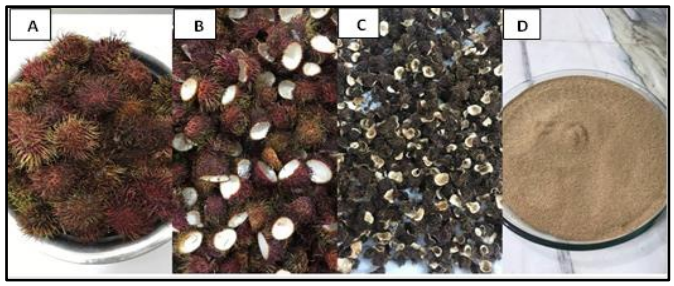

Figure 2. Stages of drying rambutan peels (A: fresh rambutan fruit; B: rambutan peel; C: dry peel; D: dry peel powder)

2.5 Statistic analysis

SPSS software was used to analysis the results, and we tested the correlation coefficient by means of the analysis of variance by complete randomized design (CRD). We used the least significant difference (L.S.D) at $P<0.01$ to show the significance of the results [25]. These modifications aim to ensuring reproducibility and understanding of the experimental procedures.

3. RESULTS

The results of G2 showed that treatment with TAA led to a significant increase ($P<0.01$) in the levels of urea, creatinine, and MDA, while it showed a significantly decrease ($P<0.01$) in the levels of antioxidants GSH and SOD compared to G1, as shown in Tables 1 and 2. The results of G3 and G4 showed no significant differences ($P>0.01$) in levels of GSH, SOD, MDA, Urea, and Creatinine compared to G1 as shown in Tables 1 and 2.

Table 1. The effect of thioacetamide and rambutan peel aqueous extract on creatinine and urea in serum of male rat

Parameter	G1 Control Group	G2 Treat with 200mg/kg TAA	G3 with 25mg/kg *NI* Peel Aqueous Extract	G4 Treat with 200mg/kg TAA +25mg/kg *NI* Peel Aqueous Extract
Creatinine (µm/l)	38.70 ± 3.16 a	80.80 ± 6.43 b	36.40 ± 4.43 a	42.00 ± 6.62 a
Urea (mmol/L)	5.41 ± 0.45 a	9.70 ± 0.89 b	5.00 ± 0.59 a	5.72 ± 0.73 a

Mean ± standard error

Table 2. The effect of thioacetamide and rambutan peel aqueous extract on GSH, MDA and SOD in serum of male rat

Parameter	G1 Control Group	G2 Treat with 200mg/kg TAA	G3 with 25mg/kg *NI* Peel Aqueous Extract	G4 Treat with 200mg/kg TAA +25mg/kg *NI* Peel Aqueous Extract
GSH (mg/dl)	16.77 ± 0.61 a	9.70 ± 2.34 b	22.96 ± 2.06 a	16.22 ± 0.78 a
MDA (mg/dl)	0.35 ± 0.06 a	0.84 ± 0.11 b	0.32 ± 0.04 a	0.37 ± 0.06 a
SOD (mg/dl)	63.70 ± 7.35 a	34.20 ± 7.02 b	68.56±6.92 a	61.50 ± 4.06 a

Mean± standard error

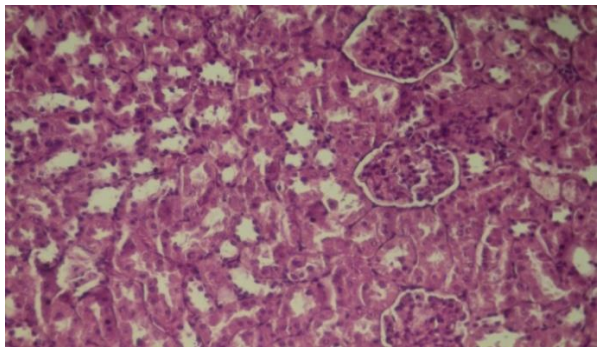

Figure 3. Section of kidney of G1 showed normal glomerulus and urinary tubules (H&E 200×)

