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Biochemical Evaluation of Parsley with or without Alfacalcidol on treatment of Renal Dysfunction Experimentally Induced by Potassium Bromate

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Abstract

This study was done to investigate the ameliorative effect of parsley extract and/or alfacalcidol 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 extract 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 (alfacalcidol treated group) rats injected once with KBrO3 at a dose of (130 mg/kg B.wt, I/P) and after 3 days treated with alfacalcidol at a dose of (0. 2µg /day / 6 weeks.) orally. Group 5:(parsley extract plus alfacalcidol 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 alfacalcidol (0.2µg/ day / 6 weeks) orally. Our results showed that rats injected with pot. Bromate revealed a significant increase in serum creatinine activity, urea, uric, and potassium concentration in addition to increase of MPO, NO and MDA concentration in renal tissue on the other hand, a significant decrease in serum sodium concentration and renal tissue (SOD and GPx) were observed. Treatment with parsley extract or alfacalcidol or their combination revealed decrease in serum creatinine, urea, uric, potassium, MPO, NO renal tissue MDA, on the other hand, significant increase in serum sodium level and renal tissue SOD, GPx activities were observed. Parsley extract or alfacalcidol act as a potentially promising agent used to treat nephrotoxicity. Parsley extract may be a novel natural products for management of nephrotoxicity.

Keywords: *KBrO3, nephrotoxicity, parsley, alfacalcidol, Na, MPO, antioxidants*

1. INTRODUCTION

The Kidney is a vital organ in the body which purifies the blood by excreting nitrogenous waste and toxic components through the urine. It helps maintaining electrolyte balance, homeostasis, blood pressure **(Pandit *et al.*, 2018).**

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, 2019**).

Nephrotoxicity is a disorder whose primary feature is impairment of the normal functions of the kidney. The clinical manifestations of toxic nephropathy vary from a mild reduction in renal function to a sever progressive toxicity culminating in end-stage renal disease as hematuria and proteinuria **(Blowey, 2005).**

Potassium bromate (KBrO3) is widely used as a food additive and is a major water disinfection by-product. Several studies have shown that it causes nephrotoxicity in humans and experimental animals, it is an oxidizing agent that exists as a white crystal powder **(Opara *et al.*, 2018).**

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**).

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, a bright green biennial shrub is widely used traditionally as a food additive and herbal remedies for many ailments (**Mohamad *et al.*, 2009**). Parsley (Petroselinum crispum) is a member of Apiaceous family that has been employed in the food, pharmaceutical, perfume, and cosmetic industries (**Azab *et al.*, 2019).**

Parsley (Petroselinum crispum,) is used as a culinary, garnishing and medicinal herb in the Mediterranean region of Southern Europe **(Dorman *et al.*, 2011)**. Parsley extract was reported to produce a diuretic effect and good antioxidant activity **(Kreydiyyeh and Usta, 2002).** 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 an analog of vitamin D3, alfacalcidol was the first vitamin D analog produced in the 1970, available for treatment of renal osteodystrophy in all stages of chronic kidney disease. **(Brandi, 2017)**

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 has potent anti-inflammatory, antiproliferative, prodifferentiation and antibacterial properties in various cells and tissues **(Tatjana *et al.*, 2016**).

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 some biochemical parameters.

2. MATERIALS AND METHODS

2.1. 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- Alfacalcidol (1µg) capsules under trade name (One Alpha) was purchased from Minapharm company, Egypt

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

Dose: 0.2 µg/kg b.w orally

3- Parsley Extract:

Preparation of aqueous parsley extract:

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

2.2. Experimental Animals

All experiments were approved by the Ethical Committee of Benha University. Fifty male Wistar rat (150 ± 20g) were supplied by the animal house, 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.

2.3. 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**: **(nephrotoxic group):** rats are injected with single dose of potassium bromate (130 mg/kg B.wt, I/P).
- **Group 3**: **(parsley extrac treatedt group):** rats injected once with potassium bromate 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**: **(alfacalcidol treated group):** rats injected once with potassium bromate 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**: **(alfacalcidol + parsley extract treated group):** rats injected once with potassium bromate 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 alfacalcidol (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 centrifuged at 2500 r.p.m for 15 minutes. Clean and sterile serum were aspirated in epindorf and kept in deep freeze till biochemical examination of urea **(Tietz, 1976)**, uric acid **(Zhao *et al.*, 2006)**, creatinine **(Henry, 1974)**, Sodium **(Natelson, 1957)**, Potassium **(Terri and Sesin 1985)**, MPO (**Nishikimi *et al.*, 1972)** and nitric oxide **(Paglia and Valentine, 1967)**.
- Rats were sacrificed by cervical dislocation, then, dissected and both kidneys were removed, washed with saline and blotted between filter papers.
- Briefly, renal tissues were divided into appropriate portions, homogenized with a glass homogenizer in 9 volume of ice-cold 0.05 mM potassium phosphate buffer (pH7.4) to make 10% homogenates. The homogenates were centrifuged at 6000 r.p.m for 15 minutes at 4°C then the resultant supernatant were used for the determination of the following parameters: superoxide dismutase **(Mesbah *et al.*, 2004)**, glutathione-peroxidase (**Montgomery and Dymock, 1961)** and malondialdehyde **(Pulli *et al.*, 2013)**.

