Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[8] July 2020 : 87-93

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

ORIGINAL ARTICLE **OPEN ACCESS**

The possible Ameliorating and Antioxidant Effects of Curcumin against Cyclosporine-Induced renal Impairment in Rats Kidney

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ABSTRACT
Curcumin has several medical importance e.g. against biliary disorders, anorexia, hepatic disorders, sinusitis, diabetic wounds and rheumatism. The current study was designated to examine the possible valuable effects of curcumin in preventing acute renal failure and related oxidative stress caused by chronic administration of cyclosporine in rats. The study included two experiments; the first one was carried out to follow up the changes that could occur in the kidney function as a result of cyclosporine administration. Cyclosporine administration exerted significant elevation of serum urea, creatinine, potassium, parathormone, malodialdehyde and dimethylarginine. Meanwhile, cyclosporine showed significant decline in the level of serum sodium and total nitric oxide, the content of kidney reduced glutathione and the activities of glutathione peroxidase, catalase and superoxide dismutase versus the levels in normal rats. In the second experiments, the nephritic rats were treated with curcumin and remarkable changes have been occurred on those parameters. It was concluded that curcumin has a beneficial effect as antioxidant against the oxidative stress and renal dysfunction which induced by chronic administration of cyclosporine in rats.
Keywords: Curcumin, Cyclosporine, Renal Impairment, Oxidative Stress, Antioxidant

Received 11.04.2020 Revised 05.05.2020 Accepted 19.07.2020

INTRODUCTION

Cyclosporine A (CsA) is a hydrophobic cyclic decapeptide produced by the fungus *Tolypocladium inflatum*, considered as one of the prototype of immunosuppressants that has revolutionized the management of allotransplantation [1, 2]. CsA combines low myelotoxicity with efficacy in preventing allograft rejection and other associated host diseases [3]. Nephrotoxicity and hypertension are the major adverse effects that often limit cyclosporine treatment following solid organ transplantation and autoimmune diseases [4]. The functional changes of cyclosporine are dose dependent and are usually reversible after short term of treatment [5]. CsA has been shown to enhance the generation of hydrogen peroxide in vitro and lipid peroxidation in vitro and in vivo. Antioxidants have been shown to be protective in cyclosporine nephrotoxicity [1]. Such evidence suggests an important role of reactive oxygen metabolites in toxic acute renal failure which may provide therapeutic opportunities for preventing or treating acute renal failure in humans. Cumulative data suggest that reactive oxygen metabolites have a role as one of the postulated mechanisms in the pathogenesis of cyclosporine nephrotoxicity. CsA enhances generation of hydrogen peroxide in cultured hepatocytes [6] and mesangial cells [7]. In vivo and in vitro studies indicate that cyclosporine reduces renal microsomal NADPH cytochrome P450 and renal oxidized/reduced glutathione ratio in kidney cortex as well as renal microsomes and mitochondria [8, 9]. Antioxidants such as α-tocopherol, ascorbate, silibinin, lazaroid, propionyl carnitine and superoxide/catalase, have been shown to ameliorate cyclosporine-induced renal toxicity [6, 10].

Curcumin (diferuloylmethane) is one of the most commonly used spices in the world. Curcumin is the active ingredient in the traditional herbal remedy and dietary spice turmeric (*Curcuma longa*), being responsible for its biological actions. Current traditional medicine claims the use of *Curcuma longa*

powder against biliary disorders, anorexia, hepatic disorders, sinusitis, diabetic wounds and rheumatism [11]. Numerous studies now show that curcumin exhibit anti-inflammatory and anti-human immunodeficiency virus [12], anti-bacterial [13] and nematocidal activities [14]. Different in vitro and in vivo studies increasingly establish the antioxidant properties of curcumin [15]. It is well documented that curcumin scavenges superoxide anions [16], peroxynitrite radicals [17, 18] and quenches singlet oxygen [19]. Curcumin has also been shown to inhibit hydrogen peroxide-induced cell damage [15]. For therapeutic importance of curcumin see for review [20, 21, 22, 23]. However, few studies have examined the beneficial effect of curcumin on renal dysfunctions.

