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THE PROTECTIVE ROLE OF GINGER AGAINST HEPATOTOXICITY OF CYCLOSPORINE A

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ABSTRACT

In this study, we investigated the possible protective role of the *ginger* extract in reducing hepatic and renal toxicity of cyclosporine A in rats. Levels of total protein and albumin had a significant decrease after treatment with cyclosporine A compared to the control. Levels of ALT, AST, and LDH increased significantly after treatment with cyclosporine A compared to the control. Results showed that ginger extract decreased the toxic effects of cyclosporine A.

KEYWORDS

Cyclosporine, Ginger and Hepatotoxicity.

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INTRODUCTON

Cyclosporine A (CsA) belongs to calcineurin inhibitors used in patients after kidney, liver, heart, lung, and heart-lung transplants for graft-versus-host disease (GVHD) prophylaxis (Tedesco and Haragsim, 2012)[1]. Moreover, CsA is used to treat the majority of autoimmune diseases, in dermatology to treat psoriasis, autoimmune dermatitis, or chronic idiopathic urticaria (Khattri *et al*, 2014)[2].

Cyclosporine is a lipophilic, cyclic endecapeptide with a molecular weight of 1202 Daltons (Kahan, 1989)[3]. 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, hyperbilirubinemia, increased production of bilesalts, and impaired secretion of lipids (Abboud and Kaplowitz, 2007)[4].

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)[3]. CsA can cause metabolic and electrolyte disorders, thatis, weight gain, hyperglycaemia, hyperlipidaemia, hypercalcaemia, and hypomagnesaemia (Serkova *et al*, 2004)[5]. These effects are thought in part due to calcineurin inhibition in nonlymphatic tissues (Williams and Haragsim, 2006)[6]. The electrolyte disturbances are believed due to alterations in tubular function and thereby ion homeostasis (Naesens *et al*, 2009)[7].

Ginger (Zingiber officinale Roscoe, Zingiberacae) is one of the most commonly used spices around the world, especially in the South-Eastern Asian countries. Ginger is also a medicinal plant that has been widely used in Chinese, Ayurvedic and Unani-Tibb medicines, since antiquity, for a wide array of ailments that include arthritis, rheumatism, sprains, muscular throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis (Ali *et al*, 2008)[8].

Ginger (Zingiber officinale) has been consumed since antiquity and is known to play diverse biological roles including anti oxidation, anti-inflammation, hypolipidemia, anti-carcinogenesis, anti-nausea, antithrombosis, and antibacterial process (Stoilova *et al*, 2007)[9].

It has been reported that nephroprotective activity of aqueous ethanol extract of Zingiber officinale against cisplatin-induced acute renal toxicity in mice. Since a high dose acetaminophen- induced hepatotoxicity was resulted from the generation of free radicals during its metabolism at liver. The possible protection by aqueous ethanol extract of Zingiber officinale may be due the polyphenolic compounds (6-gingerol and its derivatives), which have a high antioxidant activity (Ajith *et al*, 2007)[10].

The intake of ginger (Zingiber officinale Roscoe) significantly decreased the concentration of thiobarbituric acid-reactive substances (TBARS), lipid peroxidation and the formation of malonaldehyde in rats (Ippoushi *et al*, 2007)[11].

MATERIAL AND METHODS

Male white rats weighing 220-230g were used in the experiment. Rats were obtained from the Faculty of Science and were housed 7 per cage. After the period of acclimation, rats were divided into three equal groups. 7 animals were used in each group. The first group was provided with commercial diet and tap water and used as control. Second group was treated with cyclosporine A (15mg/kg BW) in olive oil by gavage twice a week, group 3 was treated with the combination of cyclosporine A and ginger (100mg/kg BW (Santosh *et al*, (1996)[12], El-Sharaky *et al*, (2009)[13]. Rats 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[14], Kwak and Mun, 2000[15]). Weights of Animals were measured daily after treatment for 21 days. After 21days of an experiment all animals were killed for obtaining blood samples for biochemical analysis.

RESULTS AND DISCUSSION

Table No.1 total protein and albumin showed a lower values after treatment with cyclosporine A compared to the control. Levels of total protein, albumin showed recovery after treatment with the combination of cyclosporine A and ginger.

Table No.2 shows levels of Alanine transaminase (ALT) and aspartate transaminase (AST). ALT and AST increased significantly in serum of male rats after treatment with cyclosporine A. levels of ALT and AST returned to their normal levels after treatment with the combination of cyclosporine A and ginger (G).

Table No.3 show levels of urea and creatinine in serum of male rats. Levels of urea and creatinine significantly higher after treatment with cyclosporine A. Levels of urea and creatinine were significantly decreased after treatment with ginger (G) compared with cyclosporine A group.

Table No.4 show levels of GSH and GST in serum of male rats. Levels of glutathione and glutathione s-transferase decreased by the effect of cyclosporine

A. their values returned to the normal values after treatment with ginger.

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 ginger extract and there was no significant difference between control group and group treated with the combination of cyclosporine A and ginger. The same results were obtained by Mohsenikia *et al*, (2012)[16], which agree with our study.

