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The possible protective role of *Thymus vulgaris* against hepatotoxicity and nephrotoxicity of cyclosporine A

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Abstract

In this study, we investigated the possible protective role of the *thymus vulgaris*extract in reducing hepatic and renal toxicity of cyclosporine A in rabbits. Levels of total protein and albumin showed a significant depression after treatment with cyclosporine A compared to the control. Levels of bilirubin increased significantly after treatment with cyclosporine A compared to control. Levels of ALT, AST, ALP, ACP and LDH showed a significant increase after treatment with cyclosporine A compared to the control. Results showed that *Thymus vulgaris* extract had a protective role by alleviating the toxic effects of cyclosporine A.

Keywords: Nanoparticles, Encapsulated, Nanopolymers

Introduction

Cyclosporine is a lipophilic, cyclic endecapeptide with a molecular weight of 1202 Daltons (Kahan, 1989[1]). In plasma, it is 90% protein bound, mostly to lipoproteins, but also to albumin and globulins. In blood, cyclosporine is extensively distributed in erythrocytes. There are differences in bioavailability of cyclosporine in large part due to significant inter individual variability in intestinal absorption, a process that is further influenced by food ingestion, diabetes, gastric motility problems, and diarrhea among other things (Naesens*et al*., 2009[2]).

Cyclosporine A (CsA) belongs to calcineurin inhibitors used in patients after kidney, liver, heart, lung, and heart-lungtrans plants for graft-versus-host disease (GVHD) prophylaxis (Tedesco and Haragsim, 2012[3]).Moreover, CsA is used to treat the majority of autoimmune diseases, in dermatology to treat psoriasis, autoimmune dermatitis, or chronic idiopathic urticaria (Colombo *et al.*, 2010[4];Khattri*et al.*, 2014[5]).

Experimental studies and clinical observations reveal that CsA can lead to drug-induced liver injury (DILI). The functional changes include elevated serum levels of liver transaminases and alkaline phosphatase, cholestasis, hyper bilirubinemia, increased production of bilesalts, and impaired secretion of lipids (Abboud and Kaplowitz, 2007[6]).

In addition to its effects on immune function, CsA possesses several other toxic effects. The most notable is acute and chronic nephrotoxicity, but also include hypertension, hyperlipidemia, gingival hyperplasia, hyperkalemia, neurotoxicity, hypo- magnesaemia, hyperuricemia, and thrombotic microangiopathy (Kahan, 1989[1]).

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CsA can cause metabolic and electrolyte disorders, that is, weight gain, hyperglycaemia, hyper lipidaemia, hypercalcaemia, and hypomagnesaemia (Serkova*et al*., 2004[7]).

These effects are thought in part due to calcineurin inhibition in non lymphatic tissues (Williams and Haragsim, 2006[8]). The electrolyte disturbances are believed due to alterations in tubular function and thereby ion homeostasis (Naesens*et al*., 2009[2]).

Material and Methods

Twenty eight male white rabbits weighing 800-900 g were obtained from the Public market, Almarj City, Animals were housed 7 per cage and kept on commercial diet and tap water (*ad libitum*). After two weeks of acclimation, animals were divided into four equal groups, 7 animals in each group. The first group was used as control (commercial diet and tap water). Second group was treated with cyclosporine A (15 mg/kg BW) in olive oil by gavage twice a week, group 3 was treated with *thymus vulgaris* 100ml/kg BW daily, group 4 was treated with the combination of cyclosporine A and *Thymus vulgaris*.

Rabbits were orally administered their respective doses by gavage for twenty one days. CsA, and olive oil doses and way of administration were established according to previous studies (Battino*et al.*, 2003[9]; Kwak and Mun, 2000[10]). Animals were weighed daily while receiving treatment for 21 days. On the 22th day of an experiment all animals were anesthetized with methyl alcohol and blood samples were obtained for biochemical analysis.

Preparation of *Thymus vulgaris* extract

Plant material was shade dried and powered with herbal grinder. The powdered material was stored in well closed cellophane bags at 4 ºC in the refrigerator. The powdered plant was extracted by method of cold maceration. The powder was soaked in distilled water for 48 hours with occasional shaking. It was passed through muslin cloth and then filtered through the filter paper. The extract was dried with the help of rotary evaporator (Mushtaq*et al.*,2013[11]).

