ROLE OF FRANKINCENSE *BOSWELLIA SACRA* AS A PROTECTIVE KIDNEY DYSFUNCTION INDUCED BY ADENINE ON ALBINO RATS

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Abstract

This study was amid to investigate the protective role of Frankincense (F) on Adenine (AD)-induced nephrotoxicity on the serum concentrations of urea and creatinine, malondialdehyde (MDA) with superoxide dismutase (SOD), besides histological and histochemical changes in the kidney of male albino rats. Twenty-four adult male albino rats were assigned randomly in to four groups (n=6 of each): Group 1 (Control) take only normal saline (0.9% NaCl), Group 2 (AD group 150 mg/kg b.w.), Group3 (AD +F 10% w/v), Group 4 (AD +F 20% w/v). The treatment was given daily via gavage for 30 days. AD group showed a significant elevation of serum urea, creatinine, and MDA while reduced SOD in comparison with the control group. Kidney sections of rats treated with AD group showed dilation of bowman's capsule space, segmentation, degeneration of glomerulus and there was hemorrhage, necrosis, hyperplasia with crystallization, and proteinaceous remnant in some uriniferous tubules. Histochemical, AD group caused fibrosis area of kidney tissue and carbohydrates. On the other hand, both groups of Frankincense in combination with AD revealed a significant reduction in the serum urea, creatinine, and in MDA level with increase in SOD level. In conclusion, these results suggest that Frankincense have a noticeable protective and antioxidant effect against AD renal toxicity.

Keywords: Creatinine, MDA, Nephrotoxicity, SOD, Urea.

Introduction

A serious and growing global health concern is the clinical condition known as chronic kidney disease (CKD), which is defined by progressive renal failure[1]. Kidney failure can be brought on by urinary tract infection, complete loss of renal function, Diabetes, cardiovascular disease, and other conditions. Rodent models are used to study the pathophysiology of CKD and to create treatment approaches[2]. 500 million people (1 in 10 adults) globally have chronic renal disease, and nearly half of those over 75 have a high risk of morbidity and mortality. Two important elements of the disease's pathophysiological foundations that have an impact on both humans and animals are inflammation and oxidative stress[3]. In CKD patients and experimental animals, inflammatory mediators with high plasma concentrations, including C-reactive protein and tumor necrosis factor, diverse cytokines, and other indicators of oxidative stress were found[4]. Our results suggest that apoptosis is essential for the development of CKD[5].

Adenine, a purine nucleobase, is essential for the biochemical and physiological processes that take place inside of cells. Under physiological circumstances, xanthine oxidase catalyzes the conversion of adenine to 2, 8-dihydroxyadenine (DHA) in the liver, and DHA is ultimately excreted from urine. However, excessive DHA production will cause kidney damage because it is poorly soluble under urine

pH and crystallizes and deposits in renal tubules or interstitial tissues[6]. Adenine is now frequently utilized to create an experimental mouse model of chronic renal failure (CRF) [7].

Although they are excellent sources of antioxidants, the antioxidant defense system is the most frequently used mechanism for herbal treatment[8]. A CKD is also caused by oxidative stress[9]. In addition, herbs have anti-inflammatory properties, diuresis, immunomodulation, proteinuria reduction, and stimulation of renal repair mechanisms in CKD patients[10]. Several herbs, like Frankincense (Gum olibanum), were utilized to treat renal function, stones, and inflammation in the Middle East[11].

As many as 24 plant species (out of 25) in the genus Boswellia are the biological sources of frankincense, also known as Gummi Boswellii or olibanum (family Burseraceae). Between the tropical parts of Africa and the desert woods of Punjab and West Bengal in India, a wide geographic area is home to representatives of this genus. The so-called "incense trade route," the world's oldest caravan route, delivered oleo-gum resin of one of this genus' most significant and well-known species, B. sacra, to the eastern Mediterranean[12]. It extended from Mediterranean ports via the Levant, Egypt, North Africa, Yemen, and Oman on the Arabian Peninsula, as well as all the way to India and even farther[13].

