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Oxidative Stress of Cyclosporine on Kidney Functions and Antioxidant Role of Cinnamon

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ABSTRACT
In this study, the oxidative effect of cyclosporine A (Cyc A) with or without cinnamon extract on kidney functions and some antioxidant enzymes in male rabbits was investigated. Levels of Na and K were depressed significantly after treatment with cyclosporine A compared to the control. A significant increase was found for Ca levels during treatment with cyclosporine A. Levels of TBARS showed a significant increase after treatment with cyclosporine A compared to the control. Levels of GSH and GST were significantly lower after treatment with cyclosporine A. Levels of these parameters were affected by the effect of cinnamon extract. It is well known that glutathione-S-transferase (GST) and glutathione play an important role in the detoxification of toxic metabolites, where GSH is catalysed by GST. One of the hypotheses explaining the detoxifying function of GST is the binding between GSH and endogenous or exogenous toxic substances; it plays an important role in the storage and excretion of xenobiotic compounds.

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INTRODUCTION

Cyclosporine (CsA), a neutral lipophilic cyclic undecapeptide isolated from the fungus Tolypocladium inflatum gams. CSA has a wide spectrum of biological effects, which are anti-parasitic, fungicidal, and anti-inflammatory. It is a powerful immunosuppressive agent [1]. Several studies have shown that the chronic treatment of patients with cyclosporine-based immunosuppressants has adverse renal function. The drug may have effects like afferent glomerulo-arteriolar constriction with a hemodynamically mediated decrease in the glomerular filtration rate. Also, solute transport alterations and thrombotic microangiopathy related to the direct endothelial injury may happen [2]. Glomeruloarteriolar constriction with a hemodynamically mediated decrease in the glomerular filtration rate. Also, solute transport alterations and thrombotic microangiopathy related to the direct endothelial injury may happen [2].

CsA is an important immunosuppressive agent that is an essential part of the drug regimen in transplant patients and the treatment of diseases involving the immune system [3]. However, its clinical and experimental use is limited by several side effects such as nephrotoxicity, cardiotoxicity, hypertension, and hepatotoxicity [4]. Different authors suggest that reactive oxygen species (ROS) production, oxidative stress, depletion of the hepatic antioxidant system, and an increase in malondialdehyde (MDA) are possible mechanisms of CsA hepatotoxicity [5]. Fortunately, there are several antioxidant mechanisms that can neutralize free radicals in living organisms. The defence mechanisms for antioxidants are grouped into enzymatic mechanisms, which include glutathione peroxidase, catalase, and superoxide dismutase, and non-enzymatic antioxidants that can deal with free radicals and neutralize them [6]. Cinnamon is one of the very important and powerful antioxidants.

The antimicrobial activity of several plant-derived compounds has been reported to be synthesized in the secondary metabolism of the plant and is produced as a result of interactions between plants, microbes, and animals [7]. Plant-derived antimicrobials do not exhibit the side effects often associated with the use of synthetic chemicals [8]. The World Health Organization (WHO) estimates that more than 80% of healthcare needs in developing countries are met through traditional healthcare practices [9].

The main properties of cinnamon are astringent, warming, stimulating, carminative, antiseptic, antifungal, antiviral, blood purifying, and aiding digestion. Cinnamon has properties that make it a good medicinal plant. Cinnamon oil has very powerful medicinal effects, and there are many uses for it. Cinnamon oil is an aromatic used to remove the unpleasant taste of other drugs [10]. Cinnamon's medicinal properties are due to terpenoids found in the spice's essential oil. Of these

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terpenoids found in cinnamon are Eugenol and cinnamaldehyde. Cinnamaldehyde and cinnamon oil vapors are very potent antifungal agents [10].

METHODS

Thirty male white rabbits, each weighing between 500 and 800 grams, were sourced from the public market in Al-Bayda City. The rabbits were divided into five groups. Rabbits were grouped into six rabbits per cage.A commercial diet and tap water were provided according to general guidelines. After a two-week acclimation period, the rabbits were divided into five equal groups, with six animals in each group. The first group served as the control, receiving only the commercial diet and tap water. The second group was administered olive oil. The third group was given cyclosporine A (15 mg/kg body weight) in olive oil.

