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A review on role of *Moringa oleifera* in kidney protection

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Abstract
The major aim of this article is to review the Kidney protection activities of Moringa oleifera (*M. oleifera*). This review covers the Nephro protective activities of *M. oleifera* including Diabetic therapeutic area. This review highlights the importance of *M. oleifera* extract in Kidney, brain and liver protection. The literature review about this plant Nephro protective activity was conducted between 2012 and 2023 through Pubmed and Google.

Keywords: *Moringa oleifera*, Kidney, extract, diabetic, toxicological

1. Introduction
Kidney diseases are regarded as one of the major public health issues in the world. Recent reports have shown the Nephro protective effect of *M. oleifera* from various parts of the world. As the disease's growth rate accelerates, it has become a global concern. The majority of incidents occur in low and lower-middle income countries. The kidneys gradually lose their ability to function in chronic kidney disease (CKD) patients, and the glomerular filtration rate (GFR) falls below 60 mL/min per 1.73 m^2. Mainly people who have been already suffering from diabetes, heart disease, or high blood pressure are at a high risk of developing CKD. Few drugs, such as prolyl hydroxylase domain inhibitors against anemia in CKD, can be used to treat CKD complications. The main pathologies involved in kidney complications are inflammation, oxidative stress, apoptosis, and fibrosis. Unfortunately, no potential drug for treating kidney diseases exists.
Therefore, the search for a potential drug with fewer side effects to combat this disease is becoming increasingly important. Furthermore, it contains numerous bioactive phytochemicals such as flavonoids, saponin, vanillin, omega fatty acids, carotenoids, ascorbates, tocopherols, beta-sitosterol, moringine, kaempferol, and quercetin that have been reported in its flowers, roots, fruits, and seeds, and can play a variety of roles in medicine.
Despite the great progress of *M. oleifera* in this Kidney protection field in recent years, less attention has been given to the effectiveness of *M. oleifera*, particularly against kidney related diseases. This review provides a hypothesis on how *M. oleifera* would be effective in the anti-inflammation and antioxidant processes of the kidney, with the least amount of side effects.

2. Anti-inflammation and Antioxidant processes of the kidney
Md Jamal Uddin *et al*. [1] were studied to investigate the causative factors involved in kidney disease and the therapeutic aspects of *M. oleifera*, as well as the effectiveness of *M. oleifera* in the anti-inflammation and antioxidant processes of the kidney while minimizing all potential side effects. In addition, they proposed a hypothesis to improve *M. oleifera* based drug development. This study was updated by searching the key words *M. oleifera* on kidney diseases and *M. oleifera* on oxidative stress, inflammation, and fibrosis in online research databases such as PubMed and Google Scholar. The following validation checking and scrutiny analysis of the recently published articles were used to explore this study. The recent existing research has found that *M. oleifera* has a plethora of health benefits. Individual medicinal properties of *M. oleifera* leaf extract, seed powder, stem extract, and the whole extract (ethanol/methanol) can up-increase the activity of antioxidant enzymes like superoxide dismutase (SOD),catalase (CAT), and glutathione (GSH), while decreasing the activity of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and COX-2. In their study, they have investigated the properties of this plant against kidney diseases based on existing knowledge

with an updated review of literature. Considering the effectiveness of *M. oleifera*, this study would be useful for further research into the pharmacological potential and therapeutic insights of *M. oleifera*, as well as prospects of Moringa-based effective medicine development for human benefits. Considering the harmful effects of synthetic resources and their non-renewable nature, the use of natural resources as a source of medicine has received a lot of attention in recent years.