Gum olibanum also normalizes systolic and diastolic blood pressure and heart rate and has been utilized in Arabic medicine for acute renal failure. Also, it inhibits the progression of renal failure, participates in antioxidant and/or anti-inflammatory activity, and normalizes plasma concentrations of urea and creatinine when used in drinking water[14].

Different species of frankincense gum have a variety of terpenes that make up around 60% of the lipophilic resin, 10% volatile oil, and 30% hydrophilic gums (mixture of polysaccharides).The pentacyclic triterpenic acids, tetracyclic triterpenic acids, and diterpenes make up the lipophilic resin component, with the main constituents being 11-ketoboswellic acid and 3-acetyl-11-ketoboswellic acid. The pentose and hexose sugars in the gum's hydrophilic fraction are combined with certain oxidizing and digesting enzymes. Galactose, arabinose, and 4 methylglucuronic acid are all present in polysaccharides that are also present. Pinene, phellandrene, and thujene are found in volatile oil [15]. The main active ingredients in B. sacra water extract were reported to be 1,8-cineole (eucalyptol), 1-octanol, L-menthol, 3-cyclohexen-1-ol, octanoic acid, thymol, and carvacrol[16].

Hence, our study aims to evaluate the effectiveness of the aqueous extract of frankincense on chronic adenine-induced renal failure in the rat model.

Materials and methods:

Animals

Twenty-four male albino rats (200-250g) were breeding in the animal house of the University of Salahaddin / College of Education /Department of Biology; Rats were kept in conventional cages at room temperature (RT) of 25±3°C with a 12 hours dark/light cycle. They had allowed to standard laboratory feed and water *ad libitum*. Then they were distributed into four groups, six rats for each[17].

Chemicals

In this study, chronic kidney disease was induced by oral gavage of adenine (150 mg/kg/day: GE7863, Glentham Life Sciences Ltd, UK) the powder was dissolved in 0.9% sodium chloride (2ml for 200g body weight). Fresh solutions were prepared daily for a period of 30 days. Dried Somalian frankincense (*B. sacra*) bought from local source in Arbil city was as a gum and stored in airtight plastic containers at 5°C until needed. Frankincense extract was made by soaking 10g and 20 g of powder in 100 mL of distilled water respectively, settled for 24 h, and then filtered to give 10% and 20% w/v extract orally given treated rats for 30 days.

Experimental Protocol

After two weeks of acclimation, before starting the experiment. The animals were separated in to four equal groups, each with six animals, and were handled as follows: The first group of control rats was taken orally with normal saline (0.9% NaCl). The second group was administered orally with AD (150 mg/kg,b.w) . The third group: was treated orally with F (10%, w/v) plus AD (150 mg/kg,b.w). The fourth group: was treated orally with F (20%, w/v) plus AD (150 mg/kg,b.w). At the end of the scheduled 30th day of the experiment, all the animals were sacrificed.

Blood samples collection

At the end of the experiment, all the animals were fasted overnight. Blood samples were collected direct cardiac puncture after ketamine (75 mg/kg i.p.) and xylazine (5 mg/kg i.p.) was used to anaesthetize fasting animals then transformed to tubes without ethylene diamine trichloroacetic acid (EDTA) and left for clotting. Blood samples were centrifuged at 3000 g for 15min. Sera were collected and stored at - 20°C to evaluate serum urea, creatinine which measured by kits purchased from Cobas Roche co. (Mannheim, Germany) and for determination of Malondialdehyde (MDA) by Colorimetric method/ (Elabscience, Cat. No. E-BC-K025-S, TBA method) and Superoxide dismutase (SOD) assay kit by Hydroxylamine method/USA- Cat No:(E-BC-K022-S) according to Mojarradgandoukmolla, S. and Akan, H.[17].

