CHAPTER FIFTEEN

Cardioprotective Properties of Kiwifruit

Asim K. Duttaroy[1]
Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Blindern, Oslo, Norway
[1]Corresponding author: e-mail address: a.k.duttaroy@medisin.uio.no

Contents

Abstract

Beneficial effects of consumption of fruit and vegetables on the cardiovascular system have been reported. Fruit and vegetable components affect the cardiovascular system in both antioxidant and nonantioxidant ways. The mechanisms of their actions are, however, still not well understood. The compounds present in fruits and vegetables may function individually or in concert to protect lipoproteins and vascular cells from oxidation or by other mechanisms such as reducing plasma lipid levels, high blood pressure, and platelet hyperactivity. Emerging data indicate that kiwifruit is beneficial in the prevention of cardiovascular disease, as consumption of two or three fruit per day for 28 days or more lowers platelet hyperactivity, plasma lipids, and blood pressure in human volunteers. These studies suggest that kiwifruit may provide a new dietary means as part of a preventive or therapeutic strategy to favorably modify cardiovascular risk factors. The relevance of lowering the cardiovascular risk factors by kiwifruit in human health is discussed.

1. INTRODUCTION

Epidemiological studies have shown an inverse association between fruit and vegetable intake and risks of cardiovascular disease (CVD), morbidity, and mortality (Dutta-Roy, 2002; Gaziano et al., 1995; Joshipura et al., 1999). Daily consumption of fruit and vegetables increases serum concentrations of

Advances in Food and Nutrition Research, Volume 68
ISSN 1043-4526
http://dx.doi.org/10.1016/B978-0-12-394294-4.00015-8

the major antioxidants and vitamins (β-carotene, vitamins C and E) and plant folate (Brevik et al., 2011; Garcia et al., 2010; van Kappel et al., 2001). In addition, a number of compounds such as isoflavones, diosgenin, resveratrol, quercetin, catechin, sulforaphane, tocotrienols, and carotenoids are also absorbed during the digestion of fruit and vegetables. These nutrients, which are abundant in fruits and vegetables, may contribute to the inverse association of the intake of these foods with the risks of stroke and mortality from CVD (Knekt et al., 1994; Tribble, 1999). Functional changes, such as reduced serum homocysteine and markers of protein, lipid, and DNA oxidation, have also been reported (Brevik et al., 2011). In addition, the positive effects on markers of inflammation, immunity, and CVD risk factors (such as plasma lipids, endothelial function, blood pressure, platelet reactivity) have been demonstrated (Bohn et al., 2010; Karlsen et al., 2012). These nutrients may function individually or in concert to protect lipoproteins and vascular cells from oxidation, and also in nonantioxidant pathways such as those reducing plasma lipid levels (low-density lipoprotein (LDL) cholesterol, triglycerides), and platelet activity (Dutta-Roy, Crosbie, & Gordon, 2001; Duttaroy & Jorgensen, 2004).

Hyperlipidemia, hypertension, and hyperactivity of platelets are some of the critical contributors to CVD mortality and morbidity (Grundy et al., 2005). Platelet aggregation is fundamental to a wide range of physiological and pathological processes, including the induction of thrombosis and arteriosclerosis (Dutta-Roy, 1994; Kaplan & Jackson, 2011). The modification of platelet activity can reduce the incidence and severity of CVD (Camera et al., 2012; Kaplan & Jackson, 2011). Platelet hyperactivity is also associated with the risk factors for CVD such as smoking, hypertension, hypercholesterolemia, diabetes, obesity, and aging (Dutta-Roy, 2002). The utility of an increasing range of antiplatelet therapies in the management of the above disease states further emphasizes the pivotal role platelets play in the pathogenesis of CVD (Dutta-Roy, 2002). Hypertension has been identified as the leading risk factor for mortality worldwide and is ranked third as a cause of disability-adjusted life-years (Ezzati, Lopez, Rodgers, Vander Hoorn, & Murray, 2002). Dietary changes can significantly reduce all these CVD risk factors (Obarzanek et al., 2001). This concept has stimulated research into the reduction of CVD risk factors by several means, including dietary supplementation.