Blood biochemical parameters and enzyme activities

Plasma was obtained by centrifugation of samples at 860 xg for 20 min, and was stored at -20°C until used for analyses. Stored plasma samples were analyzed for total protein (TP) by the Biuret method according to Armstrong and Carr (1964[12]). Albumin (A) concentration was determined by the method of Doumas *et al*., (1977[13]). Plasma glucose, urea and creatinine concentrations were measured by the method of Trinder (1969[14]), Patton and Crouch (1977[15]) and Henry *et al*., (1974[16]), respectively. Plasma total bilirubin was measured using the method of Pearlman and Lee (1974[17]).

The activities of plasma aspartate transaminase (AST; EC 2.6.1.1) and alanine transaminase (ALT; EC 2.6.1.2) were assayed by the method of Reitman and Frankel (1975[18]). Alkaline phosphatase (AlP; EC 3.1.3.1) activity was determined in plasma according to the method ofPrincipato *et al*., (1985[19]). Acid phosphatase (AcP; EC 3.1.3.2) activity was determined according to the method of Moss (1984[20]).

Statistical analysis

Statistical analysis was carried out by Minitab software statistics. Significance was assessed using two samples T-test analysis. $P<0.05$ is considered significant (Paulson[21], 2008).

Result and Discussion

Table (1) shows levels of total protein , albumin and bilirubin in serum of male rabbits. Levels of total protein and albumin showed a significant depression after treatment with cyclosporine A compared to the control. Levels of bilirubin showed significant increase after treatment with cyclosporine A.

Levels of total protein, albumin and bilirubin showed recovery after treatment with the combination of cyclosporine A and *Thymus valgaris*.

Table 1: Mean ±SE of serum biochemistry of male rabbits treated with cyclosporine A (cyc A), *thyums vulgaris* (T.vul) and their combination cyc A and T.vul.).

parameter	control	Cyc A	T.vul	cycA+T.vul
Total protein	8.2^{b}±0.14	6.5^{a}±0.14	7.9^{b}±0.14	7.8^{b}±0.13
Albumin	5.4^{b}±0.12	4.5^{a}±0.14	5.2^{b}±0.08	4.8^{b}±0.1
Bilirubin	0.75^{b}±0.01	1.3^{a}±0.11	0.81^{b}±0.01	1.1^{b}±0.1

Values are expressed as mean ± SE. mean values within an arrow not sharing a common superscript letter were significantly different ($P<0.05$).

Table (2) shows levels of Alanine transaminase (ALT) and aspartate transaminase (AST).ALT and AST increased significantly in serum of male rabbits after treatment with cyclosporine A. levels of ALT and AST returned to their normal levels after treatment with the combination of cyclosporine A and *thymus vulgaris*.

Table 2: Levels of Alanine transaminase (ALT) and aspartate transaminase (AST)

parameter	control	CycA	T.vul	CycA+T.vul
ALT	$16.3^{b} \pm 0.25$	$24.7^{a} \pm 0.22$	$15.5^{b} \pm 0.18$	$13.1^{b} \pm 0.25$
AST	$25.1^{b} \pm 0.21$	$33.4^{a} \pm 0.22$	$22.7^{b} \pm 0.27$	$29.4^{b} \pm 0.23$

Values are expressed as means ±SE. Mean values within arrow not sharing a common superscript letter were significantly different (P<0.05).

Table (3) shows that levels of alkaline phosphatase (AlK) and acid phosphatase (AcP) increased significantly after treatment with cyclosporine A compared with the control. Levels of ALP and ACP decreased significantly after treatment with the combination of CsA and *Thymus vulgaris* compared to the group treated with cycA alone.

Table 3: Levels of alkaline phosphatase (AlK) and acid phosphatase (AcP)

Parameter	Control	Cyc A	T.vul	CycA+T.vul
AlK	$71.3^{b} \pm 0.27$	$81^{a} \pm 0.3$	$69.6^{b} \pm 028$	$78.3^{a} \pm 0.28$
AcP	$12.5^{b} \pm 0.12$	$20.7^{a} \pm 0.23$	$11.7^{b} \pm 0.33$	$15.1^{b} \pm 0.18$

Valus are expressed as mean ± SE, mean values within an arrow not sharing a common superscript letter were significantly different (P<0.05.

