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Role of Selenium and Metformin in Attenuating Lead Acetate Induced Renal Damage in Male Wistar Rats

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KEYWORDS

Nephrotoxicity, Selenium, Oxidative Stress, Metformin, Renal Toxicity.

ABSTRACT:

Nephrotoxicity is one form of toxicity which damages kidney due to the toxic or harmful agents or substances is called as nephrotoxicity. Pollutants that lead to renal toxicity are termed as nephron toxicants. Renal toxicity is a condition in which kidney fails to perform its proper function. Lead Acetate is used to induced nephrotoxicity or renal failure on male Wistar rats. It makes easy to study the therapeutics effects on nephrotoxicity. This study shows how Selenium and Metformin are effective in treating kidney damage in combination. Selenium is a kind of trace mineral element. It has antioxidant property which help in reducing oxidative stress level. Selenium also used to treat kidney failure by reducing MDA (Malondialdehyde). It is utilized to treat nephrotoxicity because of its medicinal properties.

Metformin drug which is used as oral antihyperglycemic agent which help in reducing level of blood glucose in a diabetic person. Metformin also has some properties which is used to treat nephrotoxicity. It has properties like anti-inflammatory, antioxidant, and have reno protective effect. By reducing oxidative stress metformin is used to diagnose renal or nephrotoxicity. Metformin helps in improving function of mitochondrial and modulating pathways of inflammatory. In combination Metformin and Selenium give effective result in treating renal damage or nephrotoxicity. Histopathological examination of kidneys of different groups have also shows the effective result.

INTRODUCTION

Nephrotoxicity is a kind of toxicity which damages kidney due to the toxic or harmful agents or substances is called as nephrotoxicity. Pollutants that lead to renal toxicity are termed as nephron toxicants. Many types of toxicants which impacts on renal and disrupts its function leading to renal toxicity which may results to other problems or any types of diseases or systemic toxicities. Renal toxicity is a condition in which kidney fails to perform its proper function. In our body there are metabolic wastes that are carry out within the body by the process named excretion or elimination. For elimination, the organs include urinary bladder, renal or kidney or etc. Several agents or elements such as medicines, pollution, chemicals and others results in renal toxicity or nephrotoxicity. Agent that gives rise to renal toxicity is named as nephrotoxins. Nephrotoxicity affects the organ kidney that plays an essential part in body which is blood filtration, homeostasis, elimination of toxins, balancing of fluid and besides these contributes to variety of roles or function. Nephrotoxicity or renal toxicity comes under chronic type of toxicity. It means, it lasts long time or whole life. Nephrotoxicity manifest in various forms like glomeruli damage, diabetic kidney disease, acute renal injury, tubular acidosis, renal inflammation and more.

Most of the common disease in today's time is renal failure and the reason behind this is intake of chemicals daily into the body. It enters by contaminated water, chemicals present in soil which affects fruits, vegetables, cosmetics, pollutant or the air we breathe. Body is affected by these chemicals which are hazardous to us and damages the organs of the body. Many organs include in elimination especially Kidney, it plays an essential role in elimination. Kidney disease is also named as nephrotoxicity which is occur due to injury,

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poisonous or in term of diseases. It is due to heavy metals also like lead, arsenic, cadmium, mercury, ethylene glycol, bromate, trichloroethylene etc. To protect renal toxicity controls high blood pressure, being active, take healthy diet, maintains good weight, diabetes, and live healthy lifestyle by ignoring fast food, alcohol, smoking or more. (1,2,3)

The symptoms of nephrotoxicity include loss of appetite, edema, lower volume of urine, chest pain, high blood pressure and frequent fatigue.

