Review Article

Phytochemicals and Prevention of Cardiovascular Disease: Potential Roles for Tropical and Subtropical Fruits

พฤกษเคมีกับการป้องกันโรคหัวใจและหลอดเลือด: บทบาทสำคัญของผลไม้ในเขตร้อน

Yuttana Sudjaroen

Faculty of Science and Technology, Sunandha Rajabhat University

ยุทธนา สุดเจริญ

คณะวิทยาศาสตร์และเทคโนโลยี มหาวิทยาลัยราชภัฏสวนสุนันทา

Abstract

Phytochemical-rich fruits of tropical and subtropical region have the potential ability to limit the development cardiovascular diseases. The fruits contain a variety of phytochemicals that could contribute to these protective effects, mainly flavonoids such as catechin, quercetin, rutin, etc. These constituents of fruits are likely to act by antioxidant, antithrombotic, and vasoprotective effects. The evidence suggests a potential role for dietary fruits from tropical and subtropical region in the prevention of cardiovascular diseases. The presence of a large number of minor dietary factors that protect against disease reinforces the recommendation to increase the intake of plant foods rather than any specific supplement.

Keywords **:** Phytochemicals, Antioxidant, Tropical fruits, Cardioprotective effects

บทคัดย่อ

ผลไม้จากเขตร้อนอุดมไปด้วยพฤษเคมี ซึ่งสามารถป้องกันการเกิดโรคหัวใจและหลอดเลือดพฤกษเคมีจากผลไม้มีมากมายหลายชนิด สารที่มีมากที่สุดคือสารกลุ่มฟลาโวนอยด์ ได้แก่ คาทีชิน ควอซีทิน ลูทีน เป็นต้น ซึ่งมีคุณสมบัติทำหน้าที่เป็นสารต้านอนุมูลอิสระ ต้านการเกิดลิ่มเลือด และ ช่วยให้หลอดเลือดแข็งแรง มีข้อมูลที่สนับสนุนว่าผลไม้เมืองร้อนสามารถป้องกันโรคหัวใจและหลอดเลือดได้อย่างมีประสิทธิภาพปัจจัยดังกล่าวนำไปสู่การแนะนำให้บริโภคอาหารจากพืชมากกว่าการได้รับจากอาหารเสริมอย่างจำเพาะเจาะจง

คำสำคัญ **:** พฤษเคมี ฤทธิ์ต้านอนุมูลอิสระ ผลไม้เมืองร้อน ฤทธิ์ป้องกันโรคหัวใจและหลอดเลือด

Introduction

Coronary Heart Disease (CHD) is a multifactorial disease which involves a number of interrelated risk factors (Table 1); however, a major environmental influence is diet (1). Dietary factors that contribute to disease prevention include the reduction in the intake of saturated fat and increase in the consumption of plant-based diet containing fruits, vegetables and grains. These observations have been translated into guidelines and appear consistently in the dietary goals of many countries and organizations that promote cardiac health, such as the American Heart Association (2). The inverse association between fruit and vegetable intake and CHD is consistent. It has been suggested that the lower rate of CHD is attributed to such factors as the displacement of food that are high in salt, caloric density and saturated fat by fruits and vegetables; the increase in intake of dietary fiber, minerals and vitamins, all of which exhibit antioxidant action; and an increase in intake of plant-derived constituents known as phytochemicals.

The main focus of this brief review is to summarize the involvement of selected phytochemicals in the prevention of CHD; in particular, examples will be sourced the data on fruits especially from tropical region such as South East Asia.