CSA was given by gavage twice a week. The fourth group received cinnamon extract, while the fifth group was administered a combination of cyclosporine A and cinnamon extract. The treatment of rabbits and their respective doses was made orally via gavage for thirty days. The dosages of cyclosporine A and olive oil, as well as the method of administration, were made according to [11]. The animals were weighed daily throughout the 30-day treatment period. At the end of the experiment, all animals were anesthetized with methyl alcohol, then slaughtered for the collection of blood samples.

Preparation of aqueous extract of cinnamon

A total of 200 grams of cinnamon bark powder was dissolved in 1 liter of distilled water, boiled for 10 minutes, then cooled and filtered through double layers of gauze to produce a 20% aqueous extract of cinnamon. The cinnamon was sourced from a medicinal plant market for medicinal herbs in Al-Banda city. A dosage of 0.2 ml per kg of body weight was administered to animals three times a week.

Kidney function tests

Urea was determined according to the method of [12]. Creatinine was determined by kinetic test without deproteinization according to the Jaffe method [13]. The activity of Glutathione S-transferase (GST; EC 2.5.1.18) was determined according to the method of [14]. Plasma thiobarbituric acid-reactive substances (TBARS) were measured by the method of [15].

Statistical analysis

Statistical significance of the difference in values between control and treated animals was calculated by the F test with 5% significance level. Data from the present study were statistically analyzed by using data analysis carried out by Minitab software [16].

RESULTS

Table 1 shows levels of Na^+, K^+, and Ca^+ in the serum of male rabbits. A significant depression in the levels of Na and K was shown after treatment with cyclosporine A compared to the control, while levels of Ca increased significantly after treatment with cyclosporine A.

Levels of Na and K were depressed after treatment with the combination of cyclosporine A and cinnamon extract. Levels of Cash owed were higher after treatment with the combination of cyclosporine A and cinnamon extract compared with cyclosporine A alone.

Table 2 shows levels of urea and creatinine in the serum of male rabbits. Levels of urea and creatinine were significantly higher in the serum of male rabbits after treatment with cyclosporine A. Their levels were depressed after treatment with the combination of cyclosporine A and cinnamon extract, but still significantly different compared to the control.

TBARS, glutathione and glutathione S-transferase

(Table 3) shows levels of TBARS, glutathione, and glutathione-S-transferase in the serum of male rabbits. Levels of TBARS were significantly higher after treatment with cyclosporine A compared to the control. Their levels showed significant depression after treatment with the combination of cyclosporine A and cinnamon extract. GSH and GST showed a significant depression after treatment with cyclosporine A (Cyc A). Their levels showed significantly higher values after treatment with the combination of cyclosporine A and cinnamon extract (CycA+Cinn).

Table 1. Levels of Na, K, and Ca in the serum of male rabbits treated with cyclosporine (cyclosporine A) and a combination of cyclosporine A and cinnamon extract (Cyc+Cinn).

Parameter	control	Cinn	Oil	Cyc A	Cyc +Cinn
Na^+	$141.6^{a}\pm0.71$	$143.2^{a}\pm0.73$	145.4 ± 1.32^{a}	$118.4^{b}\pm1.07$	$127.4^{b}\pm1.13$
K^+	$5.3^{a}\pm0.21$	$5.4^{a}\pm0.25$	$5.7^{a}\pm0.19$	$3.2^{c}\pm0.20$	$4.6^{b}\pm0.33$
Ca^+	$5.2^{a}\pm0.20$	$5.3^{a}\pm0.15$	$5.7^{a}\pm0.13$	$6.5^{a}\pm0.23$	$4.1^{b}\pm0.20$

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

Table 2. Levels of urea and creatinine in serum of male rabbits treated with cyclosporine A (Cyc A) and a combination of cyclosporine A and cinnamon extract (CycA+Cinn).

parameter	control	Cinn	Oil	Cyc A	Cyc A +Cinn
urea	$314.6^{c}\pm1.9$	$318^{c}\pm1.8$	$323.4^{c}\pm1.43$	$351.6^{a}\pm1.1$	$332.8^{b}\pm1.24$
creatinine	$10.2^{b}\pm0.35$	$9.6^{b}\pm0.3$	$10.1^{b}\pm0.28$	$18.5^{a}\pm0.34$	$15.9^{a}\pm0.53$