Table (4) show levels of LDH and glucose. Levels of LDH and glucose showed significant increase after treatment with cyclosporine A in serum of male rabbits. there was a significant decrease in the level of glucoseby the effect of thymus vulgaris compared to group treated with cyclosporine A and group that treated with their combination (Cyc A and T.vul).

Table 4: Levels of LDH and glucose

Parameter	Control	Cyc A	T.vul	CycA+T.vul
LDH	$939^{b} \pm 0.70$	$1110.6^{a} \pm 1.28$	$933.40^{b} \pm 1.43$	$1061^{c} \pm 3.1$
Glucose	$116^{b} \pm 1.41$	$125^{a} \pm 1.5$	$77.8^{c} \pm 0.86$	$101.6^{b} \pm 1.07$

Values are expressed as mean ±SE, mean values within an arrow not sharing a common superscript letter were significantly different (P<0.05).

Table (5) show levels of urea and creatinine in serum of male rabbits. Levels of urea and creatinine increased significantly after treatment with cyclosporine A. Levels of urea and creatinine were significantly decreased after treatment with *Thymus vulgaris* compared with cyclosporine A group.

Table 5: Levels of urea and creatinine in serum of male rabbits

Parameter	Control	CycA	T.vul	CycA+T.vul
Urea	$49.6^{b} \pm 0.23$	$59.3^{a} \pm 0.26$	$47.6^{b} \pm 0.23$	$54.1^{a} \pm 0.30$
Creatinine	$0.7^{b} \pm 0.09$	$1.2^{a} \pm 0.01$	$0.6^{b} \pm 0.12$	$0.9^{a} \pm 0.13$

Values are expressed as mean ± SE, mean values within an arrow not sharing a common superscript letter were significantly different (p<0.05).

Our results showed that levels of total protein and albumin were significantly decreased after treatment with cyclosporine A. levels of total protein and albumin increased after treatment with *thymus vulgaris*extract and there was no significant difference between control group and group treated with the combination of cyclosporine A and Thymus vulgaris. These results were in agreement with the results

obtained by Mohsenikia*et al.* (2012[22]), after treatment of rats with cyclosporine A.

The protein depression might be due to loss of protein either by reduced protein synthesis or increased proteolytic activity or degradation (Yeragi*et al.*, 2003[23]). A significant increase in serum protein levels was observed after thymus vulgaris administration in CsA treated rats as compared with CsA group. Similar results were observed by (Hussein *et al.*,2014[24]) after administration of green tea to CsAt reated rats. These results were also shown by Mohsenikia*et al.* (2012[22]) after administration of Vitamin C to rats after treatment with CsA.

Our findings revealed that administration of CsA increased levels of AST, ALT, and bilirubin and these findings are consistent with the results of experimental studies of other authors, which show that elevated levels of these parameters confirmed functional liver damage (Korolczuk*et al.*, 2016[25]) and Erarslan*et al.*(2011[26]).

According to Issabeagloo *et al.*,(2012[27]) hepato cellular damage affects most liver function tests including serum amino transferase, alkaline phosphatase, bilirubin and albumin and causes release of these enzymes into circulation. Return of these above enzymes to their normal values following green tea extract, *thymus vulgaris* or vitamin C treatment may be due to prevention of intracellular enzyme leakage resulting in cellular membrane stability or cellular regeneration. Effective control of bilirubin and albumin show early improvement of functional and secretory mechanism of hepatic cells (Hussein *et al.*, 2014[24]).

CsA administration to rats resulted in a significant increase in serum marker enzyme (LDH) activity as compared to control. Also Heikal*et al.*, (2013[28]) demonstrated that LDH can be used as an indicator of cellular damage and cytotoxicity by toxic agents. In fact, elevation in LDH activity indicates cell lysis and death as well as switching from anaerobic glycolysis to aerobic respiration. LDH activity resulted from overproduction of superoxide anions and hydroxyl radicals which cause oxidative damage to cell membrane and increase membrane permeability (Hussein *et al.*, 2013[24]).

