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Garlic oil attenuates the cardiac apoptosis in hamster-fed with hypercholesterol diet

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ABSTRACT

Hypercholesterolemia is a well established risk factor for cardiac cell apoptosis. The purpose of this study is to evaluate the effects of garlic oil on cardiac apoptosis induced by a hypercholesterol diet.

Twenty-four male Golden-Syrian hamsters at 3 months of age were randomly divided into three groups, control, cholesterol and garlic oil groups received a chow diet, chow diet with 2% cholesterol, and chow diet with 2% cholesterol and 1% garlic oil for 8 weeks, respectively.

The TUNEL-positive apoptotic cells, and several apoptotic proteins were significantly induced in the excised left ventricle in cholesterol group, whereas significant reduction was observed in cholesterol plus garlic oil group. The IGFI receptor dependent survival pathway was inhibited in cholesterol group whereas it was obviously reversed in cholesterol plus garlic oil group. Our results suggest that administration of garlic oil shows protective effects on cardiac apoptosis in rats with high cholesterol intake.

1. Introduction

High cholesterol is a well-established risk factor for many heart disorders and cardiac cell apoptosis (Cullen, Rauterberg, & Lorkowski, 2005; Harjai, 1999). Cardiac apoptosis diminishes the contractile mass, leading to heart failure. In addition, cardiac non-myocytes apoptosis also contributes to maladaptive remodelling and the transition to decompensate congestive heart failure (Khoynezhad, Jalali, & Tortolani, 2007). Apoptosis, a physiological program for cellular suicide, may contribute many cardiac disorders in a wide range of clinical settings (Haunstetter & Izumo, 1998). The occurrence of apoptosis has been reported to contribute to the loss of cardiomyocytes in cardiomyopathy and is recognised as a predictor for adverse outcomes in subjects with cardiac diseases or heart failure (Narula et al., 1999). Stress-induced cardiomyocyte apoptosis is associated with Fas-dependent and mitochondrial-dependent apoptotic pathway activities. Both of these two apoptotic pathways are regulated by the Bcl family proteins. Activation of these two apoptotic pathways result in decreasing anti-apoptotic protein Bcl2 and increasing pro-apoptotic protein Bak (Bcl-2 homologous antagonist killer) (Azhar, Liu, Zhang, & Wei, 1999). Protein kinase B (Akt) is one major upstream of the Bcl2 family and phosphorylated Akt appears to promote apoptosis inhibition (Liu, Kim, Yang, Jemmerson, & Wang, 1996).

The mitochondrial dependent pathway plays an important role in apoptosis by releasing cytochrome *c* and activating caspase 9, which activates caspase 3 responsible for cleavage action (Narula et al., 1999). In end-stage cardiomyopathy, cytosolic cytochrome *c* is also accumulated (Scheubel et al., 2002). In addition, the Fas death receptor-induced apoptotic pathway is thought to be involved in cardiac disease pathogenesis (Bishopric, Andreka, Slepak, & Webster, 2001; Haunstetter & Izumo, 1998). This pathway is initiated by death receptor agonists, including the Fas ligand. Fas oligomerisation results in the activation of caspase 8, which is upstream of caspase 3, causing apoptosis activation (Reddy & Clark, 2004). Additionally, caspase-8 can cleave Bcl-2 homology domain3 (BH3)-interfering domain death agonist (Bid), and the cleaved Bid then causes the release of mitochondrial cytochrome *c*, leading to pro-caspase-9 activation which then activates pro-caspase-3 (Aggarwal, Bhardwaj, & Takada, 2004; Bishopric et al., 2001).

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Therefore, as a common component of apoptotic signaling, caspase 3 mediates both mitochondrial dependent and death receptor dependent apoptotic pathways.

Various Western drugs have been widely used in the treatment of cardiac diseases; however, these drugs show different types of side effect. For example, Losartan, one of angiotensin II receptor antagoists, shows side effect such as headache, diarrhoea or nasal congestion (Tocci, Sciarretta, Facciolo, & Volpe, 2007). Captopril, one of angiotensin-converting enzyme inhibitors shows side effect such as headache, fatigue or dizziness (Hanes & Weir, 2007). Verapamil, one of calcium channel blockers, shows side effect such as headache, fatigue or swelling (O'Rourke, 2007). In recent years, growing studies investigated the cardio protective effects of natural products which have been used as drugs or diet supplements over a long history in many medical experiences. Various oriental herb extracts or dietary supplements such as garlic have been applied in preventing cardiac abnormality or disorders. However, the garlic oil mechanisms on cardiac protective effects have not been fully discovered yet.