Table 1 Risk Factors for Coronary Heart Disease

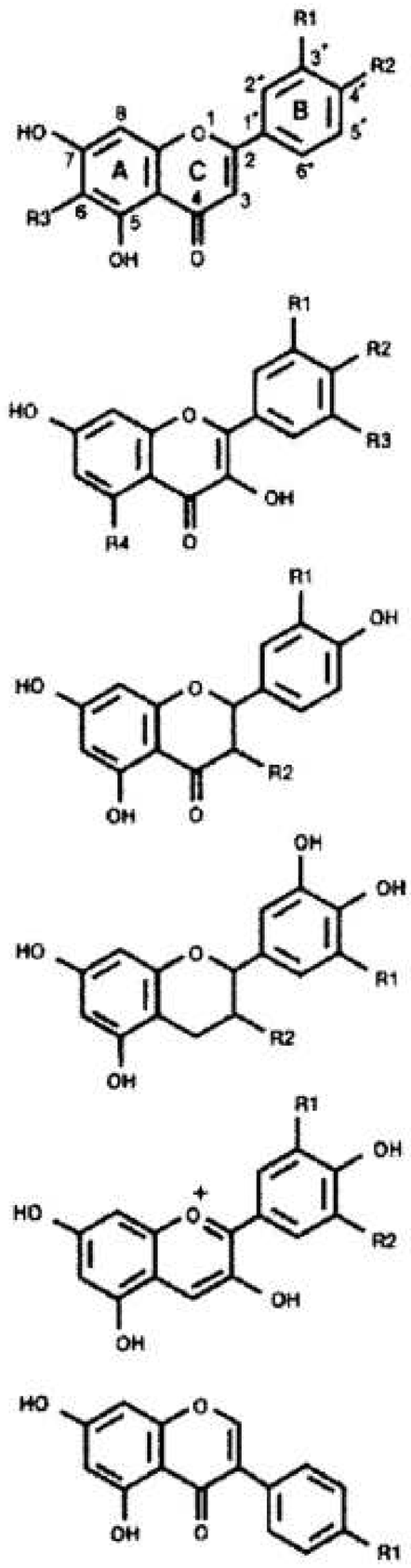
Irreversible	Potentially reversible
Gender	Cigarette smoking
Age	Lack of exercise
Genetics	Dyslipidemia
	Obesity, diabetes
	Hypertension
	Thrombotic risk
	Oxidizability of LDL

I. Bioactive phytochemicals

Phytochemicals are a broad array of compounds that coexist with nutrients in plant foods; some are considered to play a role in the prevention of chronic diseases by acting either independently, synergistically with other phytochemicals or with nutrients that coexist in the plant. Ralph and Proven (3) have conveniently grouped phytochemicals into three categories that include:

1. Product of phenylpropanoid pathway

These compounds, commonly referred to as polyphenols, are derived from cinnamic acid and include the xanthones and flavonoids. The basic structural unit of the flavonoid family (Fig. 1) comprises two benzene rings linked through a heterocyclic pyran or pyrone ring (C ring); variations in the C ring and the extent of hydroxylation define the major classes (4).



Flavone	R1	R2	R3
Apigenin	H	OH	H
Baicalein	H	H	OH
Luteolin	OH	OH	H

Flavonol	R1	R2	R3	R4
Fisetin	OH	OH	H	H
Galangin	H	H	H	OH
Quercetin	OH	OH	H	OH
Kaempterol	H	OH	H	OH
Myricetin	OH	OH	OH	OH
Isorhamnetin	H	OH	OMe	OH

Flavanone	R1	R2
Eriodictyol	OH	H
Naringenin	H	H
Taxifolin	OH	OH

Flavanol	R1	R2
Catechin	H	OH
Epicatechin	H	OH
EGCG	OH	Gallate

Anthocyanidin	R1	R2
Cyanidin	OH	H
Malvidin	OMe	OMe
Peonidin	OMe	H

Isoflavone	R1
Genistein	OH

Fig. 1 Structures of the major classes of foods flavonoids. Positions of hydroxyl groups on A and B rings are listed for select examples within each class.

2. Products of isoprenoid pathway

These include the carotenoids, steroids, terpenes, and phytosterols (5). Phytosterols are present in a broad range of plant foods, are not absorbed effectively from intestine, but can bind cholesterol and prevent it from being absorbed.

3. Organosulfur compounds

These include glucoinolates and allicins, the latter found in *Allium* vegetables such as onions, chives, and garlic. Although the published literature mainly reveals their roles in cancer prevention, compounds derived from allicin (including sulfides and disulfides) are reported to inhibit endogenous cholesterol synthesis.

II. Phytochemicals, CHD and epidemiological studies

Studies of phytochemical intake and its relationship to CHD in humans have been limited by the lack of availability within food composition databases of reliable information on the content of phytochemicals and, in particular, of flavonoids. A second and equally important problem has been the inability of dietary questionnaires to detect differences in the balance of evidence supports the view that flavonoids have protect effect on CHD (Table 2) in populations where the underlying risk of disease is not excessively high (6-9). The exceptions are described in reports from Wales and Finland, where the intake of saturated fat is known to be predominant risk factor for CHD.

Table 2 Risk of cardiovascular disease for high versus low flavonoid intake[a]

Gender	Men	Men	Men/women	Men
Age (y)	65-84	50-69	30-69	40-75
Outcome	CHD mortality MI incidence	Stroke Incidence	CHD mortality	CHD mortality MI incidence
Follow-up (y)	5	15	20-25	6
N in cohort	805	552	5,133	34,789
RR	0.32[b] 0.52	0.27[b]	0.67 (men) 0.73 (women)	0.63 1.09
Ref.	6	7	8	9

RR: Relative Risk; CHD: Coronary Heart Disease; MI: Myocardial Infarction.

