



Research Article

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Assessment of The Potential Role of Parsley (*Petroselinum Crispum*) Leaves Extract in Ameliorating Cyclosporin A- Induced Nephrotoxicity in Rats

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ABSTRACT

Background: Cyclosporin A (CsA) is immunosuppressive drug, but nephrotoxicity has been a major limiting factor. The present study aimed to evaluate the protective effect of parsley leaves extract and silymarin against nephrotoxicity induced by Cyclosporin A in rats. **Methods:** sixty male albino rats divided into six groups (n=10). Group I control group. Group II received single dose of CsA (50mg/kg weight, orally/day). Group III received parsley leaves extract (250mg/kg b.wt orally/day). Group IV received CsA and parsley leaves extract as in group II and III. Group V silymarin group received silymarin (100 mg/kg b.wt orally/day). Group VI received CsA and silymarin as in group II and V. Serum urea, uric acid and Creatinine were measured. Biomarkers of oxidative stress, antioxidant status, DNA damage, apoptosis and inflammatory-mediators had been measured in kidneys tissues. **Results:** Administration of Cyclosporin A to rats induced nephrotoxicity associated with a significant increase in serum urea, uric acid and Creatinine. Significant increase in MDA, NO, 8-OHdG, caspase-3, NF- κ B, TNF- α and significant decrease of GST in kidney tissues. Histopathological examination of animal treated with CsA exhibited disruption of normal kidney architecture; cellular disorganization, intracellular vacuoles, and formation of many inflammatory cells. Co-administration of parsley leaves extract or silymarin+ CsA attenuated all of the parameters near to the normal. However, pronounced attenuation was recorded in animals co treated with parsley leaves extract. **Conclusion:** The study suggested that the anti-oxidant and anti-inflammatory effect of parsley leaves extract may prevent CsA-induced nephrotoxicity via decreasing the oxidative stress, and repairing the histopathological changes.

Key words: Cyclosporin A, Nephrotoxicity, Parsley Leaves, Silymarin.

INTRODUCTION

Cyclosporin A (CsA) is a very strong immunosuppressant drug most exceedingly used in the management of organs transplantation and autoimmune diseases. It has many significant immunological properties that make it an appealing agent for immunosuppression [1]. It is found to inhibit both lymphocyte sensitization by allogeneic target cells in addition to in vitro cell-mediated lysis. In therapeutic doses, CsA causes diverse side effects including renal and liver toxicity [2].

Although nephrotoxicity mechanisms are not completely defined, there is a confirmation allude of the part of reactive oxygen species (ROS) in its pathogenesis. Intense CsA medication induces reversible decrease of the renal blood stream and glomerular filtration rate (GFR) that is identified with afferent arteriolar vasoconstriction. This might refer to increment vasoconstrictor variables for example, endothelin, thromboxane, angiotensin II or a diminish to vasodilators factors such as, prostacyclin and nitric oxide (NO). In addition, CsA block's mitochondrial calcium discharge prompting an increment to intracellular free calcium that might represent those CsA vasoconstriction impact [3].

Medicinal plants and herbs expect a paramount section that help avoidance or preventing kidney disorders. Parsley (*Petroselinum crispum*, Family: Umbelliferae / Apiaceae) is used in Mediterranean and Southern Europe as a culinary, garnishing and medicinal herb. Parsley leaves are rich of glucosidal flavonoids

especially apigenin, which have anti-inflammatory activity for renal inflammation in particular; antioxidant and anti-cancer activities [4]. It is important to note that the parsley contains more vitamin C than orange and some citrus fruits. 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 [5].

Bioflavonoid silymarin is the basic component of *Silybum marianum* (milk thistle). Silymarin has a number of pharmacological actions including antioxidant and immunomodulatory, anti-inflammatory, hepatoprotective, nephroprotective antibacterial, antimutagenic, antifibrotic, antiallergic, antithrombotic, antiviral and vasodilatory actions [6]. To the best of our knowledge, the nephroprotective impact about parsley leaves extract and silymarin against CsA prompted nephrotoxicity has not been scientifically investigated. The aim of the current study was to evaluate the nephrotoxic effect of Cyclosporin A administration on rat kidneys. The study also was extended to explore the potential impact of parsley leaves extract and silymarin as a protective agent with antioxidants, anti-inflammatory properties, in a trial to minimize or prevent the nephrotoxic effect of CsA on oxidative stress, inflammation, DNA damage and apoptosis. Histopathological studies of rat kidneys tissues were examined to confirm the biochemical investigations.

