

# Bioflavonoids and Cardiovascular Health: Tea, Red Wine, Cocoa and Pycnogenol®

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## ABSTRACT

Green tea, red wine, cocoa, and a pine bark extract are a few natural sources of potent antioxidants that belong to a group of extracts containing significant amounts of bioflavonoids. They bestow a number of health benefits, including the ability to reduce risk factors associated with cardiovascular disease. For example, Pycnogenol®, a pine bark extract, has shown significant heart protective activities in humans. It lowers platelet aggregation in smokers, reduces hypertension in non-smokers, lowers mediators such as thromboxane, and strengthens arteries. It is sold commercially as an alternative medicine. Thus, the antioxidant nature of bioflavonoids has been shown to play a role at inhibiting low-density lipoprotein oxidation, modulating inflammation associated with atherosclerosis and affecting platelet aggregation.

## INTRODUCTION

According to the Centers for Disease Control and Prevention, the principal components of cardiovascular disease are heart disease and stroke. Approximately 61 million

Americans, 25% of the population, live with the effects of stroke or heart disease, making these diseases the first and third causes of deaths each year, respectively. The most common risk factor for cardiovascular and cerebrovascular morbidity and mortality is hypertension. According to recent estimates, one in four adults in the United States has high blood pressure, but because there are no overt symptoms, nearly one-third of these individuals is unaware of their increased risk. Hypertension is defined as a systolic blood pressure above 139 mm Hg and a diastolic pressure above 90 mm Hg.<sup>1</sup> The Joint Committee on Detection-Evaluation and Treatment of High Blood Pressure has included a borderline, or 'mildly hypertensive', category as defined by systolic blood pressure of 130 to 139 mm Hg and a diastolic blood pressure between 85 and 89 mm Hg. Because mild forms of hypertension can predict progression to more severe disease,<sup>2</sup> it is advantageous to prevent mildly hypertensive blood pressures from rising to critical levels.

In addition to pharmacological therapies, nutritional counseling or intervention is part of the typical strategy used to treat hypertension. To decrease associated risk factors, The American Heart Association Nutrition Committee recommends a diet rich in fruits and vegetables, and low in sodium, saturated fats, and cholesterol. Fruits, vegetables, and edible plants not only contain numerous vitamins and minerals that play significant roles in good health, they also possess a number of antioxidants and iron chelating agents known as bioflavonoids. The antioxidant activities of bioflavonoids have been shown to reduce risk factors associated with cardiovascular disease.<sup>3</sup> Populations that consume a high level of these foods have reduced incidence of cardiovascular mortality and morbidity. This review analyzes the role of several foods and plant extracts in lowering cardiovascular disease risks.

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## Leaves from *Camellia sinensis*:

### Green Tea and Black Tea

Leaves from the *Camellia sinensis* plant are used to make both green tea and black tea. To obtain green tea, leaves are steamed for 1 minute and then allowed to dry.<sup>4</sup> Black tea, however, is obtained by leaving the leaves at room temperature for 16 to 20 hours before drying them.<sup>4</sup> The steaming process inactivates polyphenol oxidase in the green tea leaves, leaving them rich in polyphenols, especially catechins. The primary catechins found in green tea are epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate.<sup>5</sup> The fermentation process of black tea leaves results in the conversion of catechins to theaflavins, such as theaflavin, theaflavin-3-gallate, theaflavin-3,3'-digallate, and thearubigin polymers.<sup>5</sup> It has been shown that the antioxidant capabilities of catechins in green tea and thearubigins in black tea are comparable, suggesting that the differences in processing the leaves have little effect on the health benefits of the bioflavonoids.<sup>6,7</sup>

### Can tea affect cardiovascular function?

The findings of epidemiological studies concerning tea consumption and cardiovascular health have been perplexing. Some studies suggest a cardiovascular benefit from drinking tea; others suggest adverse effects from tea consumption, and some suggest no effect on cardiovascular health.<sup>8</sup> In an attempt to evaluate the contradictory information from a number of epidemiological studies concerning tea and cardiovascular health, Peters et al.<sup>9</sup> conducted a meta-analysis of tea consumption in relation to stroke, myocardial infarction, and all coronary heart disease of 10 cohort studies<sup>10-19</sup> and 7 case-controlled studies.<sup>20-26</sup> Their meta-analysis found an 11% decrease in the incidence of myocardial infarction with an increase of 3 cups of tea consumption daily. In addition, they concluded that elevated tea consumption increased the risk of stroke in Australia and heightened risk for coronary disease in the United Kingdom, but decreased the incidence of both in other regions. Arts et al.<sup>27</sup> suggested that the inconsistencies seen in epidemiological studies might be due to the lack of control for catechin intake from other dietary sources. In their Zutphen Elderly Study,<sup>27</sup> catechin consumption from all sources was controlled in a cohort of 806 men. The data suggested that increasing the daily intake of catechin by 7.5 mg from dietary sources other than tea resulted in a 20% decrease in the risk of ischemic heart disease. These data suggest that in future studies, the amount of bioflavonoids consumed from all sources should be tightly controlled.

