

## “HOW F&V COULD BE BENEFICIAL FOR HEALTH?”

### Editorial

A high intake of fruits and vegetables (F&V) is a strong determinant of health and results in a low risk for cardiovascular diseases and some forms of cancer. Scientific evidence supporting the health benefits of F&V is primarily derived from epidemiological studies. What is missing is a profound understanding of the bioactive constituents in F&V, the underlying mechanisms, and the dose-response relationship. The articles introduced in this Ifava Newsletter further enhance our understanding of why F&V are so healthy.

Liu *et al.* investigate the contribution of fruits to the overall intake of antioxidants. Their data suggest that some fruits are really “superfruits” due to their high antioxidative potential. Whether these effects measured in test tubes are still relevant after the intestinal digestion of fruits, has yet to be studied in humans. Esmailzadeh *et al.* report that a high intake of F&V protects against non-specific chronic low-grade inflammation. This type of inflammation occurs in obese subjects and is associated with an increased risk of cardiovascular diseases. A high F&V intake is also associated with lower blood pressure. He *et al.* suggest in their article that F&V as a major dietary source of potassium contribute to blood pressure reduction. Together these articles exemplify the different types of bioactive constituents in F&V. For the consumer, the maximum health benefit clearly results from a daily intake of at least 400 grams of various F&V.

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# Cellular antioxidant activity of fruits

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Free radical-induced oxidative stress has been hypothesized to be a major factor in the development of several degenerative chronic diseases. Oxidative stress can cause oxidative damage to large biomolecules such as lipids, proteins, and DNA, resulting in an increased risk for inflammatory diseases, cardiovascular disease (CVD), cancer, diabetes, Alzheimer's disease, cataracts, and age-related functional decline. To prevent or slow the oxidative stress induced by free radicals, sufficient amounts of antioxidants need to be consumed (Liu, 2004).

Fruits, vegetables, whole grains, and other natural products contain a wide variety of antioxidant compounds (phytochemicals), such as phenolics, flavonoids, and carotenoids, and may help protect cellular systems from oxidative damage and also lower the risk of chronic diseases (Liu, 2004). The benefits of fruits, vegetables, and whole grains have been consistently supported by epidemiological studies reporting that regular consumption of these foods is associated with a reduced risk of developing chronic diseases such as cancer and CVD. Bioactive non-nutrient phytochemicals in fruits, vegetables, whole grains and other plant foods have been linked to the reduced risk for major chronic diseases, including cancer and CVD.

Due to the potential of antioxidants to decrease the risk of developing cancer and other chronic diseases, it is important to be able to measure antioxidant activity using biologically relevant assays.

Antioxidant research has been expanded dramatically since the mid-1990s with the development of many chemical assays measuring phytochemical content and total antioxidant activity of pure compounds, foods, and dietary supplements. These assays include: total phenolics Folin-Ciocalteu (F-C) assay, oxygen radical absorbance capacity (ORAC), total radical absorption potentials (TRAP), total oxyradical scavenging capacity (TOSC), peroxyl radical scavenging capacity (PSC), trolox equivalent antioxidant capacity (TEAC), ferric reducing/antioxidant power (FRAP) and 2,2-diphenyl-picrylhydrazyl (DPPH) radical methods. However, none of these takes into account the bioavailability/uptake and metabolism of the antioxidants.

Biological systems are much more complex than the simple chemical mixtures employed and antioxidant compounds may operate via multiple mechanisms. The different efficacies of compounds in the various assays attest to the functional variation. In addition, the mechanisms of action of antioxidants go beyond the antioxidant activity scavenging free radicals in disease prevention and health promotion (Liu, 2004). The best measures are from animal models and human studies; however, these are expensive and time-consuming and not suitable for initial antioxidant screening of foods and dietary supplements. Cell culture models provide an approach that is cost-effective, relatively fast, and addresses some issues of uptake, distribution, and metabolism.

