A Review and Critical Analysis of the Scientific Literature Related to 100% Fruit Juice and Human Health[1,2]

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ABSTRACT

The association between the consumption of pure (100%) fruit juice (PFJ) and human health is uncertain. The current review summarizes data published between 1995 and 2012 related to PFJ with a focus on juices that are widely available and studied in forms representing native juice without supplemental nutrients or enhanced phytochemical content. The effects of apple, cranberry, grape, grapefruit, orange, and pomegranate PFJ intake on outcomes linked to cancer, cardiovascular disease, cognition, hypertension, inflammation, oxidation, platelet function, urinary tract infection, and vascular reactivity are reviewed. Implications for bodyweight regulation are also addressed. The collective data are provocative although challenges and unanswered questions remain. There are many plausible mechanisms by which PFJ might be protective, and investigation of its effects on human health and disease prevention must remain an active area of research. *Adv Nutr* 2015;6:37–51.

Keywords: juice, oxidation, lipid, endothelium, cognitive

Introduction

Guidelines for health promotion and disease prevention in the United States and around the world include recommendations to consume a variety of fruits and vegetables each day (1). Evidence suggests an association between a diet rich in fruits and vegetables and improved health as well as reduced risk of major chronic illnesses in humans (1). Furthermore, ongoing research demonstrates that bioactive compounds in plant sources modulate important disease-related processes by a variety of mechanisms (2).

Although it is universally accepted that fruit and vegetable intake is protective, there is no clear consensus about the effects of consuming the juices that are extracted from them (1, 3). Concerns about the lower fiber content and the higher caloric density per serving have prompted suggestions that fruit juice intake should be limited as a poor substitute for fruit and that fruit juice is comparable to sugar-sweetened beverages. In contrast, an analysis of scientific evidence published in 2006 suggested that expressed fruit juices without added nonjuice components, sweeteners, etc. [defined as pure juice or 100% fruit juice (PFJ)[3]], retain the majority of nutrients and phytochemicals of the whole fruit and therefore may have important potential to benefit human health (3). There is recent evidence linking PFJ to positive outcomes on biomarkers, mechanisms, and risk factors associated with common chronic diseases in humans although many questions remain.

Methods

This review summarizes scientific literature published between 1995 and 2012 related to the potential effects of PFJ intake in humans, ranging from single dose tests to clinical trials. The report emphasizes PFJs that are *1)* widely available, *2)* commonly consumed as a single juice preparation (rather than blended with other juices), and *3)* investigated in forms of expressed fruit juice, free of additives, enrichment, or fortification (however, commercial or research preparations formulated to represent native juices as consumed by humans are included). In cases in which it was unclear whether PFJ was examined, because of vague terminology and/or descriptors, the study was not included in the review.

The combination of constituents naturally present in PFJ may act synergistically such that the effects of the "whole juice" differ from the sum of the parts (1). As such, work with isolated phytochemicals/compounds, synthesized and mixed compound preparations, and enriched or processed

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[3] Abbreviations used: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; FMD, flow-mediated dilation; FRAP, ferric-reducing antioxidant power; HFS, high fructose corn syrup; PFJ, pure (100%) fruit juice; PSA, prostate-specific antigen; ROS, reactive oxygen species; UTI, urinary tract infection; 8-*epi*-PGF$_{2\alpha}$, 8-epi-prostaglandin 2α.

extracts was excluded. Furthermore, studies of bioavailability are not included although important work has shown that metabolites are found in plasma and urine after PFJ consumption. When known, the primary biochemical constituents associated with the observed outcomes or proposed mechanisms related to PFJ intake will be presented, recognizing that much work needs to be done to determine effective concentrations and forms in vivo.

Five fruit juices that met the inclusion criteria include apple, citrus (orange and grapefruit), grape, and pomegranate juice. Cranberry juice is typically consumed as a "cocktail" including sweeteners to offset the tart flavor. Studies that examined such mixtures are included in the review because of the wide availability of cranberry juice in this form. Data were collected from searches of the National Center for Biotechnology Information PubMed and Medline databases for peer-reviewed publications published between 1 January 1995 and 31 January 2012 that focused on several common public health conditions and related mechanisms. Key search terms included full and truncated forms of the words fruit(s) and juice(s) for each fruit (apple, citrus, cranberry, grape, grapefruit, orange, pomegranate) as well as (in alphabetical order) age, aging, Alzheimer's, arthritis, asthma, birth defects, bodyweight, bone, brain, cardiovascular disease, cataracts, cholesterol, chronic obstructive pulmonary disease, cognitive, coronary, dermatological, diabetes, diverticulosis, endothelial, eye, gastrointestinal, hypertension, immunity, inflammation, life span, lipid, longevity, neurodegenerative, obesity, oxidation, platelet, skin, and urinary tract. Related articles linked to the retrieval lists were autoprompted during the search and reviewed for relevance. References cited in retrieved articles were also searched.

Data are presented only for conditions in which at least 2 peer-reviewed publications were available that included investigations of PFJ and oxidation, inflammation, vascular reactivity, lipid metabolism, hypertension, platelet reactivity, cancer, cognitive function, Alzheimer's disease, and urinary tract infection. Values are expressed as mean ± SD for all variables unless indicated.

The review concludes with a brief discussion of the implications of PFJ intake on bodyweight regulation and associated metabolism followed by a general summary and conclusions related to PFJ consumption and human health.

Oxidation and Related Markers

An imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense systems appears to be an important factor in chronic illnesses such as cardiovascular disease, cancer, diabetes, and many others because of disruptions in the synthesis, repair, and maintenance of DNA, proteins, lipids, and other cellular components affected by ROS (4). The effects of PFJ on oxidant stress and antioxidant status or function have been extensively reported with use of a variety of analytic measures to assess the formation of free radicals, and/or primary and secondary oxidation products or substrate changes as summarized below (5–32).

PFJ intake increases antioxidant capacity in serum within an hour after consumption, and the effect may be sustained for several hours afterward, depending on the volume and type of juice, subject characteristics, type of assay, and other unknown factors. Apple, orange, and grape juice (150 mL prepared from homogenized fruit) were among 8 fresh fruit juices that exhibited a maximal antioxidant effect within 30 min of intake in 10 healthy men (aged 24 ± 1 y) (5). A significant reduction in ROS generation/oxidant stress in plasma ($P < 0.05$) indicated by fluorescent probe (2,7-dichlorofluorescin) was sustained for 90 min (apple and orange juices) and 2 h (grape juice) after intake (5).

Apple juice (300 mL) extracted from Golden Delicious or Catarina apples in Brazil was consumed by 9 healthy, normal

weight women, aged 21–27 y (6). Antioxidant capacity, based on ferric-reducing antioxidant power (FRAP) and oxidation of 2,2′-azinobis 3-ethylbenthiazolin-6-sulfonic acid was significantly increased within 1 h of consuming each juice, ranging from 4.2% to 10.6% over baseline and compared to water ($P < 0.05$). Nonspecific biomarkers of lipid peroxidation in serum, including hydroperoxides, and TBARSs were reduced comparably by both juices and were inversely correlated with serum antioxidant capacity ($r = -0.80$, $P < 0.05$). Interestingly, however, serum uric acid and vitamin C each increased by 11%, but only the former was correlated with serum antioxidant capacity (Golden Delicious: $r = 0.73$, Catarina: $r = 0.90$, $P < 0.05$) and inversely associated with lipid peroxidation ($r = -0.53$, $P < 0.05$) (6). Other investigators found a positive correlation between increased uric acid concentrations and measures of antioxidant capacity in plasma, ranging from $r = 0.65$ to $r = 0.85$, 1–4 h post-intake ($P = 0.01$) after rapid consumption of 1 L of apple juice (Table 1) (7). Although the large volume of apple juice and the 10–15 min intake period may limit the generalization of these findings, such reports underscore the importance of determining which bioactive components mediate antioxidant effects, particularly in the absence of a rise in presumed antioxidants (phenolic compounds) in plasma or serum in these subjects.