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 nephrotoxic group showed a significant increase of serum creatinine activity, urea, uric acid and K concentration. While serum Na concentration was decreased when compared with normal control. This elevation was significantly reduced after treatment with parsley or alfacalcidol or both.

Table1. *Effect of parsley, alfacalcidol or both treatment on serum urea, uric acid, Na, K concentrations and creatinine activity in KBrO3-induced nephrotoxicity experimentally in rats*

Experimental Group	Urea (mg/dl)		Uric acid (mg/dl)		Creatinine (mg/dl)		Sodium (mEq/L)		Potassium (mEq/L)	
	3 Weeks	6 Weeks	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}	141.87 ± 0.61 ^{a}	140.67 ± 0.67 ^{a}	4.13 ± 0.17 ^{c}	4.19 ± 0.15 ^{c}
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}	108.31 ± 0.56 ^{c}	113.00 ± 0.58 ^{d}	7.52 ± 0.28 ^{a}	6.27 ± 0.23 ^{a}
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}	109.38 ± 0.12 ^{c}	125.39 ± 0.70 ^{c}	7.02 ± 0.06 ^{b}	5.85 ± 0.05 ^{b}
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}	111.49 ± 0.26 ^{b}	126.72 ± 0.15 ^{c}	6.82 ± 0.05 ^{b}	5.68 ± 0.04 ^{b}
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}	112.53 ± 0.53 ^{b}	129.36 ± 0.32 ^{b}	6.56 ± 0.04 ^{b}	5.53 ± 0.03 ^{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 increase of renal tissue concentration of MPO, MDA and serum NO concentration. On the other hand decrease in renal tissue SOD and GPx activities were observed in KBrO3-induced nephrotoxicity in rats. Treatment with parsley extract or one-alpha or both resulted in significant decrease in these parameters.

Table2. *Effect of parsley, one alpha or both treatments on renal tissue MPO, MDA, SOD, GPx and serum NO concentrations in KBrO3-induced nephrotoxicity in rats*

Experimental Group	Myeloperoxidase (pg/mL)		MDA (nmol/g tissue)		SOD (mg/dL)		GPx (mg/g tissue)		NO (µmol/mL)	
	3 Weeks	6 Weeks	3 Weeks	6 Weeks	3 Weeks	6 Weeks	3 Weeks	6 Weeks	3 Weeks	6 Weeks
Control group	86.01 ± 2.40 ^{c}	93.83 ± 2.62 ^{c}	56.44 ± 2.96 ^{d}	60.47 ± 3.18 ^{c}	29.88 ± 4.12 ^{a}	27.75 ± 3.83 ^{a}	3.49 ± 0.31 ^{a}	3.27 ± 0.29 ^{a}	26.16 ± 2.30 ^{d}	24.53 ± 2.1 ^{c}
Nephrotoxic group	206.93 ± 34.76 ^{a}	172.44 ± 28.97 ^{a}	141.37± 10.44 ^{a}	113.09 ± 8.35 ^{a}	10.75 ± 2.19 ^{b}	12.90 ± 2.63 ^{c}	1.23 ± 0.17 ^{c}	1.53 ± 0.21 ^{b}	85.80 ± 4.14 ^{a}	71.50 ± 3.45 ^{a}
Parsley extract treated group	179.20 ± 22.39 ^{ab}	149.33 ± 18.66 ^{ab}	108.85 ± 5.05 ^{b}	87.08 ± 4.04 ^{b}	11.76 ± 1.93 ^{b}	14.12 ± 2.31 ^{bc}	1.35 ± 0.17 ^{c}	1.69 ± 0.22 ^{b}	67.53 ± 4.03 ^{b}	56.27 ± 3.36 ^{b}
One alpha treated group	154.27 ± 8.75 ^{ab}	128.56 ± 7.29 ^{abc}	116.09 ± 2.57 ^{b}	92.87 ± 2.05 ^{b}	12.79 ± 1.95 ^{b}	15.35 ± 2.34 ^{bc}	1.50 ± 0.23 ^{bc}	1.87 ± 0.29 ^{b}	57.22 ± 3.52 ^{b}	47.68 ± 2.94 ^{b}
Parsley extract + One alpha treated group	124.50 ± 7.63 ^{bc}	103.75 ± 6.36 ^{bc}	85.14 ± 5.47 ^{c}	68.11 ± 4.37 ^{c}	18.82 ± 1.96 ^{b}	22.58 ± 2.35 ^{ab}	2.14 ± 0.14 ^{b}	2.68 ± 0.18 ^{a}	40.55 ± 3.82 ^{c}	33.79 ± 3.18 ^{c}

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).