The aim of the current study was designated to examine the possible beneficial effects of curcumin in preventing the acute renal failure and the related oxidative stress caused by chronic administration of cyclosporine in rats.

MATERIAL AND METHODS

Study design: Fifty mature male Wistar albino rats (130-140g) were obtained from the animal facility of The Faculty of Medicine, Mutah University. They were randomly housed in cages and maintained under standard conditions 12:12 light: dark cycle at room temperature 24±1^{o}C, and 50%±10% relative humidity. All animals were fed standard laboratory control diet and drinking tap water *ad libitum*. The experiments were conducted according to the ethical norms approved by the Faculty Ethics Committee. The study included two experiments; the first one was carried out to follow up the changes that could occur in kidney as a result of cyclosporine treatment. To achieve this purpose, a comparison was carried out between two groups. The first group included five normal control rats injected daily with olive oil subcutaneously for 21 days. The second group included five animals; they received CsA (20 mg/kg/day, subcutaneously) dissolved in olive oil for 21 days [2]. CsA was obtained from Sigma-Aldrich Chemical Co. (United Tetra Group, Amman, Jordan). In the second experiment, the animals were divided into three groups (ten rats each) all with renal toxicity induced by CsA administration, 20 mg/kg/day subcutaneously, dissolved in olive oil for 21 days. The first group of animals was left without further treatment to serve as a control group (recovery nephrotoxicated group). The second group of CsA toxicated rats was treated orally with curcumin 15 mg /kg body weight. The third group of CsA toxicated rats was treated with curcumin 30 mg /kg body weight. Curcumin was obtained from Sigma-Aldrich Chemical Co. (United Tetra Group, Amman, Jordan).

Serum assessments: Serum urea and creatinine were assayed colorimetrically using commercial kits (Randox Ltd Co. UK) [24, 25]. Blood sodium and potassium were analyzed by emission flame photometry after suitable dilution [26]. Serum parathormone was assayed by ELISA kit (ICN Pharmaceutical Co. USA) using solid phase component [27]. Plasma ADMA [28], serum total nitric oxide [29] and malodialdehyde [30] were assayed by ELISA technique using commercial kits (Oxis Inc., USA).

Homogenization: Kidneys were obtained at the end of each experimental period and washed with saline solution (0.9% NaCl). They were homogenized in ice cold 0.25 M sucrose containing 1 mM diethylenetriamine penta-acetic acid (1:1w/v). Each sample was centrifuged for 20 minutes at 20000 g and 4^{o}C. The supernatant was aspirated to determine reduced glutathione (GSH) [31] and the activities of glutathione peroxidase (Gpx) [32]. Also, catalase (CAT) was assayed following the method of Johansson and Borg [33], and superoxide dismutase (SOD) as described by Oyanagui [34], using ELISA technique with commercial kits (IBL Gesellschaft, Hamburg, Germany).

Statistical analysis: Results were expressed as mean± SEM. Data were analyzed using Student t test in the first experiment [35]. Two-way analysis of variance (ANOVA) followed by Duncan's multiple range test in the second experiment [36]. Groups were considered to be significantly different at $P \leq 0.05$.

RESULTS AND DISCUSSION

In the current study, rat was used as an animal model for induction of acute renal failure by cyclosporine injection at a dose equivalent to that used clinically in man. It was found that injection of cyclosporine at a dose of 20 mg/kg body weight/day for 21 days, developed injury in the proximal tubular epithelial cells of kidney that caused acute renal failure [2]. As shown in Table 1, acute renal failure was characterized by disorders in some biochemical parameters in cyclosporine treated rats. Serum urea and creatinine increased to about 210% to 230%, respectively, over their corresponding values in the control group (Table 1). Which is comparable with those obtained by Tirkey et al [2]. Therefore, these changes reflected the severity of renal insufficiency. These biochemical alterations, occurred in association with the sudden fall in glomerular filtration rates, may be attributed to the entrance of CsA to the proximal tubular epithelial cells. Therefore binds to anionic phospholipids in the target cells, consequently causing abnormalities in the function and metabolism of multiple intracellular membranes and organelles [37]. Furthermore, this could be supported by the increased lipid peroxidation in kidney cortex showed in

