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Intake of hot water–extracted apple protects against myocardial injury by inhibiting apoptosis in an ischemia/reperfusion rat model

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ABSTRACT

Intakes of apple and its products are shown to reduce the risk of coronary heart disease by delaying occlusion of coronary arteries. In our previous study, we showed that apple pectin protected against myocardial injury by prohibiting apoptotic cascades in a rat model of ischemia/reperfusion. Thus, we hypothesized that water-extracted apple, into which apple pectin was released from the cell wall, might exhibit the same efficacy as apple pectin. To test this hypothesis, we fed rats either cold water– (400 mg kg⁻¹ d⁻¹) or hot water–extracted apples (HWEA; 40, 100, and 400 mg kg⁻¹ d⁻¹). Three days later, the rats were subjected to myocardial injuries by ligating the left anterior descending coronary artery (30 minutes), and subsequently, the heart (3 hours) reperused by releasing the ligation. Only the rats that were supplemented with HWEA (400 mg kg⁻¹ d⁻¹) showed significant reductions in infarct size, which was 28.5% smaller than that of the control group. This infarct size reduction could be partly attributed to the prevention of steps leading to apoptosis. These steps are manifested by a higher Bcl-2/Bax ratio, lower procaspase-3 conversion to caspase-3, and inhibition of DNA nick generation, which reflects the extent of apoptosis. The findings indicate that HWEA supplementation reduces myocardial injury by inhibiting apoptosis under ischemia/reperfusion conditions. In conclusion, this study suggests that apple intake, specifically boiled apple, might reduce the risk of coronary heart disease by inhibiting postocclusion steps, such as myocardial injury after artery occlusion, as well as preocclusion steps, such as atherosclerotic plaque formation.

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1. Introduction

Myocardial infarction (MI) is an irreversible heart muscle injury that is due to myocardial cell death from prolonged

ischemia with or without reperfusion [1] (Fig. 1). Myocardial ischemia is caused by a severely reduced blood supply to the heart and is typically produced through coronary atherosclerotic plaque ruptures, thrombus formation in the lesion, and

Abbreviations: AAR, area at risk; BZ, border zone; CAS, coronary artery syndrome; CHD, coronary heart disease; CWEA, cold water–extracted apple; DCM, dichloromethane; HWEA, hot water–extracted apple; IA, infarct area; IS, infarct size; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; MI, myocardial infarction; oxLDL, oxidized low-density lipoprotein; RS, risk size; TFA, trifluoroacetic acid; TTC, 2,3,5-triphenyltetrazolium chloride; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling; WEA, water-extracted apple.

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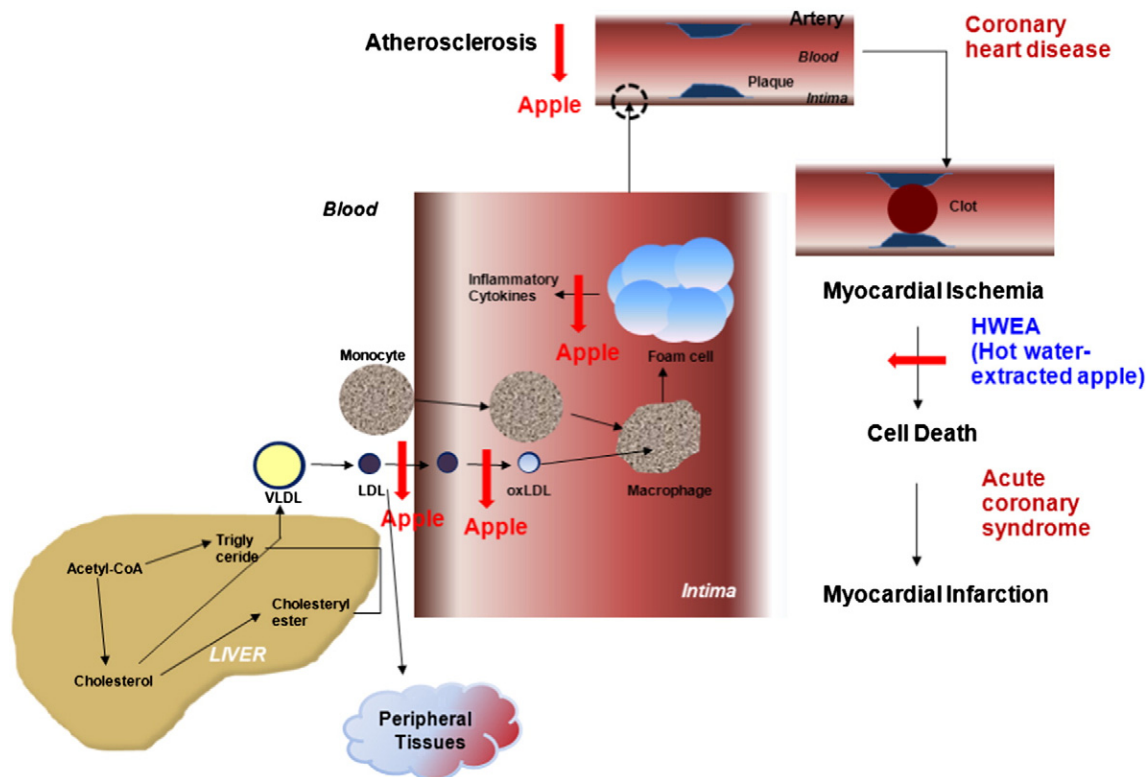


