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Nephroprotective Effect of Aqueous Extract of Anisoon (*Pimpinella anisum*) and Brinjasif (*Achillea mellifolium/Artemesia vulgaris*) Management of Renal Failure in Experimental Animals Induced Paracetamol

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ABSTRACT

BACKGROUND: The nephrotoxicity is due to the poisonous effect of some toxic chemicals and certain type of drugs on the kidneys. In Nephrotoxicity, the toxic metabolites retain in the body leading to severe complications like ARF, CRF etc. [1,2,3] **AIM AND OBJECTIVE**: Evaluate the Efficacy of combined drug Anisoon and Brinjasif, in management of renal failure and Paracetamol induced nephrotoxicity in Albino Wistar rats. **MATERIALS & METHODS:** Albino Wistar rats were divided into 5 groups and each group comprises of six rats Nephrotoxicity was induced by injection Paracetamol 200mg/kg by intraperitoneal.[4] The combined aqueous extract of Anisoon (*Pimpinella anisum*)[5] and Brinjasif (*Achillea mellifolium*).[6] Medium Dose (25.68 mg/kg) and Low dose (17.12 mg/kg) were used as nephroprotective drug in the study.[7,8] **RESULT:** Elevated levels of serum creatinine, urea, blood urea nitrogen, creatinine clearance were observed as indicatives of nephrotoxicity in paracetamol (200mg/kg bwt) administered rats. Animals, which are pre-treated with aqueous extract Anisoon and Brinjasif of combined drug (Medium Dose 25.68 mg/kg and low dose 17.12 mg/kg), restored the elevated levels of renal function markers to near normalcy when compared to paracetamol alone treated animals. Values are expressed as mean +SEM (N=5). Statistical Analysis was performed by one way ANOVA. The results were compared with control ($p<0.05$), Negative group ($p<0.05$) significantly increased. The test group medium dose 25.68 mg/kg and low Dose 17.12 mg/kg had significant $p<0.05$ lower level of urea and creatinine compared to negative group. HPE of rat kidney section of negative group shows impaired renal morphology cystic dilatation along with tubular degeneration and accumulation of fluids. Concurrently treated group showed normal appearance of glomerulus and tubules of kidneys.
CONCLUSION: The findings in the present study suggest that combined extract of Anisoon and Brinjasif is a potential Nephroprotective that reduce paracetamol induced nephrotoxicity.

INTRODUCTION:

The nephrotoxicity is due to the poisonous effect of some toxic chemicals and certain type of drugs on the kidneys. In Nephrotoxicity, the toxic metabolites retain in the body leading to severe complications like ARF, CRF etc.[1] Consequences of drug toxicity might include both glomerular and tubular injuries leading to acute or chronic functional changes.[2] Kidney damaged goes unnoticed in early stage, because there are no warning signs in the early stages of the disease, Unfortunately, most people don't realize they have a problem until their kidney functions have decreased to this level. That the patient's condition requires life-saving procedures such as dialysis or transplantation.[3] Now-a-days, heart disease and diabetes provide the first and second leading cause of death in the world, respectively and people are suffering from these diseases are likely to be more prone to kidney disease. There is great urgency for a nonconventional, affordable therapy for patients who cannot afford expensive dialysis or kidney transplant to keep them alive. With this background our research work aimed to find out the different anti-uremic and nephroprotective phytocompounds from different plant extracts such as hydro-methanolic root extract of *Asparagus racemosus*, methanolic bark extract of *Terminalia arjuna*, methanolic root extract of *Withania somnifera* which had been effective in the reduction of uremic toxins from acetaminophen induced chronic renal failure rats. Acetaminophen is a commonly used antipyretic agent which, in high doses, causes renal tubular damage and uremia. An acute acetaminophen overdose may result in a potentially fatal hepatic and renal necrosis in humans and experimental animals.[29,30,31] Etiopathological basis of Acetaminophen nephrotoxicity has recently been used for kidney disease research. It is necessary to establish proper doses and durations of Acetaminophen for inducing nephrotoxicity.[32,33,34] Therefore, objectives of this study was to establish the standardization of the threshold dose of acetaminophen induced kidney disease following OECD guidelines.[4,28,29,38,39]

The term renal failure denotes inability of the kidneys to perform excretory function leading to retention of nitrogenous waste products from the blood. Acute and chronic renal failure are the two kinds of kidney failure. When a patient needs renal replacement therapy, the condition is called end-stage renal disease (ESRD).

1. Acute Renal Failure (ARF):

Acute renal is a syndrome characterized by rapid onset of renal dysfunction, chiefly oliguria or anuria, and sudden increase in metabolic waste-products (urea and creatinine) in the blood with consequent development of uremia.