EPIDEMIOLOGY

Renal toxicity within the population happens or seen in many several ways such as trauma, injuries, infections, blockages, physical damage and many more. Globally, there is a sharp increase in renal or kidney toxicity due to the presence of causative or toxic agent that is more prone to this state or condition. More than 10 % of world's population experiencing a long-term kidney or renal disease. Current research involves worldwide that over 800 million or crores individuals suffer from this kind of toxicity named as nephrotoxicity. Nephrotoxicity is cause mostly by drugs like gentamycin, lead acetate, amikacin etc. Death rate increases day by day across the globe due to nephrotoxicity. Nephrotoxicity is a result in kidney damage or improper function of renal which take part in the development of nephrotoxicity. Rate of mortality was increased by different condition and circumstances; renal toxicity is one of them. (4)

PATHOPHYSIOLOGY

Toxicity caused by heavy metals like mercury, lead, zinc is called nephrotoxicity or renal toxicity. Which results in increasing free radicle formation and high oxidative stress, which subsequently leads to an increase in Nuclear Factor Kappa B. Increase in NF-KB increases the inflammation which results in nephrotoxicity. (5)

MATERIAL AND METHODS

Hypothesis

Null Hypothesis (H0):

Selenium and Metformin does not attenuate lead acetate induced renal damage in rats and has no significant effect on oxidative stress, renal function, or histopathology changes.

Alternative Hypothesis (H1):

By lowering oxidative stress, maintaining renal function, and limiting histopathological modification, selenium and metformin mitigate lead acetate-induced kidney injury in rats.

Methodology

Male Wistar rats are used for this research to assess the pharmacological actions regarding combination drugs including Selenium and Metformin against renal toxicity or nephrotoxicity which is induced by Lead Acetate. Animals are categorized into six different groups which are normal group, diseased group, Test group I, II,III and standard group. After the study all these groups are compared to see the final result.

Test Group Drugs:

Metformin: In order to cure nephrotoxicity Metformin is used as an investigation medication and is taken orally at a dose of 100 mg/kg. 100 milliliters of distilled water were used to dissolve 2.2 grams of metformin in order to create the stock solution.

Selenium: To treat nephrotoxicity Selenium is used as a test drug with a dose of 1.5mg/kg that is administered by oral route. For the preparation of stock solution, 12mg of selenium was dissolved in 80 ml of carboxymethyl cellulose (CMC) solution.

Dosing Protocol

Induction of Nephrotoxicity: After 7-10 days of acclimatation period Lead Acetate is induced orally with a dose of 60mg/kg daily for 28 days. For preclinical study induction to that disease is necessary. Lead Acetate is given to disease group, test group I, II, III and standard group to check whether the drugs are useful for treating disease or not. Normal group receives only saline.

Treatment of Nephrotoxicity

The total study is about 28 days. The last 10 days of studies we administered metformin and last 5 days of study we administered selenium to the rats in test groups and standard group.

Male Wistar rats were distributed up into six-rat groups, each of which was separated based on the dosage protocol:

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Group I: Normal group

This group were only given normal saline and food for 28 days.

Group II: Diseased group

This group was given Lead Acetate for 28 days for the induction of nephrotoxicity at a dose of 60mg/kg by oral route.

Group III: Test Group I

This group was given Lead Acetate for 28 days (60mg/kg) and Selenium for last 5 days (1.5mg/kg) of study by oral route.

Group IV: Test Group II

This group was given Lead Acetate for 28 days (60mg/kg) and Metformin for last 10 days (100mg/kg) of study by oral route.

Group V: Test Group III

This group was given Lead Acetate for 28 days (60mg/kg) and Metformin (100mg/kg) for 10 days + Selenium (1.5mg/kg) for 5 days of study by oral route.

Group VI: Standard Group

This group was given Lead Acetate for 28 days (60mg/kg) and Ethylenediamine tetra acetic acid (1mg/kg) for last 7 days of study by oral route.

For sacrificing rats we use overdose of anesthesia and kidney was isolated in the formaldehdye from the body of rats for histological. On 29th day of experiment kidney was collected from all groups. After kidney was collected they were placed in 10% of formalin solution for determining analysis of serum or blood. Blood was collected from the rats of all groups on the 29th day of experiment. And isolated for serum related parameters are evaluated. Some of the serum parameters are Blood Urea, Blood Urea Nitrogen, Creatinine and Inorganic Phosphorus. There are some tests performed through blood that are monocyte, neutrophil, platelet count haemoglobin, eosinophil, basophil and lymphocyte.

