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Effect of Cyclosporine A on some Blood Parmeters, Liver and Kidney Function Enzymes and the protective role of Cinnamon extract in rabbits

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Abstract:
This study investigated the biochemical and hematological effects of cyclosporine A (CsA) and the protective role of cinnamon extract in rabbits. Cyclosporine A, an immunosuppressant used in transplantation, is known to cause organ toxicity, especially in the liver and kidneys, often through oxidative stress. Our results showed that CsA treatment significantly decreased total protein and albumin, indicating compromised liver function. It also caused significant increases in liver enzymes (AST, ALT, LDH) and bilirubin, all signs of substantial liver damage. Furthermore, CsA led to reductions in red blood cell count and hemoglobin, affecting hematological parameters.Notably, co-administration of cinnamon extract effectively mitigated these adverse effects. Cinnamon is recognized for its antioxidant and anti-inflammatory properties, which counteract CsA-induced oxidative stress. The extract helped normalize liver enzyme levels and improved hematological parameters, demonstrating its protective efficacy against CsA-induced toxicity. This highlights cinnamon's potential as a natural adjunct to lessen the side effects of cyclosporine A therapy.

Keywords: Cyclosporine A, Cinnamon Extract, Liver Enzymes, Kidney, Hematological Parameters

تأثير السيكلوسبورين أ على بعض معايير الدم وأنزيمات وظائف الكبد والكلى والدور الوقائي المحتمل للمستخلص المائي للقرفة على ذكور الأرانب

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الملخص
بحثت هذه الدراسة في التأثيرات البيوكيميائية والدموية لسيكلوسبورين أ (CsA) والدور الوقائي لمستخلص القرفة لدى الأرانب. يُعرف السيكلوسبورين أ، وهو مثبط للمناعة يُستخدم في عمليات زرع الأعضاء، بأنه يُسبب سميةً للأعضاء، وخاصةً في الكبد والكلى، غالبًا من خلال الإجهاد التأكسدي. أظهرت نتائجنا أن علاج السيكلوسبورين أ أدى إلى انخفاض ملحوظ في إجمالي البروتين والألبومين، مما يُشير إلى ضعف وظائف الكبد. كما تسبب في زيادات ملحوظة في إنزيمات الكبد (AST، ALT، LDH) والبيليروبين، وجميعها علامات على تلف الكبد الشديد. علاوة على ذلك، أدى السيكلوسبورين أ إلى انخفاض في عدد خلايا الدم الحمراء والهيموغلوبين، مما أثر على المعايير الدموية. والجدير بالذكر أن الإعطاء المتزامن لمستخلص القرفة خفف بشكل فعال من هذه الآثار الجانبية. تشتهر القرفة بخصائصها المضادة للأكسدة والالتهابات، والتي تُقاوم الإجهاد التأكسدي الناتج عن السيكلوسبورين أ. ساعد المستخلص على تطبيع مستويات إنزيمات الكبد وتحسين المعايير الدموية، مما يُظهر فعاليته الوقائية ضد السمية الناتجة عن السيكلوسبورين أ. ويسلط هذا الضوء على إمكانات القرفة كمكمل طبيعي لتقليل الآثار الجانبية لعلاج السيكلوسبورين أ.

الكلمات المفتاحية: سيكلوسبورين أ، مستخلص القرفة، إنزيمات الكبد، الكلية، المعايير الدموية.

Introduction

Cyclosporine A (CsA) belongs to calcineurin inhibitors used in patients after kidney, liver, heart, lung, and heart-lung transplants [1]. Moreover, CsA is used to treat the majority of autoimmune diseases, in dermatology to treat psoriasis, autoimmune dermatitis, or chronic idiopathic urticaria [2]. The major adverse side effect of CsA is acute

and chronicnephrotoxicity. CsA can cause metabolic and electrolyte disorders, that is, weight gain, hyperglycaemia, hyperlipidaemia, hypercalcaemia, and hypomagnesaemia [3]. In CsA-induced liver injury, functional and morphological changes are observed. The functional changes include elevated serum levels of liver transaminases and alkaline phosphatase, cholestasis, hyperbilirubinemia, increased production of bile salts, and impaired secretion of lipids [4].
The use of antioxidants in experimental animals exposed to CsA reduces liver functional and morphological damage [5], which suggests the involvement of oxidative stress as one of the mechanisms of hepatotoxicity.

Cinnamon
One method of restoring antioxidants is suggested to consume natural compounds with antioxidant capacity [6]. Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils [7]. Cinnamon has been used as anti-inflammatory and antitermitic [8], nematicidal [9], mosquito larvicidal [10], insecticidal [11], antimycotic [12], and anticancer agent [13].
It was reported that various extracts of cinnamon, such as ether, aqueous, and methanolic extracts that have shown considerable antioxidant activities [14]. The aqueous and alcoholic extract (1:1) of cinnamon potentially significantly inhibits fatty acid oxidation and lipid per oxidation in vitro [15]. Different flavonoids isolated from cinnamon have free-radical-scavenging activities and antioxidant properties [16]. A recent study investigated the antioxidant properties of several parts (i.e., the leaves, barks, and buds) of C. cassia. The ethanolic extract of all of the plant parts had significant antioxidant properties compared with the extraction using the supercritical fluid [17].