Measures of the rate and lag time of copper-induced LDL oxidation are used as surrogate markers of antioxidant capacity in plasma suggesting a potential effect on components in the blood. A crossover trial in healthy men and women (12 men and 13 women, mean age: 39.8 ± 1.9 y) showed that 375-mL commercial apple juice or 340-g cored fresh apple each day for 6 wk did not affect fasting lipid measurements, but apple juice was associated with a significant increase in lag time of copper-induced LDL oxidation and a slight reduction in conjugated diene production ($P < 0.05$) (8).

The effects of a single serving of 240-mL cranberry juice cocktail [representing typically consumed including 27% cranberry juice, 80-mg vitamin C, and high fructose corn syrup (HFS)] were compared to a control beverage containing HFS and vitamin C but no cranberry concentrate in 10 healthy subjects (mean BMI: 26 kg/m², age range: 25–28 y) (9). The FRAP in plasma increased after cranberry juice intake and remained significant compared to reduced FRAP for 7 h after consumption of the control beverage ($P < 0.05$). The authors suggested that 27% cranberry juice might attenuate a pro-oxidant effect of HFS after short-term exposure.

Cranberry juice has been shown to affect paraoxonase, a lipo-lactonase (esterase) in plasma associated with stabilizing HDL and proposed to be antiatherogenic by several mechanisms. A double-blind, randomized trial evaluated the effect of 240-mL daily cranberry juice vs. placebo for 12 wk in 58 men with type 2 diabetes (mean age: 54.8 ± 9.1 y; BMI: 28.8 ± 3.6) (10). Compared to baseline, there was a significant increase in activity of apoA1 and paraoxonase-1 ($P < 0.01$) and an increase in each compared

TABLE 1 Summary of findings related to PFJ consumption and oxidative status[1]

Reference	Study design, duration[2]	Type of juice	Subjects (healthy unless specified)[3]	Results[4]
Ko et al., 2005 (5)	Single-dose postprandial	Apple, orange, grape, 150 mL	$n = 10$, ♂, 24 ± 1 y	↓ DCF at 90 min (apple, orange) and 2 h (grape)
Vieira et al., 2012 (6)	Single-dose postprandial	Apple, 300 mL	$n = 9$, ♀, 21–27 y	↑ FRAP, ABTS, uric acid, and ascorbic acid at 1 h vs. baseline and water control; ↓ LH and TBARS
Godycki-Cwirko et al., 2010 (7)	Single-dose postprandial	Apple, 1 L cloudy; clear; ± polyphenols	$n = 12$, ♀♂, 32 ± 5 y	All juices ↑ FRAP, DHHP-scavenging, uric acid over 4 h post-intake ($P = 0.01$)
Hyson et al., 2000 (8)	Crossover, 6 wk juice vs. whole apple	Apple, 375 mL/d	$n = 25$, ♀♂, 40 ± 2 y	Delay LDL oxidation, ↓ conjugated diene production; ↔ fasting lipids
Vinson et al., 2008 (9)	Single-dose postprandial	Cranberry, 240 mL/d (27% juice cocktail)	$n = 10$, ♀♂, 25–28 y	↑ FRAP vs. control beverage (maintained up to 7 h after consumption)
Shidfar et al., 2012 (10)	Double-blind, placebo-controlled, 12 wk	Cranberry, 240 mL/d	$n = 10$, type 2 diabetic ♂, 55 ± 9 y	↑ apoA1 and paraoxonase activity, ↓ glucose and apoB vs. baseline and vs. control (P range < 0.0001 to < 0.05). ↔ Lp(a)
Stein et al., 1999 (11)	Pre- and post-test, 2 wk; juice 2 h before post-test	Grape (Concord), 7.7 mL/kg per day	$n = 15$, ♀♂, CAD/hypertension, dyslipidemia, 63 ± 13 y	Delay LDL oxidation; ↑ total cholesterol ($P = 0.043$), ↑ TG ($P < 0.001$), ↑ insulin ($P = 0.004$); ↑ FMD ($P = 0.003$; see Table 2)
Vinson et al., 2000 (12)	Pre- and post-test; high or low vitamin C (7 d each), or no vitamin C	Grape (Concord), 2 × 200 mL daily (+76 mg vitamin C vs. juice 6 mg vitamin C) vs. no vitamin C (orange juice similar protocol)	$n = 8$, ♀♂, 20–55 y, high and low vitamin C; $n = 6$, ♀♂, 20–34 y in no vitamin C group	Delay LDL oxidation in all groups; not sustained after 7-d washout. ↔ LDL oxidation after orange juice
O'Byrne et al., 2002 (13)	Pre- and post-test, 2 wk juice, plus grape vs. α-tocopherol group	Grape (Concord), 10 mL/kg or 400 IU α-tocopherol/d, dietary flavonoids restricted	Grape group, $n = 15$, ♀♂, 28 ± 3 y vs. α-tocopherol, $n = 17$, ♀♂, 28 ± 5 y	Grape vs. α-tocopherol ↓ plasma protein carbonyls, ↑ TG; both groups ↑ ORAC ($P < 0.001$), delayed LDL oxidation rate ($P < 0.01$), ↑ LDL oxidation lag time ($P < 0.001$), ↔ endogenous urinary F2-isprostane, ↔ AAPH-induced plasma protein oxidation
Yuan et al., 2011 (14)	Pre- and post-test, 2 wk	Grape, 300 mL + apple, 300 mL/d	$n = 25$, ♀♂, 20–23 y	↑ Plasma T-AOC ($P < 0.01$), ↓ plasma MDA, ↔ carbonyls, ↑ erythrocyte CAT and GSH-Px, ↔ SOD, ↔ urinary 8-OHdG, ↔ DNA damage in lymphocytes
Gonzáles-Flores et al., 2012 (15)	Pre- and post-test, 5 d	Grape (Tempranillo), 200 mL/d	$n = 6$/age group, ♀♂, 20 ± 10, 45 ± 10, 75 ± 10 y	↑ Urinary aMT6s, ↑ ATBS
Castilla et al., 2006 (16)	Pre- and post-test, 2 wk	Grape (concentrated Bobal), 100 mL/d	$n = 26$, hemodialysis, 62 ± 3 y ♀♂; $n = 12$, no juice, hemodialysis, 59 ± 4 y	Juice ↑ TEAC, ↓ oxidized LDL within week 1, sustained day 14 ($P < 0.001$) vs. no juice, ↔ TEAC, ↔ oxidized LDL
Castilla et al., 2008 (17)	Pre- and post-test, 2 wk	Grape (concentrated Bobal), 100 mL/d ± 800 IU vitamin E, or vitamin E alone vs. placebo control	$n = 8$ each group, hemodialysis ♀♂, 33–79 y	All but placebo ↓ oxidized LDL ($P < 0.01$), grape juice only ↑ HDL ($P < 0.001$), ↑ apoA-1 ($P < 0.01$), juice ± vitamin E ↓ total and LDL cholesterol, apoB vs. baseline ($P < 0.0001$), juice ↓ plasma MCP-1, ↔ VCAM-1, hsCRP, complement C3 protein

(Continued)

TABLE 1 (Continued)