Kiwifruit contain very significant amounts of vitamin C, vitamin E, folic acid, and various phytochemicals, such as anthocyanidins and flavonols, described in earlier chapters in this volume. They also contain soluble fiber,

which may alter absorption and resorption of dietary lipids. The common green kiwifruit, *Actinidia deliciosa* cv. 'Hayward', has been used as a "model" fruit in several trials to examine effects on biomarkers relevant to both cancer and CVD. The more recently available "gold" kiwifruit *Actinidia chinensis* cv. 'Hort 16A', differs significantly in phytochemical contents from the green kiwifruit. Comparison of the antioxidant effects *in vitro* demonstrated that gold kiwifruit had the stronger antioxidant effects (Iwasawa, Morita, Yui, & Yamazaki, 2011).

2. CARDIOPROTECTIVE PROPERTIES OF KIWIFRUIT

2.1. *In vitro* studies

In vitro studies using extracts of different fruits showed antiaggregation activity, mainly in kiwifruit and tomato (Dutta-Roy et al., 2001; Duttaroy & Jorgensen, 2004). Among all fruits tested for their *in vitro* antiplatelet activity, tomato and kiwifruit had the highest activity followed by grapefruit, melon, and strawberry, whereas pear and apple had little or no activity (Table 15.1). Incubation of KFE (expressed as weight of pulp used to prepare kiwifruit extract (KE)) inhibited ADP-induced platelet aggregation in a dose-dependent manner (Fig. 15.1). The *in vitro* platelet aggregation experiments suggest that green and gold kiwifruit extracts inhibit both ADP- and collagen-induced whole-blood platelet aggregation. The fruit extract may contain a wide variety of different types of compounds that have antiplatelet activity and that affect different mechanisms of activation and aggregation. The antiplatelet effects of fruit are independent of their antioxidant activity. Incubation with KE inhibited ADP-induced platelet aggregation in a dose-dependent manner in platelet-rich plasma. KE also inhibited collagen-induced platelet aggregation; however, the levels of inhibition were lower compared with those observed with ADP-induced platelet aggregation (Duttaroy & Jorgensen, 2004). Arachidonic acid-induced platelet aggregation was also inhibited by KE. The compounds responsible for the observed activity in KE were isolated as a mixture and subfractionated. The ability of these subfractions to modify the platelet response to stimulation by different agonists was evaluated by examining changes in platelet aggregation. These compounds in kiwifruit are water soluble and heat stable, and their molecular mass is less than 1000 Da (Duttaroy & Jorgensen, 2004).

Table 15.1 *In vitro* anti-aggregatory activity of extracts of different fruits

Fruit	% of inhibition
Kiwifruit	89
Tomato	70
Grapefruit	51
Melon	30
Plum	25
Banana	21
Avocado	21
Mango	19
Cranberry	18
Orange	18
Nectarine	15
Pineapple	12
Pear	5
Apple	2

Platelet aggregation was monitored in the presence of ADP and different fruit extracts. Inhibition of platelet aggregation is expressed as the decrease in the area under the curve compared with the control. For details, see Dutta-Roy et al. (2001).

2.2. Human trials

Several human intervention trials have been carried out using kiwifruit (Brevik et al., 2011; Chang & Liu, 2009; Duttaroy & Jorgensen, 2004; Karlsen et al., 2012). In one human trial, 30 (12 males and 18 females) healthy volunteers aged 20–51 years were included (Duttaroy & Jorgensen, 2004). Exclusion criteria were the presence of overt vascular, hematological, or respiratory disease; hypertension; infection; and frequent consumption of drugs which affect platelet function (e.g., aspirin, paracetamol, ibuprofen, steroids, or habitual consumption of omega-3 fatty acid supplements). Subjects were allocated randomly to two groups ($n = 15$), each of which was given green kiwifruit doses in different orders. One group took two kiwifruit per day in the first period and three kiwifruit per day in the second period, whereas the second group took three and two kiwifruit. Each volunteer consumed two and three kiwifruit per day for successive 28 day