Fig. 1 – Proposed roles of apple in the prevention of MI. The steps leading to the generation of MI involve the following events; very LDL (VLDL) formed in and secreted from the liver to the blood is transformed into LDL. High LDL level in the blood promotes LDL accumulation in the coronary artery intima, subsequently leading to LDL oxidation. The oxLDL is engulfed by the macrophages originated from the monocytes. The macrophages are transformed into the foam cells after excessive ox LDL accumulation in the macrophages. The foam cell proliferation accompanied by smooth muscle cell recruitment and proliferation by inflammatory cytokines that are secreted from the foam cells is responsible for the atherosclerotic plaque formation. As a result, the arteries narrow, and blood flow to the heart is reduced, which is referred to as CHD. Abrupt rupture of unstable plaques leads to the thrombus formation in the lesion. In the most severe events, the arteries are fully blocked by the thrombus, and an ischemic condition ensues. Extensive cell death due to insufficient ATP production by oxidative phosphorylation results in MI, which is a subset of coronary artery syndrome. Previously, apple intake has been shown to block preocclusion steps including high blood LDL level, LDL oxidation, inflammation, and atherosclerotic plaque formation. In this study, we showed that intake of HWEA blocked postocclusion steps including myocardial cell death. The figure was drawn using Power Point program (Microsoft Corp., Redmond, WA, USA).

artery occlusion [2] (Fig. 1). During preocclusion, atherosclerotic plaques are formed by oxidized low-density lipoprotein (LDL) accumulation in blood wall intima, oxidized LDL (oxLDL) engulfment by macrophages, and subsequent macrophage transformation to foam cells [3,4]. Once myocardial ischemia is induced by artery occlusion, the postocclusion steps occur. Mitochondrial oxidative phosphorylation is rapidly interrupted by insufficient oxygen supply, which results in a lack of ATP that is required for myocardial cell survival [5]. Consequently, myocardial cells become injured and die through apoptosis and necrosis [6,7]. In the intrinsic apoptotic cascades triggered by myocardial ischemia, a decrease in Bcl-2/Bax ratio initiates release of cytochrome c into the cytosol, and cytochrome c, in turn, enhances conversion of procaspase-3 to caspase-3. Finally, caspase-3 further activates other proteases, activation of which results in the exhibition of various features of apoptosis, including DNA nick generation [8,9].

Pectin is a complex polysaccharide that is composed of several domains, one of which is homogalacturonan and

accounts for approximately 60% of the total pectin amount [10]. Pectin, along with cellulose and xyloglucan, is a major constituent of primary cell walls in dicotyledonous plants, such as apples, and it constitutes approximately 30% to 35% of the cell walls by weight [10–12]. Pectin is also the primary macromolecular component in middle lamella, which glues cells together [13]. Pectin is a soluble dietary fiber that is fermented by microbial flora which inhabit the large intestine. Fermentation of pectin yields metabolic products, such as butyrate [14,15] and hydrogen [16]. These products are known to provide protection against ischemia/reperfusion injury in rat models. Intramuscularly injected butyrate attenuates myocardial injury [17], and hydrogen produced from fermentation of pectin reduces hepatic injury [16].

Intake of dietary fiber, including apple pectin, is shown to be associated with a reduced risk of coronary heart disease (CHD) [18]. In addition, apple intake is associated with a lower risk of cardiovascular disease [19,20], including acute coronary syndrome, a cardiovascular disease subgroup that

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