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# Molecular Changes Associated with Parsley and/or One Alpha Treatment of Renal Dysfunction Induced Experimentally in Rats

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**Abstract**

*This study was done to investigate the ameliorative effect of Parsley extract and one-alpha on KBrO3 induced nephrotoxicity in rats. Fifty rats were classified into 5 groups: Group 1 :( normal control group): rats injected once with normal saline I/P. Group 2: (nephrotoxic group) rats injected with single dose of KBrO3 (130 mg/kg B.wt, I/P). Group 3:(parsley treated group) rats received KBrO3 then after 3 days treated with parsley extract at a dose of (400 mg/kg.b.wt /day/6 weeks ) orally. Group 4 (one alpha treated group) Rats injected once with KBrO3 at a dose of ( 130 mg/kg B.wt, I/P) and after 3 days treated with one-alpha at a dose of (0. 2µg /day / 6 weeks.) orally. Group 5: (parsley extract + one alpha treated group) Rats injected once with by KBrO3 at a dose of ( 130 mg/kg B.wt, I/P) and after 3 days treated with both of parsley extract (400mg/kg b.wt/day/6 weeks) and one – alpha (0.2µg/ day / 6 weeks) orally. Nephrotoxic group showed a significant increase in serum creatinine activity urea and uric acid concentration when compared with normal control in addition to significant increase of renal tissue NOs, TNF- α, L-AGAT and caspase-3 concentration, on the other hand, serum 1-α hydroxlase activity showed significant decrease of nephrotoxic group in comparison to normal control. Treatment with parsley or one alpha or both revealed return of these parameters to nearly normal level. Parsley or one alpha may thus be used as a potentially promising agent to inhibit nephrotoxicity and may be a novel natural products for management of nephrotoxicity.*

**Abbreations:** *KBrO3: Pottasium Bromate,* ***TNF-α:*** *Tumour Necrosis Factor alpha,* ***L-AGAT:*** *L-Arginine: Glycine Amidinotransferase,* ***Caspase****: cysteine-aspartic proteases,* ***NOS:*** *nitric oxide synthase*

**Keywords:** *KBrO3, nephrotoxicity, parsley, one alpha, NOs, TNF- α, L-AGAT.*

## 1. INTRODUCTION

Kidney is an important organ within the human body. They guard blood volumes, filter the blood to form urine, regulate water, electrolytes, acid/base balance, produce some hormones and participate in metabolism of others. At rest an estimated 20% of cardiac output flows through the kidney where they are filtered and reconditioned, Nephrotoxicity is toxicity in kidneys due to poisonous effect of some substances such as toxic chemicals and medications that affect renal function by more than one way **(Eman N.S, 2019)**.

Nephrotoxicity caused by KBrO3) Potassium bromate (seems to be attributed to the oxidative stress caused by generation of reactive oxygen species **(Mahmoud *et al*., 2015)**.

The toxic effects of KBrO3 are attributed to its ability to induce oxidative stress (OS) leading to enhanced production of reactive oxygen species (ROS) which are important mediators of tissue injury, The oxidative stress of potassium bromate (KBrO3) induces injuries in different tissues and organs through reaction with proteins, lipids and nucleic acids. Production of reactive oxygen species (ROS) due to KBrO3 causes many diseases, such as cancer, ageing and diabetes mellitus, and renal cell damage **(Rahmat *et al*., 2012) (Khan *et al*., 2004)**.

The oxidative stress induced by KBrO3 far exceeds the cellular antioxidative defense capacity leading to marked nephrotoxicity in humans and animals and carcinogenicity in experimental animals. Therefore, the search for safe and effective synthetic and/or naturally occurring ROS scavengers and antioxidants is of major clinical importance **(Ahmad *et al*., 2012)**.

Medicinal plants and herbs play an important role in the prevention and treatment of kidney diseases. Parsley, is a bright green biennial

shrub widely used traditionally as a food additive and herbal remedies for many ailments **(Mohamad *et al.*, 2009)**. It has been employed in the food, pharmaceutical, perfume, and cosmetic industries **(Azab *et al.*, 2019)**.