CsA is calcineurin inhibitor, the most limiting side effects of calcineurin inhibitors is inhibition of nitric oxide production, through a calcineurin regulating and dephosphorylation (Kou *et al.*, 2002[29]).

Administration of *thymus vulgaris* extract to CsA treated rats resulted in significant decrease in serum enzymes AST, ALT, LDH, ALK and ACP when compared with CsA group. These results were in agreement with the results obtained by Kumar *et al.*, (2010) [30], who recorded that increased activities of AST, ALT, LDH are well known diagnostic indicators of hepatic injury in such cases as liver damage with hepato cellualr lesions. These enzymes are released from liver into blood stream. These results were in agreement with the results obtained by Grespan*et al.* (2014[31]), who found that pretreatment of mice with 250 and 500 mg/kg Thymus essential oils for 7 days markedly reduced serum ALT, AST and ALP prior to acetaminophen administration. Also, pre-treatment with green tea significantly lowered the levels of these enzymes and values were comparable with control group (Kumar *et al.*, 2010[30]). Co-administration of *thymus vulgaris* prevented the injury in CsA treated animals where hepatocytes regained their normal appearance (fetouh and Ibrahim, 2013[32]).

Our results showed that CsA treatment for 21 days significantly increased the serum urea and creatinine as compared with the control group. Adminstration of *Thymus Vulgaris* significantly prevented this rise in serum urea and creatinine. These results were in agreement with the results obtained by (Tirky*et al.*, 2005[33]), who found that administration of CsA to rats for 21 days significantly increased the serum urea and creatinine, but Chronic curcumin treatment significantly and dose-dependently prevented this rise in serum urea and creatinine as happened with *Thymus Vulgaris.*

The exact mechanism of CsA-induced hypertension and nephrotoxicity remain obscure but several studies suggest that a defect in intracellular calcium handling (Cheng*et al.*, 2002[34]), magnesium deficiency (Mervaala*et al.*, 1997[35]), oxidative stress (Satyanarayana and Chopra, 2002[36]), and nitric oxide (NO) system (De Nicola *et al.*, 1993[36]) are involved. Acute renal failure due to CsA is widely attributed to the generation of reactive oxygen species (ROS) by CsA.

Administration of *Thymus vulgaris* to CsA treated rabbits resulted in a significant decrease in serum glucose levels compared with the other two groups but the group treated with *Thymus vulgaris* only had the least value of glucose because *Thymus vulgaris* had antihyperglcemic effect. These results were in agreement with the results obtained by Mushtaq*et al.*, (2013[11]),who evaluated the hypoglycemic effect of aqueous extract of Thymus serpyllum in glucose-fed mice for one month. In his study prevention of blood glucose elevation in mice fed with chronic glucose might be due to the increased clearance of glucose by the aqueous extract. Oxidative stress has also been considered as an explanation for the tissue damage that accompanies chronic hyperglycemia (Robertson *et al.*, 2004[37]).

Thymus vulgaris has been reported to exhibit antioxidant activity and antioxidants have been considered as treatment of diabetes (Cunningham, 1998[38]). The chronic high blood glucose level produces stress and leads to the formation of oxygen reactive species. It is suggested that the phytochemical constituents of the aqueous extract demonstrated a protective effect on the β-cells against the oxidative damage of high glucose concentration. Previous studies have shown that the certain phytochemical compounds e.g flavonoids of antioxidant plants play a protective role against the reactive oxygen species (ROS) that have cytotoxic effect on vital organ of the body, in particular the pancreas (Robertson *et al*., 2003[39]).

Midoui and Champlain (2002[40]) suggested the involvement of oxidative stress in the development of insulin resistance. Tsuneki*et al*., (2004[41]) and Babu*et al*. (2006[42]) observed that, green tea reduced blood glucose level in both type I and II of diabetic rat models. The antihyperglcemic effect of green tea constituents was ascribed to the activities of basal insulin (wu*et al.*, 2004[43]) and inhibition of intestinal glucose transporter (Kobayashi *et al.*, 2000[44]) and decrease the expression of genes that control gluconeogenesis (Waltner-Law *et al.*, 2002[45]).

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