2. Chronic Renal Failure (CRF):

Chronic renal failure is a syndrome characterized by progressive and irreversible deterioration of renal function due to slow destruction of renal parenchyma, eventually terminating in death when sufficient number of nephrons has been damaged. Acidosis is the major problem in CRF with development of biochemical azotaemia and clinical uraemia syndrome.[25,26]

INCIDENCE:

As per Global Burden of Disease (GBD) study in 2015, about 1.2 million people died from kidney failure, an increase of 32% since 2005. In 2010, an estimated 2.3–7.1 million people with end-stage kidney disease died without access to chronic dialysis. Additionally, each year, around 1.7 million people are believed to die from acute kidney injury. Overall, an estimated 5–10 million people die annually from kidney disease, most often it is attacked by a variety of micro-organism, drugs, and chemicals that alter the renal functions with adverse effects on the human health. [27,40.41]

Hence with this background we decided to explore the nephroprotective role of combined drugs *Pimpinella anisum* and *Achillea millefolium* in a murine model of Paracetamol-induced renal damage.[7]

Pimpinella anisum (anise, aniseed), a plant belonging to the *Umbelliferae* family [5,6], is an age old medicinal plant. Aniseed, a native of the Eastern Mediterranean region, is grown to a small extent in India as a culinary herb. They are also used as an important raw material for pharmaceutics, perfumery, food and cosmetic industries. It has been reported that essential oil and extracts of *Pimpinella anisum* have a wide range of biological activities. In folk medicine, Pimpinella species have been used as appetizing, hypnotic, expectorant, nephroprotective, hepatoprotective, carminative, aromatic, disinfectant, and galactagogue. Their association with health benefits. Plants are a large source of new bioactive molecules with therapeutic potentials. Studies have shown that many dietary polyphenolic constituents

derived from plants are more effective antioxidants in vitro than vitamins E or C, and thus might contribute significantly to the protective effects in vivo. Aniseed is shown to have great health benefits due to the presence of considerable amounts of phenolic compounds that possess varying degrees of antioxidant activity. However literature research revealed that the nephroprotective activity of *Pimpinella anisum* seeds has not been established and its probable role has only been postulated with no positive evidence. Brinjasif (*Achillea Millefolium Linn*), popularly known as "yarrow" belongs to the Achillea, the genus widespr all over the world. Achillea contains around 130 flowering and perennial species. These pl have hairy and aromatic leaves and flat clusters of small flowers on the top of the stem. Name Achillea is referred to the Achilles in the literary Trojan War of the Iliad who u yarrow to treat the soldier's wounds. Its species have been used by the people traditional medicine over hundreds of years. Brinjasif (*Achillea Millefolium Linn*) has be internally used as herbal teas for headaches, hepato-biliary disorders, gastrointest complaints, menstrual irregularities and as appetizer and externally as lotion or ointment against skin inflammation, wounds and abrasions.[42,43,44] The present review highlights the data on *Achillea millefolium* in Unani classical literature, its phytochemistry and research studies.[35] The medicinal properties of *Achillea millefolium* are worldwide recognized and the plant is included in the national pharmacopeia of countries such as Germany, Czech Republic, France and Switzerland.[8,9,10,11,12,13,14]

UNANI PERSPECTIVE OF KIDNEY DISEASES [15,16]

In Unani System of medicine kidney diseases are caused due to three reasons [16]

1. Su'i Mizaj-i-Kulya

2. Su'i Tarkeeb

3. Tafarruq wa Ittesal

Normally, the mizaj (temperament) of the kidney is har ratab (hot and wet). If any deviation in the mizaj occurs, it produces the disease condition of the same type. This may be (i) Sue mizaj har (hot), means when the hot temperament of the kidney exceeds to its own normal hot temperament, (ii) Sue mizaj barid (cold), normally kidney hasn't cold temperament, if it becomes less hot than the normal, it is a diseased condition. (iii) Sue mizaj ratab (wet), normally it is wet, but in case of exceeding its normalcy it becomes diseased. (iv) and Sue

mizaj yabis (dry) when the temperament of the kidney changes towards the yaboosat.[16,17,18,19]

ZAUF-E-KULLIYA (WEAKNESS OF KIDNEY) [19,20,21,22,23]

Zauf-e-Kulliya is a disorder where the kidneys are unable to separate or differentiate between water and other substances from the blood and pass them as such into the urinary bladder, according to unani doctors. The liver supplies the kidney with this blood. Finally excreted urine Haematuria and ascites are the results of poor renal absorption. Excessive waste products may sometimes decrease the absorptive faculty.

According to Azam Khan Zauf-e-Kulliya is a condition in which Kidneys are completely or partially incapable of performing their functions. According to some other Unani physicians kidneys cannot perform their normal filtration process due to weakness of Quwwat-e-Masika (Retentive faculty) or Quwwat-e-Hazima (Digestive faculty) and result in Ghussali (Blood stained) urine. Qarshi also described Sammiyat-e-Baul (toxic urine), as a condition in which the urinary toxic substances accumulate in the blood and affect the nervous systems which results in coma, delirium etc.

TREATMENT AS PER UNANI CONCEPT FOR KIDNEY DISORDERS:

Elimination of the puterified humours (Akhlat) by way of Emala (diversion) which may be achieved by Fasad (Venesection), Qai (Vomiting), Ishaal (purgation), and Idraar (diuresis). Muhallil-e-auram (anti-inflammatory) drugs are used in case of inflammatory disease of the kidney.

Beside these measures, Muqwwi-e-Kulliya (nephrotonics) drugs are used for the treatment of these disorders. In fact the concept of tonics is unique in Unani system of medicine. Several drugs have been described as tonic for various impairments of the organ. These drugs strengthen and tone up the particular organ and protect them against the harmful substances. [20,21,23,24]

MATERIAL AND METHODS:

Research work was approved by IAEC Institutional Animal Ethical Committee) Reg. No. 1070/GO/Re/S/CPCSEA) Dated:29/8/2020 at Government Nizamia Tibbi College (GNTC) charminar Hyderabad, the activity was conducted in Animal House Dept of ilmul Advia

GNTC Charminar. Hyderabad animal was purchased from. ICMR-NIN Animal Facility Reg No- 154/Go/RBIBt-S/R-L/1999/CPCSEA,T.S,HYD.