Parsley (Petroselinum crispum), which is a leafy vegetable belongs to the family Umbelliferae (Apiaceae) is known as a rich source of vitamins and minerals especially vitamins C, A and E; iron, calcium, phosphorus and manganese as well as many active chemical compounds. Therefore, it has many medicinal uses, the leaves are diuretic and are giving during the urinary tract infection while the fruit has a diuretic effect too in low doses but higher doses increase the contractility of the intestinal smooth muscles, bladder and uterus **(Yousuf *et al.*, 2014).**

Parsley leaves are rich in Apigenin and its glucosidal flavonoids that were found to possess anti-inflammatory especially for renal inflammation; antioxidant and anticancer activities **(Papay *et al.*, 2012)**. In addition, the aqueous extract of parsley reduced the number of calcium oxalate deposits and therefore parsley can be used for kidney and bladder stones **(Saeidi *et al.*, 2012) (Huang *et al.*, 2013)**.

Alfacalcidol (1α (OH)D3) is a synthetic vitamin D3 analogue, exerting full biological activity of calcitriol, it display immunomodulatory activities providing a beneficial effect in immunoinflammatory diseases, it have potent anti-inflammatory, antiproliferative, prodifferentiation and antibacterial properties in various cells and tissues **(Tatjana *et al.*, (2016)**.

The active D-hormone analog alfacalcidol is already hydroxylated at the crucial 1 -position. After intestinal resorption it will be automatically hydroxylated in the liver at the 25-position to become 1, 25-dihydroxycholecalciferol. That means alfacalcidol is a prodrug of the D-hormone and bypasses the strongly regulated activation in the kidney. The therapeutic potential of this interesting prohormone in osteoporosis is still today often underestimated. Due to pleiotropic effects on a number of target tissues its **(Ring and Schacht, 2017)**.

Therefore, this work aimed to evaluate using natural product as (parsley extract) alone and in combination with alfacalcidol treatment on KBrO3 induced nephrotoxicity in rats via estimation of molecular gene expression.

## 2. Materials and Methods

### 2.1. Experimental Animals

All experiments were approved by the Ethical Committee of Faculty of Veterinary Medicine, Benha University. Fifty male Wistar albino rat (150 ± 20g) were supplied by the animal house of Faculty of Veterinary Medicine, Benha University, Egypt. They were acclimatized in our animal facility for one week under controlled environmental conditions before the experiment. Fresh daily supplies of food and tape water were served ad libitum.

### 2.2. Chemicals and Antioxidant

All chemicals were of analytical grade and obtained from standard commercial suppliers. The antioxidant and chemicals used in the present study were:

**1-**Potassium bromate (KBrO3) was purchased from El-Gomhorya Company, Cairo, Egypt for induction of nephrotoxicity.

**Dose**: single dose of potassium bromate 130 mg/kg.b.wt., **(Khan and Sultana, 2004)**.

**2-** One–Alpha was purchased from MINAPHARM company concentration is (1µg) capsules.

**Preparation**: capsule dissolved in a vehicle (medium-chain triglyceride, MCT), and diluted to a given concentration) and was given orally at. **(Shiraishi *et al.*, 2000)**

**Dose**: 0.2 µg/kg b.w orally.

**3- Natural product (parsley):**

**Preparation of aqueous parsley extract:**

Freshly prepared parsley leaves extract were done at a dose of 400mg/kg by decoction **(Hemmes, 1992).**

### 2.3. Experimental Design

Fifty Rats were classified into 5 groups (10 each) as follow:

- **Group 1: (normal control group):** normal rats injected I/P once with saline and act as control.
- **Group 2: (nephrotoxoic group):** Rats are injected with single dose of potassium bromate (130 mg/kg B.wt, I/P).
- **Group 3: (parsley extract treated group):** Rats injected once with by KBrO3 at a dose of (130 mg/kg B.wt, I/P) and after 3 days administrated parsley

extract at a dose of (400 mg/kg b.wt /day / 6 weeks) orally.

- **Group 4: (one-alpha treated group):** Rats injected once with by KBrO3 at a dose of (130 mg/kg B.wt, I/P) and after 3 days treated with one-alpha at a dose of (0.2µg /day / 6 weeks.) orally.
- **Group 5: (one-alpha + parsley extract treated group):** Rats injected once with by KBrO3 at a dose of (130 mg/kg B.wt, I/P) and after 3 days treated with parsley (400mg/kg b.wt/day/6 weeks) and one – alpha (0.2µg/ day / 6 weeks) orally.