RESULTS

1. BLOOD CREATININE LEVEL

Groups	Creatinine level in (mg/dl)
Normal Control group	0.5500 ± 0.3271
Diseased Control Group	1.525 ± 0.01871
I test Group	1.225 ± 0.01871
II test Group	1.045 ± 0.01871
III test Group	1.105 ± 0.01871
Standard group	0.8650 ± 0.01871

Table no.01: showing the creatinine level of rats

Tukey's Multiple Comparison Test

S. No.	Comparison	Mean Difference	95% CI of Difference	Significant?	Adjusted P Value
1	Disease Group vs Normal Control	0.975	0.908 to 1.042	Yes	< 0.0001
2	I test group vs Disease	–0.300	–0.367 to –0.233	Yes	< 0.0001
3	II test group vs Disease	–0.480	–0.547 to –0.413	Yes	< 0.0001
4	III test group vs Disease	–0.420	–0.487 to –0.353	Yes	< 0.0001

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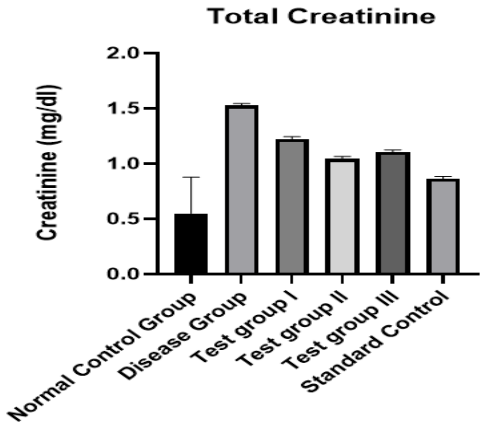
5	Standard Control vs Disease	–0.660	–0.727 to –0.593	Yes	< 0.0001
6	II test group vs Normal Control	0.495	0.428 to 0.562	Yes	< 0.0001



Graph no.01: showing the difference in creatinine level among various groups.

2. BLOOD UREA LEVEL

Groups	**Blood Urea level in (mg/dl)**
Normal Control group	31.53 ± 0.01871
Diseased Control Group	74.50 ± 1.871
I test Group	53.32 ± 0.01414
II test Group	51.13 ± 0.01871
III test Group	60.73 ± 0.01871
Standard group	56.50 ± 1.871

Table no.02: showing the blood urealevel of rats

Tukey's Multiple Comparison Test

S. No.	**Comparison**	**Mean Difference**	**95% CI of Difference**	**Significant?**	**Adjusted P Value**
1	Disease Group vs Normal Control	42.97	41.04 to 44.90	Yes	< 0.0001
2	I Test group vs Disease	–21.18	–23.11 to –19.25	Yes	< 0.0001
3	II Test group vs Disease	–23.37	–25.30 to –21.44	Yes	< 0.0001
4	III Test group vs Disease	–13.77	–15.70 to –11.84	Yes	< 0.0001
5	Standard Control vs Disease Group	–18.00	–19.93 to –16.07	Yes	< 0.0001
6	II test group vs Normal Control	19.60	17.67 to 21.53	Yes	< 0.0001

Graph no.02: illustrating the variation in blood urea level across several groups.

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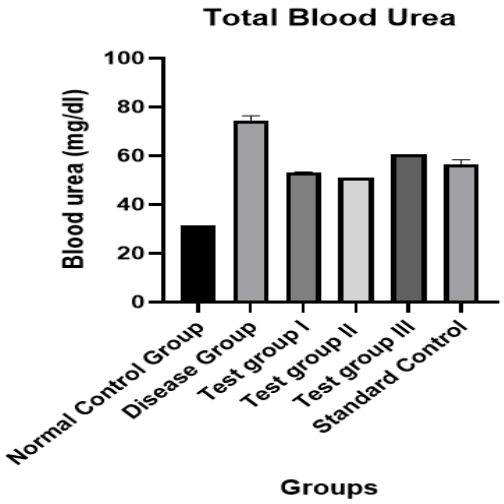

Graph no.02: illustrating the variation in blood urea level across several groups.