Reference	Study design, duration[2]	Type of juice	Subjects (healthy unless specified)[3]	Results[4]
Sánchez-Moreno et al., 2003 (18)	Single dose plus pre- and post-test, 2 wk	Orange (fresh), 500 mL single dose; 500 mL/d	n = 12, ♀♂, 20–32 y (subset n = 3 smokers)	Single dose ↑ plasma vitamin C in ♂ (P = 0.001) and ♀ (P = 0.009), ↓ plasma 8-epi-PGF$_{2\alpha}$ in ♂, greater effects in smokers
Johnston et al., 2003 (21)	Crossover × 3, juice vs. vitamin C supplement	Orange, 250 mL, 500 mL, 72 mg vitamin C	n = 11, ♀, 21–39 y	↑ Plasma vitamin C after 500-mL juice (P = 0.0001) and 72-mg vitamin C (P = 0.001), ↓ TBARS after 250-mL juice and vitamin C (P = 0.01)
Deopurkar et al., 2010 (22); Ghanim et al., 2010 (23)	Repeat single-dose tests	Orange, 300 kcal equivalent vs. 300 kcal quantity of cream or glucose	n = 10/group, ♀♂, 20–40 y; n = 12/group, ♀♂, 25–47 y	Juice ↓ ROS generation by mononuclear cells, attenuated rise in plasma endotoxins and mRNA for TLR2, TLR4, and SOD-protein at 1, 3, 5 h vs. glucose or cream beverage, suppressed monocyte p38 MAPK protein, mRNA for/and plasma MMP-9
Codoñer-Franch et al., 2008 (24)	Pre- and post-test, 4 wk	Mandarin, 500 mL/d	n = 48, hypercholesterolemic children, 8–12 y	↓ Plasma MDA, carbonyl groups (P < 0.01), ↑ reduced glutathione, vitamin C (P < 0.00001), vitamin E (P < 0.001)
Guo et al., 2008 (25)	Pre- and post-test, 4 wk	Pomegranate vs. apple, 250 mL/d	n = 26, ♀♂, >60 y	Both juices ↓ plasma MDA (P < 0.01), pomegranate ↓ FRAP, carbonyl content, ↔ oxidation LDL, GSH
Shema-Didi et al., 2012 (26)	Double-blind, placebo-controlled, 12 mo	Pomegranate, 100 mL 3 × wk, during first hour of dialysis	n = 66 juice vs. n = 35 placebo, hemodialysis ♀♂, >18 y	↓ CD11b, myeloperoxidase, oxidized fibrinogen, MDA, IL-6, TNF-α (P < 0.03–0.001), fewer infections juice vs. placebo
Rock et al., 2008 (27)	Pre- and post-test, 4 wk	Pomegranate, 50 mL/d concentrate	n = 10 ♂, n = 10 postmenopausal ♀ (age not specified)	♂ Only ↓ TBARS, AAPH-induced serum lipid peroxidation, ↑ FRAP, thiol groups, ↑ paraoxonase free and HDL-related activity (binding, catalytic), ↔ lipids, glucose, Hb A$_{1c}$
Rosenblat et al., 2006 (28)	Pre- and post-test, 12 wk vs. control	Pomegranate, 50 mL fresh diluted 1:5 (v:v)	n = 10, diabetic ♂ vs. 10 ♂, 50 ± 10 y	↓ Plasma peroxides, C-peptide, ↑ thiols, paraoxonase arylesterase activity vs. control/baseline (P < 0.01)

[1] AAPH, 2,2'-azobis(2-amidinopropane)dihydrochloride; aMT6s, 6-sulfatoxymelatonin; ABTS 2,2'-azino-di-[3-ethylbenthiazoline sulphonate); CAD, coronary artery disease; CAT, catalase; DCF, 2,7-dichlorofluorescin; DHHP, 1,1-diphenyl-2-picrylhydrazyl; FMD, flow-mediated dilation; FRAP, ferric-reducing antioxidant power; GSH-Px, glutathione peroxidase; Hb A$_{1c}$, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; LH, lipid hydroperoxides; Lp(a), lipoprotein (a); MCP-1, monocyte chemoattractant protein; MDA, malondialdehyde; MMP-9, matrix metallopeptidase 9; ORAC, oxygen radical absorbance capacity; PFJ, pure (100%) fruit juice; p38 MAP, mitogen-activated protein kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; T-AOC, total antioxidant capacity; TEAC, Trolox equivalent antioxidant capacity; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; urinary 8-OHdG, 8 hydroxydeoxyguanosine; VCAM-1, vascular cell adhesion molecule-1; 8-epi-PGF$_{2\alpha}$, 8-epi-prostaglandin 2α.

[2] Study design was randomized unless otherwise indicated.

[3] Values are mean age ± SD or range, rounded to nearest whole number.

[4] P < 0.05 unless otherwise indicated; ↑, increase; ↓, decrease; ↔, no effect; ♀, women; ♂, men.

to controls ($P < 0.0001$ and 0.05, respectively). Serum glucose and apoB concentrations declined from baseline ($P < 0.01$ and 0.05, respectively) and also decreased compared to control ($P < 0.05$).

Concord grape juice exerts antioxidant effects as first shown in 15 men (mean age: 62.5 ± 12.7 y) with documented coronary artery disease (CAD) and heterogeneous backgrounds including 10 with hypertension, 11 with dyslipidemia, 10 on lipid-lowering medications, and 12 who took daily vitamin E and C supplements (11). After 2 wk of daily juice intake (7.7 mL/kg), resistance of LDL to oxidation was significantly greater than baseline ($P < 0.05$) despite increases in plasma total cholesterol ($P = 0.043$), TG ($P < 0.001$), and insulin concentrations ($P = 0.004$) compared to baseline. Flow-mediated dilation (FMD) of the brachial artery also improved (see Vascular Reactivity and Inflammation). However, because juice was consumed 2 h before all measurements, it was not possible to differentiate between acute or long-term effects.

Concord grape juice (400 mL with 76-mg vitamin C per day) was consumed by 8 healthy men and women (aged 20–55 y) in 2 divided servings for 7 d followed by 1 wk of placebo containing 6-mg vitamin C. A second group of men and women ($n = 6$, aged 20–34 y) drank 400-mL/d grape juice without vitamin C and placebo (12). Both juices containing grape juice increased lag time of LDL oxidation by 27% ($P < 0.05$) compared to placebo; the effect was not sustained after a washout period. Orange juice was also studied in a group of comparable subjects and did not affect LDL oxidation.

Fifteen healthy adults who consumed Concord grape juice throughout the day (10 mL/kg for 2 wk) were compared with a test group ($n = 17$) who supplemented with 400-IU α-tocopherol (13). Grape juice increased plasma concentrations of phenolic compounds (total and conjugated) by 17% ($P < 0.01$) and 22% ($P < 0.001$), respectively. Oxygen radical absorbance capacity and lag time to LDL oxidation also increased ($P < 0.001$). The rate of LDL oxidation ($P < 0.01$) and concentration of plasma protein carbonyls were reduced ($P < 0.05$), although several other markers were unaffected (Table 1). Grape juice intake was associated with increased concentrations of TG in the blood ($P < 0.05$).

The effects of grape and apple juice (300 mL of each daily) were tested in 25 healthy men and women (aged 20–23 y) (14). Total antioxidant capacity in plasma was increased ($P < 0.01$), whereas malondialdehyde, a general marker of lipid peroxidation, was reduced after 2 wk ($P < 0.05$). Antioxidant enzymes in erythrocytes, including glutathione peroxidase and catalase, increased significantly, although other markers were unchanged (Table 1).

Juice from Tempranillo grapes, stabilized by high hydrostatic pressure, was examined in 3 age groups ($n = 6$ in each) of young (20 ± 10 y), middle-aged (45 ± 10 y), and elderly (75 ± 10 y) healthy subjects (15). Consuming 200 mL of juice for 5 d resulted in a significant rise in urinary concentrations of 6-sulfatoxymelatonin, a metabolite of melatonin with antioxidant properties, and increased antioxidant capacity of urine in all ages groups, based on peroxidation of 2,2′-azino-di-[3-ethylbenthiazoline sulphonate] ($P < 0.05$).

Consuming 100 mL/d of red grape juice (concentrated bobal variety) increased Trolox equivalent antioxidant capacity and reduced oxidized LDL within the first week (16). The effects were sustained at 2 wk compared to baseline ($P < 0.001$) in patients on hemodialysis (13 men and 13 women, mean age: 62 ± 3.4 y). Young, healthy subjects (10 women and 5 men, mean age 34.4 ± 3.3 y) also experienced these effects compared to no effect in control (no juice) subjects on hemodialysis (12 men and women, mean age: 59.2 ± 3.8 y) (16). Other studies assessed the effects of this regime with and without 800-IU daily vitamin E compared to vitamin E alone or placebo (17). There was a decrease in oxidized LDL cholesterol concentration in all groups ($n = 8$ each) except placebo after 1 wk of treatment and sustained for 2 wk ($P < 0.01$). Greater beneficial effects on plasma lipids were observed in subjects receiving 100-mL/d grape juice than juice plus vitamin E (Table 1). Monocyte chemoattractant protein-1 was the only inflammatory marker reduced by grape juice alone ($P < 0.05$) (see Table 1).