### How can tea affect cardiovascular health?

Nitric Oxide (NO) plays a significant role in vasculature integrity. The vasculature modulates vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle cell proliferation.<sup>28</sup> Increased oxidative stress can result in a loss of NO activity and compromised vascular

integrity. In situations of oxidative stress, lipids in arterial wall cells, including macrophages, are exposed to oxidation. An increase in antioxidant concentrations can restore nitric-oxide-dependent responses.<sup>29</sup> Even though bioflavonoids possess potent antioxidant capabilities<sup>3</sup> to restore nitric-oxide-dependent responses in the vasculature, the antioxidant properties of tea bioflavonoids must survive the processes of digestion and absorption and eventually end up in plasma. Langley-Evans<sup>30</sup> investigated plasma antioxidant potential after consumption of tea and found that consuming black tea increased plasma antioxidant capabilities in humans by 50 to 70%. Likewise, Duffey et al.<sup>31</sup> examined the flow-mediated dilation of the brachial artery of patients with coronary artery disease 2 hours after they consumed 450 ml of black tea, and after they consumed 900 ml of black tea daily for 4 weeks. Both short-term and long-term tea consumption resulted in vasomotor function values comparable to those from healthy individuals. These data suggest that antioxidants from tea can be found in plasma and can exert both short-term and long-term vascular benefits.

The oxidative modification hypothesis of atherosclerosis suggests that LDL oxidation plays a causative role in early atherogenesis.<sup>32-38</sup> Supporting this hypothesis, oxidized LDL has been identified in atherosclerotic lesions.<sup>39</sup> It has also been shown that 'oxidized macrophages' can readily oxidize LDL<sup>40,41</sup> and potentiate atherosclerosis. Flavonoids inhibit LDL oxidation in several ways. They can act as scavengers of free radicals. In addition, they can chelate transition metal ions, thereby reducing the metal's potential to generate free radicals. That action protects vitamin E and carotenoids in the LDL particle.<sup>42</sup> Flavonoids have been shown to protect against low density lipoprotein (LDL) oxidation both in vitro<sup>8,43-45</sup> and in vivo. Oxidation of LDL was inhibited in vivo after dietary consumption of several nutrients rich in flavonoids, including catechins from purple grape juice<sup>46</sup> and tea polyphenols.<sup>47-49</sup>

A growing body of evidence indicates that bioflavonoids from tea maintain levels of antioxidant capabilities in the plasma that exert beneficial effects on the cardiovascular system. It has also been shown that the antioxidant capabilities of bioflavonoids act in a number of ways to restore vasculature integrity and inhibit atherogenesis. However, continued investigation is required to identify which bioflavonoids or combinations of bioflavonoids are necessary to optimally reduce cardiovascular disease.

### Beans of *Theobroma cacao*: Cocoa

Cocoa, a major component of chocolate, is another source of bioflavonoids associated with improved cardiovascular health. The primary bioflavonoids found in cocoa are catechin, epicatechin, and procyanidins.<sup>50,51</sup> Flavonoids in cocoa increase antioxidant capabilities of solutions in vitro and slow the oxidation of LDL.<sup>52,53</sup> Protecting LDL from oxidation is one cardioprotective action of cocoa flavonoids.

Inflammation in vascular tissue due to ‘oxidized macrophages’ can further damage a compromised vasculature. Mao et al. reported that cocoa procyanidins reduce the production of inflammatory cytokines and increase levels of anti-inflammatory cytokines.<sup>54</sup> Reduced production of inflammatory cytokines leads to less tissue damage, hence decreasing atherogenic conditions.

Catechin, epicatechin, and procyanidins also modulate platelet aggregation in vitro.<sup>55</sup> Platelets play a role in early stages of atherosclerosis.<sup>56</sup> Platelet hyperactivity and aggregation are also associated with coronary artery disease.<sup>57</sup> In a recent crossover study with 16 healthy adults, Pearson et al. found that flavanol-rich cocoa inhibited epinephrine-stimulated platelet activation and function.<sup>58</sup> Although the inhibitory effects of cocoa were found to be slightly less than those seen with low dose aspirin, they were significant nonetheless.