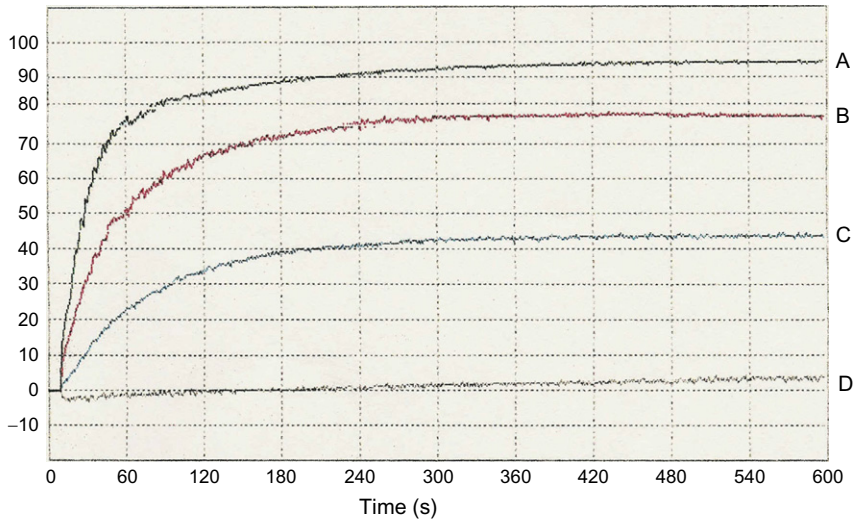

Figure 15.1 Effect of different amounts of KE on *in vitro* platelet aggregation by ADP. Kiwifruit were peeled and the pulp was homogenized. The homogenate was then centrifuged at 3000 × *g* for 10 min. The supernatant was collected and the pH was adjusted to 7.4 with sodium hydroxide. The pH-adjusted KE was then used for *in vitro* platelet aggregation experiments. PRP (450 μL) was incubated with different amounts (0, 5, 10, and 20 mg) of KE for 15 min at 37 °C prior to the addition of ADP (8 μM). (A) Control; (B) 5 mg KE; (C) 10 mg KE; and (D) 20 mg KE. For details, see Duttaroy and Jorgensen (2004).

periods separated by at least 2 week washout periods. During the supplementation period, no statistically significant change in their mean BMI was observed. The kiwifruit was well tolerated, without any adverse effect. Plasma vitamin C levels in these volunteers increased significantly. Vitamin C values increased from 65.92 ± 9.1 (day 0) to 102 ± 23.1 μM (day 28) and from 68 ± 15.2 μM to 92.38 ± 14.7 μM after consuming two and three kiwifruit per day, respectively (Duttaroy & Jorgensen, 2004). Table 15.2 shows the platelet aggregation response to different concentrations of ADP and collagen at day 0 and at 28 days after consuming two or three kiwifruit per day. Platelet response to both low and high concentrations of ADP or collagen was inhibited by kiwifruit consumption. Consuming two kiwifruit daily inhibited platelet aggregation induced by ADP significantly (18% in case of 4 μM ADP and 15% in case of 8 μM ADP) compared with those at day 0 ($p < 0.05$). A similar reduction in platelet aggregation was observed in response to collagen when volunteers consumed two or three kiwifruit per

Table 15.2 Effect of kiwifruit consumption on platelet aggregation

	% Aggregation			
	Two kiwifruit per day		Three kiwifruit per day	
Agents	**Day 0**	**Day 28**	**Day 0**	**Day 28**
ADP, 4 μM	70 ± 3.2	53 ± 3.2*	69 ± 1.8	55 ± 2.1*
ADP,8 μM	69 ± 3.1	55 ± 4.1*	68 ± 2.3	52 ± 3.2*
Collagen, 4 μg/ml	68 ± 4.2	52 ± 2.3*	67 ± 3.1	53 ± 3.1*
Collagen, 8 μg/ml	70 ± 3.9	51 ± 4.3*	70 ± 2.2	50 ± 3.5*

*$p < 0.05$.
For details, see Duttaroy and Jorgensen (2004).

day for 28 days. Mean total plasma levels of cholesterol, LDL, and HDL were unchanged from days 0 to 28 in both groups, whereas triglyceride concentrations were significantly lowered on day 28 (1.16 ± 0.45 mmol/L at day 0 vs. 0.87 ± 0.29 mmol/L at day 28, $p < 0.05$, and 1.19 ± 0.35 mmol/L vs. 0.84 ± 0.35 mmol/L, $p < 0.05$, where volunteers consumed two and three kiwifruit per day, respectively). After the washout period (minimum 2 weeks), plasma triglyceride concentrations returned to the baseline level (Duttaroy & Jorgensen, 2004).