MATERIAL AND METHODS

Chemicals:

Silymarin (Silybon-70), Manufactured via Micro Labs Ltd. Cyclosporin A (Manufactured by Sandimmune, Neoral). Other chemicals and reagents used were of analytical grade.

Animals:

Sixty male rats (Wistar strain), weighing 180-200 g were used. The rats were acquired from Experimental Animal Care Center of King Fahad Medical Research Center, King Abdulaziz University. Animals were stored in special cages under standard stipulations (20–22 °C, humidity (60%) and 12 hour cycles of dark and light). Rats were supplied with standard pellet chow with free access to tap water for one week before the experiment for acclimatization. Animal handling was performed in accordance with the guidelines provided by the Experimental Animal Laboratory and approved by the Animal Care and Use Committee of the King Abdulaziz University, Faculty of Science.

Preparation of Parsley extracts:

The isolated leaves of parsley were washed with water to get rid of the dust and different outside materials. The extraction method was following the method of Albayrak et al. (2010) [7].

Experimental design:

The rats were separated into 6 groups, 10 rats per group:

Group I: Traditional animals have provided with feed and standard water ad libitum.

Group II: Nephrotoxic group, provided with CsA (50mg/kg weight, orally)[8], for ten successive days beside standard feed and water spontaneously.

Group III: Rats which was supplemented with parsley leaves extract (250mg/kg b.wt orally) [9].

Group IV: Treated with parsley leaves extract orally at the same time with CsA for 10 days as in group II and III.

Group V: Animals provided with silymarin orally (100 mg/kg b.wt) one time daily for 10 days [10].

Group VI: Animals provided with CsA as in group II in a line with silymarin as reference drug orally as in group V.

After the experiment was ended, rats were fasted night long (12-14 hours). Blood samples were collected in tubes for clotting and serum separation. The tubes were centrifuged at 2000 g for fifteen minute and therefore the isolated serum was saved at -20 °C. The animals were scarified under anesthesia and consequently, the kidneys were gathered, washed with cold saline and kept at -20°C. Specimens of the kidneys were removed out, the tubes were centrifuged at 2000 g for 15 minutes and the isolated serum was therefore stocked at -20 °C. in 10 percent formalin and used for histopathological studies.

Biochemical investigations:

Serum urea, uric acid and creatinine were assayed using commercial assay kits according to the manufacturer's instructions. In kidney tissues the existence of oxidative stress was detected by estimating levels of Malondialdehyde and Nitrite using assay kits as stated by the manufacturer's instructions. Antioxidant enzyme

Glutathione S-Transferase had been measured by assay kits following the instructions furnished by means of the manufactures. DNA damage and apoptosis were investigated by measuring 8-hydroxydeoxyguanosine (8-OHdG) and Caspase-3 using ELISA kits in step with the producer's instructions. The inflammatory-mediators, Nuclear Factor- κ B (NF- κ B), and Tumor Necrosis Factor- α (TNF- α) had been measured using the ELISA kits assay following the instructions furnished by means of the manufactures.

Histopathological examination:

Small pieces of kidneys immediately settled in 10% formaldehyde processed by using ethanol, after which installed in paraffin. The paraffin areas were cut into 5 μ m thick cuts and recolored with hematoxylin and eosin for microscopic examination [11].

Statistical analysis:

Data information was examined by comparing the values of the various treatment groups with the values of the individual controls. The results have been demonstrated as mean \pm SE. Significant differences between the values were evaluated using the one-way analysis of variance (ANOVA) followed by using Bonferroni's test post-ANOVA.

RESULTS

Biochemical investigations:

The levels of serum urea, uric acid and creatinine of control and other studied group were illustrated in Figure 1. The statistical analysis showed significant increase ($p \leq 0.01$) in the CsA group compared with control group. Significant difference ($p \leq 0.01$) was noticed between the CsA group and the other medicinal groups. Significant difference ($p \leq 0.01$) was determined between the parsley leaves extract + CsA group and the silymarin + CsA group.