Chocolate has long been referred to as comfort food, psychological compensation for an unpleasant situation. Recent evidence suggests that the bioflavonoids in cocoa can influence cardiovascular health by antioxidant capabilities that protect LDL from oxidation<sup>52,53</sup> and decrease production of inflammatory cytokines.<sup>54</sup> The bioflavonoids in cocoa can also affect the platelet hyperactivity and hyperaggregation associated with atherosclerosis.<sup>58</sup> Some finished cocoa and chocolate products may contain sufficient amounts of antioxidants to favorably influence oxidant defense,<sup>59</sup> qualifying chocolate as a healer of both mind and body.

### **Cabernet Sauvignon: Red Wine**

The French paradox: the French population consumes diets relatively high in saturated fats and alcohol with little exercise, yet has a disproportionately lower incidence of heart disease than other western societies. That large amounts of red grape products, especially red wine,<sup>60</sup> possess bioflavonoids capable of cardioprotective benefits, sheds some light on the French paradox.

### **How can red wine protect cardiovascular health?**

In humans, polyphenols from red wine have been shown to be absorbed, to bind LDL, and to protect LDL from oxidation.<sup>61</sup> It has also been suggested that absorption rate and type of flavonoids present in red wine are important factors for protection of LDL from oxidation.<sup>62</sup> Resveratrol, a polyphenol present in red wine, has been shown to inhibit superoxide radicals and hydrogen peroxide production, and to decrease the release of arachidonic acid from stimulated macrophages.<sup>63</sup>

In a study by Kerry et al., red wine was incubated with plasma to determine whether the bioflavonoids in the wine could protect plasma LDL from oxidation. The LDL isolated from the plasma, post-incubation, had a 60% increase in lag time following copper-mediated oxidation, and uptake of this LDL by cultured macrophages was 3-fold lower than control LDL.<sup>64</sup> This group also fractionated red wine into

phenolic acids, catechins, monomeric anthocyanidins, flavonols, and polymeric anthocyanidins, and found that all groups of bioflavonoids delayed LDL oxidation. However, they determined that catechins and monomeric anthocyanidins had the most significant antioxidant activity.<sup>64</sup> In a recent study, Rifici et al. determined that LDL oxidation is inhibited by the polyphenols in red wine and not by ethanol.<sup>65</sup> This group also looked at the effects of individual bioflavonoids present in red wine on LDL oxidation, and determined that catechin and epicatechin, at the concentration found in red wine, are the major contributors to its antioxidant activity.<sup>65</sup>

Oxidation of LDL and its subsequent uptake by arterial wall macrophages likely contribute to atherosclerotic plaques.<sup>66</sup> As bioflavonoids in red wine can hinder the oxidation of LDL and its subsequent uptake by arterial wall macrophages, they protect against atherogenesis and defend the integrity of the vasculature. Such conclusions suggest that the French paradox is not as ironic as was first assumed.

### **Extract from *Pinus pinaster*: Pycnogenol®**

An important source of bioflavonoids and related compounds is an extract from the bark of *Pinus pinaster*, French maritime pine bark. Its extract, composed of water-soluble compounds extracted by a patented procedure, is commercially available (Pycnogenol®, Horphag Research). The most prevalent components belong to a class of flavonoids called proanthocyanidins: catechin, epicatechin, and taxifolin, as monomers, dimers, trimers, and oligomers consisting of catechin and epicatechin units. Additionally, the mixture contains polyphenolic organic acids. The antioxidant functions of *Pinus pinaster* bark extracts are effective in reducing factors associated with increased risk of cardiovascular disease, oxidation of LDL, and a dysfunctional endothelium, which otherwise can result from damage by free radicals.

### **How can French maritime pine bark extract affect cardiovascular health?**

The cardioprotective benefits of pine bark extract are: protection of endothelial cells,<sup>67,68</sup> enhancement of endothelial-derived vasorelaxation,<sup>69</sup> strengthened capillaries and preserved vascular integrity,<sup>70-74</sup> inhibition of platelet aggregation,<sup>75,76</sup> and inhibition of thromboxane A.<sup>77</sup> Addition of the French maritime pine bark extract to LDL from healthy individuals inhibited copper-induced LDL oxidation in vitro. It also protected cultured endothelial cells from oxidative damage caused by t-butyl hydroperoxide.<sup>68</sup> The extract protects endothelial cells by acting as a free radical scavenger, by increasing cellular levels of glutathione, and by enhancing endogenous antioxidant enzymes.<sup>67</sup> These studies demonstrate that endothelial cells take up compounds from the extract in the culture medium, suggesting a mechanism for these water-soluble antioxidants to protect the cardiovascular endothelial lining in vivo.