animals with CsA nephrotoxicity [38]. The most frequent and clinically important adverse effect of cyclosporine is nephrotoxicity [39]. Nephrotoxic usually manifested as increased Blood Urea Nitrogen Test (BUN) and serum creatinine concentrations. Those nephrotoxic effects of cyclosporine have been observed in 25-32, 38 or 37% of patients receiving the drug for kidney, heart or liver allografts, respectively [40]. On the other hand, elevations of BUN and serum creatinine concentrations resulting from cyclosporine therapy appears to be dose dependent, and are usually reversible upon discontinuance of the drug [41].

There are remarkable disturbances in serum electrolytes (p<0.05) in CsA treated rats compared with normal control rats (Table 1). For instance, lower values of serum sodium in CsA treated rats than controls indicates inability of the kidneys to conserve sodium and chloride. Conversely, the reversed increase of potassium appeared to be due to reduced excretion of potassium, which aggravated by leakage of intracellular potassium into blood stream. This can be attributed to CsA induced lesions in renal tubular epithelium [42]. On the other hand, the exact mechanism of cyclosporine-induced hypertension and nephrotoxicity remains obscure. Several studies suggested many reasons were involved; a defect in intracellular calcium handling [42], magnesium deficiency [43], oxidative stress [44], and nitric oxide system [45]. Therefore, acute renal failure caused by CsA is credited to the generation of reactive oxygen species (ROS). The present study revealed that chronic administration of CsA for 21 days caused a marked impairment of renal functions, along with significant oxidative stress within kidneys. Causing a major decline in the GSH content of kidney alongside the activities of kidney Gpx, CAT and SOD (Table 1), which is comparable with the results obtained by others [2, 15, 46]. These findings could be attributed to not only the increase in lipid peroxidation but also to the increased free radicals production reported by others [47]. Furthermore, CsA increases renal nerve activity resulting in vasoconstriction in kidneys [48], and also causes vasoconstriction directly in isolated renal tubules [49]. Additionally, CsA blocks mitochondrial calcium release, including a drastic enhancement in intracellular free calcium, which could account for the vasoconstrictive effect of cyclosporine [50]. These alterations could theoretically lead to a classical hypoxia-reoxygenation injury involving oxygen free radicals. In addition, ROS could be derived directly from CsA or during its metabolism by cytochrome P450 system [7]. It has been demonstrated that cyclosporine increased level of superoxide in endothelial and mesangial cells [8]. On the other hand, couple of studies suggested that CsA induces apoptosis characterized by internucleosomal DNA cleavage due to endonuclease activation. Because oxidants are capable of inducing apoptosis in various types of cells [51], including renal tubular epithelial cells [52], it is conceivable that reactive oxygen metabolites may play a role in apoptotic mechanism of CsA -induced nephrotoxicity.

The current investigation revealed that curcumin significantly decreased the elevated levels of serum creatinine and urea after chronic administration of CsA for 21 days. Earlier studies have shown that curcumin pretreatment decreases ischemia-reperfusion induced rise in serum creatinine levels [53]. Chronic administration of CsA, also, produced oxidative stress and increased the lipid peroxidation in kidneys as seen in the level of serum MDA, that effect was ameliorated by curcumin treatment and is on line with various previous reports, which showed the decrease in lipid peroxidation possibly by the antioxidant mechanism of curcumin [54]. Moreover, it was reported that the protective effects of curcumin on circulating lipids in plasma and lipid peroxidation products in alcohol and polyunsaturated fatty acid-induced toxicity [55]. From the data presented in (Table 2), with the progress of time after cyclosporine has been discontinued, serum urea, creatinine, potassium, parathormone, ADMA and MDA decreased ($p< 0.05$) significantly during the treatment with curcumin as compared to the nephrotoxic group. Although the levels of these variables were still significantly ($p< 0.05$) higher than saline injected rats. Conversely, serum sodium and total nitric oxide increased ($p< 0.05$) significantly during curcumin treatment as compared to the nephrotoxic animal group (Table 2). Those findings are compatible with the data obtained by Tirkey et al [2] and Ghosh et al [56]. In spite of all the similarities in the results obtained in our study and the results reported in the study of Tirkey et al [2], however, there are certain differences between the two studies, including the number of the enrolled animals, their grouping and the duration of administration of drugs. In our study a total of 50 rats were enrolled in the study compared to almost 30 rats in their study. Furthermore, there are some different parameters measured in the two studies, and the values obtained of the similar parameters were different.