3. BLOOD URIC ACID LEVEL

Groups	Blood Uric acid level in (mg/dl)
Normal Control group	4.525 ± 0.01871
Diseased Control Group	9.525 ± 0.01871
I test Group	7.425 ± 0.01871
II test Group	5.625 ± 0.01871
III test Group	5.925 ± 0.01871
Standard group	4.513 ± 0.01366

Table no.03: showing the blood Uric acid level of rats

Tukey's Multiple Comparison

S. No.	Comparison	Mean Difference	95% CI of Difference	Significant?	Adjusted P Value
1	Disease Group vs Normal Control	5.000	4.947 to 5.053	Yes	< 0.0001
2	I test group vs Disease	–2.100	–2.153 to –2.047	Yes	< 0.0001
3	II test group vs Disease	–3.900	–3.953 to –3.847	Yes	< 0.0001
4	III Test group vs Disease	–3.600	–3.653 to –3.547	Yes	< 0.0001
5	Standard Control vs Disease Group	–5.012	–5.065 to –4.959	Yes	< 0.0001
6	III test group vs Normal Control	1.400	1.347 to 1.453	Yes	< 0.0001

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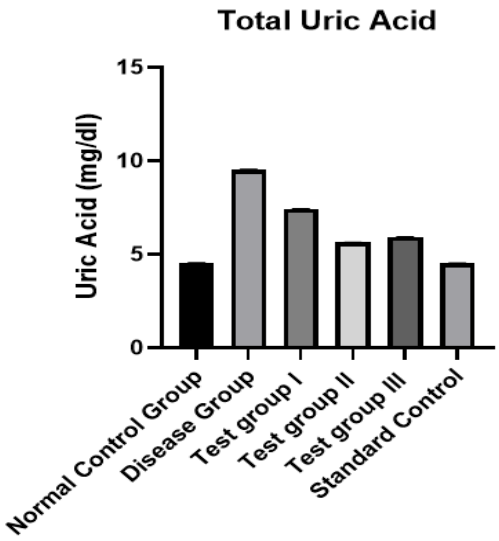

Graph no.03: demonstrating how different groups' blood urea levels differ from one another.

4. BLOOD HAEMOGLOBIN LEVEL

Groups	Blood Haemoglobin level in (g/dl)
Normal Control group	16.25 ± 0.1871
Disease Group	6.500 ± 1.871
Test Group I	12.54 ± 0.01472
Test Group II	15.50 ± 1.871
Test Group III	16.53 ± 0.01871
Standard group	15.46 ± 0.03615

Table no.04: showing the blood Haemoglobin level of rats

Tukey's Multiple Comparison Test

S. No.	Comparison	Mean Difference	95% CI of Difference	Significant?	Adjusted P Value
1	Disease Group vs Normal Control	–9.75	–10.17 to –9.33	Yes	< 0.0001
2	Test Group I vs Disease Group	6.04	5.62 to 6.46	Yes	< 0.0001
3	Test Group II vs Disease Group	9.00	8.58 to 9.42	Yes	< 0.0001
4	Test Group III vs Disease Group	10.03	9.61 to 10.45	Yes	< 0.0001
5	Standard Control vs Disease Group	8.96	8.54 to 9.38	Yes	< 0.0001
6	Test Group III vs Normal Control	0.28	–0.14 to 0.70	No	> 0.05