Materials and methods
Thirty male white rabbits weighing 500-800 g were obtained from the public market, Al-Bayda city, animals were housed 6 per cage and kept on commercial diet and tap water (*ad libitum*). After two weeks of acclimation, animals were divided into five equal groups, 6 animals in each group. The first group was used as control (commercial diet and tap water). Second group was treated olive oil. Third group was treated with cyclosporine A (15 mg/kg BW) in olive oil by gavage twice a week, group 4 was treated with cinnamone xtract.Fifth group was treated with the combination of cyclosporine A and cinnamon extract.
Rabbits were orally administered their respective doses by gavage for thirty days. CsA, and olive oil doses and way of administration were established according to previous studies [18,19]. Animals were weighed daily while receiving treatment for 30 days. On the 31th day of an experiment all animals were anesthetized with methyl alcohol. After killing of animal's blood samples were obtained immediately for biochemical analysis.
Preparation of aqueous extract of cinnamon:
A total of 200 g of each powder of cinnamon barks were dissolved in 1 L of distilled water and boiled for 10 min, cooled and filtered through double layers of gauze to obtain cinnamon aqueous extracts 20% [20]. Cinnamon was purchased from public market for medicinal herbs in Al-Bayda city. Animals were treated with cinnamon extract0.2 ml/kg BW three times a week.

Measured parameters
Blood biochemical parameters and enzyme activities
Plasma was obtained by centrifugation of samples at 860 g 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 [21]. Albumin (A) concentration was determined by the method of [22]. Plasma glucose, urea and creatinine concentrations were measured by the method of [23,24,25], respectively. Plasma total bilirubin was measured using the method of [26].
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 [27]. Alkaline phosphatase (AlP; EC 3.1.3.1) activity was determined in plasma according to the method of [28].

Statistical analysis
Statistical analysis was carried out by Minitab software statistics. Statistical significance of the difference in values of control and treated animals was calculated by F test with 5% significance level. $P<0.05$ is considered significant [29].

Results
Biochemical parameters
Table (1) shows levels of total protein, albumin and bilirubin in serum of male rabbits. Levels of total protein and albumin showed a significant decrease after treatment with cyclosporine A compared to the control. Levels of bilirubin showed significant elevation after treatment with cyclosporine A. Levels of total protein; albumin

showed an increase in their level but still less than the control. Levels of billirubin showed a decrease but still significantly different from control after treatment with the combination of cyclosporine A and cinnamon extract.

Table (1): serum biochemistry of male rabbits treated with cyclosporine A and combination of cyclosporine A (cyc A) and cinnamon extract (Cinn).

parameter	control	Cinn	Oil	Cyc A	Cyc A +Cinn
T. protein	$30.4^{a}\pm1.03$	$31.1^{a}\pm 0.43$	30.9 ± 0.49^{a}	$22.7^{b}\pm0.88$	$24.3^{b}\pm0.65$
Albumin	$36.9^{a}\pm1.2$	$37.0^{a}\pm0.74$	$37.4^{a}\pm0.51$	27.0 ± 1.08^{b}	$30.4^{b}\pm1.1$
Bilirubin	$1.6^{b}\pm0.014$	$1.5^{b}\pm.070$	1.7 ± 0.11^{b}	$2.6^{a}\pm0.16$	$2.0^{a}\pm0.10$

Values are expressed as means ±SE. Mean values within 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) and lactate dehydrogenase (LDH). ALT, AST and LDH increased significantly in serum of male rabbits after treatment with cyclosporine A. levels of ALT and AST and LDH decreased but still highly significant from control after treatment with the combination of cyclosporine A and cinnamon extract.

Table (2): Alanine transaminase, aspartate transaminase (AST) and LDH in serum of male rabbits treated with cyclosporine A (cyc A) and combination of cyclosporine A and cinnamon extract (cycA+Cinn).

parameter	control	Cinn	Oil	Cyc A	CycA+Cinn
ALT	$18.5^{c}\pm1.35$	$18.3^{c}\pm0.59$	$19.4^{c}\pm0.57$	$36.9^{a}\pm1.9$	$28.7^{b}\pm1.00$
AST	$117.4^{c}\pm1.68$	$119.6^{c}\pm0.92$	$120.4^{c}\pm0.92$	$148.4^{a}\pm1.3$	$132.3^{b}\pm1.0$
LDH	$535.4.4^{c}\pm1.2$	$550.8^{c}\pm1.6$	$552.4^{c}\pm2.3$	$715.2^{a}\pm1.9$	$636.2^{b}\pm1.6$

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 levels of red blood cells, white blood cells and hemoglobin of male rabbits. Levels of red blood cells and hemoglobin decreased significantly after treatment with cyclosporine A, while levels of white blood cells decreased significantly after treatment with cyclosporine A. Levels of red blood cells and hemoglobin increased significantly after treatment with the combination of cyclosporine A and cinnamon extract compared to control. Levels of white blood cells decreased significantly compared to control after treatment with the combination of cyclosporine A and cinnamon extract but still significantly different from control and cyc A treatment.