Therefore, there is an urgent need for cell culture models to support antioxidant research prior to animal studies and human clinical trials, as indicated at the First International Congress on Antioxidant Methods

(Liu and Finley, 2005). To address this need, we developed a cellular antioxidant activity (CAA) assay to measure the antioxidant activity of pure phytochemicals, dietary supplements, and foods (Wolfe and Liu, 2007 and 2008).

## Principle of the Cellular Antioxidant Activity (CAA) Assay

The CAA assay utilizes 2',7'-dichlorofluorescein diacetate (DCFH-DA) as a probe in cultured human HepG2 liver cancer cells (Wolfe and Liu, 2007). Non-polar DCFH-DA is taken up by HepG2 cells by passive diffusion and deacetylated by cellular esterases to form polar 2',7'-dichlorofluorescein (DCFH), which is trapped within the cells. Peroxyl radicals generated from 2, 2'-azobis (2-amidinopropane) (ABAP) lead to the oxidation of DCFH to form a fluorescent compound dichlorofluorescein (DCF). The level of fluorescence formed within the cells is proportional to the level of oxidation (Wolfe and Liu, 2007). Pure phytochemical compounds, antioxidants and fruit extracts quench peroxyl radicals and inhibit the generation of fluorescent DCF. The decrease in cellular fluorescence compared to the control cells indicates the antioxidant capacity of the compounds.

## Cellular antioxidant activity of CAA

Twenty-five common fruits consumed in the United States were evaluated for their antioxidant activity in the CAA assay (Wolfe et al, 2008). In general, the CAA values of the berries (wild blueberry, blackberry, strawberry, blueberry, raspberry, and cranberry) and pomegranate tended to be the highest. Wild blueberry had the highest CAA value, followed by pomegranate and blackberry, which had similar CAA values. Strawberry, blueberry, and raspberry were next, and were not significantly different from each other. These were followed by cranberry, plum, cherry, mango, apple, red grape, kiwifruit, pineapple, orange, lemon, grapefruit, peach, pear, nectarine, and honeydew. Honeydew, cantaloupe, and banana had the lowest activities of all the fruits tested in the CAA assay. Apples were found to be the largest contributors of fruit phenolics to the American diet, and apple and strawberries were the top providers of cellular antioxidant activity.

## Fruits consumption to increase antioxidants intake

Antioxidant activity provided by fruits may be important in the prevention of cancer and other chronic diseases. Therefore, increasing fruit consumption is a logical strategy to increase antioxidants intake and decrease oxidative stress, and may lead to reduced risk of cancer. Measuring the antioxidant activity of fruits in cell culture is an important step in screening for potential bioactivity and is more biologically representative than data obtained from chemistry antioxidant activity assays. Further testing is needed to confirm the relationship between CAA values for fruits and their modulation of oxidative stress markers in vivo.



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# Fruit and vegetable intake, C-reactive protein and the metabolic syndrome

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The metabolic syndrome is a cluster of metabolic risk factors in individuals. This syndrome is highly prevalent worldwide<sup>1,3</sup>. Individuals with the syndrome are at greater risk of morbidity and mortality due to cardiovascular disease and diabetes<sup>4,5</sup>. The dietary determinants of this syndrome remain to be identified<sup>6,7</sup>. Systemic inflammation, as measured by plasma C-reactive protein (CRP) concentrations, may directly affect cardiovascular disease through several mechanisms.

## Fruits and vegetables associated with CRP levels?

Dietary intake of fruits and vegetables may reduce risk of the metabolic syndrome through beneficial combinations of antioxidants, fiber, potassium, magnesium and other phytochemicals. Fruits and vegetables have been associated with reduced risk of coronary heart disease but the mechanisms have not been well understood. Fruit and vegetable consumption may reduce the risk of coronary heart disease in part through lowering CRP. We conducted a cross-sectional study, among 486 female teachers aged 40-60 y living in Tehran, to assess the association of consumption of fruits and vegetables with blood CRP levels and the prevalence of the metabolic syndrome.