### 2.4. Sampling

*2.4.1. Blood samples*

- Blood samples were collected twice after overnight fasting from retro- orbital plexus of eyes after 3 and 6 weeks from onset of treatment, blood samples were collected on clean tubes, then centrifugated at 2500 r.p.m for 15 minutes. Clean and sterile serum were aspirated in epindorf and kept in deep freeze till biochemical examination to check of urea **(Tietz, 1976)**, uric acid **(Zhao *et al.*, 2006),** creatinine **(Henry, 1974)**, and 1-α hydroxlase Hewison, 2000.

*2.4.2. Tissue sample*

- Rats were sacrificed by cervical dislocation, stomach was opened and viscera was out then, both kidneys were isolated, washed with saline and blotted between filter papers.

- Two kidneys was preserved in a deep freezer at 80 c in plastic bags for histopathological examination to check cytogenetics and PCR analyzes: TNF- α (Tumor necrosis factor), L-AGAT (L-arginine –glycine amidinotransferase), caspase 3, NO synthases was measured by **(Livak and Schmittgen, 2001)**

### 2.5. Statistical Analysis

The results were expressed as mean ± SE using SPSS software program version 16 (SPSS© Inc., USA). The data were analyzed using one-way ANOVA to determine the statistical significance of differences among groups. Duncan's test was used for making a multiple comparison among the groups for testing the inter-grouping homogeneity. Values were considered statistically significant when $p<0.05$.

## 3. RESULTS

The obtained results presented in table (1) revealed that KBrO3-induced nephrotoxicity in rats resulted in a significant increase of serum creatinine activity, urea and uric acid concentration. While serum 1-α Hydroxylase showed significant decrease when compared with normal control rats. Parsley extract treatment showed significant decrease in serum creatinine activity and non significant decrease in serum urea and uric acid concentration while non significant incease in serum 1-αhydroxylase activity. Treatment with one-alpha resulted in significant decrease in serum creatinine activity and urea concentration in comparison with nephrotoxic group

Treatment with both parsley extract and one – alpha showed significant decrease of all parameters when compared with nephrotoxic group

**Table1.** *Effect of parsley extract, one alpha or both treatment on serum urea, uric acid concentration, creatinine and 1-α Hydroxylase activites in KBrO3-induced nephrotoxicity in rats*

| Experimental Group | Urea (mg/dl) | | Uric acid (mg/dl) | | Creatinine (mg/dl) | | 1-α Hydroxylase (pg/mL) | |
|---|---|---|---|---|---|---|---|---|
| | 3 Weeks | 6 Weeks | 3 Weeks | 6 Weeks | 3 Weeks | 6 Weeks | 3 Weeks | 6 Weeks |
| **Control group** | 17.05 ± 1.56 $^{c}$ | 18.94 ± 1.73 $^{c}$ | 1.74 ± 0.34 $^{c}$ | 1.64 ± 0.32 $^{b}$ | 1.02 ± 0.22 $^{b}$ | 0.95 ± 0.20 $^{b}$ | 62.45 ± 3.18 $^{a}$ | 56.78 ± 2.90 $^{a}$ |
| **Nephrotoxic group** | 63.60 ± 7.30 $^{a}$ | 53.00 ± 6.08 $^{a}$ | 4.15 ± 0.69 $^{a}$ | 3.46 ± 0.58 $^{a}$ | 5.80 ± 1.65 $^{a}$ | 4.97 ± 1.41 $^{a}$ | 20.80 ± 3.95 $^{b}$ | 26.00 ± 4.93 $^{c}$ |
| **Parsley extract treated group** | 47.10 ± 6.24 $^{ab}$ | 39.25 ± 5.20 $^{ab}$ | 3.22 ± 0.28 $^{ab}$ | 2.68 ± 0.23 $^{ab}$ | 2.03 ± 0.41 $^{b}$ | 1.74 ± 0.35 $^{b}$ | 24.25 ± 2.55 $^{b}$ | 30.31 ± 3.18 $^{bc}$ |
| **One alpha treated group** | 41.03 ± 3.47 $^{b}$ | 34.19 ± 2.89 $^{b}$ | 3.08 ± 0.31 $^{ab}$ | 2.56 ± 0.26 $^{ab}$ | 2.01 ± 0.37 $^{b}$ | 1.73 ± 0.32 $^{b}$ | 23.69 ± 2.54 $^{b}$ | 29.61 ± 3.18 $^{bc}$ |
| **Parsley extract + One alpha treated group** | 34.93 ± 6.24 $^{b}$ | 29.11 ± 5.20 $^{b}$ | 1.97 ± 0.38 $^{bc}$ | 1.64 ± 0.32 $^{b}$ | 1.47 ± 0.24 $^{b}$ | 1.26 ± 0.20 $^{b}$ | 32.05 ± 4.40 $^{b}$ | 40.06 ± 5.50 $^{b}$ |