Healthy men and women ($n = 12$, aged 20–32 y, normal BMI) were tested after consuming a single serving of 500-mL freshly-squeezed orange juice (250-mg vitamin C) and after 2 wk of daily intake (18). Although vitamin C concentrations increased in all subjects, only men experienced a 27% reduction in plasma concentrations of 8-epi-prostaglandin 2α (8-epi-PGF$_{2\alpha}$), a marker of nonspecific phospholipid oxidation, at day 14 ($P < 0.05$). Plasma 8-epi-PGF$_{2\alpha}$ was inversely correlated with plasma vitamin C concentrations at baseline ($r = -0.60$, $P = 0.05$) but not on day 14 ($r = -0.55$, $P = 0.06$) (18). A small subset of male smokers ($n = 3$) experienced a greater increase in plasma vitamin C (93%) and a significant reduction in 8-epi-PGF$_{2\alpha}$ after 7 d of orange juice intake and sustained on day 14 ($P = 0.04$ for each). Similar findings were associated with consumption of 500-mL orange juice subjected to different processing techniques including high-pressure treatment (19) and pulsed electric field treatment (20).

Orange juice intake was associated with antioxidant activity comparable to vitamin C supplementation in a randomized 3×3 crossover study in which healthy, normal weight women, ($n = 11$, aged 21–39 y) consumed, in random order 250- or 500-mL orange juice or a vitamin C supplement (72 mg/d) for 2 wk each, separated by 2-wk washouts (21). General lipid peroxidation concentrations (TBARS) were reduced by 47% (250-mL juice, $P = 0.013$), 40% (500-mL juice, $P = 0.083$), and 46% (vitamin C, $P = 0.015$).

Orange juice modulated antioxidant and anti-inflammatory properties at the cellular and molecular level at 1, 3, and 5 h after consumption than isocaloric (300-kcal equivalent) beverages of cream or glucose. Orange juice was the only test beverage that did not invoke an inflammatory response in plasma or isolated monocytes of healthy subjects ($n = 12$) (22) and attenuated the rise in blood glucose and several

markers of inflammation associated with a high-fat, high-carbohydrate meal (900 kcal) during the postprandial period (Table 1) (23).

Mandarin juice improved the antioxidant status of hypercholesterolemic children (22 girls, 26 boys, aged 8–12 y) after consumption of 500 mL/d for 28 d (24). Plasma concentrations of malondialdehyde and carbonyl groups were reduced compared to baseline ($P < 0.01$), and plasma concentrations of reduced glutathione, vitamin C ($P < 0.00001$), and vitamin E ($P < 0.001$) were elevated suggesting that mandarin juice might spare other cellular antioxidant systems.

Twenty-six elderly men and women (>60 y) were randomly assigned to drink 250 mL/d of either freshly prepared pomegranate juice or commercial apple juice (25). After 4 wk, plasma concentrations of malondialdehyde were lower in both groups ($P < 0.01$), and only pomegranate juice increased FRAP and reduced carbonyl content in plasma compared to baseline ($P < 0.05$). Other markers were unaffected (Table 1).

Pomegranate juice (100 mL) was provided during the first hour of dialysis, 3 times per week compared to placebo in a randomized, double-blind, placebo-controlled 12-mo trial (26). Quarterly follow-up assessments showed an accumulating benefit of pomegranate juice on all primary and secondary outcomes including reduction in several biomarkers of oxidative stress and inflammatory markers after 1 y of juice intake compared to placebo (see Table 1) as well as improvements in carotid artery ultrasonography in a subset of mobile patients (18 patients in the juice group and 13 in the placebo group). The incidence of infection(s) requiring hospitalization was also significantly lower in the juice group, particularly second hospitalizations ($P = 0.01$).

A trial including 10 nonsmoking men and 10 postmenopausal women, all treated with statins, examined the effects of pomegranate juice (50-mL concentrate) consumption after 4 wk (27). A concurrent group of men ($n = 10$) received a pomegranate extract of polyphenolic compounds for comparison. Juice intake lowered TBARSs by 19% after 2 wk and 25% after 4 wk, as well as reduced 2,2′-Azobis(2-amidinopropane) dihydrochloride–induced serum lipid peroxidation by 15% at 4 wk ($P < 0.05$) in men but not women. Concentrations of thiol groups and FRAP in plasma were increased by 25% after 2 wk and 35% after 4 wk ($P < 0.05$). Several beneficial effects on paraoxonase-related measurements were observed in men but not women (Table 1), and most effects were still evident for 4 wk after discontinuing the juice.

A study of type 2 diabetic men ($n = 10$) vs. healthy controls ($n = 10$), aged 50 ± 10 y, also demonstrated that pomegranate juice (50-mL fresh-squeezed concentrate diluted 1:5 (v:v) for 3 mo) improved several markers of oxidation in the study group compared to controls and baseline (Table 1) (28). In the diabetic subjects, pomegranate juice consumption did not adversely affect markers of diabetic control and actually reduced plasma concentrations of C-peptide (cleavage product of proinsulin).

In contrast to the above, other investigations of antioxidant effects in humans have not shown a benefit or have produced mixed results. A randomized crossover study including 3 test periods [600-mL daily orange juice supplementation, washout, and no orange juice for 3 wk in women ($n = 16$) aged 20–27 y] did not affect functional indicators of antioxidant status despite increased plasma concentrations of vitamin C and several carotenoids during the study period (29).

In another study of young healthy women aged 18–40 y, 750-mL/d cranberry juice consumed for 2 wk had no significant effect on plasma lipids, total homocysteine, or plasma or urinary markers of antioxidant status compared to baseline or placebo group (30).

Dalgard et al. (31) reported that 4 wk of consuming orange juice (250 mL) and blackcurrant juice (250 ml) increased concentrations of plasma vitamin C in 24 men and women with peripheral artery disease in Denmark but did not affect other markers or serum concentrations of paraoxonase.

A small study ($n = 6$) of pomegranate juice designed to examine bioavailability did not show any effect on plasma lipids or several markers of antioxidant activity (2,2′-azinobis 3-ethylbenthiazolin-6-sulfonic acid; 1,1-diphenyl-2-picrylhydrazyl; and FRAP) in healthy humans who consumed 1 L of pomegranate juice for 5 d (32).

In vitro work aimed at ranking the relative antioxidant capacity of fruits/juice has produced inconsistent results with some methods ranking antioxidant capacity of selected fruits/juice as relatively poor, whereas others show better antioxidant activity for the same fruits/juice (33). The pros and cons of various assays to determine in vitro antioxidant activity and the inconsistent correlation between in vitro outcomes and in vivo antioxidant activity have been discussed (33) and will not be discussed in the current report.

Collectively, the results of the above underscore the importance of understanding how health-related outcomes are affected by the volume and duration of juice intake in addition to factors affecting bioavailability and bioactivity. Furthermore, short-term antioxidant effects are not conclusively linked to reduced risk of long-term chronic disease. A comprehensive understanding of the impact of PFJ on other disease-related mechanisms and the link(s) to disease risk are important in elucidating the true effects of PFJ intake.

Vascular Reactivity and Inflammation

Impaired endothelial function and associated inflammation, oxidation, platelet reactivity, and cell proliferation are processes involved in the pathogenesis of atherosclerosis and cardiovascular disease (4). Many researchers have assessed the response of endothelium to PFJ, commonly using measurements of brachial reactivity as a surrogate for endothelial function in coronary arteries.

As described earlier, Concord grape juice consumption (7.7 mL/kg) increased FMD of the brachial artery by 4.2 ± 4.4% ($P = 0.001$) in 15 men with CAD. This suggests

improved endothelial function in coronary arteries after 2 wk of intake, although juice was also consumed 2 h before assessing FMD function (11). In another study, the effects of either a "high" dose (8 mL/kg, $n = 11$) or "low" dose (4 mL/kg, $n = 11$) of Concord grape juice for 28 d were assessed in subjects (mean age: 64 ± 10 y) with angiographically documented CAD, severe endothelial dysfunction, and mild hypertension who were treated with statins, β-blockers, and calcium-channel blockers (34). Each dosage of grape juice significantly improved FMD of the brachial artery by >100% compared to baseline ($P = 0.036$) but not lipids or other markers (Table 2). The addition of 400-IU vitamin E for 28 d to both groups did not further improve FMD. In this small study, the authors did not adjust for the different medication regimes or the degree of underlying endothelial dysfunction/hypertension.