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

Table 3. Levels of TBARS, GSH, and GST of male rabbits treated with cyclosporine A (Cyc A) and a combination of cyclosporine A and cinnamon extract (cycA+Cinn).

parameter	control	Cinn	Oil	Cyc A	Cyc A +Cinn
TBARS	0.54^{b}±0.01	0.55^{b}±0.01	0.57^{b}±0.01	0.96^{a}±0.02	0.90^{a}±0.01
GSH	0.58^{a}±0.01	0.57^{a}±.01	0.57^{a}±0.01	0.47^{b}±0.03	0.50^{b}±0.02
GST	1.7^{a}±0.07	1.56^{a}±0.09	1.6^{a}±0.09	1.4^{b}±0.09	1.5^{b}±0.07

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

DISCUSSION

Our results were consistent with the findings of [17], which showed marked elevation of serum urea and creatinine concentrations, suggesting a significant functional impairment of kidneys in cyclosporine A-treated rabbits. This suggestion was supported by the findings of [18], who observed that plasma urea and creatinine indicate several disturbances in kidney levels of urea and creatinine. Administration of cinnamon extract to rabbits normalized levels of urea and creatinine. These results were in agreement with the results of [18]. After administration of green tea to rats.

Administration of cyclosporine A to rabbits resulted in a significant decrease in serum electrolytes (sodium and potassium) as compared with the control group. These results are nearly similar to the study of [19], who found that there is a relationship between sodium depletion and cyclosporine A treatment. Also [20]. Reported that hypokalaemia was more frequent under cyc A treatment. Cyc-induced nephrotoxicity has been characterized by a 20-30% reduction in glomerular filtration rate and up to 40%reduction in renal blood flow, resulting in elevated serum creatinine levels, decreased creatinine clearance, and reduction in sodium and potassium [21]. It has been reported that the decrease in Na-K ATPase activity caused by cyc A is thought to be one of the mechanisms for the observed potassium ion secretion defects [22, 23] reported that chronic treatment of rats with CsA induced nephrotoxicity by increasing Kidney function parameters. The relationship between anemia and chronic kidney disease is thoroughly documented [24]. Also, anemia is common after treatment with cyclosporine in liver-transplant patients, which may be due to inhibition of erythropoietin production induced by cyclosporine [25].

In this study, levels of TBARS increased significantly with the cyclosporine A treatment, while levels of GSH and glutathione S-transferase decreased. It is well known that endogenous antioxidant enzymes are responsible for preventing and neutralizing the free radical-induced oxidative damage. The antioxidant enzymes, such as GST, constitute a major supportive team of defense against free radicals [26]. Targeting and modulating these physiological defense mechanisms by chemopreventive agents has become a part of many therapeutic strategies. In the present study, CsA administration significantly decreased the activity of these antioxidant enzymes; thus, providing more evidence for the involvement of oxidative damage in CsA-induced hepatotoxicity and nephrotoxicity. The implication of reactive oxygen species in CsA hepatotoxicity and nephrotoxicity was strengthened by the fact that many free radical scavengers provide marked functional and histopathological protection against CsA nephrotoxicity [27].

In a study of the wound healing action of an ethanol extract of cinnamon, the significant increase in wound healing was attributed to the antioxidant activity [28]. Cinnamon constituents have powerful antioxidant action and may have a potential effect against free radical damage to cell membranes [29]. Cinnamon has a marked antioxidant effect and may be beneficial in alleviating the complications of many illnesses related to oxidative stress in humans [30].

Increased levels of TBARS were consistent with the results of [31], who found that levels of lipid peroxidation products (TBARs and hydroperoxides) were significantly higher in streptozotocin diabetic rats. It is well known that glutathione-S-transferase (GST) and glutathione play an important role in the detoxification of toxic metabolites, where GSH is catalyzed by GST [32]. One of the hypotheses explaining the detoxifying function of GST is the binding between GSH and endogenous or exogenous toxic substances; it plays an important role in the storage and excretion of xenobiotic compounds [33].

CONCLUSION

The results showed that the cinnamon played a role in alleviating of harmful effects of cyclosporine A and increasing the potential of antioxidant enzymes.

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