Table (3): shows Levels of red blood cells, hemoglobin and white blood cells of male rabbits treated with cyclosporine A (Cyc A) and combination of cyclosporine A and cinnamon extract (cycA+Cinn).

parameter	control	Cinn	oil	Cyc A	Cyc A+ Cinn
RBCs	$5.8^{a}\pm0.15$	$5.6^{a}\pm0.12$	$5.8^{a}\pm0.14$	$4.8^{b}\pm0.30$	$5.5^{b}\pm0.16$
WBCs	$9.6^{a}\pm0.13$	$9.2^{a}\pm0.30$	$9.5^{a}\pm0.23$	$7.2^{b}\pm0.25$	$8.0^{c}\pm0.16$
HG	$13.6^{a}\pm0.35$	$13.3^{a}\pm0.14$	$13.6^{a}\pm0.19$	$9.7^{b}\pm0.24$	$11.6^{c}\pm0.33$

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

Discussion

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 cinnamon extract and there was no significant difference between control group and group treated with the combination of cyclosporine A and cinnamon extract. These results were in agreement with the results obtained by [30], 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 [31], who found that CsA administered orally (100 mg kg^{-1} day^{-1}) to rats for 21 days caused marked decreases in total serum protein and albumin accompanied by rise in alkaline phosphatase and bilirubin.

The higher values of total protein, albumin and globulin indicate acute/chronic inflammation or infections caused by hepatitis B and C [32]. Albumin is about 60% of total serum protein responsible for various physiological functions. It has been reported in research that total protein, albumin and globulin level may decrease due to liver

dysfunction, diarrhea, malnutrition and malabsorption, acute hemolytic anemia, nephrosis, alpha-1-antitripsin deficiency; severe and loss through the urine in acute kidney disease [33].
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 [34,35]. According to [36], hepatocellular 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 administration of cinnamon extract, 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.
CsA administration to rats resulted in a significant increase in serum marker enzyme (LDH) activity as compared to control. Also [37], demonstrated that LDH can be used as an indicator of cellular damage and cytotoxicity by toxic agents. In fact, elevation in LDH activity indicates cellists 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. CsA is calcineurin inhibitor, the most limiting side effects of calcineurin inhibitors is inhibition of nitric oxide production, through a calcineurinregulating and dephosphorylation [38]. Administration of cinnamon extract to CsA treated rabbits resulted in significant decrease in serum enzymes AST, ALT, LDH, when compared with CsA group. These results were in agreement with the results obtained by [39], who recorded those increased activities of AST, ALT, LDH are well known diagnostic indicators of hepatic injury in such cases as liver damage with hepatocellualr lesions. These enzymes are released from liver into blood stream. The depression in serum enzymes AST, ALT, LDH after treatment with cinnamon were in agreement with the results obtained by [40], 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 [39]. Co-administration of thymus vulgaris prevented the injury in CsA treated animals where hepatocytes regained their normal appearance [41]. The present results showed that cinnamon extract ameliorates the biochemical alterations induced by cyclosporine A in rabbits. These findings are in accordance with the result of [42], who reported that the increased activities in serum ALT and AST of rats were suppressed by ethanolic extract of cinnamon.
The current study has revealed that treatment of rabbits with CsA for one month caused a significant decrease in RBCs count and hemoglobin. These results were in agreement with results obtained by [43], who found that treatment of rats with CsA for four weeks caused a significant decrease in Hb, Hct, and MCHC and MCHC. These results are in accordance with previous studies. Oral treatment of male rats with 10–20 mg/kg mycophenolate mofetil (an immunosupressive drug) for two weeks induced a significant reduction of RBCs count [44]. A clinical report showed that a significant decrease in Hb concentration following an increase in the plasma concentration of cyclosporine [45]. The most common cause of unexplained anemia may be due to bone marrow suppression induced by Immunosuppressive drugs [43].

Conclusion:
Importantly, treatment with cinnamon extract showed a protective effect against CsA-induced toxicity. These results align with earlier studies that reported the hepatoprotective and antioxidant properties of cinnamon and other natural compounds. This protective effect may be attributed to the antioxidant and anti-inflammatory properties of cinnamon, which counteract oxidative stress and cellular damage caused by CsA. Overall, the findings of this study suggest that cinnamon extract has a promising therapeutic potential in reducing the adverse effects of CsA on liver function and hematological parameters.

Recommendations:
Further research is recommended to explore the underlying mechanisms and to evaluate the clinical applicability of cinnamon extract as a complementary treatment in patients receiving CsA or other immunosuppressive drugs.

Disclaimer
The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest
There are no financial, personal, or professional conflicts of interest to declare.

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