Grape juice consumption for 14 d (500 mL/d) significantly improved FMD compared to baseline ($P < 0.05$) in 8 men and 8 women (mean age: 51.6 ± 8.1 y) but did not change mean brachial artery diameter or nitroglycerin-mediated dilation (35). Intercellular adhesion molecule-1 was the only marker in plasma that was significantly reduced among several that were measured compared to baseline ($P < 0.05$; Table 2).

Thirty adolescents with metabolic syndrome (gender not specified, mean age: 13.4 ± 1.1 y) consumed either unsweetened home-prepared grape juice (18 mL/kg per day) or 240-mL natural pomegranate juice each day for 1 mo (36). There was a significant acute (4 h after consumption) and long-term (1 mo) effect of both juices on FMD measured 90 s after cuff deflation and 3–4 min after 400-mg sublingual nitroglycerin. Grape juice was the only treatment associated with improved basal brachial artery diameter after 1 mo (37). Pomegranate juice reduced inflammatory markers IL-6, E-selectin, and vascular cell adhesion molecule-1 acutely and after 1 mo compared to baseline ($P < 0.05$), whereas grape juice intake reduced E-selectin and IL-6 at 1 mo only ($P < 0.05$). Changes in FMD were correlated with changes in serum concentrations of intercellular adhesion molecule-1 and E-selectin (4 h and 1 mo FMD) and IL-6 (1 mo FMD) ($P < 0.05$). The lack of a control group in this study is a limitation.

Morand et al. (38) examined the effects of orange juice consumption on vascular reactivity in 23 overweight men between the ages of 50 and 65 y, one-third of whom were hypertensive. The randomized crossover study included 3 dietary periods of 4 wk each: 500-mL orange juice, control drink plus hesperidin (hesperidin-7-0-rutinoside, the predominant flavanone in orange juice), and placebo control drink. Orange juice and hesperidin intake were associated with significantly greater endothelium-dependent vasodilation 6 h after consumption, which correlated with plasma hesperetin concentrations ($r = 0.43$, $P = 0.039$). Orange juice consumption was associated with a significant reduction in diastolic blood pressure compared to placebo ($P = 0.023$) and comparable to a reduction after 4 wk of the hesperidin-control drink, suggesting a role for hesperidin in mediating vascular reactivity. Bodyweight did not change and several

markers of antioxidant capacity as well as glucose, insulin, lipids, and inflammatory markers in plasma did not differ between groups (Table 2). These investigators examined genetic expression in isolated monocytes from 10 subjects after orange juice and hesperidin control drink consumption. They reported similar effects on more than half of the disease-related genes examined, although the changes associated with hesperidin alone were only 2–3% of the magnitude associated with juice.

The effects of a composite of juice from 3 red orange varieties (Tarocco, Sanguinelllo, and Moro) in 19 subjects (aged 27–56 y with ≥2 criteria for metabolic syndrome) were compared to 12 healthy controls in a randomized, crossover, single-blinded study (39). At baseline and after 7 d of placebo, FMD of the brachial artery was lower in subjects than controls, but after 7 d of juice intake FMD became comparable between the groups ($P < 0.005$). Basal blood concentrations of high-sensitivity C-reactive protein , IL-6, and TNF-α were also higher in subjects than controls ($P < 0.005$) but decreased significantly after 1 wk of juice intake ($P < 0.001$). There was no effect of juice on bodyweight, fasting, or postprandial glucose concentrations, or protein carbonyls in plasma. The filtering, freezing, and pasteurization of the squeezed juice, as well as the short intervention and washout period between treatments (3 d), were limitations of this investigation.

An analysis of carotid ultrasound measurements after 12 mo of 240-mL daily pomegranate juice intake did not show a difference between subjects with cardiovascular risk factors ($n = 146$, mean age: 60.8 ± 7.3 y) and placebo-matched controls ($n = 143$) (40). Several markers of oxidation, plasma lipids, and inflammatory markers were unaffected by long-term juice consumption (Table 2). Post hoc exploratory analyses on subgroups of subjects in the highest tertiles of plasma lipids showed lower intimal thickening in the anterior wall and reduced composite measurements of thickening in subjects consuming pomegranate juice (P range < 0.001–0.03). These findings aligned with earlier work by the same group that showed pomegranate juice reduced progression in patients with confirmed stenosis, suggesting that the juice might be protective for those at greater risk (41).

In summary, the available data suggest that some PFJ mediates effects on endothelial reactivity, although the mechanism(s) responsible for these observations and the potential clinical benefits are unclear.

Lipids and Related Metabolism

Elevated plasma lipids and aberrations in lipid metabolism are well-established risk factors for cardiovascular disease (42). A number of studies have focused on the effect of PFJ on lipid markers as the primary outcome.

A study of 26 healthy men (aged 25–60 y) found a significant increase in plasma HDL cholesterol concentrations ($P < 0.001$) and apoB concentrations ($P < 0.002$) and no effect on apo A1 after 1 mo of consuming 150-mL red grape juice twice a day (43) (Table 3). There was also a 19%

TABLE 2 Summary of findings related to PFJ consumption and vascular reactivity and inflammation[1]

Reference	Study design, duration[2]	Type of juice	Subjects (healthy unless specified)[3]	Results[4]
Stein et al., 1999 (11)	Pre- and post-test, 2 wk	Grape (Concord), 7.7 mL/kg	n = 15 (12 ♂), CAD/hypertension, dyslipidemia, 63 ± 13 y	↑ FMD brachial artery (P = 0.003) (juice dose consumed 2 h prior)
Chou et al., 2001 (34)	Pre- and post-test, 4 wk; additional 4 wk ± vitamin E	Grape (Concord), 2 doses: 8 mL/kg (high), 4 mL/kg (low); 400 IU vitamin E (added to each after 4 wk)	n = 11 high dose, n = 11 low dose, CAD on medication, mild hypertension ♂, 64 ± 10 y	↑ FMD brachial artery vs. baseline both high and low dose (P = 0.04), no additional benefit with vitamin E, ↔ plasma lipids, glucose, insulin, oxidation of LDL cholesterol
Coimbra et al., 2005 (35)	Pre- and post-test, 2 wk	Grape (purple), 500 mL/d	n = 16, ♀♂, hypercholesterolemia, 52 ± 8 y	↑ FMD brachial artery vs. baseline, ↓ ICAM-1, ↔ mean brachial diameter or NMD, ↔ plasma lipids, glucose, platelet aggregation, or VCAM-1
Hashemi et al., 2010 (36) Kelishadi et al., 2011 (37)	Pre- and post-test: acute 4-h post-intake (4 h) and long-term 4 wk (4 wk)	Pomegranate, 240 mL/d or grape, 18 mL/kg per day	n = 30, metabolic syndrome, adolescents, 13 ± 1 y, (gender not specified)	Pomegranate and grape ↑ FMD and NMD brachial artery at 4 h and 4 wk vs. baseline, grape ↑ brachial diameter 4 wk, pomegranate and grape ↓ IL-6, E-selectin 4 wk, pomegranate ↓ VCAM-1 at 4 wk, pomegranate ↓ IL-6, E-selectin, VCAM-1 at 4 h, ↔ bodyweight
Morand et al., 2011 (38)	Crossover × 3 (4 wk each), plus test 6 h after consumption	Orange vs. control beverage + placebo vs. control beverage containing hesperidin	n = 23, overweight, 33% hypertensive ♂, 50–65 y	↑ EDR 6 h after consumption correlated with plasma hesperetin (r = 0.434, P = 0.04), ↓ BP orange vs. placebo (P = 0.023), ↔ bodyweight, FRAP, urinary-8-isoprostane, insulin, lipid, inflammatory markers
Buscemi et al., 2012 (39)	Crossover single-blind, 7 d vs. control subjects	Orange (composite 3 varietals, Tarocco, Sanguinello, Moro), 500 mL/d	n = 19, ≥2 criteria for metabolic syndrome, ♀♂, 27–56 y vs. 12 healthy controls ♀♂	Juice normalized FMD in brachial artery in subjects (P < 0.005), ↓ blood concentrations hsCRP, IL-6, TNFα (P < 0.001), ↔ plasma protein carbonyls, bodyweight, fasting postprandial glucose
Davidson et al., 2009 (40)	Double-blind, parallel arm, 18 mo	Pomegranate, 240 mL/d	n = 146, ≥1 risk factor for CVD, ♀♂, 61 ± 7 y vs.143 matched controls, 61 ± 8 y	↔ Plasma lipids, inflammatory or oxidative markers, 12-mo carotid ultrasound. Group with highest lipids had reduced measures of intimal thickening in anterior wall (P < 0.001–0.03)