3. Impact of Cobalt chloride

The impact of cobalt chloride was studied by Mohamed M. Abdel-Daim *et al*. [2]. They studied the protective efficacy of *Moringa oleifera* ethanolic extract (MOEE) against the impact of cobalt chloride ($CoCl_2$) exposure on the rat's kidney. Fifty male rats were assigned to five equal groups: a control group, a MOEE-administered group (400 mg/kg body weight (bw), daily via gastric tube), a $CoCl_2$-intoxicated group (300 mg/L, daily in drinking water), a protective group, and a therapeutic co-administered group that received MOEE prior to or following and concurrently with $CoCl_2$, respectively. The antioxidant status indices (superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH)), oxidative stress markers (hydrogen peroxide (H_2O_2), 8-hydroxy-2-deoxyguanosine (8-OHdG), and malondialdehyde (MDA)), and inflammatory response markers (nitric oxide (NO), tumor necrosis factor (TNF-α), myeloperoxidase (MPO), and C-reactive protein (CRP)) were evaluated. The expression profiles of pro-inflammatory cytokines (nuclear factor-kappa B (NF-kB) and interleukin-6 (IL-6)) were also measured by real-time quantitative polymerase chain reaction (qRT-PCR). The results showed that $CoCl_2$ exposure was associated with significant elevations of oxidative stress and inflammatoryindices with reductions in the endogenous tissue antioxidants' concentrations. Moreover, $CoCl_2$ enhanced the activity of the NF-κB inflammatory-signaling pathway that plays a role in the associated inflammation of the kidney. MOEE ameliorated $CoCl_2$-induced renal oxidative damage and inflammatory injury with the suppression of the mRNA expression pattern of pro-inflammatory cytokine-encoding genes. MOEE is more effective when it is administered with $CoCl_2$ exposure as a prophylactic regimen. The MOEE administration exhibited protective effects in counteracting $CoCl_2$-induced renal injury in rats.

4. Morphology and functions of Kidneys in Rats

A detailed study made by Ameen *et al*. [3] on *M. oleifera* extract on kidneys. They tested the hypothesis that *M. oleifera* impairs the morphology and functions of the kidney in rats. Twenty four adult male Wistar rats were employed in the study. Rats of Control Group I received physiological saline while rats of Groups II-IV received 250, 500 and 750 mg/kg body weight of methanolic extract of *Moringa oleifera* respectively for twenty one days. No behavioural anomalies were observed in rats of Groups I-IV. Rats of Control Group I gained statistically significant increased bodyweight while rats of Groups II-IV experienced non-significant decreased bodyweight during experimental procedure. ($p \leq 0.05$). No statistical significant differences ($p \leq 0.05$) were observed in the analyses of the relative weights of kidneys of rats of Groups I-IV. Histological examinations showed normal cyto-architecture of the kidneys of rats of Group I while the Capsular spaces of the kidneys of rats of Groups II-IV appeared wider than those of Group I. Statistical analyses showed significant higher levels ($p \leq 0.05$) of Alanine and Aspartate Transaminases, and serum urea in rats of Groups II-IV in a non-dose-dependent manner when compared to rats of Group I. The findings are consistent with the stated hypothesis.

5. Renal Ischemia-Reperfusion (IR) Injury

Akinrinde *et al.* [4] were studied to investigate the protective effect of the methanol extract of *M. oleifera* in a rat model of renal ischemia-reperfusion (IR) injury. Forty two wistar rats were randomly assigned to six groups of seven rats each, as follows: A, control group; B, sham-operated group; C, IR group; D, IR + low dose (200 mg/kg) MO; E, IR + high dose (400 mg/kg) MO and F, IR + Vitamin C (200 mg/kg). Unilateral ischaemia was induced by occluding the left renal artery for 45 minutes followed by reperfusion up to 24 hours. *Moringa oleifera* significantly ($p<0.05$) ameliorated IR-induced increases in malondialdehyde (MDA), protein carbonoyls (PC) and advanced oxidation protein products (AOPP), while also decreasing serum BUN and Creatinine levels. More-over, the low dose of MO caused reductions in renal NO and H_2O_2 levels, while increasing renal GPx and GST activities. Histopathology revealed marked improvement of tissue alterations induced by IR with both doses of MO. In this study, the methanol extract of *M. oleifera* effectively attenuated the deleterious effects of renal IR via alleviation of tissue oxidative stress.