Tissues preparation

After sacrificing the animals, a longitudinal incision was made from the ventral side of the rat, and the kidneys were taken from the rats, they were fixed in 10% neutral buffered formalin for 48 hours, purified with xylol, embedded in paraffin, paraffinized kidney tissue blocks were processed and cut by a microtome at 5 μm thickness, then deparaffinized, and counterstained by staining with hematoxylin and eosin dye (H&E), and after being prepared, they are examined under a microscope to study histological changes. Alcian blue-periodic acid Schiff (AB-PAS) (pH2.5) staining kit (Solarbio co., Beijing, China) was used to detect polysaccharides such as glycogen, and muco-substances such as glycoproteins, glycolipids, and acidic mucins. Collagen or fibrosis in kidney tissue sections was determined by Masson's trichome staining technique, kit from (Solarbio co., Beijing, China), according to Sobin[18].

Statistical Analysis

Statistical analyses were conducted using the Statical Product for Service Solution version 28 (Spss Gmbh, Munich, Germany). Data are presented as means and standard errors of the means (mean SEM). Before performing an ANOVA, the data's normality and homogeneity were determined by one-way direction (ANOVA), and Tukey's test was used to see whether there were any differences between the experimental groups. A probability level of $P<0.01$ and $P<0.05$ were considered as statistically significant.

Results:

Table (1) showed, there were significant increase ($P<0.05$) in urea and creatinine levels of AD group when compared with control group. On the other hand, in both doses treated groups of Frankincense, there were a significant decrease($P<0.05$) in both urea and creatinine levels when compared with AD treated group and near to control group. Further, in AD administrated group, MDA level was caused a significant increase($P<0.05$) when compared with the control group. In contrast, there were significant decrease($P<0.05$) in MDA level in both F treated groups when compared with the AD administered group and near to the control group but still significantly higher than control group. In addition, there was significant decrease ($P<0.05$) in SOD level of AD group when compared to control group. While there was a significant increase ($P<0.05$) in both doses treated groups of Frankincense when compared to AD treated group and also there were significant increase ($P<0.05$) of both treated groups of Frankincense when compared with control group

Groups	Urea Conc. mg/dl	Creatinine conc. mg/dl	MDA Conc. nmol/ml	SOD Conc. U/ml
Control	49.10±0.90b	0.50±0.06b	15.64±0.59d	95.31±0.40c
AD	157.10±9.01a	2.13±0.54a	77.25±4.04a	76.18±0.77d
AD +F 10%	61.53±0.47b	0.53±0.03b	51.18±0.33b	124.21±0.83b
AD +F 20%	69.60±1.30b	0.60±0.06b	32.16±0.91c	155.63±0.78a

P-value	0.001	0.007	0.001	0.001

Table 1. The effect of different treatments on urea, creatinine, MDA, and SOD levels in the serum (mean ± SEM).

The different letters in the same column means significant differences ($p<0.05$)

Histological examination of Kidney

Histologically, AD affected on the kidney tissue and caused dilation of Bowmans capsule space, sloughing of lining epithelium of uriniferous tubules, segmentation, and degeneration of glomerulus (Fig.1). In the medulla there were hemorrhage, degeneration inside uriniferous tubules, necrosis of some uriniferous tubules, proteinaceous remnant inside some uriniferous tubule, hyperplasia of uriniferous tubules epithelium with crystallization and damaged urinary tubules (Fig.1).

Histochemical results revealed that AD group caused thickness in basement membrane of uriniferous tubules and fibrosis in the interstitial tissue, beside that mucopolysaccharides showing weak response to PAS stain in the glomerulus and urinary tubule, appeared in weak red magenta color and increased acidic mucin (blue color) over neutral mucin with thickness of bowman's capsule parietal membrane also thickness of uriniferous tubules basement membrane (Fig. 2).

Treatment with Frankincense in both doses accompanied by AD ameliorated the adverse effects of AD in kidney tissue. In low dose of Frankincense treated group showing moderate appearance of fibrosis in the interstitial tissue and around glomerulus, while in high dose of Frankincense treated group showing more normal structure and retained to the healthy collagen fiber (Fig. 2).On the other hand low dose of Frankincense treated group showing positive retention of the mucopolysaccharides, the faint color represents thickness of bowman's capsule parietal membrane and degenerated urinary tubules, while in high dose of Frankincense treated group revealed for moderate positive response to PAS stain in the glomeruli and urinary tubules when compared with AD group tissue sections.