The result of control and other studied groups of Nitrite, Malondialdehyde (MDA) and Glutathione S-Transferase (GST) levels in kidney tissues were illustrated in Figure 2. The statistical analysis showed significant increase ($p \leq 0.01$) in Nitrite and MDA levels in CsA group compared with control group. Significant difference was noticed ($p \leq 0.01$) between the CsA group and the other groups. Moreover, there was significant difference ($p \leq 0.01$) between the parsley+CsA group and the silymarin+CsA group. GST level showed significant decrease ($p \leq 0.01$) in CsA group compared with control group, and the level ($p \leq 0.01$) was ameliorated after treatment with medicinal plants compared with CsA group. In addition, there was significant difference ($p \leq 0.01$) between the parsley+CsA group and the silymarin+CsA group.

The result of kidney tissues 8-hydroxydeoxyguanosine (8-OHdG), Caspase-3(CASP3) Nuclear Factor- κ B(NF- κ B) and Tumor necrosis factor- α (TNF- α) levels of different studied groups were illustrated in Figures 3 and 4. The statistical analysis of 8OHdG, Caspase-3, NF- κ B and TNF- α levels showed significant increase ($p \leq 0.01$) between the control group and CsA group. While significant ($p \leq 0.01$) ameliorating effect was noticed in the medicinal plants treated groups compared with CsA group. Moreover, there was significant difference ($p \leq 0.01$) between the parsley+CsA group and the silymarin+CsA group.

Plant.

From all the above results the percentage of changes in the levels of the studied parameters showed elevation in the CsA groups and were ameliorated in parsley leaves extract and silymarin groups except in the GST that it showed an adverse response. Co-administration of parsley leaves extract with CsA was more pronounced than the percentage of change in co-treatment with silymarin as shown in table 1.

Table 1: Percentage of changes of all the studied parameters:

Parameters \ Groups	CsA	Parsley leaves extract + CsA	Silymarin+ CsA
Serum Urea	↑ 257%	↓ 38%	↓ 29%
Serum Uric Acid	↑ 110%	↓ 51%	↓ 19%
Serum Creatinine	↑ 278%	↓ 57%	↓ 49%
Nitrite	↑ 80%	↓ 36 %	↓ 26%
MDA	↑ 102%	↓ 42%	↓ 35 %
GST	↓ 64%	↑ 95%	↑ 37%

8-OHdG	↑ 240%	↓ 46 %	↓ 39%
CASP-3	↑ 206%	↓ 24%	↓ 15%
NF-κB	↑ 157%	↓ 31 %	↓ 15%
TNF-α	↑ 82%	↓ 26 %	↓ 19%

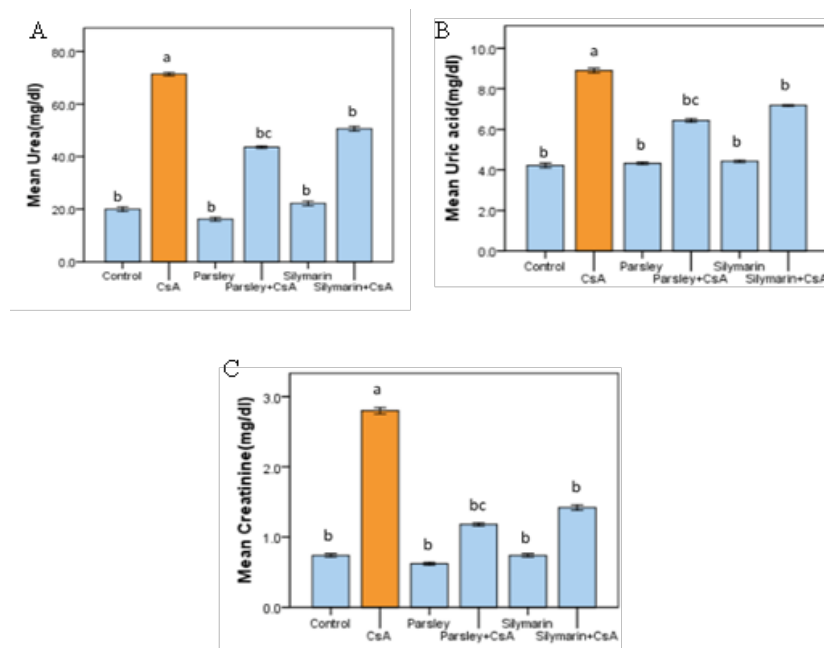


Figure 1: Effect of parsley leaves extract and Silymarin on urea (A), uric acid (B) and creatinine(C) levels (mg\dl) in CsA induced nephrotoxicity in rats. Data are presented as mean \pm S.E. of 10 rats
 a Statistically significant difference between the control group and CsA group.
 b Statistically significant difference between the CsA group and the other groups.
 c Statistically significant difference between the parsley leaves extract +CsA group and the silymarin+CsA group.