Garlic (*Allium sativum*) has been reported to have a variety of cardio vascular protective effects, including a reduction in plasma cholesterol and preventing fat-induced hyperlipidemia (Ali & Thomson, 1995; Saravanan & Prakash, 2004). The major active constituent of garlic is the compound allicin (allyl 2-propene thiosulfinate) which is formed when garlic cloves are crushed (Cho, Rhee, & Pyo, 2006; Ogita, Fujita, Taniguchi, & Tanaka, 2006). Methyl and allyl sulfide derivatives of allicin are the major components of garlic oil (GO) formed by the steam distillation of mashed garlic and used as on alternative medicine.

In this study, to understand the garlic oil effect on cardiac protection, we examined Fas-dependent and mitochondria-dependent apoptotic signaling pathways of cardiac tissues from hamsters fed a high cholesterol diet. We further suggest that the cardiac protective effect of garlic oil is mediated by inhibiting both the mitochondria-dependent and Fas-dependent apoptotic signaling pathways.

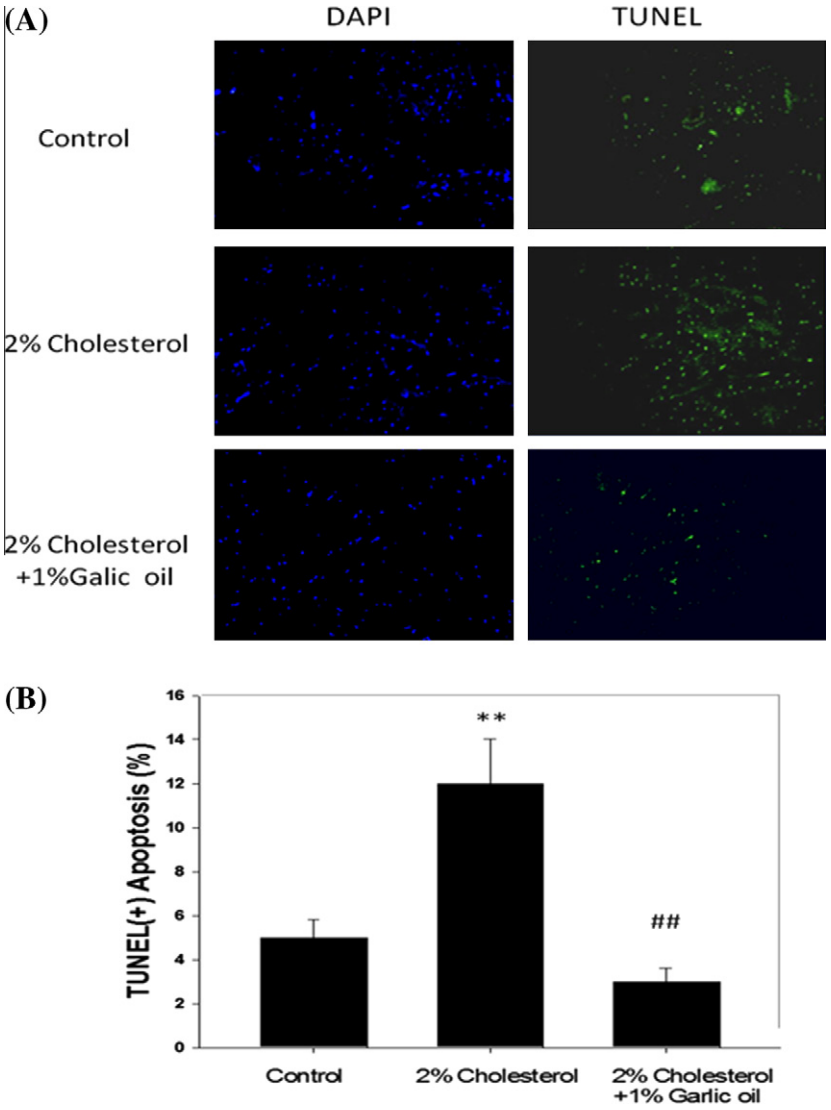

Fig. 1. (A) Representative stained apoptotic cells from cardiac sections from the left ventricles in control, cholesterol and garlic oil group hamsters were measured by staining with 4′,6-diamidino-2-phenylindole (DAPI) (left panels, blue spots) and terminal deoxynucleotidyltransferase UTP Nick End labelling (TUNEL) assay (right panels, green spots). The images were magnified by 400×. (B) Bars represent the percentage of TUNEL positive cells relative to total cells (6 rats × 30 scope field count in each group). $^{**}P < 0.01$, significant differences between control and cholesterol group. $^{\#\#}P<0.01$, significant differences between cholesterol and garlic oil groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)