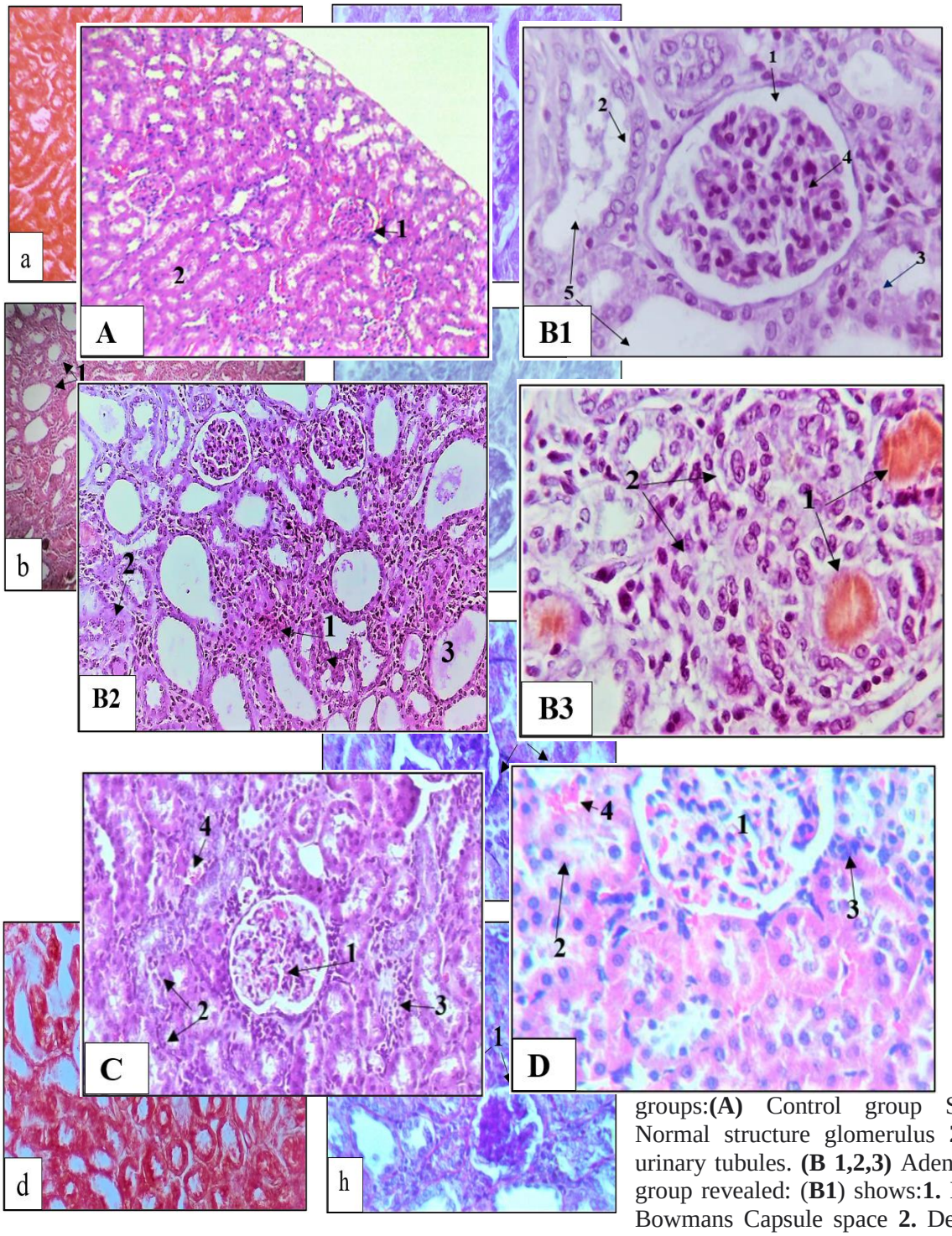
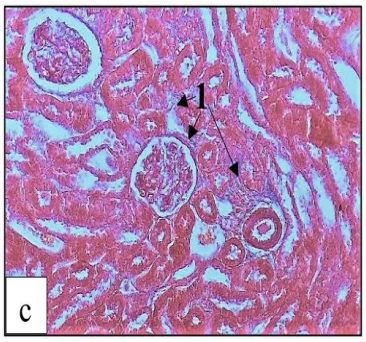