[a] Σ Quercetin, kaempferol, myricetin, luteolin, apigenin.

[b] Statistically significant.

Further support for the cardioprotective effect of flavonoids has been obtained from a reexamination of food records from 16 cohorts within seven countries (10). During a 25-year follow-up period, an inverse association was observe between CHD mortality and flavonoid intake; this explained a small but significant portion (8%) of the variance in CHD deaths, independently of alcohol and antioxidant vitamins. CHD mortality was observed to be lowest in Japan with an estimated average flavonoid intake of 61 mg/day, mainly derived from green tea.

III. Contribution of tropical and subtropical fruits to phytochemical intake and CHD prevention

Generally, there are insufficient data on the phytochemical content of foods, but a selection of phytochemicals to be found in tropical and sub tropical fruit is shown in Table 3. Despite the limitations of the data, it is established that these fruits contain active compounds and are capable of impacting favorably on heart disease prevention.

The phytochemical composition of avocado (Table 3), combined with its main fatty acid, oleic acid (18:1), represents a potential for lowering plasma cholesterol (10) and increasing antioxidant status. An added benefit may result from content of phytosterols. Moreover, the presence of chlorogenic and caffeic acids in avocado increases the antioxidant capacity of plasma. In the same way, Jackfruit *(Artocarpus heterophyllus)* contains antioxidants and phytosterols (Table 3) and its flavonoids, particularly the flavonones, have antioxidant activity (4).

Table 3 Examples of phytochemicals found in tropical and subtropical fruits

Common and sciencetific names	Phytochemical ingredients
Avocado (*Persea americana*)	Caffeic acid, chlorogenic acid, coumaric acid, cycloartenol, dopamine, phytosterols
Durian (*Durio zibethinus*)	Dimethyl trithiolane, methylbutanoate
Guava *(Psidium guajava*)	Ascorbigen, bisabolene, cadinene, cinnamyl-acetate, ellagic acid, humulene, leucocyanidin, limonene
Jackfruit (*Artocarpus heterophyllus*)	Dihydromorin, cycloartenone, heterophylol, flavonones
Lime (*Citrus aurantiifolia*)	Borneol, bergamotene, bisabolene, camphene, cineole, citronellal, coumarin, limonene, methoxypsoralen, naringin
Litchi (*Litchi chinensis*)	Cyanidin, damascenone, guaiacol, malvidin, quercetin
Longan (*Dimocarpus longan*)	Acetonylgeraniin
Mango (*Mangifera indica*)	Mangiferic acid, mangiferine, neoxanthophyll, phytin, xanthophyll
Mangosteen (*Garcinia mangostana*)	Catechins, deoxygartanin, gartanin, mangostin, phytin
Papaya (Carica papaya)	Germacrene, isocaryophyllene, kryptoflavin, myrcene, ocimene, phellandrene, terpinene
Passionfruit (*Passiflora edulis*)	Alkaloids, flavonoids, Harman, xanthophyll
Pineapple (*Ananas comosus*)	Ananasic acid, chaviol, ellagic acid, phytosterols, serotonin, vanilin
Rambutan (*Nephelium lappaceum*)	Damascenone
Starfruit (*Averrhoa carambola*)	Cryptochrome, damacenone, phytofluene

Citrus fruits provide a diverse range of flavonoids (11). Naringenin, a flavonone, has been shown to posses chloresterol-lowering and anticancer properties (12). The naringin content of lime juice has been estimated to be ~100 μg/g (13), and the lime is also a source of limonene, a biologically active terpene. Other bioactive substances in lime (Table 3) include coumarins that possess anticoagulatory and anti-inflamatory properties.

Caroteniods are the dominant products of the isoprenoid pathway in mango. Phytochemicals in mango have been implicated in protection from cancer (14). Mango impacts favorably on a number of metabolic functions such as the production of a low plasma glucose concentration relative to other tropical and subtropical fruits commonly consumed in Thailand (15), and also to an increase in plasma

vitamin C (16). Although few data are available on the phytochemical composition of rambutan, the cholesterol-lowering effect (17) of this fruit may associated with its phytosterol content.

IV. Molecular targets

The mode of action of phytochemicals in prevention of CHD is multifaceted and is dependent on the chemical natures of individual phytochemicals in question and on the consequences of their complex interactions. The most extensively studies group is undoubtedly the flavonoids.