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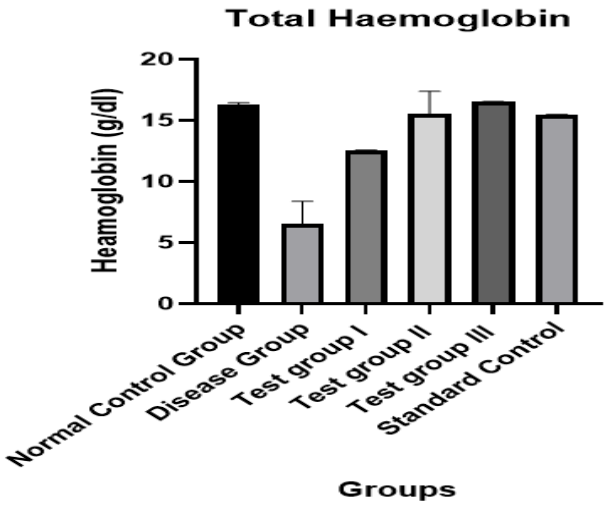

Graph no.04: showing the difference in Haemoglobin level among various groups.

Analyzed variations in body weight among several groups

Groups	No of Rats	Day 1 (gm)	Day 7 (gm)	Day 14 (gm)	Day 21 (gm)	Day 28 (gm)
Group 1: Normal Control (NC)	Rat 1	100	102	110	125	135
	Rat 2	75	80	85	100	120
	Rat 3	75	80	90	110	125
	Rat 4	170	175	177	177	180
	Rat 5	150	155	155	160	160
	Rat 6	120	125	130	140	140
Group 2: Diseased Control (DC)	Rat 1	130	120	115	100	90
	Rat 2	110	106	101	92	85
	Rat 3	150	145	141	140	120
	Rat 4	100	96	90	80	73
	Rat 5	130	126	120	100	90
	Rat 6	125	122	118	110	100
Group 3: Test Group 1 (TG1)	Rat 1	120	115	125	122	121
	Rat 2	130	128	125	122	120
	Rat 3	100	96	96	98	101
	Rat 4	125	122	120	119	115
	Rat 5	80	85	99	100	102
	Rat 6	130	131	135	135	137
Group 4: Test Group 2 (TG 2)	Rat 1	140	135	136	140	145
	Rat 2	100	105	105	107	110
	Rat 3	80	78	83	85	89
	Rat 4	130	132	135	135	140

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	Rat 5	100	95	94	99	110
	Rat 6	160	160	159	164	165
Group 5: Test Group 3 (TG 3)	Rat 1	130	132	133	135	140
	Rat 2	120	119	123	126	130
	Rat 3	120	122	121	125	129
	Rat 4	100	115	112	118	120
	Rat 5	90	95	93	95	100
	Rat 6	130	132	129	135	140
Group 6: Standard Group (SG)	Rat 1	150	152	155	157	160
	Rat 2	145	142	145	148	152
	Rat 3	130	131	133	135	140
	Rat 4	100	98	97	100	103
	Rat 5	120	118	120	123	130
	Rat 6	100	99	98	101	105