Figure 1: Cross section in the kidney of the treated groups:**(A)** Control group Shows: **1.** Normal structure glomerulus **2.** Healthy urinary tubules. **(B 1,2,3)** Adenine treated group revealed: (**B1**) shows:**1.** Dilation of Bowmans Capsule space **2.** Degeneration of Uriniferous tubules **3.** Sloughing of lining epithelium of uriniferous tubules **4.** Segmentation and degeneration of glomerulus and **5.** Dilation of uriniferous tubules. **(B2)** Shows: **1.** Hemorrhage inside uriniferous tubules in the medulla **2.** Necrosis of some Uriniferous tubules **3.** Proteinaceous remnant inside some uriniferous tubule. **(B3)** Shows: 1. Hyperplasia of uriniferous tubules epithelium with crystallization 2. Urinary tubules damaged. **(C)** Adenine (150 mg/kg) + Frankincense (10% w/v) treated group shows reasonable improvement in kidney tissue with: 1. Glomerular segmentation 2. Desquamation of Some Uriniferous tubules 3. Infiltration of inflammatory cells 4. Hemorrhage. **(D)** Adenine (150 mg/kg) + Frankincense (20% w/v) treated group revealed nearly normal tissue with: 1. Glomerular segmentation and hemorrhage 2. Damage of Some Uriniferous tubules 3. Infiltration of inflammatory cells 4. Hemorrhage. (100,400X), H&E.

Figure 2: Kidney section (a,b,c,d) stained with trichome Masson's technique to detect collagen or fibrosis

where blue represents the collagen deposition. **a:** Normal content in the control group, **b:**AD treated group showed positive blue staining is apparent in 1. Thickness in basement membrane of uriniferous tubules and 2. fibrosis in the interstitial tissue. In **c:** AD+F10% showing moderate appearance of 1. fibrosis in the interstitial tissue and around glomerulus. **D:** AD+F20% group showing more normal structure. H&E (100X). (e, f, g, h) stained with PAS-alcian blue for the detection of neutral mucins (PAS) and acidic mucins (alcian blue) **e:** control group normal distribution of neutral and acidic mucins (magenta). **f:** AD group showing weak response to PAS stain in the glomerulus and urinary tubule, appeared in weak red magenta color and increased acidic mucin (blue color) over neutral mucin1.thickness of bowman's capsule parietal membrane.2. thickness of uriniferous tubules basement membrane. **g:** AD+F10% group showing positive retention of the mucopolysaccharides, the faint color represents 1. thick of bowman's capsule parietal membrane and degenerated urinary tubules. **h:**AD+F20% revealed for moderate positive response to PAS stain in1. the glomeruli and urinary tubules. H&E(400X).



Discussion:

According to table (1) of this investigation, as compared to the control group, oral administration of AD significantly raised serum levels of urea and creatinine. According to [19], one of the diseased indicators of the kidneys is the presence of elevated amounts of urea and creatinine in the blood. Adenine is a well-known model medication that promotes renal tubule and degeneration leading to kidney failure, which is characterized by inhibited nitrogen compound excretion, including creatinine and urea[20].

The metabolic byproduct of creatine and phosphocreatine is creatinine, and the liver produces urea from ammonia. Both metabolites are carried to the kidney for excretion through glomerular filtration, whereas impairment of the glomerulus will lead to the accumulation of hazardous metabolites followed by the formation of kidney failure[21]. The findings of other investigations [22,23]are consistent with our findings. Previous research has demonstrated that administering adenine orally or through food can cause reproducible renal impairment[24-27].