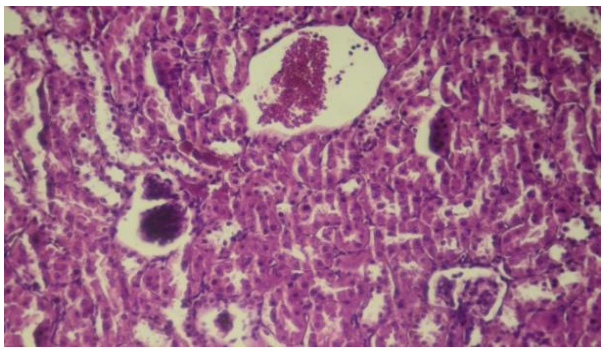

Figure 4. Histological section of G2 was inject 200 mg / kg of TAA was showed shrinkage and lysis of urinary glomerulus with hemorrhage (H&E 200×)

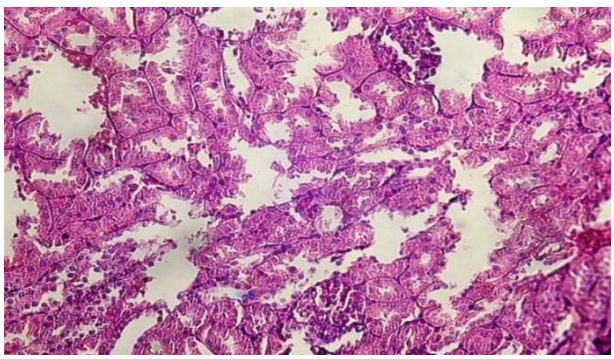

Figure 5. Histological section of G2 was injected 200 mg / kg of TAA was showed Destruction of urinary tubules and cellular necrosis with degeneration of renal tubules endothelial cells (H&E 400×)

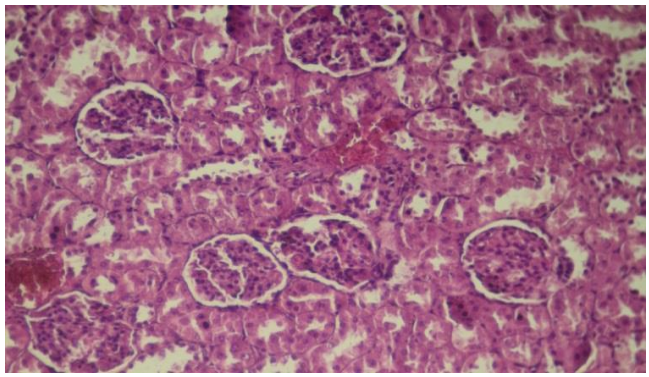

Figure 6. Histological section of G3 was gavage 25 mg/kg *NI* showed the normal structure of kidney tissue and the normal of nephron with presence of hemorrhage (H&E 200×)

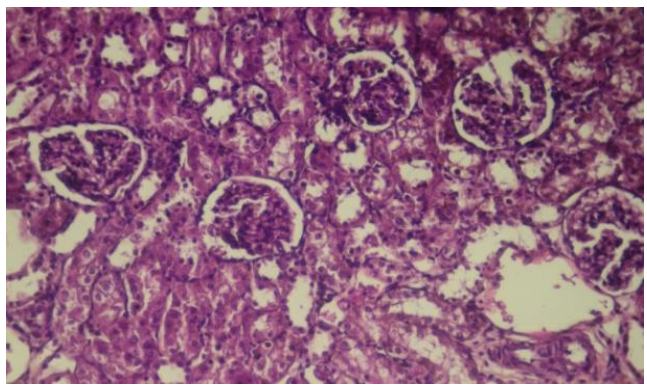

Figure 7. Histological section of G4 injected of TAA 200 mg / kg + 25 mg / kg of *NI* peel aqueous extract was shows natural makeup of the glomerulus and tubules with some degenerative change in kidney tissue (H&E 200×)

The histological structure of G1 showed normal architecture and urinary tubules as shown in Figure 3, whereas, the histological results of rat treat with TTA for 90 day showed necrosis of glomeruli and shrinkage, increase in bowman's space, acute cellular swelling of renal tubules with interstitial hemorrhage as shown in Figures 4 and 5. Histological result of G3 showed normal structure of nephron and urinary tubules as shown in Figure 6. sections of G4 treated with TAA and *NI* peels aqueous extract showed enhancements in the changes induced by TAA, normal structure of glomeruli and urinary tubule as shown in Figure 7.