It has been demonstrated that curcumin inhibits the generation of superoxide radicals [57]. In the current study, CsA administration caused marked deterioration of endogenous antioxidant profile as evidenced by the decrease in SOD and CAT activities, which was reversed by curcumin treatment [16]. Furthermore, GSH a major non-protein thiol in living organisms plays a crucial role in coordinating the antioxidant defenses process in the body. The obtained results in the current study (Table 3), indicated that administration of CsA lowered the level of GSH in the kidney, while, curcumin treatment caused improvement in the levels of GSH validating the antioxidant effect of curcumin. The prolonged use of

curcumin, also, improved the levels of the two key antioxidant enzymes SOD and CAT in cyclosporine administrated rats. Peroxynitrite anions have been generated by the reaction of nitric oxide with superoxide anions. These peroxynitrite anions oxidize biomolecules, which finally leads to lipid peroxidation and tubular cell damage [58]. Large amounts of nitric oxide can lead to the depletion of cellular ATP which can inactivate enzymes that contain iron-sulfur clusters, such enzymes involved in the electro transport chain [59]. Nitric oxide damages DNA, and this in turn, stimulates the DNA repair enzyme poly-ADP-ribose synthetase [60]. Other studies have shown that administration of CsA induces apoptosis in various renal cell lines [61], and this effect is mediated by the induction of iNOS. Consistent with further studies where curcumin is reported to inhibit iNOS gene expression in isolated BALB/c mouse peritoneal macrophages and also, in the livers of lipopolysaccharide injected mice [60]. The current study showed that CsA-induced nitrosative stress was significantly and dose dependently and attenuated by curcumin. It is also, known that ROS mediates lipid peroxidation of lipid structures within tissues [18, 59], resulting in subcellular damage, as observed in histopathological examination.

In conclusion, this study demonstrated that curcumin through its marked antioxidant activity coupled with favorable hemodynamic effects salvages CsA nephrotoxicity depending on both the dose and the time of treatment.

Table 1: Effects of cyclosporine administration on some physiological and biochemical parameters in rats

Parameter	**Control group Number = 5 rats**	**Cyclosporine group Number = 5 rats**
Urea (mg/dL)	18.34±0.46	34.22±0.98*
Creatinine (mg/dL)	0.382±0.012	1.23±0.043*
Sodium (meq/L)	129.91±2.34	122.76±1.64*
Potassium (meq/L)	4.23±0.004	5.44±0.21*
Parathormone (ng/dL)	11.540.65	18.65±0.84*
ADMA (µmol/L)	1.03±0.073	2.66±0.095*
Total nitric oxide (µmol/L)	56.44±2.23	33.87±1.54*
Malodialdehyde (nmol/dL)	0.55±0.01	0.86±0.022*
GSH (mg/g protein)	10.76±0.77	6.87±0.46*
Gpx (µmol/min/g protein)	23.54±0.86	18.68±0.78*
CAT (nmol/60 min/mg protein)	40.94±1.32	33.76±0.89*
SOD (Nu/60 min/mg protein)	4.09±0.33	3.53±0.23*

Values are expressed as mean±SE
** Means a significant (p<0.001)*

Table 2: Effect of curcumin (15&30 mg/body weight) treatment on kidney function tests in cyclosporine A-nephrotoxic rats