High levels of MDA and a sharp decline in the antioxidant enzyme activity of SOD in serum were found in the current study's results from the adenine group, indicating an oxidative stress condition. This links damage caused by free radicals to a general decline in cellular function[28]. Our findings support those of [29] and [4] who found that adenine dramatically lowered the activities of antioxidant enzymes and raised oxidative stress indicators in renal tissue. According to a recent study[30], rats fed with adenine had considerably lower SOD enzyme activity. [31], reported that the oxidative stress is a well-known consequence of an imbalance between increases in the production of reactive oxygen species (ROS) and a consequent decline in the body's natural antioxidant defense mechanisms. More and more health issues are being linked to the image[32].

Oxidative stress is caused by an excessive production of free radicals and oxidants, which damages cell membranes, genetic material, proteins, lipids, and lipoproteins (DNA). In order to better understand the potential pathways directly connected to the damaging effects of adenine on the kidney, both before and after treatment with Frankincense, we were able to evaluate several markers of lipid peroxidation in plasma. Adenine injection significantly increased oxidative stress and lipid peroxidation, according to the measured data. In previous trials, the team found that lipid peroxidation levels raised in the

kidney [33].

Adenine caused noticeable histological changes (Fig.1) in the glomerulus and kidney tubules and led to the fibrosis and neutral polysaccharides (Fig.2) in the kidney of the treated rats which deterioration of creatinine liquidation in blood and urea, as well as noted an increase in inflammatory cells because of damage to the epithelial cells of the kidney, likewise [34]. In contrast, in both doses of Frankincense there were typically architecture of renal glomeruli and renal tubules, appears few infiltrations of inflammatory cell, similarly to [35]. Frankincense abrogated the histopathological findings seen in the adenine administered groups.

Since high serum urea and creatinine levels are indicators of uremic toxins and, consequently, of kidney function impairment, frankincense aqueous extract co-administration has been successful in significantly reducing the former to nearly normal and normalizing the latter two, as shown in table (1). Moreover, frankincense possesses anti-proliferative, anti-tumor, and anti-arthritis properties these benefits may be connected to the boswellic acids' active ingredient[36].

These positive outcomes imply that oral Frankincense's anti-oxidative and anti-inflammatory characteristics are the main mechanism underlying its therapeutic impact in adenine-induced renal failure.

Conclusion:

We concluded that, Frankincense may have a role on avoiding kidney failure in rats administrated adenine by minimizing in creatinine, urea, MDA, SOD levels and histological changes.

References:

1. Mojarrad, S. Responses of liver and renal function markers against arjuna tree extract in induced Hyperlipidemia Rats. *Issue S.* 2020; *10*, p.6.
2. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. The lancet. 2021 Aug 28;398(10302):786-802.
3. Alghamdi AM, Alghamdi AM, Alsemairi SAB, Alangari AA, Alabbad MA, Alebrahim EA, et al. Sepsis-associated Acute Kidney Injury, Diagnosis, and Management, Review Article. Int J Pharm Res Allied Sci. 2021;10(3):129-36.
4. Ali BH, Al-Salam S, Al Suleimani Y, Al Kalbani J, Al Bahlani S, Ashique M, Manoj P, Al Dhahli B, Al Abri N, Naser HT, Yasin J. Curcumin ameliorates kidney function and oxidative stress in experimental chronic kidney disease. Basic & Clinical Pharmacology & Toxicology. 2018 Jan;122(1):65-73.
5. Kim DH, Park JS, Choi HI, Kim CS, Bae EH, Ma SK, Kim SW. The critical role of FXR is associated with the regulation of autophagy and apoptosis in the progression of AKI to CKD. Cell death & disease. 2021 Mar 25;12(4):320.
6. Vezirkhanov AZ, Sysoev PA, Kafarov ES. Three-Dimensional Anatomical Analysis of the Vascular System of the Human Kidney. J Biochem Technol. 2021;12(3):78-83.
7. Dos Santos IF, Sheriff S, Amlal S, Ahmed RP, Thakar CV, Amlal H. Adenine acts in the kidney as a signaling factor and causes salt-and water-losing nephropathy: early mechanism of adenine-induced renal injury. American Journal of Physiology-Renal Physiology. 2019 Apr 1;316(4): F743-57.
8. Mojarradgandoukmolla, S., Nanakali, N.M.Q. and Jabbar, A.A. Hypolipidemic and anti-oxidative activities of *Terminalia arjuna* barks against induced hyperlipidemic albino rats. *Plant Archives*. 2021; *21*(1), pp.2082-2086.
9. Rafieian-Kopaei M. Medicinal plants for renal injury prevention. Journal of renal injury prevention. 2013;2(2):63.
10. Aslan Z, Aksoy L. Anti-inflammatory effects of royal jelly on ethylene glycol induced renal inflammation in rats. International braz j urol. 2015 Sep; 41:1008-13.
11. Chand GM, Chand TA. Critical review on commonly used herbal drugs in CKD. J Med Plants Stud. 2015;3(4):44-7.
12. McCutcheon A. Adulteration of Boswellia serrata. Austin, TX: Botanical Adulterants Prevention Program. 2018.
13. Maksimović Z. On Frankincense. Archives of Pharmacy. 2021 Feb 27;71(Notebook 1):1-21.
14. Ali BH, Ziada A, Al Husseni I, Beegam S, Al-Ruqaishi B, Nemmar A. Effect of

Acacia gum on blood pressure in rats with adenine-induced chronic renal failure. Phytomedicine. 2011 Oct 15;18(13):1176-80.