6. Role of Fatty acids

Nafiu *et al*. [5] studied to investigate the nephroprotective effect of fatty acids from ethanolic extract of *Moringa oleifera* seeds (EEMOS) against gentamicin-induced kidney injury in rats. Gentamicin, an aminoglycoside drug, used for the treatment of Gram-negative bacterial infections. Despite its potency against bacterial infections, its clinical use is limited owing to nephrotoxicity effect. Forty-five male Wistar rats, 100-160 g, were divided into 5 groups as follows: Group 1 (control), 5 rats, received 0.2 ml/100 g/day of propylene glycol orally for 28 days. Group 2, 10 rats, received 100 mg/kg/day (i.p) of gentamicin (GENT) for 8 days. Group 3-5, 10 rats each, treated with EEMOS orally for 28 days at graded doses of 100, 200 and 400 mg/kg respectively after GENT treatment. Twenty four after treatment, five rats from each group were sacrificed. The remaining 5 rats were sacrificed after 2 weeks recovery period from the drugs

The result showed that GENT elicited polyuria, elevated plasma creatinine, urea, and lower plasma electrolytes and creatinine clearance levels. Measurements of 24 h urinary output demonstrated marked decrease in creatinine and potassium levels in the GENT-treated group, whereas sodium level remain unchanged. Also, GENT caused significant decrease in superoxide dismutase and an increase in malondialdehyde levels in the kidney of the rats. Histopathological examination revealed evidence of necrosis of the kidney. Treatment with EEMOS significantly ameliorated the alterations caused by GENT in the plasma, urine and kidney homogenate of the rats. Hence, the mono- and poly-unsaturated fatty acids present in EEMOS were responsible for its renoprotective ability

7. Alloxan induced diabetes

Alloxan induced diabetes in rats was studied in detail by Saleh *et al.* [6]. They studied to determine the effect of ethanolic *M. oleifera* extract on glucose ,melatonin, lipid profile, liver, and kidney function in alloxan induced diabetes

Induced Diabetes in rats. Diabetes was induced in male Wistar rats by single intra peritoneal injection of alloxan (150 mg/kg b. wt.).The diabetic rats were administered orally with EMOE at two different doses (250 and 500 mg/kg b. wt. /day) for 60 days. The alloxan treated control rats showed a significant increase in glucose (BS), total cholesterol (STC), triglycerides (STG), low density lipoprotein cholesterol (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatases (ALP), urea creatinine with a concomitant decrease in serum melatonin, lactate dehydrogenase (LDH),and high density lipoprotein cholesterol (HDL).Oral administration of MOLEt (250 and 500 mg/kg b. wt./day) for 60 days showed significant reduction in BS, STC, STG, LDL,ALP, ALT, AST and LDH, , urea creatinine levels and an elevation in serum melatonin, LDH, and HDL levels in diabetic group as compared with control group. Treatment of the diabetic rats with MOE could restore the changes of the above parameters to their normal levels.

8. Gentamycin impact

Moustapha_Ouédraogo *et al*. [7] were established the oxidative stress due to abnormal production of reactive oxygen species has been implicated in the nephrotoxicity induced by gentamicin. The nephroprotective effect of aqueous-ethanolic extract of *M. oleifera* leaves (150 and 300 mg/kg) was evaluated against gentamicin-induced (80 mg/kg) renal injury in rabbits. Serum urea and creatinine levels were evaluated as the markers of renal nephrotoxicity. At the end of the experiment, the kidneys of rabbits were excised for histological examinations and determination of lipid peroxidation levels. Serum urea and creatinine levels were reduced in the *M. oleifera* (150 and 300 mg/kg) plus gentamicin treated groups. On histological examinations, kidney of intoxicated rabbits groups which received *M. oleifera* extract showed reparative tendencies. A highly significant ($p< 0.01$) elevation was observed in lipid peroxidation (LPO) level in the kidneys of gentamicin-intoxicated rabbits whereas combined treatment of *M. oleifera* and gentamicin group showed a highly significant ($p< 0.01$) depletion in LPO. The present study indicates that aqueous-ethanolic extract of *M. oleifera* leaves attenuates renal injury in rabbits treated with gentamicin, possibly by inhibiting lipid peroxidation.