*Data are presented as (Mean ± S.E). S.E = Standard error.*

*Mean values with different superscript letters in the same column are significantly different at (P<0.05).*

The obtained results presented in table (2) revealed a significant up regulation of renal tissue TNF-α, L-AGAT, Caspase-3, NOS gene expression of KBrO3-induced nephrotoxicity in rats when compared with normal control rats. Treatment with parsley extract or one alpha or their combination revealed non significant down regulation of renal TNF-α and renal L-AGAT when compared with nephrotoxic group.

Combination treatment of parsley extract and one – alpha showed significant down regulation of L-AGAT, renal caspase 3 and NOS when compared with nephrotoxic group

**Table2.** *Effect of parsley, one alpha or both treatments on renal tissue TNF-α, L-AGAT, Caspase-3, NOS gene expression in KBrO3-induced nephrotoxicity in rats*

| Experimental Group | Renal TNF-α gene expression | Renal L-AGAT gene expression | Renal Caspase-3 Immunohisto-chemical expression | NOS (ng/mL) | |
|---|---|---|---|---|---|
| | | | | 3 Weeks | 6 Weeks |
| **Control group** | 1.15 ± 0.09 [b] | 6.47 ± 1.44 [b] | 0.06 ± 0.01 [b] | 60.13 ± 2.40 [d] | 54.67 ± 2.19 [d] |
| **Nephrotoxic group** | 1.89 ± 0.29 [a] | 16.97 ± 2.89 [a] | 0.17 ± 0.03 [a] | 108.50 ± 2.26 [a] | 98.64 ± 2.05 [a] |
| **Parsley extract treated group** | 1.59 ± 0.12 [ab] | 11.53 ± 2.02 [ab] | 0.11 ± 0.01 [ab] | 90.50 ± 4.14 [b] | 82.28 ± 3.77 [b] |
| **One alpha treated group** | 1.51 ± 0.16 [ab] | 11.56 ± 2.02 [ab] | 0.11 ± 0.02 [ab] | 74.65 ± 1.41 [c] | 67.86 ± 1.28 [c] |
| **Parsley extract + One alpha treated group** | 1.31 ± 0.12 [ab] | 8.72 ± 2.03 [b] | 0.09 ± 0.02 [b] | 69.82 ± 1.37 [c] | 63.47 ± 1.25 [c] |

## 4. DISCUSSION

Kidney dysfunction is becoming a major public health problem. Previous investigation has shown that acute renal injury and chronic kidney disease are major contributory factors to mortality and morbidity in many developing countries **(Xu *et al.*, 2018)**. Some of the pathological conditions associated with renal dysfunction include acute kidney injury (AKI), chronic kidney disease (CKD), nephrotoxicity, renal hypoxia, and ischemic reperfusion injury. Several factors may be responsible for the development and progression of renal disease/dysfunction. Degenerative diseases such as cardiovascular disease, diabetes mellitus, hypertension, and dyslipidemia have been highlighted as causative factors of renal dysfunction **(Dennis and Witting, 2017).**

The obtained results presented in table (1) revealed a significant increase of serum urea, uric acid concentration and, creatinine activity. On the other hand serum 1-α Hydroxylase was significant decrease in KBrO3-induced nephrotoxicity in rats. These results are nearly similar to those reported by of **(Rezq, 2017)** who mentioned that, injection of KBrO3 resulted in a significant elevation in serum level of Urea, Uric acid concentration and creatinine activity which reflect the functional status of the kidneys, and detect diseases that affect the kidneys, such as acute kidney failure or end-stage renal disease (ESRD), this may be due to the toxic effect of potassium bromate that lead to renal failure. Furthermore, **(Afaf *et al.*, 2008)** discussed that, increased blood Urea, creatinine activity and Uric acid concentration are strongly related with renal damage.