4. DISCUSSION

The results of the current study showed significant increase($P<0.01$) in the levels of urea and creatinine in the G2, which was injected sub peritoneal at a dose of (200 mg/kg) TAA, and these results agreed with [26, 27]. The kidneys are one of the body's organs most vulnerable to injury because of their physiological function in filtering blood from various toxins, nephrotoxicity occurs due to TAA which causes severe necrosis in the epithelial cells of the renal tubules, that leads to a decrease in the glomerular filtration rate (GFR), which leads to a decrease in the filtration of urea and creatinine from the blood and an increase in their levels in the serum [28]. Urea and creatine levels are important diagnostic markers for evaluating kidney damage. They represent the final products of protein metabolism, which are usually eliminated and excreted by the kidneys [29, 30]. Metabolism of TAA in cytochrome P450 system leads to the formation of toxic metabolites TAASO and $TAASO_2$ that lead to the breakdown of Cellular membranes and kidney failure, which causes high levels of urea and creatine [31]. The accumulation of necrotic cells in the lumen of the renal tubules due to the toxic effect of TAA possibly cause the glomerular filtration to flow back, which leads to stimulation of the inflammatory and fibrosis as well as kidney injury [32]. The use of *NI* peels aqueous extract has led to maintaining normal levels of urea and creatinine, because it contains many effective compounds such as phenolic, geraniin, corilagin, ellagic acid, rutin, quercetin, and gallic acid, which scavenge free radical and activate antioxidants enzymatic to inhibiting oxidative stress [33]. In addition, to its role in maintaining the integrity of the vital functions of renal cells and reducing the accumulation of ROS, as well as inhibiting Fibrosis and its role in healing and thus contributing to protecting the kidneys from injury [34]. Endogenous antioxidants are necessary to protect cells from damage caused by ROS. The decrease in GSH and SOD levels in G2 treated with TAA may be due to the increase in ROS caused by TAA which oxidized GSH to glutathione disulfide (GSSG), which reacts easily with free radicals, leading to GSH depletion and increased oxidative stress. The same data was confirmed by researchers [35, 36]. SOD is the first line of enzymatic defense in the body, which works directly to break down the superoxide anion free radical. O_2- to hydrogen peroxide (H_2O_2) and oxygen, led to reduces the levels of oxidative stress caused by these radical [37]. It plays an important role in eliminating toxins caused by TAA that producing the toxic reactive metabolite ($TAASO_2$), which leads to increased lipid peroxidation and its products MDA [38]. MDA is one of the final products of the lipid peroxidation process that results from the interaction of free radicals with unsaturated fatty acids in cellular membranes, which causes loss of integrity of cellular membranes and cell damage. Free radicals, especially alkyl radicals and hydroxyl OH, play an essential role in the decomposition of fat by breaking the double bond between unsaturated fat and their conversion into hydroperoxide fats and thiobarbituric acid reactive substances (TBARS) leads to production MDA [39]. MDA causes the breakdown of Cell membranes and change in the fluidity and permeability of these membranes, also causes necrotic cells and damage kidney tissue [40]. The active compounds of the *NI* peels aqueous extract show a positive effect on kidney tissue, glomerular filtration rate, and the structure of renal tubules [41, 42]. The peels of rambutan fruits have role in reducing the production of free radicals through the scavenging activity of the free hydroxyl radical (HO) and the nitrite radical (NO), as well as reducing oxidative stress caused by the action of hydrogen peroxide radical (H_2O_2) in the cells, that leads to a reduction in lipid peroxidation and thus contributes to protecting the kidney from injury [43]. Maintaining MDA levels within normal limits may be attributed to the role of rambutan peels and the active compounds, especially geranin, which is one of the most powerful antioxidants found in the peels ,which is effective in reducing MDA production, via inhibit the gene expression of peroxisome proliferator activating receptor γ (PPARγ), which is stimulated in response to the production of harmful MDA, therefore the presence of active compounds in rambutan