EXPERIMENTAL DESIGN:

Male Albino Wistar (AW) rats weighing 150-200 gm were used. The animals were procured from registered breeder Prior to experiment the animals were allowed to get acclimatization for at least one week. They were maintained under standard laboratory conditions throughout the experimental period and were provided with standard diet and water at libitum Unless otherwise indicated. They were housed in clean polypropylene cages at room temperature 25+2°C, humidity at 55-60% with 12h light: 12h dark cycle.

The animals were purchased from, ICMR-NIN Animal Facility Reg No-154/Go/RB/B 5/8 L/1999/CPCSEATS HYD. The animal care procedures and experimental protocol were in accord with the guidelines of CPCSEA.

DRUGS:

Paracetamol injection (Piramal Health Care Ltd) was used to induce renal damage.

COLLECTION AND AUTHENTICASTION OF PLANT MATERIAL:

Anisoon and Brinjasif (*Pimpinella anisum, Achillea mellifolium*) were provided by the department of Ilmul Advia, GNTC Charminar, Hyderabad. Drugs were submitted for identification and authentication to survey of Medicinal Plants Unit (SMPU) Hyderabad. NRIUMSD Identification and Authentication was done by (Botanist) of SMPU of NRIUMSD, Hyderabad vide Vouchers specimen No SMPU/CRI-hyd14645/002/01 and 14646/002/02.

PLANT MATERIAL AND PREPARATION OF EXTRACT:

The test drugs are dried in drying chamber at 40°C for 30 min to remove moisture if any. The drugs are pulverized in an electrical grinder to make a coarse powder. 200 gram of compound drug (Anisoon:Brinjasif) is taken for Aqueous extract in the Soxhlet Apparatus with 100% distilled water and for about 8 hours at a temperature of 80-90°C. The liquid extract is filtered using filter paper (Whatman No. 40) and then solvent is evaporated on Water bath (80°C). Dried extracts were weighed for yield percentage and it was found to be (Anisoon-20%,

Brinjasif -25%) in Aqueous compound crude drug. It was labeled and kept in airtight container in refrigerator for further use.

EXPERIMENTAL PROCEDURE:

After acclimatization, the animals were divided randomly into five groups of 6 animals each and placed in separate cages. The test drug, the Combined aqueous extract of *Pimpinella anisum* and Brinjasif, and the inducing drug paracetamol. 1 control group received normal saline 2. Negative group received intraperitoneal injection of paracetamol 200 mg/kg/bwt 3. High dose of combined test drug 34.24 mg/kg along with pcm 200 mg/kg/bwt 4. Medium dose of combined test drug 25.68 mg/kg along with pcm 200 mg/kg/bwt 5. Low dose of combined test drug 17.12 mg/kg along with pcm 200 mg/kg/bwt. From 1st day to 14 day.

URINE ASSESMENT:

On 14th day 6 rats from each group was kept in single metabolic cage and urine (pooled) collected for 12 hrs. Animal had free access to drinking water during the urine collection period.

SAMPLE COLLECTION AND BIOCHEMICAL ASSAYS:

Twenty-four hour after the last injection the rats were anesthetized with ketamine (60 mg/kg) and xylazine (5mg/kg) intraperitoneally [32] and blood samples were collected by cardiac puncture. The serum was rapidly separated and processed for determination of serum creatinine, serum urea, serum uric acid and blood urea nitrogen (BUN), creatinine clearance as an indicator of f kidney damage. The animals were sacrificed and both kidneys were isolated. The kidneys from all the groups were weighed and processed for histopathological examination.

HISTOPATHOLOGICAL EXAMINATION:

At the end of experiment/Study (on 15 day) all the animals were sacrificed using ether for Anaesthetizing and euthanizing the animals. Before sacrifice blood sample from each animal was collected by heart puncture for biochemical assay (S. urea, Serum Creatinine and Blood Urea nitrogen, S. electrolytes, LFT, Creatinine clearance). Blood was collected in labeled test tubes, and send to the Veterinary pathology lab by maintaining cold chains statistical analysis.

STATISTICAL ANALYSIS:

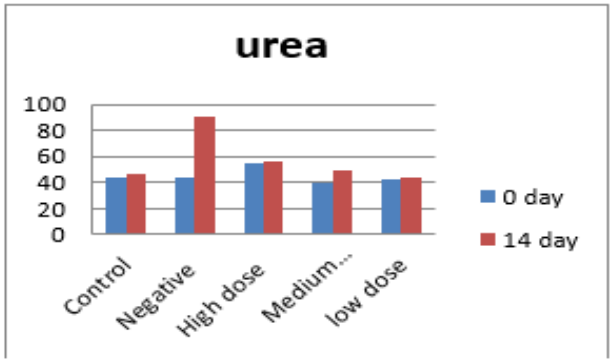
Parameters mentioned above were assessed in all the groups and findings were expressed as Mean±SEM. The different values determined were compared with each other and comparison was made using One-way ANOVA with Tukey's Multiple Comparison test. The difference of mean was considered significant at p value of 0.05 or less.