In another study, the effects of consumption of two green kiwifruit per day on the blood lipid profile, plasma antioxidants and markers of lipid peroxidation were investigated in hyperlipidemic adult men and women (Chang & Liu, 2009). Forty-three subjects who had hyperlipidemia (including 13 males and 30 females) participated in the study. They consumed two green kiwifruit per day for 8 weeks. No significant differences from baseline to 8 weeks of the intervention were detected for triacylglycerol, total cholesterol, or LDL cholesterol. However, after 8 weeks of kiwifruit consumption, the HDL-C concentration was significantly increased and the LDL cholesterol/HDL-C ratio and total cholesterol/HDL-C ratio were significantly decreased. Plasma vitamin C and vitamin E levels also increased significantly. In addition, the lag time of LDL oxidation had statistically significantly changed at 4 and 8 weeks during the kiwifruit intervention.

In another human intervention trial, it was demonstrated that consuming one gold kiwifruit per day for 4 weeks reduced whole-blood platelet aggregation in healthy volunteers (Brevik et al., 2011). Consumption of gold kiwifruit reduced plasma triglyceride levels without affecting cholesterol levels: original levels were restored after the washout period. Lowering of

Table 15.3 Effects of kiwifruit consumption on whole-blood platelet aggregation and angiotensin-converting enzyme (ACE) activity in smokers

	Control[a]		Antioxidant-rich diet ($n=33$)		Kiwifruit ($n=33$)		
Variable	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**	***p***
Whole-blood aggregation	13.0	−0.5	13.0	−1.1	13.6	−2.1*	0.009
ACE activity (U/L)	27.42	3.09	27.31	−1.4	28.45	−3.22*	0.0034

*Significantly different as compared to control ($p<0.050$, Mann-Whitney test). For details, see Karlsen et al. (2012).
[a]$N=34$ for control and 33 for both experimental diets.

plasma triglycerides by kiwifruit was observed despite the fact that the volunteers maintained their regular diet during the supplementation period.

In a randomized, controlled trial in male smokers aged 44–74 years, the effects of green kiwifruit and an antioxidant-rich diet on CVD risk factors (such as blood pressure, plasma lipids, and whole-blood platelet aggregation) were compared with a control group after 8 weeks (Karlsen et al., 2012). The kiwifruit group received three green kiwifruit per day, whereas the antioxidant-rich diet group received a comprehensive combination of antioxidant-rich foods. In the kiwifruit group, reductions of 10 mm Hg in systolic blood pressure and 9 mm Hg in diastolic blood pressure were observed. In the antioxidant-rich diet group, a reduction of 10 mm Hg in systolic blood pressure was observed among hypertensives. Additionally, a 15% reduction in whole-blood aggregation and an 11% reduction in angiotensin-converting enzyme activity were observed in the kiwifruit group (Table 15.3). No effects on these parameters were observed in the antioxidant-rich diet group. This study suggests that intake of kiwifruit may have beneficial effects on blood pressure and platelet aggregation in male smokers.

3. DISCUSSION

CVD is the leading cause of morbidity and mortality (Rao, 2002). Primary prevention and secondary prevention of CVD are public health priorities (Westerby, 2011). Substantial data indicate that CVD is a life-course disease that begins with the evolution of risk factors that in turn contribute to the development of subclinical atherosclerosis. High blood pressure, hyperlipidemia, and hyperactivity of platelets are all recognized risk factors for CVD.