**(Ali *et al.*, 2018)** reported that, Treatment of rats with KBrO3, significantly raised creatinine concentration. In addition, **(Khan *et al.*, 2012)** found that, High levels of urobilinogen, urea, creatinine, protein and albumin in urine reflect the kidney dysfunction and renal injuries induced by KBrO3 treatment **(Ogeturk *et al.*, 2005)**.

Moreover, **(Ahmad *et al.*, 2013)** found that, Administration of KBrO3 alone to rats produced a typical pattern of nephrotoxicity which was manifested by several fold increase in creatinine and BUN levels, as also reported previously **(Ahmad *et al*. 2012)**.

Treatment with parsley extract to KBrO3 induced nephrotoxicity in rats caused decrease in creatinine activity, urea and uric acid concentration. On the other hand increase in serum 1-α Hydroxylase of KBrO3-induced nephrotoxicity in rats. These results confirmed by **(Ayman *et al.*, 2015)** who found that, treatment with parsley extract showed a significant decreased in serum blood creatinine activity and urea, and uric acid concentration because parsley has a significant effect in improvement of renal disorders by reduction of generation of uremic toxins and aggregation with pathogenic bacteria.

Also, **(Abeer, 2015)** reported that, the oral ingestion of parsley extract has significantly reduced the pathologic concentration of various marker molecules of CKD by a way of probably

altering the composition of colon microbiota and generation uremic toxins. Thus, parsley extract serve as dietary supplement to maintain a natural metabolic and physiological renal mechanism and so it reduced nephrotoxicity. Furthermore, **(Khalil *et al.*, 2015)** revealed that, in an animal study- that, urea level, creatinine and uric acid levels were found to be significantly lowered by peppermint and parsley leaves oils supplementation with the same trend that recorded insignificant in these parameters. Also, **(Dhanarasu *et al.*, 2016)** reported that, The gentamicin induced neprotoxicity were confirmed by an increase in serum creatinine, uric acid, urea and blood urea nitrogen levels and severe proximal renal tubular necrosis, followed by deterioration and renal failure then these parameters were almost significantly normalized by oral administered parsley.crispum extracts and parsley.crispum leaves Decoction (groups III and IV) animals. This result is consistent with many previous studies done using other traditional plants **(El-Adawi *et al*., 2011)**.

Treatment with one-alpha to KBrO3 induced nephrotoxicity in rats caused decrease in creatinine, urea, uric acid. On the other hand increase in serum 1-α Hydroxylase of KBrO3-induced nephrotoxicity in rats. Our results agree with **(Shoben *et al.*, 2008)** who found that, treatment with alfacalcidol showed a significant decreased in serum blood urea, creatinine and uric acid and showed improvement of renal disorders. Also, **(Marianne *et al.*, 2004)** reported that, serum urea, creatinine, and uric acid values did not change and even tended to decrease. Glomerular filtration was found to increase insignificantly more markedly in the patients with renal failure in the early stages because alfacalcidol normalizes metabolic process and promotes recycling product exchange so it reduced nephrotoxicity. Alfacalcidol (1 a-hydroxy vitamin D3), a synthetic analogue of vitamin D, Alfacalcidol is hydroxylated in the liver to calcitriol (1, 25 dihydroxyvitamin D) and has a stable pharmacokinetic profile as it avoids serum peaks that may lead to elevated calcium levels and associated adverse effects **(Sachiyo *et al.*, 2010).**

The obtained results presented in table (2) revealed a significant up regulation in both increase of renal tissue **Caspase-3, TNF-α, L-AGAT, NOS gene expression** were observed after injection of potassium bromate.

These results agree with **(Rehman *et al.*, 2012)** who showed, up regulation in caspase-3 gene expression after injected of KBrO3. Increased ROS levels contribute to the apoptotic cell death every time they are generated in the context of the apoptotic process **(Liu *et al.*, 2010)**. Caspase-3 is one of the key executioners of apoptosis, as it can be activated in both intrinsic and extrinsic pathway. Activated caspase-3 has the potential of cleaving or degrading many key proteins such as fodrin, nuclear lamins and the nuclear enzyme poly (ADP ribose) polymerase (PARP).Also, **(Rehman *et al.*, 2012)** demonstrated that Caspase-3 activity was significantly up-regulated in KBrO3 treated group and pretreatment with B.monnieri significantly restored the Caspase-3 activity.