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)[17]. Similar results were observed by (Hussein *et al*, 2014)[18] after administration of green tea to CsA treated rats. (Mohsenikia *et al*, 2012)[16] found same results after treatment of rats with vitamin C and CsA.

Our findings revealed that administration of CsA increased levels of AST, ALT 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)[19] and (Erarslan *et al*, 2011)[20].

According to Issabeagloo *et al*, (2012)[21] hepatocellular damage affects most liver function tests including serum aminotransferase, alkaline phosphatase, causes release of these enzymes into circulation. Return of these above enzymes to their normal values following green tea extract, thymus vulgaris, vitamin C or ginger treatment may be due to prevention of intracellular enzyme leakage resulting in cellular membrane stability or cellular regeneration. Effective control of these parameters show early improvement of functional and secretory mechanism of hepatic cells (Hussein *et al*, 2014)[18].

When rats treated with CsA resulted in a significant increase in LDH activity in comparison with control. LDH may be used as an indicator of cellular damage and cytotoxicity (Heikal *et al*, 2013)[22]. The increase in LDH activity indicates cell lysis and death and it may indicate also 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)[18].

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)[23].

Administration of ginger extract to CsA treated rats 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 Kumar *et al*, (2010)[24] who recorded that 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 when released their levels increases in blood stream.

Grespan *et al*, (2014)[25], found that pretreatment of mice with 250 and 500mg/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)[24]. Co-administration of ginger prevented the injury in CsA treated animals where hepatocytes regained their normal appearance (Fetouh and Ibrahim, 2013)[26].

In this study CsA treatment for 21 days showed marked increase in the serum urea and creatinine in comparison with the control group. Adminstration of ginger significantly prevented this rise in serum urea and creatinine. These results were in agreement with the results obtained by (Tirky *et al*, 2005)[27], 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 ginger.

The exact mechanism of induced hypertension and nephrotoxicity caused by CsA remain obscure but several studies suggest that may be due to a defect in intracellular calcium handling (Cheng *et al*, 2002)[28], oxidative stress (Satyanarayana and Chopra, 2002)[29] or and nitric oxide (NO) system (De Nicola *et al*, 1993)[30]. The generation of reactive

oxygen species (ROS) may cause acute renal failure by CsA.

Treatment of rats with cyclosporine A caused marked decrease in levels of GSH and GST. Treatment with ginger caused recovery and returning of GSH and GST to normal levels. These results were in agreement with the results of (Siddaraju and Dharmesh 2007)[31], who reported that ginger-free phenolic and ginger hydrolysed phenolic fractions exhibited free radical scavenging, and reducing power abilities indicating strong antioxidant properties. Levelsof GSH in animals treated with Zingiber officinale is increased which may explain its mechanism of protection. Thiol group is increased by increased levels of GSH, which could effectively provide for the possible GSH mediated detoxification reactions of GPx and GST. Previously that administration of Zingiber officinale significantly enhanced GST activities in the liver of rat (Ajith *et al*, 2007)[10].

Table No.1: Mean ± SE of serum biochemistry of male rats treated with cyclosporine A (cyc A), and their combination cyc A and ginger (G)

S.No	parameter	Control	Cyc A	Cyc A +Ginger
1	T. protein	8.5 ± 0.16^{b}	6.6 ± 0.27^{a}	8.2 ± 0.15^{b}
2	Albumin	5.5 ± 0.27^{b}	4.5 ± 0.12^{a}	4.9 ± 0.20^{b}

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

Table No.2: Shows levels of AST, ALT and LDH in serum of male rats

S.No	Parameter	Control	Cyc A	Cyc A+G
1	AST (U/L)	47 ± 0.73^{b}	70 ± 3.61^{a}	53 ± 4.76^{b}
2	ALT (U/L)	55 ± 0.56^{b}	65 ± 2.27^{a}	61 ± 1.65^{b}
3	LDH(U/L)	933 ± 6.8^{a}	1133 ± 21.5^{b}	1100 ± 12.0^{b}

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

Table No.3: Shows levels of urea and creatinine in serum of male rats

S.No	Parameter	Control	Cyc A	Cyc A+G
1	Urea mg/dL	19.8 ± 0.86^{b}	29.6 ± 0.79^{a}	17.4 ± 0.61^{b}
2	Creatinine g/dL	0.75 ± 0.025^{b}	0.95 ± 0.038^{a}	0.70 ± 0.014^{b}

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

Table No.4: Shows levels of GSH and GST in serum of male rats

S.No	Parameter	Control	Cyc A	Cyc A+G
1	GSH (U/ml)	0.62 ± 0.007^{b}	0.270 ± 0.004^{a}	0.45 ± 0.006^{b}
2	GsT ***(µmol /hr/ml)***	1.00 ± 0.007^{b}	0.51 ± 0.024^{a}	0.62 ± 0.048^{b}

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

CONCLUSION

The results showed that ginger had a protective effects against toxicity of cyclosporine A. ginger is a strong antioxidant. So it is recommended with more work and researches for more declaration.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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