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Effect of combined administration of ginger (*Zingiber officinale* Roscoe) and atorvastatin on the liver of rats

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ABSTRACT

Ginger is known to possess hypolipidemic, antioxidant and hepatoprotective properties. Combination therapy often takes advantage of complementary effects of different agents. This study investigated the combined effect of ginger extract (GE) and atorvastatin on lipid profile and on atorvastatin-induced hepatic injury. Rats were randomized into: control; GE (400 mg/kg); atorvastatin (20 mg/kg) alone or with GE or vitamin E, and atorvastatin (80 mg/kg) alone or with GE or vitamin E. Administration of 80 mg/kg atorvastatin for 4 weeks had major hepatotoxic effect whereas the lower dose (20 mg/kg) seems to cause mild liver injury. Besides lowering serum total cholesterol and hepatic superoxide dismutase (SOD) and catalase (CAT), atorvastatin significantly increased serum aminotransferases, hepatic malondialdehyde (MDA) and nitric oxide (NO). Concurrent administration of GE and atorvastatin had the opposite effect. Histopathological study revealed that GE reduced liver lesions induced by atorvastatin. The results indicate that the ability of ginger to lower serum cholesterol and to decrease aminotransferases, MDA and NO is clinically important, because its chronic administration will neither lead to side-effects nor to hepatic changes as occurs with high atorvastatin doses. Therefore, combination regimens containing GE and low dose of statins could be advantageous in treating hypercholesterolemic patients which are susceptible to liver function abnormalities.

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) are group of drugs that have been recognized as the most efficient drugs for the treatment of hyperlipidemia (Wainwright 2005). Animal studies and pre-marketing clinical trials point to statins-induced significant liver problems, primarily elevations in serum aminotransferases levels. The frequency of persistent transaminases elevation is consistent with all commercialized statins, and is dose dependent (Veillard and Mach 2002). Accordingly, statins have labeling that requires the monitoring of liver enzymes (Parra and Reddy 2003). Initial toxicological studies in animals suggested that statins may cause hepatotoxicity. Although the usual doses of lovastatin did not cause significant liver injury, when given in very high doses they caused hepatocellular necrosis in rabbits (MacDonald et al. 1988). Similarly, high doses of simvastatin caused hepatocellular necrosis in guinea pigs (Horsman et al. 1990).

Atorvastatin (AT) differs from other statins in that it has a longer action and presents active metabolites which are biotransformed mainly by cytochrome P3A4 in the liver (Clarke and Mills 2006). The incidence of increased aminotransferase activity in patients who consumed high doses of AT is 0.5–3.3% (Waters 2005). Previous studies have reported severe AT-induced hepatotoxicity. Nakad et al. (1999) reported a case of AT-induced acute hepatitis, and Ridruejo and Mando (2002) reported acute cholestatic hepatitis after reinitiating treatment with AT. Pelli and Setti (2004) suggest that AT may trigger autoimmune hepatitis. A case of liver failure was reported by Perger et al. (2003).

Natural products and their active principles, as sources for new drug discovery and treatment of diseases, have attracted attention in recent years. Herbs and spices are generally considered safe and proved to be effective against various human ailments. *Zingiber officinale* Roscoe, commonly known as ginger, is one of the commonly used spices around the world (Ajith et al. 2007). Ginger contains active phenolic compounds that have antioxidant (Stoilova et al. 2007; Ahmed et al. 2008), anti-cancer (Shukla and Singh 2007), anti-inflammatory (Young et al. 2005; Habib et al. 2008) and antithrombotic properties (Thomson et al. 2002).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, atorvastatin; CAT, catalase; GE, ginger extract; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase.

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Table 1
Effect of atorvastatin (AT; 20 and 80 mg/kg) alone and in combination with ginger extract (GE; 400 mg/kg) or vitamin E (vit E, 200 mg/kg) on serum total cholesterol and triglycerides levels in rats.

Groups	Total cholesterol (mg/dl)	%Decrease in total cholesterol from control	Triglycerides (mg/dl)	%Decrease in triglycerides from control
Control	76 ± 6.1	–	51 ± 4.3	–
GE	67 ± 5.4*	11%	48 ± 2.4	5%
AT(20)	64 ± 6.3*	15%	39 ± 1.4*	23%
AT(20) + GE	54 ± 3.4*,◦	28%	38 ± 2.7*	25%
AT(20) + vit E	62 ± 4.5*	18%	40 ± 1.8*	21%
AT(80)	57 ± 2.7*	25%	32 ± 3.1*	37%
AT(80) + GE	49 ± 4.3*,#	35%	33 ± 1.5*	35%
AT(80) + vit E	55 ± 3.3*	27%	31 ± 2.1*	39%

Data represent the mean ± S.E.M. of observations from 6 rats.
*Significantly different from control group at $P < 0.05$.
#Significantly different from AT (80 mg/kg) group at $P < 0.05$.
◦Significantly different from AT (20 mg/kg) group at $P < 0.05$.