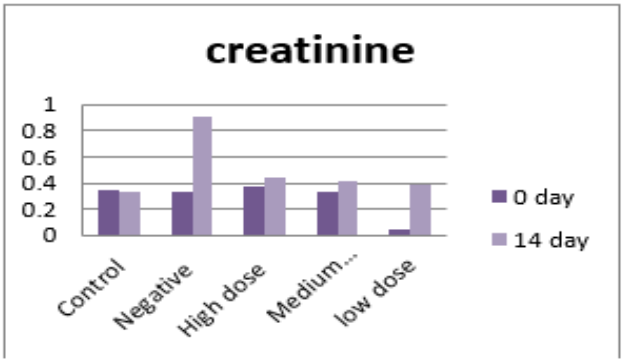
RESULTS:

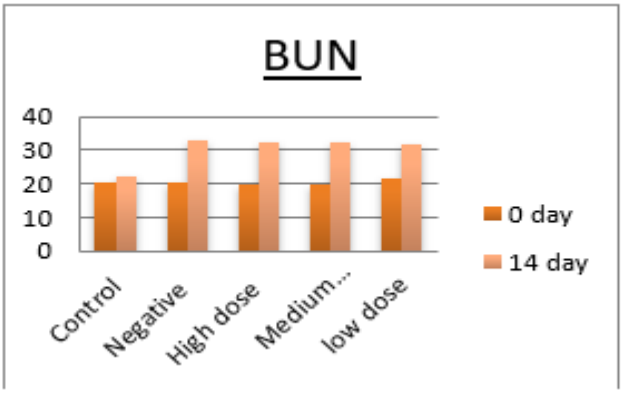
EFFECT ON BIOCHEMICAL PARAMETERS

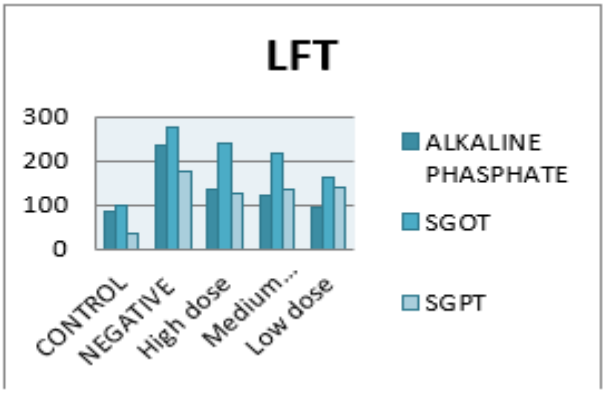
In the present study, Paracetamol (200mg/kg/bwt) when injected for daily for 14 days caused marked nephrotoxicity as is evident from showing significant ($p< 0.05$) increase in serum urea (90.23±3.29mg/dl). serum creatinine (0.0917±0.642mg/dl), blood urea nitrogen (33.1±6.200mg/dl), LFT (233.66±15.24200mg/dl), Electrolytes (179.83±6.615 mg/dl), creatinine clearance (2.5083±0.3914 mg/dl), as compared to normal control animals. The test drug, combined aqueous extract of depicted protective effects at doses 1, 2 and 4g/kg body weight by reducing the levels of serum urea, creatinine, and blood urea nitrogen, creatinine clearance as compared to Paracetamol treated group but not in a dose dependent manner. There was a significant nephroprotective effect at doses 1 and 2g/kg body weight of the test drug as evidenced by a significant decrease in serum urea, creatinine, and blood urea nitrogen, creatinine clearance ($p<0.05$) as compared to paracetamol treated group.

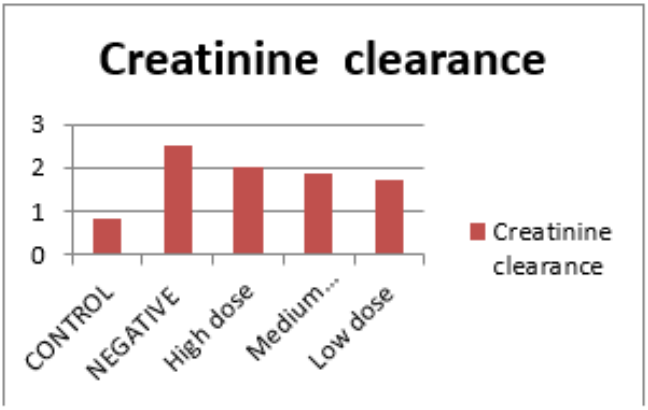
Sr.No.	**Treatment**	**Parameters**					
		Urea (mg/dl)	Creatinine (mg/dl)	BUN (mg/dl)	creatinine clearance	LFT	Electrolytes
1.	Normal control	46.1±2.3571	0.338±0.313	21.983±1.308	0.338±0.313	83.283±5.285	142.83±2.28
2.	Paracetamol 200mg/kg.bwt	90.23±3.29	0.9017±0.642	33.1±6.200	32.55±1.500	32.4±1.676	31.916±2.726
3.	Combined Test drug (High dose) 34.25mg/kg+ pcm200mg/kg/ip	55.6±3.395	0.4467±0.034	32.55±1.500	1.995±0.2445	133.05±12.895	181.66±7.27
4.	Combined Test drug (medium Dose) 25.68mg/kg+pcm 200mg/kg/ip	49.93±4.816	0.41±0.0589	32.4±1.676	1.8617±0.147	119.33±16.469	165.83±8.704
5.	Combined Test drug (low dose)17.12mg/kg +pcm200mg/kg/ip	44.416±1.634	0.41±0.0589	0.3917±0.020	1.715±0.045	94.25±8.4031	147.166±8.617