Furthermore, **(Ben Saad *et al.*, 2018)** found that, a concomitant significant increase in TNF-α and IL-6 mRNA in the cerebellum of KBrO3-treated mice. Cell surface death receptors transmit apoptotic signals initiated by specific ligands, such as Fas, TNF-α, and other related ligands which activate a caspase cascade.

Moreever, **(Ben Saad *et al*., 2018)** investigated that, TNF-α mRNA increased after KBrO3 treatment. Also, **(Ben Saad *et al*., 2018)** suggested that, KBrO3 induces oxidative stress in the cerebellum and causes lipid peroxidation, leading to a disruption of the cell membrane, loss of ATPase activity, decrease in antioxidant enzyme activity, and increase in inflammatory cytokine expression. Many studies have revealed oxidative stress to be the major cause of the inflammation stimulating the release of several proinflammatory cytokines. Redox status has also been shown to influence NF-kB regulation and hence several genes involved in cell transformation, proliferation, and angiogenesis. Although, relationship between ROS and NF-kB is complex, ROS are believed to be implicated as second messengers in the activation of NF-kB via TNF-a and other proinflammatory cytokines **(Reuter *et al.*, 2010)**

On the other hand, **(Memmedov *et al.*, 2020)** reported that, potassium bromate caused a decrease in caspase-3, caspase-8, caspase-9, cytochrome-c, TRAIL, and APAF levels in CCD 841 normal colon cells.

Amidinotransferase (transamidinase, L-arginine: glycine amidinotransferase, is an enzyme that

catalyses the first step in creatine synthesis primarily in the kidney and pancreas. The kidney is also the primary target organ for the toxic effect of potassium bromate **(Jelenka and Dusan, 2004).**

Treatment with parsley extract or Alfacalcidol or both to KBrO3 – induced nephrotoxicity in rats caused, non significant down regulation in both **Caspase-3,TNF-α, L-AGAT, NOS gene expression** when compared with KBrO3 – induced nephrotoxicity non treated group.

These results are recorded with **(Takrooni *et al.*, 2019)** who reported that, Co-administration of parsley leaves extract with CsA ameliorate the level of 8-OHdG and caspase-3. It could be stated that parsley leaves extract provided a significant protection against CsA-induced renal DNA damage and apoptosis.This outcome was in agreement with **(Sharma *et al.* 2014)** who found that plant flavone apigenin (main constituent of parsley) binds to nucleic acid bases and decrease oxidative DNA damage in prostate epithelial cells. This finding supports that parsley suppressed the DNA damage and have an anti-apoptotic role in kidney cells. This property helps to prevent kidney from free radical stress. Cell death is the final phase of cellular damage; it happens by apoptosis. Caspases are cysteine-aspartyl proteases which play an important role in apoptosis. Caspase-3, in particular, is the most important effector of caspases widely studied **(Pandurangan *et al.*, 2014)**. These results were in agreement with Wu et al (2018) who study the mechanism of Cyclosporin A nephrotoxicity. As CsA increase the level of NF-κB and TNF-α, these increases were attenuated by treatment with parsley leaves extract. These results suggest that the parsley leaves extract modulates the expressions of NF-κB and TNF-α; the results are in agreement with **(Malik *et al.* 2017)**. Using apigenin essentially reduce the levels of TNF-α, IL-1β, and TGFβ in rat's kidneys. Moreover, apigenin inhibited the activations of CYP2E1, phosphoNF-κB p65 and phospho-P38 MAPK in cisplatin-induced renal damage **(He et *al.*, 2016)**. Apigenin belongs to the flavone subclass of flavonoids and is abundant in parsley leaves extract, which confirm the anti-inflammatory effect of Parsley leaves extract.

## 5. Conclusion

The obtained results suggested that treatment with parsley extract or/and one-alpha led to improvment of renal cells functions and can reduce the nephrotoxic effect of pot. bromate which revealed by apparent reduction in serum creatinine activity, urea, uric acid, renal tissue **Caspase-3, TNF-α, L-AGAT, NOS gene expression**. On the other hand elevate in serum1-α Hydroxylase level. It could be concluded with using both combination of parsley extract as a cofactor with one alpha in treatment of renal dysfunction.

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