A. *In vitro* inhibition of LDL oxidation by flavonoids

Flavonoids inhibit the formation of Lipid Per-Oxides (LPO) at the initiation stage by acting as scavengers of superoxide anions and hydroxyl radicals. It has been proposed that flavonoids terminate chain radical reaction by donating hydrogen atoms to the peroxyl radical, forming flavonoid radicals that, in turn, react with free radicals, thereby terminating the propagation chain. In addition to these antioxidative properties, some flavonoids can act as metal-chelating-agents and inhibit the superoxide-driven Fenton reaction, an important source of active oxygen radicals (18-20). The structure-function activity of flavonoids has been reported previously (4).

A number of aglycone flavonoids are potent inhibitors of in vitro oxidative modification of LDL. Phenolic compounds isolated from red wine inhibit the copper-catalyzed oxidation of LDL in vitro, significantly more than α-tocopherol, possibly by regenerating α-tocopherol. Alternatively, chelation of divalent metal ions by flavonoids may reduce formation of free radicals induced by Fenton reactions. Hydroxylation of flavone nucleus appears to be advantage because flavone itself is poor inhibitor of LDL oxidation, whereas polyhydroxylated flavonoids such as quercetin, morin, hypoleatin, fisetin, gossypetin, and galangin are potent inhibitors of LDL oxidation.

The ability of the constituents of tea, particularly (+)-catechin, to inhibit LDL oxidation has been investgated; as expected, LDL modified by cells or copper-induced oxidation was endocytosed and degraded by macrophages more quickly than native LDL. However, in presence of (+)-catechin, the rates of endocytosis and degradation were similar to those of native LDL. In addition to the inhibition of LDL oxidation, flavonoids such as catechin, rutin, and quercetin, at levels of 10-20 mmol/L, minimize the cytotoxicity of the oxidized LDL. Moreover, cells preincubated with these flavonoids were observed to be resistant to the cytotoxic effects of previously oxidized LDL. The postulated mechanisms by which flavonoids protect against the cytotoxicity of oxidized LDL are consistent with their antioxidant and free radical-scavenging properties (4).

Coffee has been reported to inhibit LDL oxidation *in vitro*. One class of phenolic substances, the hydroxycinnamic acids, is ubiquitous in its occurrence. The most common member of this class is chlorogenic acid, which has been shown to inhibit the oxidative modification of LDL *in vitro*. Coffee, along with apples and berries, is a major source of chlorogenic acid in the human diet.

B. Antithrombotic and vasoprotective effects of flavonoids

The antioxidant action of flavonoids appear to be involved in their observed anti-thrombotic action. The antithrombotic and vasoprotective action of quercetin, rutin and other flavonoids have been attributed to their ability to bind to platelet membranes and scavenge free radical. In this manner, flavonoids restore the biosynthesis and actions of endothelial prostacyclin and Endothelial-Derived Relaxing Factor (EDRF), both of which are known to be inhibited by free radicals. However, some flavonoids may inhibit arachidonic acid

metabolism and platelet function by flavonoid-enzyme interactions rather than by antioxidant effects. In addition to their antiaggregatory effects, flavonoids appear to increase vasodilation by inducing vascular smooth muscle relaxation, which may be mediated by inhibition of protein kinase C, PDEs, or by decreased cellular uptake of calcium (18-22).

Flavonoids inhibit platelet aggregation and adhesion; it has been shown that flavonoids influence several pathways involved in platelet function, such as inhibition of cyclooxygenase and lipooxygenase and antagonism of thromboxane formation and thromboxane receptor function. One of the most potent mechanisms by which flavonoids appear to inhibit platelet aggregation is by mediating increases in platelet cyclic AMP (cAMP) levels, either by stimulating adenylate cyclase or by inhibiting cAMP Phosphodiesterase (PDE) activity (23).

The consumption of red wine is linked to decreased platelet aggregation. It is postulated that the antioxidant properties of phenolic compounds in red wine reduce platelet aggregation and inhibit lipid peroxidation in vitro. If such mechanisms are established in humans the protective effects of red wine against platelet aggregation may partly explain the long term advantages of consuming moderate amounts of red wine over other alcoholic beverages (21-23).

Conclusion

Epidemiological, clinical, and *in vitro* evidence support the hypothesis that phytochemicals benefit health. Tropical and subtropical fruits contain a broad range of such compounds, some of which are reported to protect against cardiovascular disease. The presence of a large number of minor dietary factors that protect against disease reinforces the recommendation to increase the intake of plant foods rather than any specific supplement.