## A study in Tehran

Fruit and vegetable intakes were assessed using a validated questionnaire. Anthropometric measurements including weight, height, and waist circumference were measured and blood pressure was assessed according to standard methods. Fasting blood samples were taken for biochemical measurements. Metabolic syndrome was defined as the presence of three or more of the following components<sup>8</sup>:

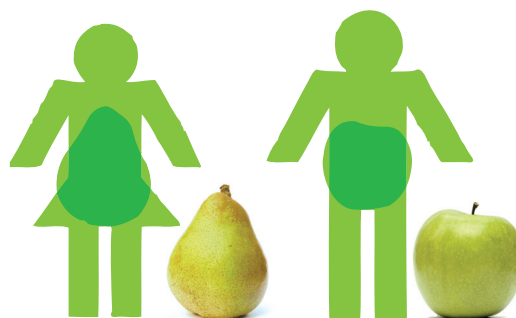
1. abdominal adiposity (waist circumference >88 cm);
2. low serum HDL-C (<50 mg/dL);

3. high serum triglyceride levels ( $\geq 150$  mg/dL);
4. elevated blood pressure ( $\geq 130/85$  mmHg);
5. abnormal glucose homeostasis (fasting plasma glucose level  $\geq 110$  mg/dL).

## Fruits and vegetables consumption associated with lower risk of metabolic syndrome

The reported mean daily intake of fruits and vegetables was  $228 \pm 79$  and  $186 \pm 88$  g/d, respectively. The food items that contributed most to fruit intakes were apples, cantaloupe, watermelon, grapes and bananas, respectively; those that contributed most to vegetable intake were onions, tomatoes, mixed vegetables, lettuce, cucumber and green beans, respectively. Both fruit and vegetable intakes were inversely associated with plasma CRP concentrations. Individuals with higher intakes of fruits had lower plasma CRP levels as compared with those with lower intakes (1.56 vs. 1.94 mg/L). This was also the case with vegetable intakes (1.47 vs. 2.03 mg/L). This inverse association remained significant even after additional control for dietary factors. Compared to those in the lowest quintile of fruit and vegetable intakes, individuals in the highest category had lower odds of having metabolic syndrome. Individuals in the highest quintile of fruits had 34% lower and those in the highest quintile of vegetables had 30% lower chance of having the metabolic syndrome<sup>9</sup>.

It is concluded that higher intake of fruits and vegetables were associated with lower risk of metabolic syndrome; part of this association may be mediated through CRP. These findings support current dietary recommendations to increase the intake of fruits and vegetables as a primary preventive measure against cardiovascular disease.



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# Potassium is beneficial to human health

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For several million years the ancestors of humans ate a diet that contained large amounts of potassium. However, with the advent of civilized societies, cooking and processing of food have greatly reduced the potassium content, and this in combination with a large increase in the consumption of processed foods and a reduction in the consumption of fruit and vegetables, have led to a significant decrease in potassium intake. In most developed countries, the average potassium intake is now around 70 mmol/day, i.e. approximately one third of our evolutionary intake<sup>1</sup>. This low potassium intake causes a rise in blood pressure, increases the risk of cardiovascular disease, renal disease and bone demineralization. Much evidence has shown that an increase in potassium intake is beneficial to human health<sup>2</sup>.



and vegetables, individuals who ate 3-5 servings/day had an 11% reduction in stroke risk and 7% reduction in coronary heart disease risk, and people who consumed more than 5 servings/day had a reduction of 26% and 17% in stroke and coronary heart disease risk respectively<sup>6,7</sup>. It was estimated that, worldwide, up to 2.6 million deaths per year were attributable to inadequate consumption of fruit and vegetables<sup>8</sup>.