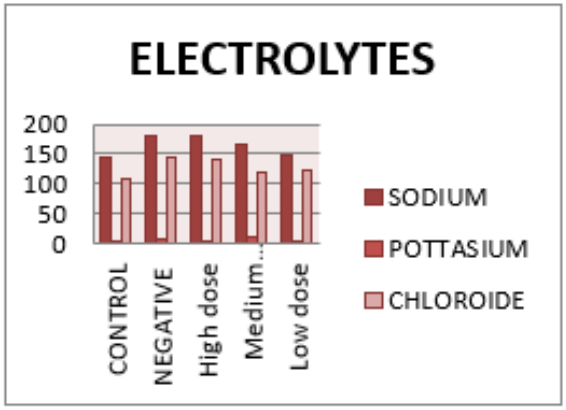












HISTOPATHOLOGICAL CHANGES:

The Histopathology of negative group which received paracetamol for 14 days kidneys shows the Foci of Cystic dilatation along with tubular degeneration and accumulation of fluids and in liver mild peri portal and peri biliary fibrosis were observed, Paracetamol is nephrotoxic as it shows the significantly damage of kidneys in High dose kidneys shows which receive test drug +paracetamol moderate tubular degeneration and dilatation was observed in cortex of kidney, in liver mild infiltration of inflammatory cells in peri portal region of liver in Medium and Low dose of test drug shows normal morphology of glomerulus and tubules of kidneys,

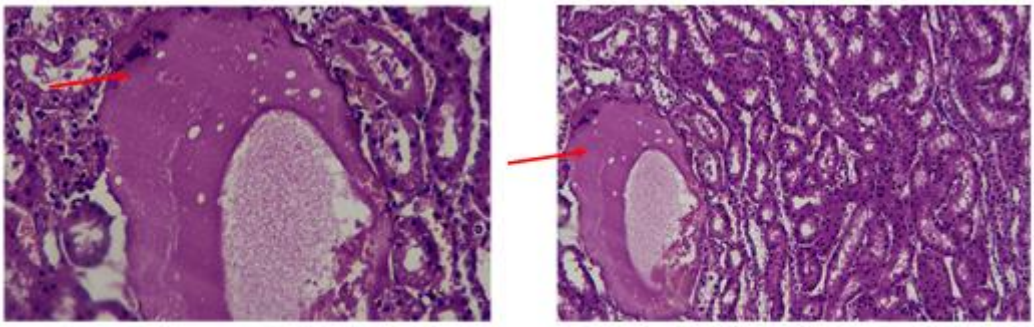
in liver shows normal morphology of hepatocytes in portal peri portal central lobular region and the control group shows no abnormalities observe in kidney and liver.

DISCUSSION:

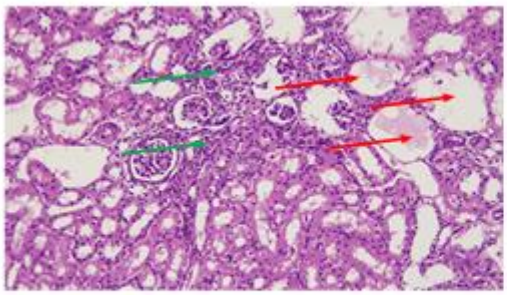
Kidney disease has become a major cause of morbidity and mortality globally in India. The estimated number of kidney-related deaths is on the rise there is a tremendous increase in the prevalence of chronic kidney disease (CKD) progressing renal disease (ESRD) termination stage. Over 500 million people worldwide or roughly one in ten people have some form of CKD. Therefore; people with kidney disease are at elevated risk of other systemic diseases that also prove to be fetal. The complex nature of renal disease and its progression to renal failure (both acute and chronic) and end-stage renal disease makes it very difficult to treat it. The biggest issue with kidney disease is its development to a stage where practically no alternative works at all but for RRT But the RRT, which involves hemodialysis and kidney transplantation, is not affordable for most renal disease patients due to its high cost and limited availability, particularly in developing and underdeveloped countries Therefore a lot of patients in these countries are left to die. This scenario prompted the medical community to find alternative steps to avoid the occurrence and early diagnosis of kidney disease. And the search for substances that can be used to preserve the function of the kidney and to prevent the development of renal disease so that it can be controlled without RRT became the focus research field. Thus the idea of nephroprotection came into being, and a range of drugs have been studied for this purpose but no standard nephroprotective drugs have been produced to date. The test drug Anisoon (*Pimpinella Anisum*) and Brinjasif (*Achillea mellifolium*) used to determine its nephroprotective impact against paracetamol induced nephrotoxicity in albino wistar rats.