Platelets are involved in the atherosclerosis process, and therefore, reduction of platelet activity decreases the incidence of CVD in diabetes, smokers, and in the metabolic syndrome (Dutta-Roy, 2002). Both *in vitro* and human studies indicate that both green and gold kiwifruit have cardio-protective effects. Consumption of kiwifruit (green and gold) lowered the platelet aggregation response in both healthy human volunteers and smokers (Brevik et al., 2011; Duttaroy & Jorgensen, 2004; Karlsen et al., 2012). In addition, both green and gold kiwifruit consumption increased plasma antioxidants and vitamin C levels. There were no correlations between individual changes in plasma vitamin C and platelet aggregation response and plasma lipid values. In addition, consumption of both green and gold kiwifruit reduced plasma triglyceride levels without affecting cholesterol levels. The inhibitory effects on platelet aggregation response and lowering effects on plasma triglyceride of kiwifruit disappeared during the washout period. This indicates that the effects of kiwifruit on platelets and blood plasma lipids are reversible.

Our *in vitro* study suggests that the kiwifruit extracts inhibit both ADP- and collagen-induced platelet aggregation. The antiplatelet potential of the fruits appeared to be the opposite of that of their reported antioxidant activity, indicating that the antiplatelet factors in fruits are quite different from their antioxidant property. The effecting compounds present in kiwifruit are heat stable and water soluble, and their mass is less than 1000 Da.

Given the role of blood lipids in the development of atherosclerosis and CVD and the positive effects of fruits and vegetables on plasma lipids (Kurowska et al., 2000; Lampe, 1999), the effects of kiwifruit on plasma lipids indicate the potential benefit of consuming these fruit. Lowering of plasma triglycerides by kiwifruit consumption was observed despite these volunteers maintaining their regular diet during the supplementation periods. None of the volunteers reported any loss of appetite or changes in their food intake during the supplementation. The search for alternative antiplatelet drugs that are devoid of adverse side effects continues. Recent studies have shown that kiwifruit are effective inhibitors of platelet aggregation and also lower plasma triglycerides in normal human volunteers. However, very little information is available whether these fruit are beneficial in hyperlipidemia, type 2 diabetes, or the metabolic syndrome, the risk factors for CVD. Therefore, further work is required in this regard.

Kiwifruit may have great potential for increasing the effectiveness of thrombosis prophylaxis. Modulation of platelet reactivity toward collagen and ADP, and plasma triglyceride levels and hypertension by kiwifruit

consumption could be of potentially prophylactic and therapeutic benefit in preventing and halting pathological processes that lead to CVD. Localization of *in vitro* activities to specific groups of water-soluble kiwifruit components has further elucidated possible antiplatelet mechanisms, and in the future, *ex vivo* studies should be performed with the extract to demonstrate bioavailability and activity *in vivo*.

REFERENCES

Bohn, S. K., Myhrstad, M. C., Thoresen, M., Holden, M., Karlsen, A., Tunheim, S. H., et al. (2010). Blood cell gene expression associated with cellular stress defense is modulated by antioxidant-rich food in a randomised controlled clinical trial of male smokers. *BMC Medicine*, *8*, 54.

Brevik, A., Gaivao, I., Medin, T., Jorgenesen, A., Piasek, A., Elilasson, J., et al. (2011). Supplementation of a western diet with golden kiwifruits (Actinidia chinensis var. 'Hort 16A':) effects on biomarkers of oxidation damage and antioxidant protection. *Nutrition Journal*, *10*, 54.

Camera, M., Brambilla, M., Facchinetti, L., Canzano, P., Spirito, R., Rossetti, L., et al. (2012). Tissue factor and atherosclerosis: Not only vessel wall-derived TF, but also platelet-associated TF. *Thrombosis Research*, *129*, 279–284.

Chang, W. H., & Liu, J. F. (2009). Effects of kiwifruit consumption on serum lipid profiles and antioxidative status in hyperlipidemic subjects. *International Journal of Food Sciences and Nutrition*, *60*, 709–716.

Dutta-Roy, A. K. (1994). Insulin mediated processes in platelets, erythrocytes and monocytes/macrophages: Effects of essential fatty acid metabolism. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *51*, 385–399.

Dutta-Roy, A. K. (2002). Dietary components and human platelet activity. *Platelets*, *13*, 67–75.