Parameter	**Group**	**Control**	**Recovery**	**Cyclosporine + curcumin 15 mg**	**Cyclosporine + curcumin 30 mg**
Urea (mg/dL)	15 days (n =5)	16.42±0.48	32.12±0.84	30.56±0.95	27.47±0.79
	30 days (n =5)	16.36±0.48	31.45±0.86	29.66±0.82	25.94±0.71
Creatinine (mg/dL)	15 days (n =5)	0.48±0.01	1.15±0.017	0.89±0.013	0.80±0.012
	30 days (n =5)	0.48±0.01	1.09±0.014	0.82±0.012	0.83±0.011
Sodium (meq/L)	15 days (n =5)	132.87±1.88	123.76±1.76	127.54±1.77	128.53±1.81
	30 days (n =5)	133.45±1.89	122.88±1.84	126.98±1.83	131.66±1.85
Potassium (meq/L)	15 days (n =5)	4.11±0.188	5.14±0.25	4.63±0.23	4.32±0.21
	30 days (n =5)	4.10±0.185	5.28±0.27	4.42±0.27	4.16±0.19
Parathormone (ng/dL)	15 days (n =5)	11.55±0.55	18.64±0.87	15.96±0.76	14.63±0.71
	30 days (n =5)	11.64±0.59	17.98±0.92	14.99±0.81	13.55±0.64
ADMA (µmol/L)	15 days (n =5)	1.23±0.091	2.88±0.092	2.44±0.083	2.21±0.081
	30 days (n =5)	1.22±0.085	2.73±0.082	2.260.079	1.99±0.083
Total nitric oxide (µmol/L)	15 days (n =5)	57.23±2.1	36.23±1.14	38.90±1.15	43.67±1.15
	30 days (n =5)	59.53±1.19	35.84±1.33	42.36±1.17	47.92±1.17

Values are expressed as mean±SE
All parameters are not significantly different (p>0.05) n= number of rats

Table 3: Effect of curcumin (15&30 mg/body weight) treatment on serum malodialdehyde and kidney GSH content, Gpx, CAT and SOD activities in cyclosporine A-nephrotoxic rats

Parameter	Group	Control	Recovery	Cyclosporine + curcumin 15 mg	Cyclosporine + curcumin 30 mg
Malodialdehyde (nmol/dL)	15 days (n =5)	0.53±0.009	0.83±0.022	0.76±0.017	0.65±0.013
	30 days (n =5)	0.53±0.009	0.78±0.016	0.73±0.014	0.58±0.013
GSH (mg/g protein)	15 days (n =5)	11.21±0.87	7.87±0.522	8.89±0.51	9.44±0.56
	30 days (n =5)	11.18±0.64	8.92±0.58	9.39±0.55	9.58±0.64
Gpx (µmol/min/g protein)	15 days (n =5)	23.67±0.93	18.43±0.80	19.56±0.85	19.34±0.63
	30 days (n =5)	24.06±0.86	18.67±0.79	20.34±0.91	21.21±0.94
CAT (nmol/60 min/mg protein)	15 days (n =5)	42.11±1.23	37.88±1.14	39.34±0.11	38.67±1.17
	30 days (n =5)	41.67±1.34	38.43±1.14	40.51±0.14	41.56±1.23
SOD (Nu/60 min /mg protein)	15 days (n =5)	5.13±0.23	3.95±0.19	4.53±0.20	4.69±0.19
	30 days (n =5)	5.45±0.19	4.22±0.18	4.98±0.0.21	5.12±0.22

Values are expressed as mean±SE
All parameters are not significantly different (p>0.05)
n= number of rats