Many studies have focused on the effect of ginger on blood lipids in animals and humans. The results of those studies show that ginger significantly reduces plasma cholesterol level (Giri et al. 1984; Fuhrman et al. 2000). It was shown previously that long term dietary feeding of ginger has hypoglycemic, hypolipidemic and anti-atherosclerotic effects in rats and cholesterol fed rabbits (Sharma et al. 1996; Ahmed et al. 2000; Bhandari et al. 2005). In addition, the hepatoprotective effect of ginger against ethanol, carbon tetrachloride and acetaminophen-induced hepatotoxicity in rats was previously documented (Yemitan and Izegbu 2006; Ajith et al. 2007; Mallikarjuna et al. 2008). To date, however, the possible modulating effect of ginger extract in the presence of statins has not been yet investigated. Hence, we aimed in the current investigation to evaluate the possible protection of GE against low and high doses of atorvastatin-induced hepatic injury in rats, aiming to benefit with both the hypolipidemic and the hepatoprotective properties of this spice.

Materials and methods

Drugs and chemicals

AT was a kind gift from EIPICO Co., Egypt. All other chemicals were of analytical grade and were obtained from commercial sources.

Preparation of ginger extract

The aqueous ethanol extract of ginger was prepared according to the method described previously (Ajith et al. 2007). In brief, rhizome of *Zingiber officinalis* Roscoe was purchased from Harazz Stores of Medicinal Plants, Cairo, Egypt, and identified by Department of Pharmacognosy, Faculty of Pharmacy, Minia University, Egypt. The rhizome (500 g) was cut into small pieces and homogenized using 50% ethanol (v/v). The homogenate was centrifuged at 1500 × *g* for 10 min and the supernatant was collected. Solvent in the pooled supernatant was completely evaporated and the residue was designated as ethanol extract. The extract was pre-solublized in saline for the *in vivo* studies.

Animals

Male Wistar rats weighing 180–200 g were purchased from Abou-Rawash Animal House, Giza, Egypt. Animals were used after acclimatization for a period of 1 week to animal house conditions and had free access to food and water. The experiments were conducted according to Institutional Animal Ethics Committee guidelines for the care and use of laboratory animals.

Experimental design

Animals were divided into eight groups as follow:

- First group was treated with saline and kept as control.
- Second group was treated with GE (400 mg/kg/day, orally).
- Third group was treated with AT (20 mg/kg/day, orally).
- Fourth group was treated with AT (20 mg/kg/day, orally) and GE (400 mg/kg, orally).
- Fifth group was treated with AT (20 mg/kg/day, orally) and vitamin E (200 mg/kg, orally).
- Sixth group was treated with AT (80 mg/kg/day, orally).
- Seventh group was treated with AT (80 mg/kg/day, orally) and GE (400 mg/kg, orally).
- Eighth group was treated with AT (80 mg/kg/day) and vitamin E (200 mg/kg, orally).

After 4 weeks of treatment, the rats were sacrificed under ether anesthesia. The blood was collected by cardiac puncture, allowed to clot for 30 min and centrifuged at 1000 × *g* for 15–20 min to separate sera. Livers were excised and homogenized in phosphate buffer saline (0.1 M, pH 7.4). The homogenate was centrifuged at 3000 × *g* for 20 min and the supernatants were stored in aliquots for subsequent determinations.

Biochemical studies

Serum total cholesterol, triglycerides, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined using spectrophotometric assay kits (Spectrum, Egypt). Liver homogenates were used for the estimation of malondialdehyde (MDA), according to the method described previously (Mihara and Uchiyama 1978), superoxide dismutase (SOD) and catalase (CAT) enzymes activities using commercially available kits (Biodiagnostic, Egypt). Also, the total nitrites/nitrates in liver homogenate were assayed as nitrites after reduction of nitrates into nitrites using the cadmium reduction method (Sastry et al. 2002). Estimation of protein content follows the method of Lowry et al. (1951).

Histopathological examination

Portions of the liver were fixed in 10% formalin and then embedded in paraffin. Microtome sections 5 μm thickness were prepared from each liver samples and stained with hematoxylin–eosin (H&E). The sections were examined for the pathological findings of hepatic changes.