[1] BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; EDR, endothelium-dependent relaxation; FMD, flow-mediated dilation; FRAP, ferric-reducing antioxidant power; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; NMD, nitroglycerin-mediated dilation; PFJ, pure (100%) fruit juice; VCAM-1, vascular cell adhesion molecule-1.
[2] Study design was randomized unless otherwise indicated.
[3] Values are mean age ± SD or range, rounded to nearest whole number.
[4] P < 0.05 unless otherwise indicated; ↑, increase; ↓, decrease; ↔, no effect; ♀, women; ♂, men.

reduction in plasma homocysteine concentrations ($P <$ 0.001), suggesting a mechanism beyond lipids by which grape juice might reduce the risk of cardiovascular disease.

Twenty-five subjects with either moderate hypercholesterolemia ($n = 20$) or normal-to-mild hypercholesterolemia ($n = 5$) participated in a 17-wk study in which they sequentially consumed 250-mL, 500-mL, and 750-mL commercial orange juice for 4 wk each, separated by 5-wk washout periods (44). There was a 21% increase in HDL cholesterol ($P < 0.001$), 16% decrease in LDL-to-HDL cholesterol ratio (driven by the higher HDL), and 30% increase in TG concentration ($P < 0.02$ each) associated with the consumption of 750-mL juice (not 250 or 500 mL) and no effect on bodyweight or other markers (Table 3). However, the general applicability of these findings is limited by the large quantity of juice (750 mL), the varied metabolic profile of the subjects, and the sequential addition of increasing doses of juice vs. randomized exposure.

A study of 26 sedentary premenopausal women who were either overweight (37% of subjects) or obese (63%) included an aerobic exercise protocol for 3 mo and consumption of 500-mL/d orange juice (frozen concentrate reconstituted at home) by half of the subjects (45). Reductions in plasma concentrations of total cholesterol (5%), LDL cholesterol (15%), and LDL-to-HDL cholesterol ratio (27%), and increased HDL (18%) were observed in the juice vs. nonjuice drinkers ($P < 0.05$; Table 3). Significant weight loss and improved anaerobic threshold were comparable between groups, although plasma lactate concentrations after anaerobic tests were lower in women who consumed orange juice suggesting greater aerobic fitness in this group ($P < 0.05$). The small sample size, self-reported compliance, and lack of placebo control in this study are important limitations.

Concentrated pomegranate juice (40 g) was provided for 8 wk to 22 subjects (8 men and 14 women) with type 2 diabetes not treated with insulin (46). There was no change in BMI or waist-to-hip ratio, but significant reductions were found in total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.006$), total cholesterol–to–HDL ratio ($P < 0.001$), and LDL-to-HDL cholesterol ratio ($P < 0.001$), the latter being inversely correlated with baseline LDL-to-HDL cholesterol ratio ($r^2 = 0.32$, $P = 0.02$) (Table 3). The amount of concentrated juice used suggests a cautious approach in diabetic subjects and the need for dose-response studies in this population.

Clear apple juice, provided as 1 of 5 treatments in a randomized crossover trial, was shown to have an adverse effect on plasma lipids in women, but not men, among 23 subjects (aged 18–69 y) (47). After 4 wk of drinking clear apple juice (500 ml/d), LDL cholesterol concentrations were significantly increased compared to controls and all other apple treatments including fresh apple, apple pomace, and cloudy apple juice (range: $P = 0.0003$–0.023 across products). There was no difference between treatments on other lipids or outcomes (Table 3). The small subsample size in addition to the high dropout rate (32%) and 2 "interruptions" (totaling 8 wk) are noteworthy concerns of this study.

TABLE 3 Summary of findings related to PFJ consumption and lipid metabolism[1]

Reference	Study design, duration[2]	Type of juice	Subjects (healthy unless indicated)[3]	Results[4]
Khadem-Ansari et al., 2010 (43)	Pre- and post-test, 4 wk	Grape (red),150 mL/d × twice a day	$n = 26$, ♂, 25–60 y	↑ HDL ($P < 0.001$), ↑ apoB ($P < 0.002$), ↔ apoA1, ↓ plasma homocysteine ($P < 0.001$)
Kurowska et al., 2000 (44)	Crossover × 3 doses, 4 wk each, 5-wk washout	Orange, 250 mL, 500 mL, 750 mL/d	$n = 20$ moderate hypercholesterolemia + $n = 5$ normal-mild hypercholesterolemia ♀♂, 55 ± 11 y	↑ HDL ($P < 0.001$), ↑ TG ($P < 0.02$), ↓ LDL:HDL ($P < 0.005$) with 750 mL/d only; ↔ other lipids, apoproteins, homocysteine, or bodyweight
Aptekmann et al., 2010 (45)	Juice vs. no juice control, 3 mo; all on exercise protocol	Orange, 500 mL/d	$n = 26$, sedentary ♀, (37% overweight, 63% obese), premenopausal, 30–48 y	↓ Cholesterol (total, LDL, LDL:HDL), ↑ HDL, ↓ plasma lactate
Esmaillzadeh et al., 2004 (46)	Pre- and post-test, 8 wk	Pomegranate, 40 g concentrated	$n = 22$, type 2 diabetic ♀♂, 53 ± 5 y	↓ Total cholesterol ($P < 0.001$), LDL ($P < 0.006$), total cholesterol:HDL ($P < 0.001$), LDL:HDL cholesterol ($P < 0.001$), ↔ bodyweight or waist:hip ratio
Ravn-Haren et al., 2013 (47)	Crossover × 4, 4 wk each	Apple, 500 mL/d (clear, cloudy) apple pomace, fresh apple, control	$n = 23$, ♀♂, 18–69 y	↑ LDL cholesterol in clear apple juice vs. control and all products ($P = 0.0003$); ↔ plasma lipids, hsCRP, glucose metabolism

[1] hsCRP, high-sensitivity C-reactive protein; PFJ, pure (100%) fruit juice.
[2] Study design was randomized unless otherwise indicated.
[3] Values are mean age ± SD or range, rounded to nearest whole number.
[4] $P < 0.05$ unless otherwise indicated; ↑, increase; ↓, decrease; ↔, no effect; ♀, women; ♂, men.

The small number of studies, in addition to the variable response in lipids associated with PFJ intake, suggests the need for further work in this area.

Hypertension

Hypertension, or high blood pressure, is an independent risk factor for cardiovascular disease that may be influenced by PFJ intake, although results are conflicting as described below. Dramatic mean reductions in diastolic (41%) and systolic (33%) pressures were observed in normotensive subjects ($n = 20$) within 5–40 min after consuming a single 250-mL serving of freshly prepared grapefruit juice ($P < 0.05$) (48). Reductions in a group of hypertensive subjects ($n = 20$) were reported to be 11% and 18% in diastolic and systolic blood pressures, respectively ($P < 0.05$). Mean arterial pressure was also lower after grapefruit juice consumption compared to either milk or a vitamin C–enriched test beverage. Orange juice had no significant effect in this study.