REFERENCES

1. Buurman WA, Daemen AJ, van der Linden CJ and Kootstra G (1987). Clinically used concentrations of CsA only partially inhibit interferon-gamma production by activated T lymphocytes. Transplant Proc., 19(1pt2):1193
2. Tirkey N, Kaur G, Vij G and Chopra K (2005). Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. BMC Pharmacology, 5: 15-25.
3. Kahan BD (1989). Cyclosporine. N. Engl. J. Med., 321(25):1725-38
4. Mason J (1990). Pharmacology of cyclosporine (sandimmune) VII. Pathophysiology and toxicity of cyclosporine in humans and animals Pharmacol., Rev., 41(3):423-34
5. Remuzzi G and Perico N (1995). Cyclosporine-induced renal dysfunction in experimental animals and humans. Kid. Int., 52(Suppl., S70-4)
6. Wolf A, Clemann N, Frieauff W, Ryffel B and Cordier A (1994). Role of reactive oxygen formation in cyclosporine A-mediated impairment of renal functions. Transplant Proc., 26(5):2902-7
7. Ahmed SS, Napoli KL and Storbel HW (1995). Oxygen radical formation during cytochrome P450-catalyzed cyclosporine metabolism in rat and human liver microsomes at varying hydrogen ion concentrations. Mol. Cell Biochem., 151(2):131-140
8. Perez de Lema G, Arribas-Gomez I, Ruiz-Gines JA, de Arriba G, Prieto A, Rodriguez-Puyol D and Rodriguez-Puyol M (1997). Reactive oxygen species mediate the effects of cyclosporine A on human cultured mesangial cells. Transplant Proc., 29(1-2):1241-1243
9. Walker G, Kunz D, Weisenberg I, Van den Bosch H and Pfeilschifte J (1996). Tetranactin inhibits interleukin 1 beta and cAMP induction of group II phospholipase A2 in rat renal mesangial cells. Eur. J. Pharmacol., 306(1-3):265-270
10. Longoni B, Giovanni L, Migliori M, Bertelli AA, Bertelli A (1999). Cyclosporine- induced lipid peroxidation and propionyl carnitine protective effect. Int. J. Tissue React. 21(1):7-11
11. Ammon HP and Wahl MA (1991). Pharmacology of Curcuma longa. Plant Med., 57(1):1-7
12. De Clercq E (2000). Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. Med. Res. Rev., 20(5):289-297
13. Pal A and Pal AK (2000). Studies on genotoxicity of turmeric extracts in bacterial system. Int. J. Antimicrob. Agents 16(4):415-417
14. Jurgens TM, Frazier EG, Schaeffer JM, Jones TE, Zink DL, Borris RP, Nanakorn W, Beck HT and Ballick MJ (1994). novel nematocidal agents from Curcuma comosa. J. Nat. Prod., 57(2):230-235
15. Biswas SK, McClure D, Jimenez LA, Megson IL and Rahman I (2005). Curcumin induces glutathione synthesis and inhibits NF-kappa-B activation and interleukin-8 release in alveolar epithelial cells: mechanism of free radical scavenging activity. Antioxid. Redox Signal 7(1-2):32-41
16. Vajragupta, Boonchoong P, Watanabe H Tohda M, Kummasud N and Sumanont Y (2003). Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. Free Radic. Biol. Med., 35(12):1632-1644
17. Kim JE, Kim AR, Chung HY, Han SY, Kim BS and Choi JS (2003). In vitro peroxynitrite scavenging activity of diarylheptanoids from Curcuma longa. Phytother. Res., 17(5):481-484
18. Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Matsumoto K and Watanabe H (2004). Evaluation of the nitric oxide radical scavenging activity of manganese complexes of curcumin and its derivative. Biol. Pharm. Bull., 27(2):170-173
19. Das KC and Das CK (2002). Curcumin (diferuloylmethane) a singlet oxygen ((1) O (2)) quencher. Biochem. Biophys. Res. Commun., 295(1):62-66