Although several nutrients, e.g. potassium, folate, fibre, antioxidants, may contribute to the beneficial effects of fruit and vegetables on cardiovascular disease, much evidence suggests that potassium plays an important role. As raised blood pressure is a major cause of cardiovascular disease, the blood pressure-lowering effect of potassium is likely to be an important mechanism. Additionally, increasing evidence suggests

that potassium may have a direct effect on reducing vascular lesions associated with cardiovascular disease<sup>9</sup>.

A recently published outcome trial demonstrated that an increase in potassium intake reduced cardiovascular mortality. The trial was carried out by Chang *et al.* in 1981 elderly veterans who lived in a veteran's retired home in northern Taiwan<sup>10</sup>. Five kitchens of the veteran retirement home were randomised into 2 groups (experimental or control) and veterans assigned to those kitchens were given either potassium-enriched salt (experimental group) or regular salt (control group) for approximately 31 months. With this intervention there was a 76% increase in potassium intake and a 17% reduction in salt intake in the experimental group, as measured by urinary potassium/creatinine ratio and sodium/creatinine ratio. Compared to those in the control group, individuals in the experimental group had a 40% reduction in cardiovascular disease mortality.

## Effect on blood pressure

Both epidemiological studies and randomised trials have shown that a higher potassium intake was related to a lower blood pressure. A meta-analysis of 32 randomised trials demonstrated that potassium supplementation, with an average increase of approximately 50 mmol in 24-hour urinary potassium excretion, resulted in a fall in blood pressure of 4.4/2.5 mmHg in individuals with high blood pressure and 1.8/1.0 mmHg in those with normal blood pressure<sup>3</sup>.

Most of the randomised trials have used potassium chloride, which is convenient for making a study double blinded by using wax encapsulated potassium chloride (Slow-K) against Slow-K placebo. However, the best way to increase potassium intake is to increase the consumption of food high in potassium, e.g. fruit and vegetables. In the DASH (Dietary Approaches to Stop Hypertension) trial, an increase in fruit and vegetable intake from an average of 3.6 to 8.5 serving/day, with a subsequent increase of approximately 30 mmol/24-hour in urinary potassium excretion, resulted in a fall of 2.8/1.1 mm Hg in blood pressure in individuals with normal or mildly raised blood pressure<sup>4</sup>.

## Effect on cardiovascular disease

A number of epidemiological studies have shown an inverse association between potassium intake and cardiovascular disease. For example, in a 12 year prospective study, Khaw *et al* demonstrated that an increase of 10 mmol/day in potassium intake was associated with a 40% reduction in the risk of stroke mortality<sup>5</sup>. This association was independent of other dietary variables and also independent of other known cardiovascular risk factors including age, sex, blood pressure, blood cholesterol, obesity, fasting blood glucose and cigarette smoking.

The consumption of fruit and vegetables has also been shown to be inversely related to cardiovascular disease in a dose-response manner<sup>6,7</sup>. Meta-analyses of prospective cohort studies showed that, compared with those who consumed less than 3 servings/day of fruit

## Other beneficial effects

Experimental studies in animals have shown that a high potassium diet may prevent or at least slow the progression of renal disease<sup>11</sup>. An increased potassium intake lowers urinary calcium excretion and could play an important role in the management of hypercalciuria and kidney stones, and is also likely to decrease the risk of osteoporosis<sup>12</sup>. Low potassium concentration in serum is strongly related to glucose intolerance and increasing potassium intake could prevent the development of diabetes that occurs in hypertensive patients who receive prolonged treatment with thiazide diuretics<sup>13</sup>. Reduced serum potassium increases the risk of lethal ventricular arrhythmias in patients with coronary heart disease, heart failure and left ventricular hypertrophy, and increasing potassium intake may prevent this<sup>14</sup>.

The best way of increasing potassium intake is to increase the consumption of fruit and vegetables, which in themselves may have beneficial effects on health (e.g. antioxidants, folic acid, etc) independent of potassium intake.

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