Dutta-Roy, A. K., Crosbie, L., & Gordon, M. J. (2001). Effects of tomato extract on human platelet aggregation in vitro. *Platelets*, *12*, 218–227.

Duttaroy, A. K., & Jorgensen, A. (2004). Effects of kiwi fruit consumption on platelet aggregation and plasma lipids in healthy human volunteers. *Platelets*, *15*, 287–292.

Ezzati, M., Lopez, A. D., Rodgers, A., Vander Hoorn, S., & Murray, C. J. (2002). Selected major risk factors and global and regional burden of disease. *Lancet*, *360*, 1347–1360.

Garcia, A. L., Mohan, R., Koebnick, C., Bub, A., Heuer, T., Strassner, C., et al. (2010). Plasma beta-carotene is not a suitable biomarker of fruit and vegetable intake in german subjects with a long-term high consumption of fruits and vegetables. *Annals of Nutrition & Metabolism*, *56*, 23–30.

Gaziano, J. M., Manson, J. E., Branch, L. G., Colditz, G. A., Willett, W. C., & Buring, J. E. (1995). A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Annals of Epidemiology*, *5*, 255–260.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., et al. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*, *112*, 2735–2752.

Iwasawa, H., Morita, E., Yui, S., & Yamazaki, M. (2011). Anti-oxidant effects of kiwi fruit in vitro and in vivo. *Biological & Pharmaceutical Bulletin*, *34*, 128–134.

Joshipura, K. J., Ascherio, A., Manson, J. E., Stampfer, M. J., Rimm, E. B., Speizer, F. E., et al. (1999). Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA: The Journal of the American Medical Association*, *282*, 1233–1239.

Kaplan, Z. S., & Jackson, S. P. (2011). The role of platelets in atherothrombosis. *Hematology/ The Education Program of the American Society of Hematology*, *2011*, 51–61.

Karlsen, A., Svendsen, M., Seljeflot, I., Laake, P., Duttaroy, A. K., Drevon, C. A., et al. (2012). Kiwifruit decreases blood pressure and whole-blood platelet aggregation in male smokers. *Journal of Human Hypertension*. http://dx.doi.org/10.1038/jhh.2011.116.

Knekt, P., Reunanen, A., Jarvinen, R., Seppanen, R., Heliovaara, M., & Aromaa, A. (1994). Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *American Journal of Epidemiology*, *139*, 1180–1189.

Kurowska, E. M., Spence, J. D., Jordan, J., Wetmore, S., Freeman, D. J., Piche, L. A., et al. (2000). HDL-cholesterol-raising effect of orange juice in subjects with hypercholesterolemia. *The American Journal of Clinical Nutrition*, *72*, 1095–1100.

Lampe, J. W. (1999). Health effects of vegetables and fruit: Assessing mechanisms of action in human experimental studies. *The American Journal of Clinical Nutrition*, *70*, 475S–490S.

Obarzanek, E., Sacks, F. M., Vollmer, W. M., Bray, G. A., Miller, E. R., 3rd, Lin, P. H., et al. (2001). Effects on blood lipids of a blood pressure-lowering diet: The Dietary Approaches to Stop Hypertension (DASH) Trial. *The American Journal of Clinical Nutrition*, *74*, 80–89.

Rao, A. V. (2002). Lycopene, tomatoes, and the prevention of coronary heart disease. *Experimental Biology and Medicine (Maywood, N.J.)*, *227*, 908–913.

Tribble, D. L. (1999). AHA Science Advisory. Antioxidant consumption and risk of coronary heart disease: Emphasison vitamin C, vitamin E, and beta-carotene: A statement for healthcare professionals from the American Heart Association. *Circulation*, *99*, 591–595.

van Kappel, A. L., Steghens, J. P., Zeleniuch-Jacquotte, A., Chajes, V., Toniolo, P., & Riboli, E. (2001). Serum carotenoids as biomarkers of fruit and vegetable consumption in the New York Women's Health Study. *Public Health Nutrition*, *4*, 829–835.

Westerby, R. (2011). An overview of cardiovascular disease risk assessment. *Nursing Standard*, *26*, 48–55 quiz 56.