20. Noorafshan A and Ashkani-Esfahani S (2013). A Review of Therapeutic Effects of Curcumin. Current Pharmaceutical Design, 19, 2032-2046
21. Hewlings SJ and Kalman DS (2017). Curcumin: A Review of Its' Effects on Human Health. Foods, 6, 92: 1-11
22. Dikkala PK and Shirisha SDSN (2018). Curcumin and Its Biological Importance: A Review. International Journal of Current Microbiology and Applied Sciences 7 (2): 1100-1105
23. Sanidad KZ, Sukamtoh E, Xiao H, McClements DJ, and Zhang G (2019). Curcumin: Recent Advances in the Development of Strategies to Improve Oral Bioavailability. Annual review of food science and technology 10: 597-617
24. Fawcett JK and Scott J (1960). Determination of blood urea using berthelot reaction. J. Clin. Path., 13:156-162
25. Seeling F and Wust T (1969). modified methodology for determination of creatinine. Z. Ernaehryg Swiss; 2(4):169-176
26. Dean JA (1960). In: Flame Photometry. 1st ed. Mc-Graw-Hill Book Co. New York.
27. Engvall E and Perlmann P (1971). Enzyme-linked immunosorbent assay (ELISA). Quantitative assay of immunoglobulin G. Immunochemistry; 8(9):871-874.
28. Schulze F, Wesemann R, Schwedhelm E, Sydow K, Albsmeier J, Cooke JP and Boger RH (2004). Determination of asymmetric dimethylarginine (ADMA) using a novel ELISA assay. Clin. Chem. Lab. Med., 42(12):1377-83
29. Nine RW, Darbyshire JE and Saavedra JE (1995). A new method for the determination of nitric oxide concentration in neutral aqueous solution. Method., 7:48-54
30. Pedeson MA, Scott CS and William AB (1990). Evaluation of lipid peroxidation in inflammatory patients. Ann. NY Acad. Sci., 559:45-62
31. Baker MA, Cerniglia GJ and Zaman A (1990). Microtiter plate assay for the measurement of glutathione and glutathione disulfide in large members of biological samples. Anal. Biochem., 190:360-365
32. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG and Hoekstra WG (1973). Selenium: Biochemical roles as a component of glutathione peroxidase. Science; 179:588-590
33. Johansson LH and Borg LAH (1988). A spectrophotometric method for determination of catalase activity in small tissue samples. Anal. Biochem., 174:331-336
34. Oyanagui Y (1984). Evaluation of assay methods and establishment kit for superoxide dismutase. Anal. Biochem., 142:290-296
35. Milton JS, Corbert JJ and Teer PM (1986). Introduction to statistics 3rded. D.C. Health and Company, Canada.
36. Snedecor GW and Cochran WG (1982). Statistical Methods 7th ed. Iowa State University Press, Ames Iowa, USA.
37. Grossman RM, Chevret S and Abi-Rached J (1996). Long-term safety of cyclosporine in the treatment of psoriasis. Arch. Dermatol., 132:623-9
38. Ameer, B and Weintraub RA (1997). Drug interactions with grapefruit juice. Clin. Pharmacokinet., 33:103-21
39. Canafax DM. and Ascher NL (1983). Cyclosporine immunosupression. Clin. Pharm., 2:515-24
40. Merion RM, White DJG and Thiru S (1984). Cyclosporine: five years, experience in cadaveric renal transplantation. N. Engl. J. Med., 310:148-154
41. Scott JP and Higenbottam TW (1988). Adverse reactions and interactions of cyclosporine. Med. Toxicol. Adverse Drug Exp., 3:107-27
42. Cheng CH, Hsieh CL, Shu KH, Chen YL and Chen HC (2002). Effect of calcium antagonist diltiazem and calcium ionophore A23187 on cyclosporine A-induced apoptosis of renal tubular cells. FEBS (Lett), 516(1-3):191-196
43. Mervaala EM, Pere AK, Lindgren L, Laakso J, Teravainen TL, Karjala K, Vapaatalo H, Ahonen J and Karppanen H (1997). Effects of dietary sodium and potassium on cyclosporine A-induced hypertension and nephrotoxicity in spontaneously hypertensive rats. Hypertension; 29(3):822-827
44. Satyanarayana PS and Chopra K (2002). Oxidative stress-mediated renal dysfunction by cyclosporine A in rats: attenuation by trimethazidine. Ren. Fail., 24(3):259-274
45. De Nicola L, Thomson SC, Wead LM, Brown MR and Gabbai FB (1993). Arginine feeding modifies cyclosporine nephrotoxicity in rats. J. Clin. Invest., 92(4):1859-1865
46. Chen J, Wanming D, Zhang D, Liu Q and Kang J (2005). Water soluble antioxidants improve the antioxidant and anticancer activity of low concentrations of curcumin in human leukemia cells. Pharmazie; 60(1):57-61
47. hong Z, Arteel GE, Connor HD, Yin M, Frankenberg MV, Stachlewitz RF, Raleigh JA, Mason RP and Thurman RG (1998). Cyclosporine A increases hypoxia and free radical production in rat kidneys: prevention by dietary glycine. Am. J. Physiol., 275(4 Pt 2):F595-604
48. Moss NG, Powell SL and Falk RJ (1985). Intravenous cyclosporine activates afferent and efferent renal nerves and causes sodium retention in innervated kidneys in rats. Proc. Natl. Acad. Sci., USA; 82(23):8222-8226
49. Lanese DM, Falk SA and Conger JD (1994). Sequential agonist activation and site-specific mediation of acute cyclosporine constriction in rat renal arterioles. Transplantation; 58(12):1371-1378
50. Avdonin PV, Cottet-Maire F, Afanasjeva GV, Loktionova SA, Lhote P and Ruegg UT (1999). Cyclosporine A up-regulates angiotensin II receptors and calcium responses in human vascular smooth muscle cells. Kidney Int., 55(6):2407-2414
51. Buttke TM and Sandstrom PA (1994). Oxidative stress as a mediator of apoptosis. Immunol., 15:7-10
52. Ueda N and Shah SV (1992). Endonuclease-induced DNA damage and cell death in oxidant injury to renal tubular epithelial cells. J. Clin. Invest., 90:2593-97
53. Shoskes DA (1998). Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. Transplantation; 66(2):147-152