These Drugs found all over the world, described by most Unani physicians such as Galen, Razi and Shaik bu ali sina as Mudirr-e-Baul (duretic), Muqawwi-e-Kuliyah (Tonic to the kidney). Muhallil-e-Awram (anti inflamatory), and astringent. It's useful in dysuria, bladder and kidney inflamation, and serves as a healing agent in the cellular injury of kidney and bladder. It is commonly used by physicians of Unani Medicine in the management of renal diseases Paracetamol was used to induce nephrotoxicity in Albino wistar rats, as these are reported even at therapeutic doses via radical formation. Its nephrotoxicity is well stablished at a dose of 2000 mg/kg. Paracetamol is an NSAIDS agent used in treatment of Analgesic, Anti pyretic. The toxic effect of Paracetamol was evidenced in the present study by elevation

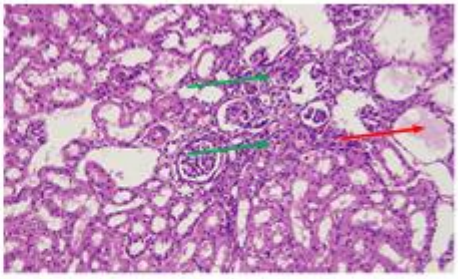
of biochemical markers of kidney function viz serum creatinine and blood nitrogen (BUN) and Histopathological examination in Paracetamol induce nephrotoxicity.



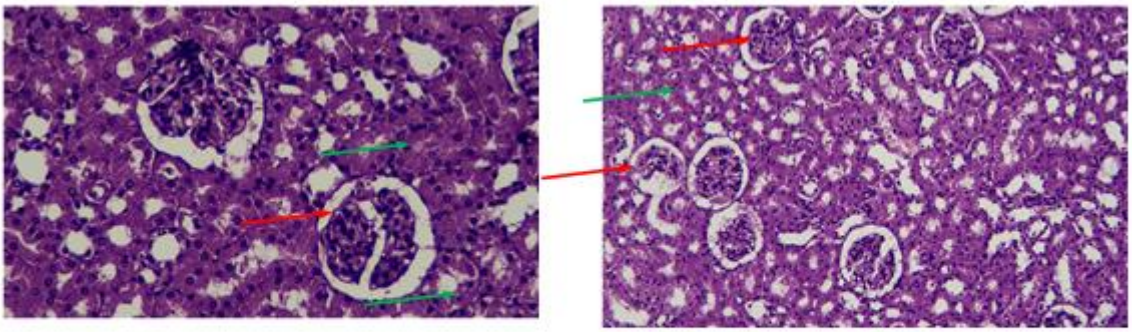
Cystic dilatation along with tubular degeneration and accumulation of fluids were observed [Red arrow]



Foci of cystic dilatation and degeneration of tubules with accumulation of fluids – red arrow in cortex region

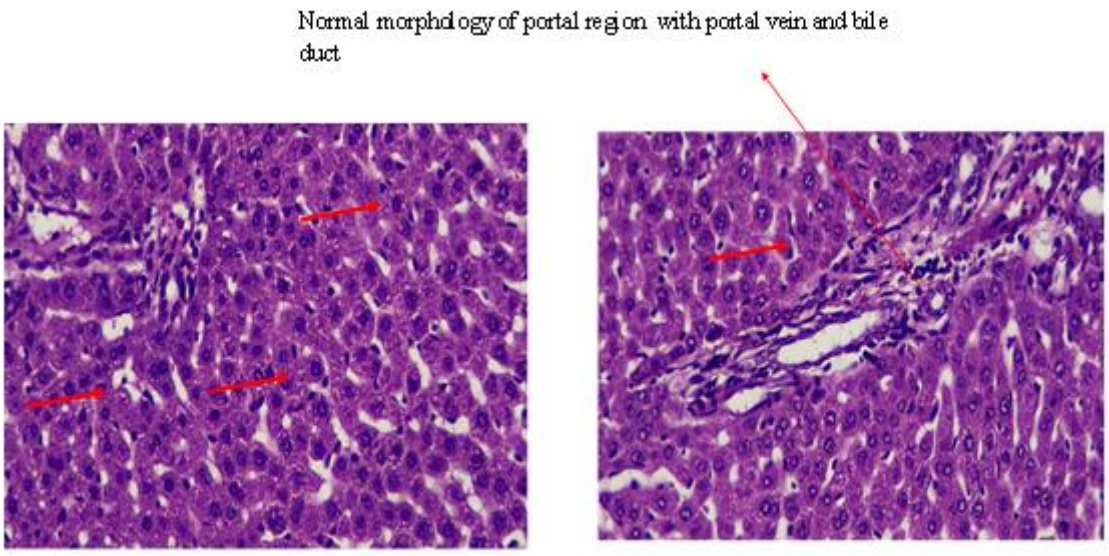


Foci of tubular/interstitial inflammation [green arrow] in cortex region



Normal morphology of glomerulus [red arrow] and tubules of kidneys in cortex region – green arrows

No abnormalities were observed in the kidneys



Normal morphology of hepatocytes were observed in the portal, periportal and centri lobular region of liver – arrow; NO abnormalities were observed in liver

On the 0 day the parameters was done S.urea, S.creatinine, BUN The values will be normal limits. Paracetamol produced nephrotoxicity even at therapeutic doses via radical formation. Its nephrotoxicity is well stablished at a dose of 2000 mg/kg. Paracetamol is an NSAIDS agent used in treatment of Analgesic, Anti pyretic. The toxic effect of Paracetamol was evidenced in the present study by elevation of biochemical markers of kidney function viz serum creatinine and blood nitrogen (BUN) and Histopathological examination in Paracetamol induce nephrotoxicity.