Inconsistent effects on blood pressure have been reported for grape juice (49, 50). Twenty-one normal weight subjects with untreated borderline hypertension (mean age: 43 ± 2 y) consumed grape juice for 8 wk (5.5 mL/kg) in a randomized, double-blind, placebo-controlled trial (49, 50). Systolic blood pressure was reduced by 7.2 mm Hg from baseline in the grape juice group ($P = 0.005$) vs. no change in placebo. However, diastolic blood pressure was reduced from baseline in both grape juice and placebo groups (6.2 mm Hg lower in grape juice group, $P = 0.001$; 3.2 mm Hg lower in placebo group, $P = 0.05$). Several other markers were unaffected including plasma lipids, total radical antioxidant potential, and erythrocyte catalase activity. There was a reduction in lymphocyte DNA damage (26%, both hydrogen peroxide exposed and spontaneous) in the grape juice group ($P < 0.01$) (50) (see section on cancer).

In another study, grape juice had no effect on several measures of blood pressure in 64 moderately hypertensive subjects participating in a double-blind, placebo-controlled, crossover study (51). After consuming 7-mL/kg Concord grape juice per day and a matched placebo beverage for 8 wk each, separated by a 4-wk washout period, the only significant finding was a change in "nocturnal dip" blood pressures compared to daytime pressures, which has been associated with lower mortality (51). There was an unexpected but significant reduction in fasting blood glucose of 2 mg/dL ($P = 0.03$) in a subset of subjects with prehypertension and reportedly good study compliance. This trial included typically understudied populations including 31% women and 46% black subjects. However, the high withdrawal rate (23%) and failure to account for alcohol intake are important limitations.

Pomegranate juice was associated with a 3% mean reduction in mean arterial, diastolic, and systolic pressure ($P < 0.001$ for each) in 24 healthy adults (16 women and 8 men, mean age: 36.1 y) after 4 wk of 30 mL/d compared to a control group (mean age: 39 y) who drank soda (52). Several other measurements were unaffected including

arterial stiffness (pulse wave velocity), heart rate, and notably, angiotensin-converting enzyme (ACE), responsible for converting the inactive peptide angiotensin I to the vasoconstrictor angiotensin II, associated with hypertension in some subjects.

The above results differ from a small uncontrolled study of pomegranate juice in hypertensive subjects (7 women and 3 men) (53), although the majority of these were being treated with ACE inhibitors and 2 with calcium channel blockers to control blood pressure. Consumption of 50-mL/d pomegranate juice for 2 wk decreased ACE activity by an average of 36% in 7 out of 10 subjects ($P < 0.05$). Blood pressure was also reduced by 5% ($P < 0.05$ for systolic), but the drop was not correlated with reduced ACE activity.

Platelet Reactivity

The functional properties of platelets are of interest because of their role in coronary thrombosis as well as initiation and progression of heart disease.

In a crossover trial, 10 subjects (aged 26–58 y) consumed 5–7.5 mL/kg (mean: 450 mL ± 120 mL/d) of either purple grape juice, orange juice, or grapefruit juice in random order for 1 wk each, separated by 1-wk washout periods (54). Grape juice reduced collagen-induced platelet aggregation in whole blood samples by 77% compared to baseline ($P = 0.0002$). At higher concentrations of collagen, this effect remained significant but not when ADP or thrombin were used as agonists. Orange and grapefruit juice did not affect platelet aggregation.

A 14-d study of 20 healthy subjects (12 men and 8 women, mean age: 30.6 ± 1.6 y) who consumed purple grape juice (7 mL/kg) showed reduced ADP ($P = 0.09$) and collagen-induced platelet aggregation ($P = 0.08$) and a significant decrease in phorbol myristate acetate–dependent platelet aggregation (33% reduction, $P = 0.002$) (55). There was also a significant increase in platelet-derived NO release ($P = 0.012$).

In contrast, a study involving healthy men who drank 500-mL/d commercial grape juice for 4 wk ($n = 24$, aged 26–45 y) found no effect on platelet aggregation in platelet-rich plasma (vs. whole blood above) (56). However, collagen was not used to induce aggregation, only ADP and thrombin, both agents that were associated with nonsignificant effects in the 14-d study of grape juice and the crossover trial with grape, orange, and grapefruit juice as described above.

Cancer

An early consensus report that summarized hundreds of primarily case-control studies suggested that diets high in fruits and vegetables were protective against several types of cancer (57), although analyses of newer cohort studies have shown a less convincing link (57, 58). The evidence related to fruit juice and cancer was deemed as "too limited in amount, consistency, or quality to draw any conclusions" based on a review of over 800 studies related to fruit and vegetable

intake and cancer (58). Very few individual trials using PFJ have been published since 1995.

A large prospective study of over 35,000 women found an inverse association between intake of all fruits and vegetables and risk of non-Hodgkin lymphoma and a 35% lower risk in women who consumed ≥2 servings/mo of apple juice/cider than women consuming none ($P = 0.026$) (59). Although a major strength of this study was the large sample size, the self-reported data were collected at a single time point several years before the analysis with use of a 127-item semi-quantitative FFQ.

A very small study ($n = 7$) of normal weight healthy women (mean age: 26 ± 2.1 y) showed that a single serving (300 mL) of pasteurized commercial orange juice reduced hydrogen peroxide–induced oxidative damage to DNA, a suggested biomarker of cancer risk, by 18% in mononuclear blood cells ($P < 0.01$) (60). The effect was present at 3 h and 24 h after consumption and not correlated with 24-h plasma vitamin C concentrations, suggesting other compounds in orange juice might account for the observation. In contrast, there was no significant reduction in DNA damage in lymphocytes, based on 8 hydroxydeoxyguanosine–to–guanosine ratio, after consumption of 750-mL/d orange juice for 3 wk in 13 men and women (aged 28–51 y) (61).

A study of the effects of 250-mL/d pomegranate juice (Wonderful variety; crushed, squeezed, and treated with pectinase) on prostate cancer was conducted in 46 men with rising prostate-specific antigen (PSA) concentrations after radical prostatectomy or radiotherapy (62). Quarterly follow-up for 2 y showed an association between juice intake and delayed PSA doubling time, a surrogate marker of prostate cancer mortality ($P < 0.0001$), and 27% lower PSA concentrations in approximately one-third of participants ($P < 0.001$). Reductions in NO metabolites (23%) and serum oxidative state (40%) were also observed at 9 mo compared to baseline ($P < 0.02$). Although the bioavailability of active components in pomegranate may be highly variable, the observed effects after a long duration of exposure suggest that follow-up work is important (63).

Although data in humans are limited, there are many plausible mechanisms by which plant-based foods might affect cancer processes in different tissues (57, 58). Cancer is a complex disease with multifactorial etiology over an extended time, and determining the effect of dietary factors on cancer remains an active area of investigation.

Cognitive Function, Memory Decline, and Alzheimer's Disease

A decline in cognitive function is among the hallmark features of Alzheimer's disease (64). Patients with moderate-to-late stages of Alzheimer's disease (aged 82 ± 5 y) were provided 250-mL/d apple juice (two 4-oz servings) for 1 mo (65). Validated assessment tests showed no change in cognitive or day-to-day function, but measures of mood and behavior were improved by 27% ($P < 0.001$) based on a 12-item neuropsychiatric inventory. Changes in scores were significant in all individual cases, independent of age ($P < 0.01$), and

focused on anxiety, apathy, agitation, depression, and delusion among others. The lack of placebo control, the short treatment period, and the small number of subjects are important drawbacks of this study.

A preliminary study showed potential for grape juice effects on neurocognitive outcomes in subjects with evidence of early memory decline (mean age: 78.2 ± 5 y) (66). Five subjects received grape juice (6–9 ml/kg, range: 444–621 ml/d in 3 equal volumes) for 12 wk compared to 7 subjects who consumed a matched placebo. Grape juice intake was associated with improved performance on the standardized California Verbal Learning Test, in particular with list-learning and a trend toward improved performance on delayed recall tasks as well as spatial memory tasks on the Spatial Paired Associate Learning Test (66).