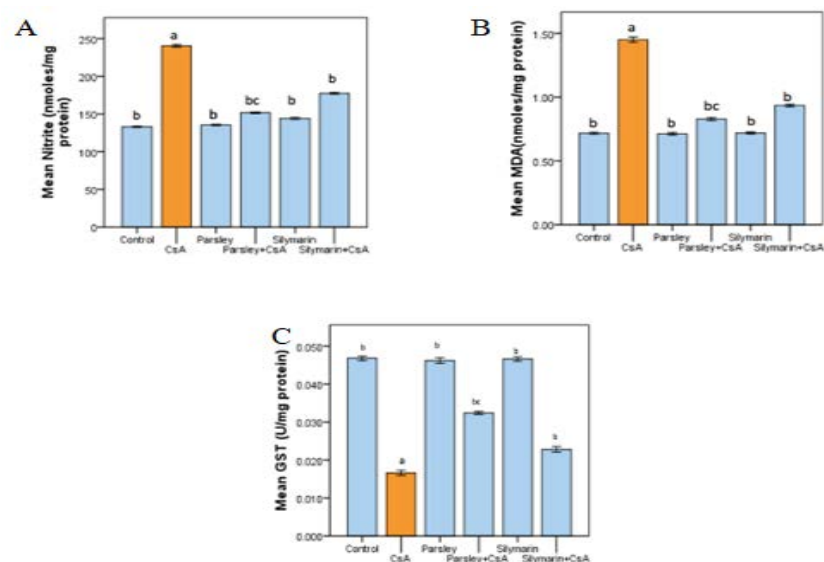


Figure 2: Effect of parsley leaves extract and silymarin on Nitrite (A) and MDA (B) levels (nmole/mg protein) (oxidative stress biomarkers) and GST (C) level (U/mg protein) (antioxidant biomarker) in CsA induced nephrotoxicity in rats. Data are presented as mean \pm S.E. of 10 rats.
 a Statistically significant difference between the control group and CsA group.
 b Statistically significant difference between the CsA group and the other groups.
 c Statistically significant difference between the parsley leaves extract +CsA group and the silymarin+CsA group.

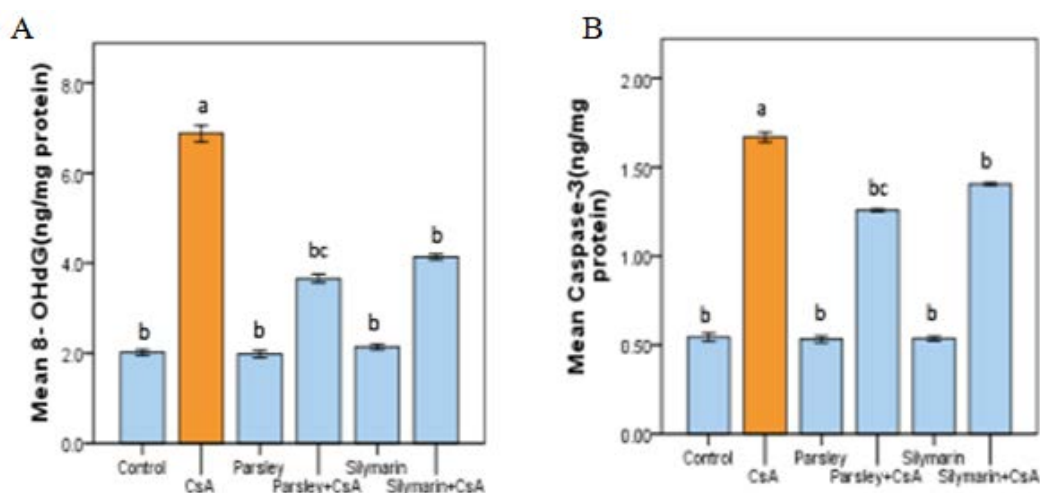


Figure 3: Effect of parsley leaves extract and silymarin on 8-OHdG (A) and Caspase 3 (B) levels (ng/mg protein) in CsA induced nephrotoxicity in rats. Data are presented as mean \pm S.E. of 10 rats
 a Statistically significant difference between the control group and CsA group.
 b Statistically significant difference between the CsA group and the other groups.
 c Statistically significant difference between the parsley leaves extract +CsA group and the silymarin+CsA group.