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 creatinine activity and urea, uric acid, K concentration. On the other hand decrease in serum Na of KBrO3-induced nephrotoxicity in rats. These results are nearly similar to those reported by **(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 evaluate 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 and uric acid are strongly related with renal damage.

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 injection**.** Also, (**Khan *et al.*, 2012)** revealed that KBrO3 injection caused marked increases in the serum levels of creatinine, BUN, total bilirubin and direct bilirubin, as reported previously **(Adewole *et al.*, 2007).** Moreover**, (Ahmad *et al.*, 2013)** found that, injection of KBrO3 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.*, 2012b).** hyponatremia is commonly defined as a serum sodium concentration below 135meq/L, but can vary to a small degree in different clinical laboratory because of nephrotoxicity **Eman, (2019)**

Furthermore, (**Rahmat *et al.*, 2012**) reported that, a hyperkalemia after the progression of renal failure in the experimental groups, indicated that this could be attributed to the decreased excretion of potassium. This decrease might have been coupled with both the loss of

intracellular potassium to extracellular fluid (due to tissues break down) and the intracellular buffering of retained hydrogen ions.

Treatment with parsley extract or alfacalcidol or both to KBrO3 induced nephrotoxicity in rats caused decrease in serum creatinine activity, urea, uric acid and potassium concentration. On the other hand an increase in serum Na level was observed when compared with to nephrotoxic group. 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, 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 nephrotoxicity 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. **(El-Adawi *et al.*, 2011)**

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. In addition, (**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 α-hydroxy vitamin D3), a synthetic analogue of vitamin D, 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 increase of renal tissue MPO, MDA and serum NO. On the other hand decrease in renal tissue antioxidants including SOD and GPx of KBrO3-induced nephrotoxicity in rats when compared with normal control. Our results agree with (**Rahmat *et al.*, 2012**) who reported that, depletion of antioxidant responses has been implicated in the kidney toxicity with KBrO3. The activities of antioxidant enzymes including SOD, CAT, GSHPx and GSH contents were significantly reduced while increased lipid peroxidation in rat. Furthermore, **(Watanabe *et al.*, 2002)** demonstrated that, KBrO3 is known to decrease the activity of an important antioxidative enzyme glutathione peroxidase, and to increase the formation of free radicals and reactive oxygen species: superoxide anion radical (O^-), Nitric oxide (NO) and peroxynitrite anion ($ONOO^-$) an increase of lipid peroxidation, in the rat kidney. Potassium Bromate is potent nephrotoxic agent that can mediate renal oxidative stress. It also enhances renal lipid peroxidation and hydrogen peroxide formation with reduction in renal antioxidant enzymes also, KBrO3 contributes to the cellular redox status and impairment of membrane protein activities in rats (**Rahmat *et al.*, 2012**).

Furthermore, (**Farombi *et al.*, 2002**) reported that, the decrease of antioxidant enzymes (SOD and CAT) are due to reactive oxygen species (ROS) produced by metabolism of KBrO3, KBrO3 depleted glutathione (GSH) content in various tissues which causes decrease in phase II metabolizing enzymes like glutathione peroxidase (GSH-Px) and a showed significantly increased renal, MDA. Moreover, KBrO3 causes significant alteration in antioxidant enzymes (SOD, GSH-Px , MDA, Myeloperoxidase) and oxidative DNA damage in kidneys of rats causing nephrotoxicity (**Khan and Sultana, 2005**). MPO activity from inflamed kidney was significantly greater than that from normal control tissue **(Malle *et al.*, 2003**)