54. Skrzdlewska E, Ostrowska J, Farbiszewski R and Michalak K (2002). Protective effect of green tea against lipid peroxidation in the rat liver, blood serum and the brain. Phytomedicine; 9(3):232-38
55. Rukkumani R, Sri Balasubashini M and Menon VP (2003). Protective effects of curcumin and photo-irradiated curcumin on circulatory lipids and lipid peroxidation products in alcohol and polyunsaturated fatty acid-induced toxicity. Phytother. Res., 17(8):925-29
56. Ghosh SS, Krieg R, Massey HD, Sica DA, Fakhry I, Ghosh S and Gehr TWB (2012). Curcumin and enalapril ameliorate renal failure by antagonizing inflammation in 5/6 nephrectomized rats: role of phospholipase and cyclooxygenase. Am J Physiol Renal Physiol, 302: F439–F454.
57. Priyadarsini KI, Maity D, Naik GH, Kumar MS, Unnikrishnan MK, Satav J and Mohan H (2003). Role of phenolic OH and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Radic. Biol. Med., 35(5):475-484
58. Sreejayan N and Rao MN (1997). Nitric oxide scavenging by curcuminoids. J. Pharm. Pharmacol., 49(1):105-107
59. Dawson TM, Dawson VL and Snyder SH (1992). A novel neuronal messenger molecule in brain: the free radical, nitric oxide. Ann. Neurol., 32(3):297-311
60. Chan MM., Huang HI, Fenton MR and Fong D (1998). In vivo inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties. Pharmacol., 55(12):1955-1962
61. Amore A, Emancipator SN, Conti G, Ricotti E, Bagheri N and Coppo R (2000). Nitric oxide mediates cyclosporine-induced apoptosis in cultured renal cells. Kidney Int., 57(4):1549-1559

CITATION OF THIS ARTICLE

AL-Qtaitat Aiman, Mwafi Nesrin, Albtoosh Amal , Al-Dalaien Said . The possible Ameliorating and Antioxidant Effects of Curcumin against Cyclosporine-Induced renal Impairment in Rats Kidney .Bull. Env. Pharmacol. Life Sci., Vol 9[8] July 2020 : 87-93