- On the 0 day the parameters was done S.urea, S.creatinine, BUN The values will be normal limits. In the serum parameters for nephroprotective effects of Anisoon and Brinjasif it was observed that plain control group animals fed with 3 ml of normal saline.

- On the 14 day the S.urea in negative group shows highly increase and significant ($p < 0.0001$) when compare to control the test drug high, medium, low is decrease and significant ($p < 0.0001$) when compare to negative group.

- The S. creatinine The negative group shows highly increase and significant ($p < 0.0001$) when compare to control, the test drug high, medium low is decreased and significant ($p < 0.0001$) when compare to negative group.

- The BUN The negative group shows increase and not significant (p=0.109) when compare to control. The test drug high, medium low is slightly decreased and not significant (p=0.109) when compare to negative group.

- The Serum Sodium: The negative group shows increase and significant (p <0.0011) when compare to control.

- The test drug high is slightly high and significant (p <0.0011) when compare to negative group.

- The medium and low is slightly decreased and significant (p <0.0011) when compare to high dose.

- The Serum Potassium: The negative group shows slightly increase and not significant(p=0.3732) when compare to control.

- The test drug high, low is similar values and not significant (p=0.3732) when compare to negative group.

- The medium dose is increased when compare to negative and high and medium dose and not significant.

- The Serum Chloride: The negative group shows increase and significant (p <0.0012) when compare to control.

- The test drug high, medium low is decreased and significant (p <0.0012) when compare to negative group.

- The Alkaline Phosphate: The negative group shows increase and significant (p <0.0001) when compare to control.

- The test drug high, medium low is decreased and significant (p <0.0001) when compare to negative group. The SGOT The negative group shows increase and significant (p <0.0001) when compare to control.

- The test drug high, medium low is decreased and significant (p <0.0001) when compare to negative group.

- The SGPT: The negative group shows increase and significant ($p < 0.0001$) when compare to control.

- The test drug high, medium low is decreased and significant ($p < 0.0001$) when compare to negative group.

- The Creatinine Clearance: The negative group shows increase and significant ($p < 0.0004$) when compare to control.

- The test drug high, medium low is decreased and significant ($p < 0.0004$) when compare to negative group.

In these results of serum analysis it assumed that low is significantly more effective than high medium and dose of test drug.

CONCLUSION

The findings in the present study suggest that combined extract of Anisoon and Brinjasif is a potential Nephroprotective that reduce paracetamol induced nephrotoxicity.

SUMMARY

The present study provides evidence that pre-treatment and co-administration of *Pimpinella anisum* and Brinjasif along with paracetamol prevents both functional and histological renal changes induced by paracetamol in rats.

REFERENCES:

1. Drug induce nephrotoxicity and its biomakers, Biomolecules and therapeutics.
2. Awdishu L, Mehta RL. The 6R's of drug induced nephrotoxicity. BMC Nephrology. 2017;18(1):124.
3. Fundamentals of medical physiology, L prakasam reddy, Paras,4 edition, pg 497.
4. Acetaminophen Induced Kidney Failure in Rats: A Dose Response Study.
5. Saini N, Singh GK, Nagori BP. Spasmolytic potential of some medicinal plant belonging to family umbelliferae: A Review. Int. J. Res. Ayurveda Pharm. 2014;5(1):74-83.
6. National farmulary of unani medicine, part 1,pg 380.
7. Jamshidzadeh, A., Heidari, R., Razmjou, M., Karimi, F., Moein, M.R., Farshad., 2015.
8. International Journal of Herbal Medicine Available online at www.florajournal.com Brinjasif (Achillea millefolium Linn): An efficacious unani medicine.
9. Botany illustrated, by Janice glimn lacy and peter b.kaufman., 2 edition, WHO. WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. Geneva, Switzerland: World Health Organization.
10. Nadim MM, Malik AA, Ahmad J, Bakshi SK. The essential oil of Achillea millefolium L. World J Agric Sci. 2011; 7(5):561-65.
11. Khare CP. Indian medicinal plants. Springer India (P) Ltd, New Delhi, India, 2007, 10-11.