9. Glycerol-induced acute kidney injury

Adeolu Alex Adedapo [8] were studied to assess the ameliorative effect of *M. oleifera* on glycerol-induced acute kidney injury in rats thus renewing interest in the development of new treatment plans. Glycerol (50% v/v in sterile saline, intramuscular) was used to induce acute kidney injury. Group A (control group) received distilled water only, the group B animals (toxicant group) received glycerol alone on the 8th day, and groups C and D animals were given 50 mg/kg and 100 mg/kg of methanol stem extract of *Moringa oleifera* respectively for seven days and glycerol on the 8th day. Group E animals on the other hand received 100 mg/kg of methanol stem extract of *Moringa oleifera* alone for seven days and on day 8 received normal saline. To assess renal damage and possible ameliorative effects of the extract, serum blood urea nitrogen (BUN), creatinine,myeloperoxidase,advancedoxidativeproducts, malo ndialdehyde, superoxide dismutase, reduced glutathione, and protein carbonyl were determined. Histopathological analysis of kidney tissues and immunohistochemical analysis of KIM-1 and NF-κB expressions were also carried out on kidney tissues. The results showed that methanol stem bark extract of *Moringa oleifera* improves glycerol-induced acute kidney injury by inhibiting markers of inflammation, oxidative stress and renal damage by modulating KIM-1 and NF-κB signaling pathways. Authors concluded that the methanol stem extract of *Moringa oleifera* blunts glycerol-induced acute kidney injury in rats through its anti-oxidant and anti-inflammatory properties.

10. *Moringa oleifera* roots

The methanolic extract of *Moringa oleifera* was studied by C.W Paul *et al*. [9]. They studied to investigate effect(s) of methanolic extract of *Moringa oleifera* lam root on Histo-architechture of Liver and Kidney, considering objectives such as determining if the effect of the extract is dose and time-dependent, and determination of LD50. 'LD50 ip' of 223.61 mg/kg was determined using modified Lorke's (1983) method. Twenty four (24) guinea pigs were used for the study. They were acclimatized and randomly distributed into groups A-C and control. They were given daily intra-peritoneal injection of methanolic extract of *Moringa oleifera* lam root was done for three (3) weeks. Doses of 3.6, 4.6 and 7.0 mg/kg were given to groups A, B and C respectively. Four pigs; one from each group were sacrificed on 8th, 15th and 22nd days. Methanolic extracts of *Moringa oleifera* lam roots was found to distort the histo-architecture of both liver and kidneys of guinea pigs. These effects are time-dependent and dose-dependent. The liver and kidney of guinea pigs in the reversal group retained histo-architectural distortions.

11. Morphology and functions of the kidney in Rats

Akinlolu *et al*. [10] were tested the hypothesis that *M. oleifera* impairs the morphology and functions of the kidney in rats. Twenty four adult male Wistar rats were employed in the study. Rats of Control Group I received physiological saline while rats of Groups II-IV received 250, 500 and 750 mg/kg bodyweight of methanolic extract of *Moringa oleifera* respectively for twenty one days. No behavioural anomalies were observed in rats of Groups I - IV. Rats of Control Group I gained statistically significant increased bodyweight while rats of Groups II - IV experienced non-significant decreased bodyweight during experimental procedure. ($P\leq0.05$). No statistical significant differences ($P\leq0.05$) were observed in the analyses of the relative weights of kidneys of rats of Groups I - IV. Histological examinations showed normal cyto-architecture of the kidneys of rats of Group I while the Capsular spaces of the kidneys of rats of Groups II - IV appeared wider than those of Group I. Statistical analyses showed significant higher levels ($p\leq0.05$) of Alanine and Aspartate Transaminases, and serum urea in rats of Groups II-IV in a non- dose-dependent manner when compared to rats of Group I. Their findings are consistent with the stated hypothesis.

12. Diabetic therapeutic area

12.1. Epigenome and Transcriptome Effects

The Epigenome and Transcriptome Effects studied by Shanyi Li *et al*. [11], They established the Moringa isothiocyanate (MIC-1) is a bioactive constituent found abundantly in *M. oleifera* which possesses antioxidant and anti-inflammation properties. However, epigenome and transcriptome effects of MIC-1 in kidney mesangial cells challenged with high glucose (HG), a pre-condition for diabetic nephropathy (DN) remain unknown. Herein, we examined the transcriptome