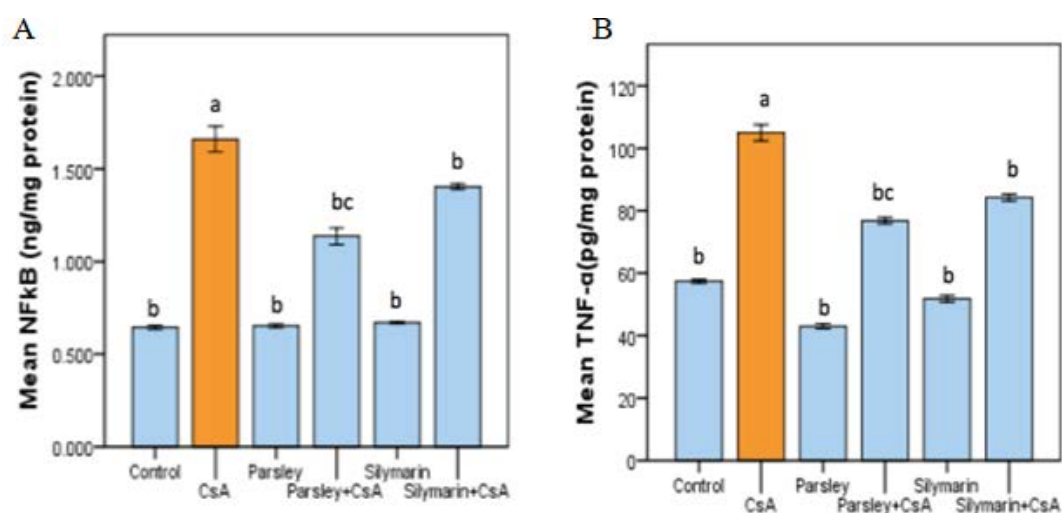


Figure 4: Effect of Parsley leaves extract and silymarin on NF-κB(A) and TNF-α (B) levels (ng/mg protein) in CsA induced nephrotoxicity in rats. Data are presented as mean \pm S.E. of 10 rats
 a Statistically significant difference between the control group and CsA group.
 b Statistically significant difference between the CsA group and the other groups.
 c Statistically significant difference between the Parsley leaves extract +CsA group and the silymarin+CsA group.

Histopathological study:

The histopathological examination of stained kidney sections of control and different studied groups were illustrated in Figure 5. Renal sections of the control group (A), revealed entirely normal histological features; each renal corpuscle was formed of a glomerular tuft of capillaries covered by Bowman's capsule. Proximal and distal convoluted tubules cells showed acidophilic cytoplasm. While renal sections of the CsA treated group exhibited disruption of normal kidney architecture; increased glomerular cellularity (B), destructed epithelium lining of Bowman's capsule, some tubules showed cell desquamation, others showed cellular disorganization, intracellular vacuoles, cast formation and many inflammatory cells. The renal sections of the parsley leave extract and silymarine treated groups (C, E) showed normal kidney histological structures. The renal sections of the CsA+ parsley leaves extract showed improvement of the morphological organization of renal cortex as in

(D). While, renal sections of the CsA+silymarine revealed regeneration of glomeruli and renal tubules but inflammatory cells infiltration still was found (F).