### Can French maritime pine bark extract affect vasodilation?

Vasodilation is an endothelial function. Nitric oxide acts as a vasodilatory signal on the adjacent smooth muscle layer. The extract's addition to media containing cross sections of rat aortas reversed epinephrine- or norepinephrine-induced vasoconstriction.<sup>69</sup> The vasodilatory effect resulted from the French maritime pine bark extract-induced increase in endothelial-derived nitric oxide. Thus, this extract may be effective in maintaining endothelial function by protecting the integrity of the endothelial lining through antioxidant mechanisms and by regulating specific endothelial functions, including the production of nitric oxide. A related benefit is improved blood flow without a concomitant increase in blood pressure, since endothelial-derived vasodilation helps regulate blood pressure. It has been shown that French maritime pine bark extract effectively improved capillary resistance in animal models.<sup>70,72,75</sup> Significant improvement was demonstrated in leg swelling following a single supplement of 360 mg of French Maritime Pine Bark extract.<sup>73</sup> Likewise, there was a decrease in complaints of pain, cramps, and the feeling of "heavy legs," following intake of 5-90 mg of the extract.

### Can French maritime pine bark extract prevent platelet aggregation?

The effects of bioflavonoids present in French maritime pine bark extract were assessed on platelet function of cigarette smokers. Cigarette smoking induces platelet aggregation for thrombus formation, which is a critical contributing factor to vascular events. It has been shown that aspirin prevented smoking-induced platelet aggregation, but not in those with stable coronary disease.<sup>7</sup> In a 2-year study, 180 post-stroke patients took 500 mg of aspirin, with 21% discontinuing medication due to side effects.<sup>79</sup> Therefore, the effects of the pine bark extract were tested on smoking-induced platelet aggregation.<sup>76</sup> Increased platelet reactivity yielding excessive aggregation 2 hours after smoking was prevented by a single dose of 500 mg aspirin or 100-150 mg of the pine bark extract.<sup>76</sup> Prevention followed a dose response relationship, starting from 25 mg. The maximum effect, the complete prevention of abnormal platelet aggregation, was achieved with 200 mg of the French maritime pine extract. Its effects persisted more than 6 days after intake of a single 200 mg dose.<sup>76</sup> We recently treated 7 heavy smokers with 200 mg/d of the pine bark extract for 8 weeks. It significantly inhibited their platelet aggregation and retarded lung congestion. Aspirin increased bleeding time a significant 41% while French maritime pine bark did not, suggesting an advantageous risk/benefit ratio.<sup>76</sup>

Procyanidins inhibit synthesis of the proaggregatory compound thromboxane A<sub>1</sub>.<sup>77</sup> Procyanidins in the pine bark extract also blocked the smoking-induced formation of thromboxane A<sub>2</sub> by stimulating production of nitric oxide in

the endothelium in asthmatics.<sup>78</sup> Thus, inhibition of platelet aggregation by nitric oxide could be part of the mechanism of its preventive effects. In a dose dependent manner, the pine bark extract inhibited epinephrine-induced platelet aggregation in vitro.<sup>75</sup> As smoking doubles plasma epinephrine concentration, prevention of epinephrine-induced platelet aggregation by the extract may also regulate the in vivo platelet activity. We recently reviewed the role of Pycnogenol in cardiovascular health<sup>80</sup> finding that it should synergize with CoQ10 to further benefit and protect the heart.<sup>81</sup>

In conclusion, the French maritime pine bark extract prevented smoking-induced platelet aggregation at a four- to five-fold lower intake and without the adverse effect of aspirin. Therefore we are currently testing additional novel tree bark and peel extracts for commercialization.

### SUMMARY

It has long been understood that eating diets rich in fruits and vegetables yields good health. We now appreciate that these natural sources of nutrition possess components other than vitamins and minerals, such as bioflavonoids, which also confer profound health benefits. Bioflavonoids found in green tea, red wine, cocoa, and pine bark extract are potent antioxidants capable of defending the integrity of the vasculature and reducing risks of cardiovascular disease. They affect platelet aggregation, inflammation, nitric oxide activity, oxidation of LDL, and uptake of oxidized LDL by macrophages in arterial wall cells. Because many of the medications used to treat cardiovascular dysfunction induce adverse side effects, finding natural products capable of protecting and/or restoring cardiovascular health is now and will be a profound contribution to mankind.

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