gene expression and epigenome DNA methylation in mouse kidney mesangial cells (MES13) using next-generation sequencing (NGS) technology. After HG treatment, epigenome and transcriptome were significantly altered. More importantly, MIC-1 exposure reversed some of the changes caused by HG. Integrative analysis of RNA-Seq data identified 20 canonical pathways showing inverse correlations between HG and MIC-1. These pathways included GNRHsignaling, P2Y purigenic receptor signaling pathway, calcium signaling, LPS/IL-1-mediated inhibition of RXR function, and oxidative ethanol degradation III. In terms of alteration of DNA methylation patterns, 173 differentially methylation regions (DMRs) between the HG group and low glucose (LG) group and 149 DMRs between the MIC-1 group and the HG group were found. Several HG related DMRs could be reversed by MIC-1 treatment. Integrative analysis of RNA-Seq and Methyl-Seq data yielded a subset of genes associated with HG and MIC-1, and the gene expression changes may be driven by promoter CpG status. These genes include Col4a2, Tceal3, Ret, and Agt. In summary, our study provides novel insights related to transcriptomic and epigenomic/CpG methylomic alterations in MES13 upon challenged by HG but importantly, MIC-1 treatment reverses some of the transcriptome and epigenome/CpG methylome. These results may provide potential molecular targets and therapeutic strategies for DN.

12.2 Streptozotocin-Induced Diabetic Nephropathy

Ying Wen *et al*. [12] evaluated the therapeutic effects of *M. oliefera* seed (MOS) extract on the kidneys of high-fat diet (HFD)-fed rats with streptozotocin-induced diabetic nephropathy and reveal its underlying mechanisms. For this study, HFD-fed rats with streptozotocin-induced diabetic nephropathy and high-glucose induced Human Renal Mesangial Cells (HRMC) were used to explore the protective effect of MOS on diabetic nephropathy *in vivo* and *in vitro.* MOS extract could inhibit the proliferation of HRMCs induced by high glucose levels. Compared with the rats in the DN group, MOS not only significantly reduced blood glucose levels and oxidative stress in the experimental rats but also improved their kidney function and reduced kidney tissue damage. Additionally, MOS extract increased GSK-3β activity and the expression of Nrf2 and HO-1. This study showed that MOS could activate GSK-3β and Nrf2/HO-1 pathways toexert antioxidant and anti-renal fibrosis activities, and delay the progression of diabetic nephropathy.

12.3 Anti - diabetic benefits

Yujiao Tang *et al*. [13] were studied to assess the antidiabetic effect of *M. oleifera* extract from Cambodia. The leaf ethanolic extract contained flavonoids (31.90 mg/mL), polyphenols (53.03 mg/mL), lycopene (0.042 mg/mL), and ß-carotene (0.170 mg/mL), and possessed 2,2-diphenyl-1-picrylhydrazyl, hydrogen peroxide, and hydroxyl radical scavenging activities of 92.40, 99.25, and 83.57 TE/μM at 1 mg/mL, respectively. Db/db mice were orally administered the leaf extract (150 mg/kg/day) for 5 weeks. *M. oleifera* treatment significantly ameliorated the altered fasting plasma glucose (from 483 to 312 mg/dL), triglyceride (from 42.12 to 23.00 mg/dL), and low-density lipoprotein cholesterol (from 107.21 to 64.25 mg/dL) compared to control group, and increased the insulin levels from 946 ± 92 to 1678 ± 268 pg/mL. The histopathological damage and expression levels of tumor necrosis factor-alpha, interleukin (IL)-1β, IL-6, cyclooxygenase-2, and inducible nitric oxide synthase in renal tissue decreased. These results indicate the potential antidiabetic benefits of *M. oleifera* ethanolic leaf extract.

13. Multi organ protection

13.1 Liver and Kidney

Ajilore B, S *et al*. [14] were studied to induce liver and kidney damage in rats using cadmium and biochemically evaluate possible protective potentials of methanolic extract of *Moringa oleifera* (MO). Twenty-one adult male rats weighing 200-250g were randomly divided into three groups (A, B and C) of seven rats each. Group A rats served as control and received normal saline orally. Group B rats were treated with cadmium chloride 2.5 mg/kg bwt subcutaneously while group C rats were pre-treated orally with extract of MO 500 mg/kg bwt before treating with cadmium chloride 2.5 mg/kg bwt subcutaneously. The rats were treated every other day regularly for three weeks. Blood samples were collected by ocularpuncture and sera used for estimations of gammaglutamyl transferase (GGT), protein, bilirubin, and urea levels. Animals were sacrificed by cervical decapitation and liver tissues were harvested and homogenized. The supernatant obtained was used to estimate GGT, protein and bilirubin levels. The liver GGT, and protein levels in rats treated only with cadmium were significantly ($p<0.05$) increased. However, administration of methanolic extract of MO one hour to cadmium exposure ameliorated the toxic effect of cadmium. The study concluded that methanolic extract of *Moringa oleifera* showed appreciable potentials in protecting against cadmium-induced liver and kidney dysfunction in rats.