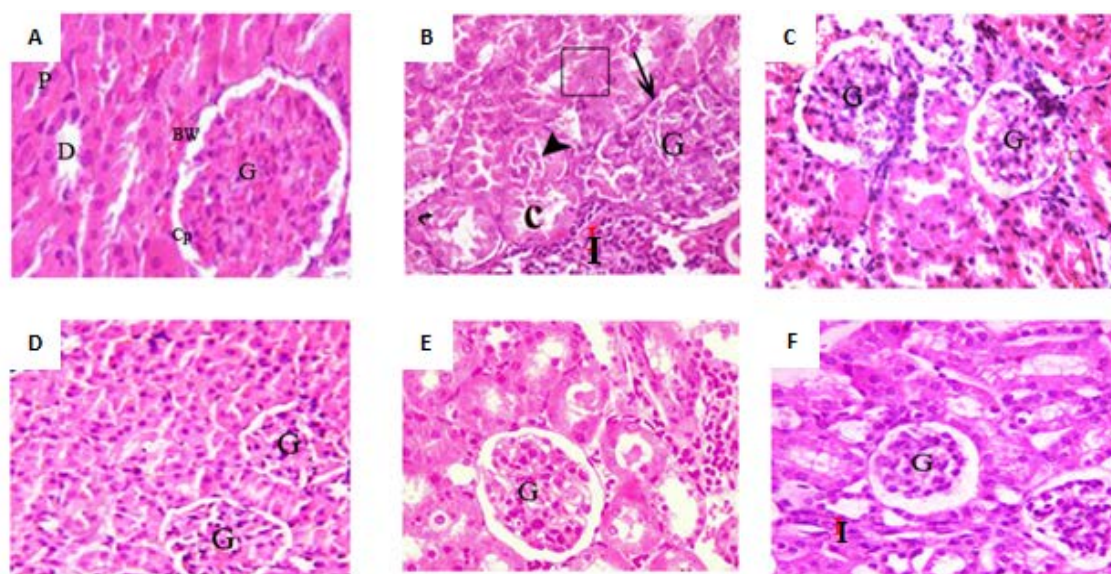


Figure 5: Histopathological findings in the kidney sections of CsA-induced and treated groups. Control, Parsley leaves extract and silymarin groups show normal kidney architecture (A, C and E) (X100). Kidney sections treated with CsA showed increased glomerular cellularity, destructed epithelium lining of Bowman's capsule (arrow), desquamation in some tubules (head arrow), tubular cellular disorganization (square) in other tubules, intracellular vacuoles (curved arrow), cast formation (c) and many inflammatory cells (I) in (B) (X100). The renal sections of the CsA+ parsley leaves extract showed nearly normal structure of the glomeruli and renal tubules in (D). (X100) While, renal sections of the CsA+silymarine showed nearly normal structure of the glomeruli and tubules and few inflammatory cells infiltrations (I) in (F). (X100)

DISCUSSION

Nephrotoxicity is a considerable clinical issue of CsA treatment, regardless of the fact of its suitable role in organ transplantation and in an assortment of immunologic disruption. Although a wide variety of mediators were suggested to represent for CsA-induced nephrotoxicity, the exact mechanism remains unclear. The accumulative data shows the role of ROS as one of the postulated mechanisms in the pathogenesis of CsA-induced nephrotoxicity [3].

In the current study the rats that received Cyclosporin A (CsA) only induced acute nephrotoxicity proved by a significant elevation in serum levels of (urea, uric acid and creatinine) compared with control group, which was in conjunction with Korolczuk et al. (2010) [12] and Elsayed et al. (2016) [13]. These findings were further evidenced by Hussein et al. (2013) [14] who attributed the elevation to the disturbances in kidney along with oxidative stress. Oxidative stress promotes vasoactive mediators that can affect renal functions directly. The increasing uric acid level clearly means that the CsA has significantly decreased the renal capacity and these increased levels of uric acid would possibly have combination with the kidney disease [15].

Co-administration of parsley leaves extract with CsA decreased significantly serum urea, uric acid and creatinine contrasted to CsA treated group. These results coincided with Mahmoud et al.; Elkhamisy et al (2015) [5, 16] using gentamicin-induced nephrotoxicity in rats. The parsley extract mechanism of action appears to be mediated by an inhibition of the Na⁺/K⁺ pump, which would lead to a decrease in Na⁺ and K⁺ reabsorption, leading to osmotic water flow into the lumen and diuresis. The diuretic effect of parsley owes to the presence of two ingredients, apiole and myristicin [17]. So, the decrease of creatinine, urea and uric acid in the outcomes results may be attributed to the diuretic impact of parsley.