References

1. Truswell AS. ABC of Nutrition. 3rd ed. London: BMJ Books; 1999.
2. American Heart Association. Heart and Stroke Statistical Update. Dallas: American Heart Association; 2000.
3. Ralph A, Provan GJ. Phytoprotectants. In: Garrow JS, James WPT, Ralph A, Eds. Human Nutrition and Dietetics. Edinburgh: Churchill Livingstone; 2000: 417-26.
4. Cook NC, Samman S. Flavonoids: chemistry, metabolism, cardioprotective effects and dietary sources. J Nutri Biochem 1996; 7: 66-76.
5. Samman S. Lipid metabolism. In Kuchel PW, Ralston GB, Eds. Schaum's Outlines of Theory and Problems of Biochemistry. New York: McGraw-Hill books Company; 1998: 362-401.
6. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. Lancet 1993; 342: 1007-11.
7. Keli SO, Hertog MGL, Feskens EJM, Hollman PCH, Kromhout S. Dietary flavonoids, antioxidant vitamins and incidence of stroke: The Zutphen Elderly Study. Arch Intern Med 1996; 154: 637-42.
8. Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. Br Med J 1996; 312: 478-81.
9. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willet WC. Relation between intake of flavonoids and risk of coronary heart disease in male health professionals. Ann Int Med 1996; 125: 384-9.
10. Colquhoun DM, Moores D, Somerset SM, Humphries JA. Comparison of the effects on lipoproteins and apolipoproteins of a diet high in monounsaturated fatty acids, enriched with avocardo, and a high carbohydrate. Am

J Clin Nutr 1992; 56: 671-7.

11. Kawaii S, Tomono Y, Katase E, Ogawa K,Yano M. Quantitation of flavonoid constitu-ents in citrus fruits. J Agric Food Chem 1999; 47: 3565-71.
12. Guthrie N, Kurowska EM. Anticancer and chloresterol lowering activies of citrus flavonoids. In: Wildman REC, REC, Ed. Hand- book of Nutraceuticals and Functional Foods. Boca Raton, FL: CRC Press; 2001: 113-26.
13. Yusof S, Ghazali HM, King GS. Naringin content in local citrus fruits. Food Chem 1990; 37: 113-21.
14. Botting KJ, Young MM, Learson AE, Harris PJ, Ferguson LR. Antimutagens in food plants eaten by Polynesians: micronutrients, phytochemicals and protection against bacterial mutagenicity of the heterocyclic amine 2-amino-3-methylimidazol [4,5-f] quinoline. Food Chem Toxicol 1999; 37: 95-103.
15. Roongpisuthipong C, Banphotkasem S, Komindr S, Tanphaichitr V. Post-prandial glucose and insulin responses tovarious tropical fruits of equivalent carbohydrate content in non-insulin dependent diabetes mellitus. Diabetes Res Clin Prac 1991; 14: 123-31.
16. Bates CJ. Prentice AM, Prentice A, Paul AA, Whitehead RG. Seasonal variations in ascor acid status and breast milk ascorbic acid levels in rural Gambian women in relation to dietary intake. Trans Royal Soc Trop Med Hyg 1982; 76: 341-7.
17. Mongkolsirikieat S, Areegitranusorn P, Limratana N, Limpaiboon T, Lulitnond V. Hypocholesterolemic effect of rambutan *(Nephelium lappaceum)* supplementation in Thai adults. Nutr Rep Intl 1989; 39: 797-803.
18. Zern TL, Fernandez ML. Cardioprotective ef fects of dietary polyphenols. J Nutr 2005; 135: 2291-4.
19. Lapointe A, Couillard C, Lemieux S. Effects of dietary factors on oxidation of low-density lipoprotein particles. J Nutr Biochem 2006; 17: 645-58.
20. Rasmussen SE, Frederiksen H, Struntze Krogholm K, Poulsen L. Dietary proanthocyanidins: occurrence, dietary intake, bioavailability, and protection against cardio vascular disease. Mol Nutr Food Res 2005; 49: 159-74.
21. Cordova AC, Jackson LS, Berke-Schlessel DW, Sumpio BE. The cardiovascular protec tive effect of red wine. J Am Coll Surg 2005; 200: 428-39.
22. Folts JD. Potential health benefits from the flavonoids in grape products on vascular dis-ease. Adv Exp Med Biol 2002; 505: 95-111.
23. de Gaetano G, De Curtis A, di Castelnuovo A, Donati MB, Iacoviello L, Rotondo S. Antithrombotic effect of polyphenols in ex-perimental models: a mechanism of reduced vascular risk by moderate wine consumption. Ann N Y Acad Sci 2002; 957: 174-88.