13.2 Brain, Liver and Kidney

Manoj Kumar *et al*. [15] *M. oleifer* leaves and seeds are reported to have ameliorative effects against metal toxicity. In the present investigation, *M. oleifera* seed powder was tested against lead-induced oxidative stress and compared against meso-2, 3-dimercaptosuccinic acid (DMSA) treatment. Male Wistar rats (100-120 g) were divided into four groups: control (2000 ppm of sodium acetate for 2 weeks), exposed (2000 ppm of lead acetate for 2 weeks), *Moringa* treated (500 mg/kg for 7 days after lead exposure), and DMSA treated (90 mg/kg for 7 days after lead exposure). After exposure and treatment periods, rats were sacrificed and the brain was separated into cerebellum, hippocampus, frontal cortex, and brain stem; liver, kidney, and blood were also collected. The data indicated a significant ($p<0.05$) increase in reactive oxygen species (ROS), lipid perioxidation products (LPP), total protein carbonyl content (TPCC), and metal content of brain regions, liver, and kidney in the exposed group compared with their respective controls. In the blood, delta-amino levulinic acid dehydratase (ALAD) activity, RBC, WBC, hemoglobin, and hematocrit showed significant ($p<0.05$) decrease on lead exposure. However, administration of *M. oleifera* restored all the parameters back to control, tissue-specifically, and also showed improvement in restoration better than DMSA treatment, indicating reduction of the negative effects of lead-induced oxidative stress.

13.3 impact on Kidney liver and Brain tissues

Hassan *et al*. [16] were made the particular investigation to observe the effects of *Moringa oleifera* 80% methanol leaf extract on the histological architecture of kidney, liver and brain tissues. Fifteen (15) rats were randomly divided into three (3) with five rats per group. Rats were exposed to 2000 mg/kg, 1000 mg/kg and 500 mg/kg of *Moringa oleifera* extract per os (p.o) along with the control group that was placed on commercial diet. There was no observed mortality

in all experimental rats but there is deleterious effect in brain, liver and kidney in those that were exposed to higher doses especially the 2000 mg/kg. It's therefore concluded that higher dose of *Moringa oleifera* is toxic while moderate doses is safe to most vital organs especially brain, liver and kidney. In their study authors realised that there is need for further investigation to identify the phytochemical constituents that are responsible for the toxic effects.

14. Toxicological evaluation

The toxicological evaluation of *M. oleifera* was studied by Ademola *et al*. [17]. They conducted to investigate toxicological effects associated with prolonged consumption of *M. oleifera* leaves as a beverage. In this study, thirty rats were used in this study. They were grouped into five groups of six rats. Rats in group I received 2 mL/kg body weight (b.w.) of corn oil (vehicle). Animals in groups II, III, IV and V received 50, 100, 200 and 400 mg/kg b.w. of methanolic extract of *M. oleifera* (MEMO) for 8 weeks. They observed that there was a significant ($p<0.05$) increase in serum total protein and globulin in a dose-dependent manner. Rats that received MEMO at 200 and 400 mg/kg b.w. showed a significant ($p<0.05$) increase in serum ALT, AST, BUN and creatinine which pointed to hepatic and kidney damage. All experimental animals that received MEMO had a significant ($p<0.05$) increase in body weight in a dose-dependent manner. They confirm for the first time that chronic administration of *M. oleifera* leaves might predispose to hepatic and kidney damage.

15. Conclusion

M. oleifera is a cheap and easily available plant. It is a rich source of essential amino acids, phytochemicals and vitamins. In traditional medicine, it has so many well-known health benefits including Nephro protective activities. *M. oleifera* along with other active herbal extract combinations gives useful nephroprotective results. In spite of having great biological importance of *M. oleifera* on Nephro protective activity and there was a limited research has been done so far. *M. oleifera* based medicine would be an excellent protective agent against several risk factors associated with kidney diseases. There is a need of further investigation about this plant and it's potentiality on Nephro protection.

16. Acknowledgement

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17. Conflict of interest statement

We declare that we have no conflict of interest.

18. References

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