HISTOPATHOLOGY OF KIDNEYS OF THE MALE WISTAR RATS

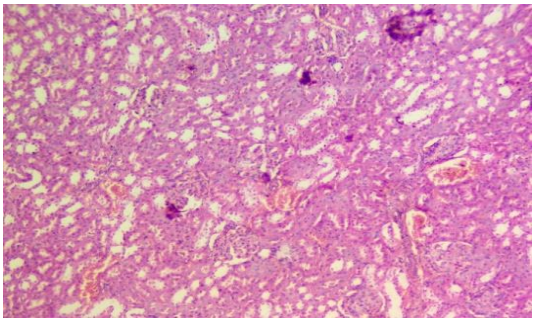

Fig.no.1- (a) Normal Control

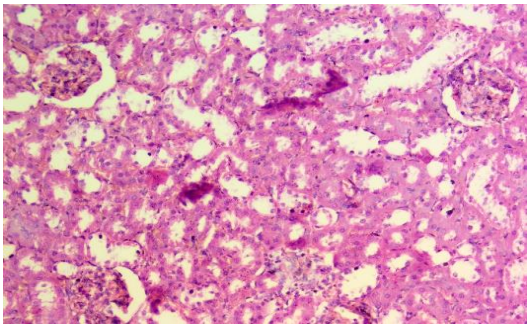

Fig.no.1- (b) Diseased Control

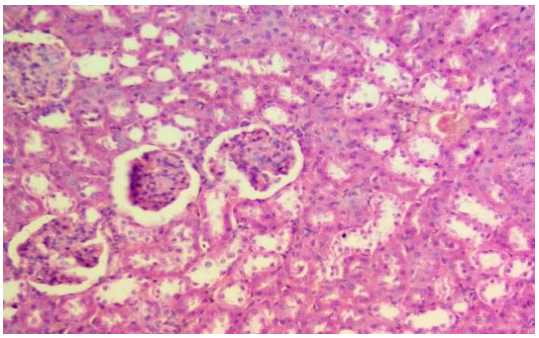

Fig.no.1- (c) Test Group I

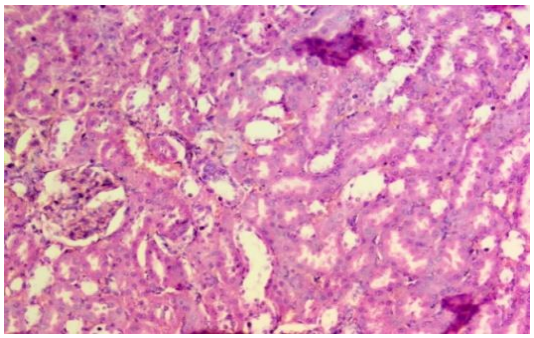

Fig.no.1- (d) Test Group II

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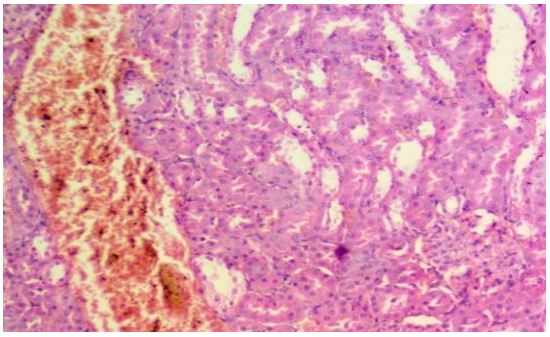

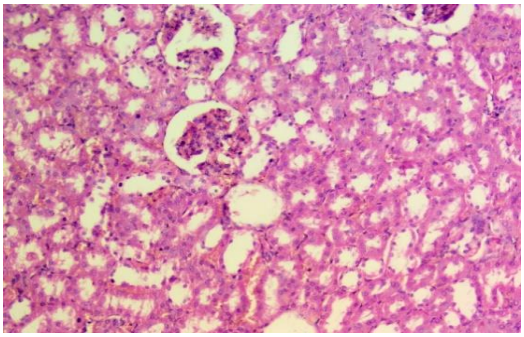

Fig.no.1- (e) Test Group III **Fig.no.1- (f) Standard Group**

Figure no.1*- Photomicrograph of histopathology examination of kidneys.*
(Fig.a) *Kidneys were found to be healthy in normal groups. Glomeruli appear normal in morphology , no cystic change noted.*
(Fig.b) *Both the kidney were found to be nephrotoxic kidney with interstitial pyelonephritis exhibiting lymphoplasmacytic interstitial filteration, congestion and hemorrhage.*
(Fig.c) *Histopathology shows mild nephrotoxic kidney having moderate lymphoplasmacytic interstitial infilteration, congestion and hemorrhage.*
(Fig.d) *Histopathology shows mild nephrotoxic kidney having mild lymphoplasmacytic interstitial infilteration, congestion and hemorrhage.*
(Fig.e) *Histopathology shows minimal nephrotoxic kidney having focal lymphoplasmacytic interstitial infilteration with congestion. The impression shows receding nephrotoxic kidney.*
(Fig.f) *Kidneys found to be healthy with signs that shows receading nephrotoxic kidney.*