Co-administration of silymarin to CsA ameliorated the kidney function, which is confirmed by reducing the increased levels of serum renal function (urea, uric acid and creatinine) compared to the CsA Group. Our result is consistent with Ghaznavi (2015) [18] who used gentamicin-induced nephrotoxicity which ameliorated with silymarin. Previous study on cyclophosphamide (CP) induced nephrotoxicity and showed a down regulation of

kidney function after treatment with *Mangifera indica* L and silymarin that can restore the kidney [19]. Thus the results confirmed the nephroprotective role of silymarin.

NO is a vasoactive component in kidney tissues that plays an important role in preserving vascular tone by suppressing the development of endothelin, a peptide that restricts blood vessels, nitric oxide and peroxynitrite, which mediates renal cell apoptosis leading to cell damage [20]. CsA administration may prompt iNOS in rat kidneys resulting of increased nitric oxide production, encouraging the development of dangerous peroxynitrite [21]. In the present study, rats that received CsA alone indicated a significant increase in nitrite level of renal tissue. This outcome was in agreement with França et al. (2014) [22] who stated that, the NO production was elevated when cells were pre-incubated with H89 followed by Cyclosporin A. The increasing of NO levels attributed to the renal vasoconstriction due to a disproportion in releasing the vasoactive substances, including decrease of vasodilator factors specifically nitric oxide [23].

Lipid peroxidation is a free radical-incited process prompting to oxidative disintegration of polyunsaturated fat [24]. Malondialdehyde (MDA) is the final products of lipid peroxidation and measure of free radical generation [25]. Concerning the impact of CsA on lipid peroxidation, the outcome indicated significant elevation in renal tissue MDA, which support the theory of oxidative stress induced by CsA. This suggestion was in the same line with Uz et al. (2011) [26] who studied the protective effect of erdosteine on Cyclosporin induced chronic nephro-toxicity in rats. Previous studies determined that CsA administration leads to excess local hydroxyl radical production, which leads to lipid peroxidation and nephrotoxicity [14].

GSTs can eliminate genotoxic or cytotoxic compounds, which can damage or interact with DNA, RNA and proteins [27]. In the present study renal tissues' GST levels significantly showed a decline in CsA group compared with the control group, which was in concurrence with Ezejiofor et al. (2016) [8]. The current study observed that parsley leaves extract provided a significant defense against CsA-induced nephrotoxicity by reducing the level of MDA. Previous studies indicated decrease in MDA by studying the nephroprotective and antioxidant effects of parsley plant parts against gentamicin-induced nephrotoxicity in rats [28, 29]. This clarify the antioxidant activity of parsley leaves extract. Similarly, silymarin showed a significant defense against CsA-induced nephrotoxicity by reducing the level of MDA, Nitrite and increasing the level of GST. The ameliorating effect of silymarin on MDA, Nitrite levels was in line with Shahbazi et al. (2012) [30] and Ghaznavi et al. (2015) [18]. Previous results confirmed that pretreatment of rats with silymarin and melatonin against gentamicin induced nephrotoxicity in rats, significantly reduce renal MDA and ROS level. Also increased antioxidant status of GST enzyme activity was recorded with Ahmed et al. (2016) [31] and Amien et al. (2015) [19] who reported that silymarin is a potent antioxidant; it neutralized free radicals and restored GST level in the tissue. This property helps to prevent kidney from free radical stress.

ROS additionally applies adverse impacts on DNA by developing 8-OHdG. 8-OHdG is the most regularly utilized markers for assessing oxidative DNA damage. 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 [32]. In the current study, 8-OHdG and apoptotic marker caspase-3 was higher in CsA treated group than control group; these results were in line with Lai et al. (2015) [33] who studied the nephroprotective benefits of using *Schisandra chinensis* extracts on CsA cytotoxicity. CsA treatment caused elevation in 8-OHdG production and upregulation of TGF- β 1, caspase-3, and LC3-II [34].

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) [35] 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. Simultaneous administration of silymarin to CsA significantly decreased the level of 8-OHdG; these results are in line with Cengiz et al. (2018) [36] and Dabak et al. (2015) [37] who study the effect of silymarin on thioacetamide or methotrexate-induced nephrotoxicity in rats respectively. Thus it may be inferred that silymarin suppresses DNA damage and it has an anti-apoptotic effect.