peels has an essential role in maintaining cell stability, inhibiting the process of lipid peroxidation, and preventing tissue damage from oxidative stress caused by various toxic substances [44]. Furthermore, to the phenolic compounds of rambutan peels that work to enhance the enzymatic defense system against oxidative stress and increase the levels of internal antioxidants, including glutathione and superoxide dismutase, thus maintaining the normal functions of the cells and protect tissues from oxidative stress [45]. On other hand, the normal of glutathione level may be due to the effectiveness of the *NI* peels aqueous extract in stimulating the biosynthesis of GSH by active compounds in rambutan peels, such as the ellagic acid, which important in production of glutathione by stimulating the enzymatic pathway gamma-glutamyl cysteine synthetase, and thus it participates in enhancing the levels of internal antioxidants [46]. Moreover, the current data demonstrated that rambutan peels have reduced the production of free radicals because of stabilizing antioxidant levels. This may be attributed to the high content of flavonoids, phenols, and others, which contribute to enhancing endogenous antioxidants and achieving stability of cell membranes and maintaining their homeostasis, this confirms the active compounds of rambutan peels as main effector in inhibiting many harmful processes that occur in the body [47]. The findings of histopathology demonstrated that injection Subperitoneal with TAA led to congestion, shrinkage of the urinary glomerulus, furthermore an increase in Bowman's space, destruction of the urinary tubules, and sloughing of the renal tubules endothelial cells. This is consistent with studies [48-50]. The harmful renal effects that have occurred may be due to of various exotic substances or medicines and toxins (TAA) that stimulates oxidative stress, and this may follow the activation of various factors that participate in kidney tissue damage and increase the production of inflammatory cytokines, lead to an imbalance between these inflammatory factors and antioxidant defense systems, which ultimately leads to tissue destruction and many pathological changes in the kidney [51]. Also, the increase in oxidative damage in kidney tissue due to the bioactivation of TAA leads to shrinkage and contraction of the mesangial cells and a change in the filtration surface area, which causes a decrease in GFR, and thus the renal cells lose their ability to remove toxins, and failure of vital kidney processes [52]. The results of histological after oral administration with the *NI* peel aqueous extract showed the normal structure of the glomerulus and urinary tubules. This may be attributed to the role of the rambutan peel in reducing of oxidative stress through active compounds such as flavonoids, geranin, gallic acid, ellagic acid and in coordination with internal antioxidants to reduce ROS and oxidative damage. That contributes to maintaining the integrity and functions of tubular cells and glomeruli [53].

The enhancement of kidney tissue and preserving renal tubule from the severe destructive effects caused by TAA may be due to the protective role of phenolic compounds that work to suppress the stimulation of inflammatory cytokines such as TNF-a by Its inhibition of the Nuclear Factor kappa (NF-κB) signaling pathway Therefore, the role of the extract and its contribution to regulating these factors make rambutan peels quality and anti-inflammatory properties in reducing cellular injuries and reducing oxidative damage of kidney tissue [54].

5. CONCLUSION

Our findings indicate that *NI* peels aqueous extract contributes to improving renal function, and this is evident through the improvement in the levels of both urea and creatine, as well as contributing to the preservation of the body's internal antioxidants, including glutathione and the superoxide dismutase enzyme. We also observed a relationship between rambutan peel and a normal level of malondialdehyde. We conclude *NI* peels aqueous extract improves the defense status against nephrotoxicity, has high antioxidant activity. it has great preventive importance in preserving kidney tissue from damage caused by TAA, and this conclusion is derived from the current data, which requires conducting more research on the therapeutic and preventive possibilities of rambutan to clarify the effectiveness and safety it provides.

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