Also, (**Neveen and Ismail, 2014**) reported that single intraperitoneal dose of KBrO3 induce oxidative stress in rats caused significant decreases in body weight gain and feed efficiency ratio. It also passively affected biomarkers of hepatorenal function, increased lipid peroxidation (MDA) and decreased the activity of antioxidant enzymes (GPX, SOD and CAT) in tissues. The production of free radicals is an integral part of body metabolism but imbalance results is oxidative stress. The excessive lipid peroxidation results in destruction of cellular membranes that could leads to cell death and degenerative disorders (**Sultan *et al.*, 2014).** Free radicals such as nitric oxide (NO) and superoxide ions are produced as second messengers, particularly by immune cells. Superoxide reacts rapidly with nitric oxide by nitric oxide synthase to produce peroxynitrite, whereas hydrogen peroxide (H_2O_2) slowly decomposes to the highly reactive hydroxyl radical. Both peroxynitrite and hydroxyl radicals are highly reactive oxidizing agents, capable of damaging proteins, lipids, and DNA (**Khan and Sultana, 2004**). Accordingly, (**Sultan *et al.*, 2012**) discussed that, there are a significant increase in myeloperoxidase, nitric oxide (NO), malondialdehyde (MDA) and showed a significant decreased in glutathione peroxidase (GPx), superoxide dismutase (SOD) and α- hydroxylase after injection with potassium bromate causing nephrotoxicity. Reactive oxygen species (ROS) may play a key role in KBrO3-induced nephrotoxicity by a significantly increased kidney MDA and NO levels while SOD, GSH and GPX levels significantly decreased, a single dose of potassium bromate at dose 130 mg/kg body weight intraperitoneal to induce renal toxicity lead to the induction of iNOS in rat kidneys resulting in an increased production of nitric oxide, leading to the formation of toxic peroxynitrite**.**

Moreover**, (Rehman *et al.*, 2012)** suggested that, KBrO3 exposure elevated the level of NO. However, pretreatment with B.monnieri prevented KBrO3 induced NO production in a concentration-dependent manner. Further, MPO is an enzyme formed mainly by polymorphonuclear leucocytes, and is linked to the degree of neutrophil infiltration in a given tissue **(Sehirli and Sener, 2010).** Following KBrO3 treatment, MPO activity was markedly elevated. This increase in MPO activity was significantly prevented by B.monnieri administration, which is consistent to the histopathopathological findings.

Treatment with parsley extract to KBrO3 induced nephrotoxicity in rats caused modulates antioxidant enzymes. Our results agree with **(Hijazi, 2017)** who showed that, treated parsley extract administration revealed, significant increase in kidney SOD, GPX and GST concentration and a significant decrease in kidney MDA.

Also, (**Khalisa *et al.*, 2017**) reported that, the administration of parsley extract has antioxidant properties. These due to that parsley and parsley oil contain active substances flavonoids, vitamins and the presence of some volatile oils, flavonoids contain antioxidant and influence immune system and anti-inflammatory in the laboratory and in animal models. Parsley leaves are rich of glucosidal flavonoids especially apigenin, which have anti-inflammatory activity for renal inflammation antioxidant. It contains many vitamins such as A, B, E and K, beta-carotene, manganese, iron, magnesium, potassium, sulfur, phosphorus, and sodium. It acts as an antioxidant, anti-rachitic, anti-infectious, diuretic, antiseptic, general stimulant and more **(Salehi *et al.*, 2019).** Furthermore**, (Abeer, 2015**) demonstrated that, oral administration of parsley extract caused a nephroprotective effect evident by significant decreases in serum levels of urea, creatinine and alkaline phosphatase enzyme in nephrotoxic rats. Parsley extract decreased serum sodium and potassium levels, tissue malondialdehyde (MDA) and increased activity of antioxidant enzymes. Parsley also increased urine volume and urinary excretion of Na+ and K+ electrolytes, denoting a diuretic activity and mitigated renal tubular necrosis induced by GM. The nephroprotective mechanisms of parsley could be attributed to inhibition of lipid peroxidation and enhancement of antioxidant enzymes activity. These results affirm the traditional use of parsley in folk medicine for the prevention of kidney diseases **(Afzal *et al.*, 2004**).

Treatment with alfacalcidol or both to KBrO3 induced nephrotoxicity in rats caused modulates antioxidant enzymes. These results are accorded with (**Tatjana *et al.*, 2016**) who reported that, the results revealed that alfacalcidol treatment, significantly reduced SOD activity and CAT activity in kidney disease. The activity of GPx was significantly lower in kidney disease before

treatment compared to controls. After therapy, GPx activity was restored to control levels, and GSH levels were significantly reduced. MDA levels in patients at the beginning of the study protocol, remained significantly elevated compared to controls **(Pantovic *et al.*, 2015**).

5. CONCLUSION

The obtained results suggested that treatment with parsley extract and alfacalcidol led to improve renal cells functions and can reduce the nephrotoxic effect of pot. bromate which revealed by apparent reduction in serum creatinine activity, urea, uric acid, K, NO concentration and renal MPO and MDA. On the other hand elevate in serum Na and renal tissue SOD and GPx level. It could be concluded with using both combination of parsley extract as a cofactor with alfacalcidol in treatment of renal dysfunction.

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