DISCUSSION

The study of experimental are concluded that selenium and metformin have antioxidant property. This experimental study of lead acetated induced nephrotoxicity in the rats are protective by the selenium and metformin which shows the potential effect in te condition of nephrotoxicity. In this study, groups are divided into control, Disease, Test group I Selenium (1.5mg/kg), Test group II Metformin (100mg/kg), Test group III Selenium + Metformin (1.5mg/kg+ 100mg/kg), Standard Group EDTA (1mg/kg). The first Control group is maintained with standard condition of bedding & foods and not induced of disease & treatment. The Disease Group is the group of disease induced and no treatment is given. This group has high toxicity is observed as compare to other groups. The confirmation test of toxicity is also done by the disease group and shows the presence of toxicity in the rats. The Test group I is the third group that are treated with 1.5mg/kg of Selenium. The Test group II is the fourth group that are treated with 100mg/kg of Metformin. The Test group III is the fifth group that are treated with 1.5mg/kg of selenium and 100mg/kg of metformin. The sixth group is standard group of EDTA treated with 1mg/kg of EDTA.

The Third, Fourth, Fifth and Sixth group are shows that toxicity level is decreased by the used of 1.5mg/kg of selenium, 100mg/kg of metformin and the Standard group of EDTA. The KFT of groups also show the levels are maintained by the used of drugs and their functions are reverse back to normal in the parameter of Urea in Blood, BUN, level of creatinine and inorganic phosphate are evaluated. The toxicity level is confirmed by the blood analysis and visible through changes in the level of blood component. The induce of toxicity in rat body represent the level of Hb (haemoglobin) is low and other level are high such as the Platelet Count & TLC. Administration of 1.5mg/kg os selenium show slightly change in the state while 100mg/kg of metformin and 1.5mg/kg of selenium together show huge differences in the result. The Rats histology of kidney images shows that clear and definite situation as above the condition are mentioned of groups. The result of KFT & Blood

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analysis was represented by the selenium and metformin that has powerful ability and capable for decreases toxicity and improve the condition. The drugs selenium and metformin show protective effect in the condition of lead induced nephrotoxicity in the rats.

CONCLUSION

The Experimental Study in which the pharmacological evaluation of Selenium and Metformin in lead acetate induced nephrotoxicity in wistar rats.

The aim and purpose of this study was to analysis the drugs Selenium amd Metformin beneficial with protective effect in nephrotoxicity condition. The Nephrotoxicity is induced by the heavy metal or chemical lead (lead acetate). The induction of nephrotoxicity through chemical can reversible the heath condition by the drugs. So, there are following conclusions are drawn below by this experimental study such as Lead component (lead acetate) possible to occur the nephrotoxicity in the body.

Administration of lead results as the nephrotoxicity symptoms is weight loss of rats in groups. Disease group that not contain any type of treatment only disease induce and compares with other groups shows more weight loss. Test group I 1.5mg/kg of selenium slightly more than disease group whereas test group II 100mg/kg receive Metformin.

The Heamoglobin level are identify that is normal in control group whereas disease group level is very low, 1.5mg/kg group level slightly high, 100mg/kg extract group level is near to heamoglobin level, and standard group level within the range of haemoglobin.

The Platelet Count and TLC (Total Leucocyte Count) levels are higher in disease group whereas other groups level is nearer and within the ranges presented.

The Nephrotoxicity is identified by the KFT (Kidney Function Test) parameters that are creatinine level in serum, urea in blood, BUN (Blood Urea Nitrogen), etc.

These tests result showed the level are higher in lead induced disease group and 1.5mg/kg of Selenium group show moderate change in condition, 100mg/kg of Metformin and 1.5mg/kg of Selenium group show the great changes in range with standard group.

Conflict of Interest: The author has no conflict of interest.

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Author Contribution

SA- Writing original

Draft VPS- Original concept

SS- Supervision

Ethical Approval: The research study was conducted at Siddhartha institute of pharmacy, Near IT park, Dehradun 248001. The animal house is CPCSEA approval. And the registration no. of the animal house – 1435/PO/RE/S/11/CPCSEA.

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