12. Ibn Baitar. Al Jameul Mufredat wa al Advia wa al Aghzia. CCRUM, New Delhi, India. 1999; III:97-102. 16. Hakeem MAH. Bustanul Mufradat. Idarae Kitab-us-Shifa, New Delhi, India, 2002, 73-74.
13. Anonymous. The Unani Pharmacopoeia of India. CCRUM, New Delhi, India, 2010: II(2):3-4.
14. Shawl AS, Srivastva SK, Tripathi S, Raina VK. Essential oil composition of Achillea millefolium.
15. Concept of Kidney Disorders & Its Treatment in Unani System of Medicine Rasikh Javaid1, Ghazala Javed2, Raheela Javaid3, Anju4, Asim Ali Khan.
16. Nephroprotective Agents Used in Unani Medicine-An Evidence Based Approach Roohi Zaman1, Anzar Alam, Shahid Shah Choudhry and Mohd Tariq , Department of Ilmul Saidla, National Institute of Unani Medicine, Bangalore, India 2Department of Moalajat, National Institute of Unani Medicine, Bangalore, India.
17. Ibne Zuhar. Kitabul Taiseer Fil mada vahwal Tadabeer (Urdu translation). Ed.
18. 1st. New Delhi: CCRUM; 1986:159 74. Ibn Sina. Al Qanoon FilTibb. Trans. Kantoori GH. Ed. 1st. New Delhi: Idara Kitabus Shifa; 2007: part-1, vol-2nd: 105, part- II, vol-3rd: 194.
19. Concept of Kidney Disorders & Its Treatment in Unani System of Medicine Rasikh Javaid, Ghazala Javed, Raheela Javaid, Anjun, Asim Ali Khan.
20. Molijath hakim wasim Ahmed Azmi part 2.pg no.429
21. Haziq masihul mulk mohd ajmal khan sahab.pg no 383
22. Tib e akbar,Hakim akbar arzani pgno 519.
23. Mizan e tib,hakim mohd akbar arzani, pg 18
24. Makzan e hikmat shams atibba dr wa hakim gulam jeelani sahab
25. davidson's principle and practice of medicine,edt by cr w Edwards, I a d Bouchier, c.Hastle,e r chilvers, 7 edition,pg 626.
26. Text book of pathology,Harsh mohan,6 edition. Pg 654.
27. The global burden of kidney disease and the sustainable development goals. Bulletin of the World Health Organization 2018; 96:414-422.
28. https://en.wikipedia.org/wiki/Kidney_failure.
29. Pracetamol-induced renal tubular injury:A role for ER stress.
30. Paracetamol: Mechanism of Action, Applications And Safety Concern Marta J"Èwiak-B Benista And Jerzy Z. Nowak Department of Pharmacology, Chair of Pharmacology and Clinical Pharmacology at the Medical University of £Ûdü, Øeligowskiego 7/9, 90-752 £Ûdü, Poland.
31. Acetaminophen-Induced Nephrotoxicity: Pathophysiology, Clinical Manifestations, and ManagementMaryann Mazer, MD, PharmD, and Jeanmarie Perrone, MD Department of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA Corina Lorz, Pilar Justo, Ana Sanz, Dolores Subirá, Jesús Egido and Albert.
32. Paracetamol: mechanisms and updates Chhaya V Sharma MB BS FRCA Vivek Mehta FRCA MD FFPMRCA.
33. Gowda KPS, Swamy BMV, Histopathological and nephroprotective study of aqueous stem bark extract of Ficus racemosa in drug induced nephrotoxic rats. IOSR Journal of Pharmacy, 2012:212) 265-70.
34. Gu, J., H. Cui, M. Behr, L. Zhang and Q.Y. Zhang *et al*., 2005. In vivo mechanisms of tissue-selective drug toxicity: Effects of liver-specific knockout of the NADPH-cytochrome P450 reductase gene on acetaminophen toxicity in kidney, lung and nasal mucosa. Mol. Pharmacol., 67: 623-630.
35. Henrich, W.L., L.E. Agodoa, B. Barrett, W.M. Bennett and R.C. Blantz *et al*., 1996. Analgesics and the kidney: Summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc Committe of the National Kidney Foundation. Am. J. Kidney Dis., 27: 162-16
36. Jones, A.F. and J.A. Vale, 1999. Paracetamol poisoning and the kidney. J. Clin. Pharm. Ther., 18: 5-8. Mandal, A., K. Das, S. Roy, K.C. Mondal and D.K. Nandi. 2013. In vivo assessment of bacteriotherapy onacetaminophen-induced uremic rats. J. Nephrol.,26:228-236.
37. Palani, S., S. Raja, R.P. Kumar, S. Jayakumar and B.S. Kumar, 2009. Therapeutic efficacy Pimpinella tirupatiensis (Apiaceae) on acetaminophen of induced nephrotoxicity and oxidative stress in male albino rats. Int. J. PharmTech Res., 1: 925-934.
38. Palani, S., S. Raja, R.P. Kumar, S. Jayakumar and B.S. Kumar, 2009. Therapeutic efficacy of Pimpinella tirupatiensis (Apiaceae) on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats. Int. J. PharmTech Res., 1: 925-934.

39. Bessems, J.G.M. and N.P.E. Vermeulen, 2001. Paracetamol (acetaminophen)-induced toxicity: Molecular and biochemical mechanisms, analogues and protective approaches. Crit. Rev. Toxicol., 31: 55-138.
40.Mills K.T., Xu Y., Zhang W., *et al*. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int.* 2015;88:950–957.
41. GBD Mortality Causes of Death Collaborators Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;385:117.
42.Lakshmi T, Geetha RV, Anitha R, Aravind KS. Yarrow (Achillea millefolium Linn) a herbal medicinal plant with broad therapeutic use-A Review. International Journal of Pharmaceutical Sciences Review and Research. 2011; 9(2):136-41.
43. Ghani N, Khazainul Advia, Idarae Kitab-us-Shifa. New Delhi, India, 2010, 361-62. 22. Ibn Sina, Al Qanoon Fil Tib. (Urdu trans. by Kantoori
44. Idarae Kitab-us-Shifa, New Delhi, India, 2007, 291. 23. Candan F, Unlu M, Bektas T, Deferera D, Polissiou M, Sokmen A *et a*l. Antioxidant and antimicrobial activity of the essential oil and methanol extract of Achillea millefolium Subsp. millefolium Afan. (Asteraceae). Journal of Ethnopharmacology. 2003; 87:215-20.