15. Al-Harrasi A, Rehman NU, Khan AL, Al-Broumi M, Al-Amri I, Hussain J, Hussain H, Csuk R. Chemical, molecular and structural studies of Boswellia species: β-Boswellic Aldehyde and 3-epi-11β-Dihydroxy BA as precursors in biosynthesis of boswellic acids. PLoS One. 2018 Jun 18;13(6): e0198666.
16. Asad M, Alhomoud M. Proulcerogenic effect of water extract of Boswellia sacra oleo gum resin in rats. Pharmaceutical biology. 2016 Feb 1;54(2):225-30.
17. Mojarradgandoukmolla, S. and Akan, H. Physiological Activity and GC" Mass Analysis of *Trigonella strangulata*, *Trigonella filipes* and *Trigonella uncinata* Against Ethanol" Induced Hepatorenotoxicity in Rats. *Pakistan Journal of Zoology*. 2023; *55*(2), p.513.
18. Sobin LH. AFIP laboratory methods in histotechnology. Washington, American Registry of Pathology. 1992:102-4.
19. Dabdoub BR, Mohammed RH, Abdulhadi HL. Ganoderma lucidum attenuates and prevents CCl4-induced hepatic and renal damage in Sprague–Dawley Rats. Systematic Reviews in Pharmacy. 2020 Dec 1;11(12):1704-9.
20. Claramunt D, Gil-Peña H, Fuente R, García-López E, Loredo V, Hernández-Frías O, Ordoñez FA, Rodríguez-Suárez J, Santos F. Chronic kidney disease induced by adenine: a suitable model of growth retardation in uremia. American Journal of Physiology-Renal Physiology. 2015 Jul 1;309(1): F57-62.
21. Wang R, Hu B, Ye C, Zhang Z, Yin M, Cao Q, Ba Y, Liu H. Stewed rhubarb decoction ameliorates adenine-induced chronic renal failure in mice by regulating gut microbiota dysbiosis. Frontiers in Pharmacology. 2022;13.
22. Törmänen S, Pörsti I, Lakkisto P, Tikkanen I, Niemelä O, Paavonen T, Mustonen J, Eräranta A. Endothelin A receptor blocker and calcimimetic in the adenine rat model of chronic renal insufficiency. BMC nephrology. 2017 Dec;18(1):1-3.
23. Cai H, Su S, Li Y, Zeng H, Zhu Z, Guo J, Zhu Y, Guo S, Yu L, Qian D, Tang Y. Protective effects of Salvia miltiorrhiza on adenine-induced chronic renal failure by regulating the metabolic profiling and modulating the NADPH oxidase/ROS/ERK and TGF-β/Smad signaling pathways. Journal of Ethnopharmacology. 2018 Feb 15; 212:153-65.
24. Diwan V, Mistry A, Gobe G, Brown L. Adenine-induced chronic kidney and cardiovascular damage in rats. Journal of pharmacological and toxicological methods. 2013 Sep 1;68(2):197-207.
25. Kim IY, Lee DW, Lee SB, Kwak IS. The role of uric acid in kidney fibrosis: experimental evidence for the causal relationship. BioMed research international. 2014 May 5;2014.
26. Fong D, Ullah MM, Lal JG, Abdelkader A, Ow CP, Hilliard LM, Ricardo SD, Kelly DJ, Evans RG. Renal cellular hypoxia in adenine-induced chronic kidney disease. Clinical and Experimental Pharmacology and Physiology. 2016 Oct;43(10):896-905.
27. Vázquez-Méndez E, Gutiérrez-Mercado Y, Mendieta-Condado E, Gálvez-Gastélum FJ, Esquivel-Solís H, Sánchez-Toscano Y, Morales-Martínez C, Canales-Aguirre AA, Márquez-Aguirre AL. Recombinant erythropoietin provides protection against renal fibrosis in adenine-induced chronic kidney disease. Mediators of Inflammation. 2020 Feb 27;2020.
28. Almalki GH, Rabah S, Arafa NMS, Bahshwan SM. Immunohistochemical Evaluation of the Euphorbia Inarticulata Extract on Liver and Kidney Tissues in Hepatocellular Carcinoma Rats. Pharmacophore. 2022;13(2):33-40.
29. Chang XY, Cui L, Wang XZ, Zhang L, Zhu D, Zhou XR, Hao LR. Quercetin attenuates vascular calcification through suppressed oxidative stress in adenine-induced chronic renal failure rats. BioMed research international. 2017 Jun 11;2017.
30. Ali BH, Al-Salam S, Al Husseni I, Kayed RR, Al-Masroori N, Al-Harthi T, Al Zaabi M, Nemmar A. Effects of Gum Arabic in rats with adenine-induced chronic renal failure. Experimental Biology and Medicine. 2010 Mar;235(3):373-82.
31. Kattoor AJ, Pothineni NV, Palagiri D,

Mehta JL. Oxidative stress in atherosclerosis. Current atherosclerosis reports. 2017 Nov; 19:1-1.

32. Dandekar A, Mendez R, Zhang K. Cross talk between ER stress, oxidative stress, and inflammation in health and disease. Stress Responses: Methods and Protocols. 2015:205-14.
33. Nemmar A, Karaca T, Beegam S, Yuvaraju P, Yasin J, Ali BH. Lung oxidative stress, DNA damage, apoptosis, and fibrosis in adenine-induced chronic kidney disease in mice. Frontiers in physiology. 2017 Nov 23; 8:896.
34. ElGendy AA, Elsaed WM. The Role of Erythropoietin, Vitamin C and L-NAME in Carboplatin-Induced Hematological and Renal Dysfunctions. Bulletin of Egyptian Society for Physiological Sciences. 2019 Dec 1;39(2):231-51.
35. Al Za'abi M, Al Salam S, Al Suleimani Y, Manoj P, Nemmar A, Ali BH. Gum acacia improves renal function and ameliorates systemic inflammation, oxidative and nitrosative stress in streptozotocin-induced diabetes in rats with adenine-induced chronic kidney disease. Cellular Physiology and Biochemistry. 2018;45(6):2293-304.
36. Noroozi S, Khadem Haghighian H, Abbasi M, Javadi M, Goodarzi S. A review of the therapeutic effects of frankincense. Journal of Inflammatory Diseases. 2018 Apr 10;22(1):70-81.