In our study the levels of inflammatory mediators NF- κ B and TNF- α , were increased in the CsA treated group compared to control group; these results were in agreement with Wu et al (2018) [38] who study the mechanism of Cyclosporin A nephrotoxicity. Previous study by Jin et al. (2017) [39] reported that Klotho gene, enhances CsA-instigated nephropathy by downregulating kidney aggravation through the PDLIM2/NF- κ B p65 pathway. In ordinary cells, NF- κ B is inefficient in cytoplasm through its cleavage with its inhibitors, p105 and I κ B α -like

proteins. The raised ROS in kidney causes the degradation of its inhibitor I κ B-alpha or proteolytic cleavage of p105, and free NF- κ B dimers translocate to nucleus and activates the target anti-inflammatory genes [40]. The study conducted by Saraswat et al. (2014) [41], after CsA administration reported a rise in the level of inflammatory cytokines such as TNF- α . Its inflammatory properties are mediated by a wide range of pro-inflammatory cytokines, including IL-1, IL-2, IL-6, IL-12 IFN- γ (interferon- γ) and TGF- β (transforming growth factor- β), generated mainly through NF- κ B activation [42].

As CsA increase the level of NF- κ B 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- κ B and TNF- α ; the results are in agreement with Malik et al. (2017) [43]. Using apigenin essentially reduce the levels of TNF- α , IL-1 β , and TGF β in rat's kidneys. Moreover, apigenin inhibited the activations of CYP2E1, phospho-NF- κ B p65 and phospho-P38 MAPK in cisplatin-induced renal damage [44]. 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. Similarly, the treatment with silymarin accompanied with CsA decreased NF- κ B and TNF- α levels. These results are in agreement with Prabu et al. (2012) [45] and Geed et al. (2014) [46] they revealed that silibinin treatment significantly attenuated the overproduction of TNF- α and reduced the expression of NF- κ B in the kidney of rat exposed to intoxication [47]. Previous study reported that renal changes and dysfunction in the kidney depend on CsA toxicity prompted oxidative stress that produces reactive oxygen species (ROS) prompting lipid peroxidation [48].

The histopathological study has shown that CsA induced renal changes. Renal sections of the CsA treated group exhibited disruption of normal kidney architecture; cellular disorganization, intracellular vacuoles and many inflammatory cells. The histopathological changes were in line with Elshama et al. (2016) [49] and Ouyang et al (2014) [50] who reported that CsA induced damage of renal tubules, by studying the protective effects of 2-deoxy-D-glucose on nephrotoxicity caused by CsA in rats. In our study the renal sections of the CsA+ parsley leaves extract showed improvement of the morphological organization of renal cortex. While, renal sections of the CsA+silymarin revealed regeneration of glomeruli and renal tubules, but inflammatory cells infiltration still was found. Which support that the protective role of parsley leaves extract was more beneficial than silymarin.

From all the above result and by computation of the percent of changes in all the studied parameters, and the ameliorating effect of parsley leaves extract and silymarin. It could be postulated that there is no significant interaction between parsley leaves extract and CsA when used in combination. It pursues that the two treatments (parsley leaves extract and CsA) can be taken together harmlessly without serious responses. It has been reported that, when the medication is taken orally it goes through the digestive system in generally same way as food and herbs taken. In this manner, when it is mixed with herb, each can modify the others pharmacokinetic profile, that is absorption, distribution, metabolism, and excretion. A few medications overlap with the Body's capacity to absorb herbs. Additionally, a few herbs and nutrition can reduce or increase the effect of a medication [51].

CONCLUSIONS

This study aimed to study the possibility of administration of CsA results in severe oxidative stress and renal damage. Parsley leaves extract and silymarin significantly ameliorated the renal dysfunction by strengthening the antioxidant status, regulating the inflammatory and DNA damage process. In addition, co-administration of parsley leaves extract with CsA showed more beneficial effect than silymarin. The results indicated that the extract of parsley leaves is effective in preventing functional impairment in a rat model induced nephrotoxicity by CsA. Finally, consumption of parsley leaves extract should be recommended to lessen nephrotoxicity of CsA. These findings may have important role in the development of new therapeutic strategy aimed at manipulating parsley leaves extract as a supplement for prophylaxis from nephrotoxicity.

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