A recent double-blind study by the group who investigated neurocognitive outcomes described above reported no difference in learning and retention between men and women who consumed either grape juice ($n = 10$, 6.3–7.8 mL/kg) or placebo ($n = 11$) for 16 wk, although the latter had more errors on recognition memory tasks ($P = 0.04$) (67). Brain imaging studies conducted on a small subset of volunteers ($n = 4$) showed greater neural activity consistent with an increased hemodynamic response in 2 regions of the brain involving working memory tasks in juice drinkers compared to placebo (67).

The potential effects of PFJ on cognitive performance, memory, and Alzheimer's disease in humans are intriguing but studies are limited. There is a need for larger reproducible investigations in this area.

Urinary Tract Infection

Urinary tract infection (UTI) is defined as the presence of pathogens in the urinary tract, diagnosed by microscopy and culture of urine samples, and is among the most common bacterial infections in the United States (68). Recurrent UTIs, defined as ≥2 episodes over 6 mo, occur in up to one-third of women after their first UTI. In 2 early reports, including a Cochrane Collaboration review, the evidence evaluating a potential link between cranberry juice consumption and UTIs was critically assessed (69, 70). Studies included in the Cochrane review were limited to those involving at least 1 mo of intervention involving a randomized controlled trial design with juice vs. placebo/no treatment and performed on susceptible men and women with recurrent lower UTIs (70). Seven studies evaluated cranberry juice including amounts ranging from 30 mL (concentration not specified) to 750 mL/d in subjects ranging in mean age from 9 to 81 y. There was a 34% reduction in risk of symptomatic UTIs and 39% lower risk in women with recurrent UTIs at 12 mo but less of an effect in elderly subjects and catheterized individuals.

An updated systematic review and meta-analysis of data incorporating recent trials (13 randomized controlled reports, 9 of which used cranberry juice) was published in 2012 (71). The authors reported a comparable 38% overall lower risk of UTIs associated with cranberry juice intake.

Subgroup analyses suggested that younger subjects, women, and those with recurrent UTIs were more likely to benefit from cranberry juice intake. Cranberry juice tended to be more protective than cranberry in other forms (capsules or tablets), although it is unclear whether this was related to the associated fluid intake and/or synergistic effects of compounds in the native juice. Lack of dose-response data limit the determination of an "optimal" dose associated with reduced risk of UTIs. Some studies reported a high attrition rate leading authors to question the practical value of consuming large quantities of cranberry juice each day. In addition, cranberry juice was not effective in the treatment of symptomatic UTIs.

A recent investigation, not included in the above analyses, evaluated the effect of cranberry juice at a dose of 5 mL/kg up to 300 mL in 2 daily doses in Finnish children ($n = 126$, 91% girls, mean age: 3.8 ± 2.5 y) compared with a group consuming a placebo beverage ($n = 129$, 91% girls, mean age: 4.5 ± 2.9 y) for 6 mo (72). The total number of UTI episodes was reduced by 43%, and UTI incidence per person year at risk was significantly lower in the juice group than placebo ($P = 0.03$). The cranberry juice group also had fewer days of antimicrobial treatment than placebo ($P < 0.001$). The number of children experiencing at least 1 recurrence of the initial UTI episode did not differ between groups. Although there was a relatively high dropout rate in this study, the results align with those in adults (70, 71) suggesting that cranberry juice might be of most benefit for individuals who are susceptible to recurrent UTIs.

Implications of PFJ on Bodyweight and Related Metabolism

Weight gain and nutrient displacement have been cited as potential concerns associated with high consumption of fruit juice intake, particularly in children. Although, importantly, some studies in this area have not distinguished between fruit juice–containing drinks and PFJ (73, 74).

Cross-sectional analyses of NHANES data from 1999 to 2000 ($n = 3618$ children, aged 2–11 y) found a lower mean BMI and higher intake of several nutrients associated with a mean daily intake of 128-mL (4.1 fluid ounces) PFJ than nonconsumers of juice (75). There were similar findings in separate reports focused on orange juice intake from 2003–2006 NHANES data in children 2–18 y of age ($n = 7250$) (76) and adults aged $\geq$19 y ($n = 8861$) (77).

A double-blind, randomized controlled investigation of 3 groups of healthy adults compared the response to grape juice intake. In 25 healthy adults (aged 18–50 y, BMI: 25–29), consumption of 480-mL/d Concord grape juice, providing an average of 17% of each subject's daily energy intake for 12 wk, did not result in significant weight gain compared to baseline. In contrast, there was a mean weight gain of 1.6 ± 0.03 kg ($P < 0.05$) in a control group of 26 subjects who drank a matched placebo lacking grape phenolics ($n = 26$) (78). Waist circumference in the grape juice group also declined significantly from baseline but not in the placebo or a matched "no juice" group ($n = 25$) ($P < 0.05$).

Twelve weeks of consuming 250-mL grapefruit juice daily was associated with 1.5 kg of weight loss in 18 obese subjects and comparable to a 1.6-kg loss in subjects consuming half a fresh grapefruit daily ($n = 19$), although only the latter was significantly different from placebo ($P < 0.05$) (79). In a subset of subjects with metabolic syndrome (34% of group), weight loss in the grapefruit juice group was significantly greater than placebo ($P < 0.02$) and comparable to fresh grapefruit intake. Two-hour insulin concentrations were also significantly lower in the grapefruit juice group than placebo ($P = 0.049$).

Grapefruit juice and fresh grapefruit, consumed as a preload before meal intake during 12 wk of calorie restriction, did not result in greater weight loss compared to a matched-weight water preload in obese subjects ($n = 68$) (80). Grapefruit juice was the only treatment associated with increased plasma HDL cholesterol concentrations compared to both baseline and the water group despite comparable weight loss in all 3 groups ($P = 0.02$). There was a notable 20% attrition in this study (weeks 6 through 9), and further work is needed to study the potential of PFJ to modify lipid metabolism in the absence of significant weight loss.

Phenolic compounds in some PFJ such as cloudy apple juice might affect metabolic processes and associated cellular processes in adipocytes, or adipocyte-derived factors known to reduce visceral fat, as well as lipid metabolism (81). Investigators have proposed that compounds in pomegranate juice might improve bodyweight regulation by modulating insulin sensitivity through PPAR-γ activation, changes in leptin and adiponectin, and inhibition of pancreatic lipase (82).

Mechanistic and observational data suggest that the association between PJF and bodyweight regulation is complex. Furthermore, the balance between the potential bioactive compounds in PFJ and the satiating capacity of PFJ/energy density relative to other beverages is not fully understood. Well-controlled prospective intervention studies focused on 100% juice are needed to determine the true impact of PFJ intake on bodyweight in humans.

Summary and Conclusions

A review published in 2006 concluded that there was no evidence that pure fruit and vegetable juices are less beneficial in coronary heart disease and cancer prevention than whole fruits (3). The current report summarizes research spanning approximately 2 decades from around the world and provides evidence suggesting that 100% juice expressed from different fruits contains bioactive components with potential to affect human health. Studies examining the effect of juice consumption are varied in design and methodology. An increasing number of investigations are focused on isolated extracts, compounds, and mixtures of components rather than the juice itself. However, a number of reports in which PFJs, free of added components, were tested and compared to isolated compounds referred to the importance of the composite mixture of bioactive components present in native juice, possibly because of additive or even synergistic interactions of compounds in pure juice.

Increasingly sophisticated methodologies have furthered our understanding of the mechanisms and molecular processes influenced by fruit juice intake. Several types of PFJs increase antioxidant capacity in plasma in the hours after consumption and in some cases on a longer term basis. Studies have also shown potential for functional antioxidant effects as well as improved lipid metabolism and reduced inflammation. Some juices may modulate risk factors for cardiovascular disease including blood pressure, endothelial function, platelet reactivity, and lipid metabolism. A growing area of study is focused on the potential role of PFJ to preserve memory and reduce cognitive decline associated with aging or neurodegenerative diseases including Alzheimer's disease. Intriguing new studies have examined the interaction between genome and juice intake, representing an area of investigation that is just beginning to be explored. Related to this is the possibility that components in fruit juice may modulate cell signaling cascades that regulate bodyweight and associated processes.

Despite the potential, there are many unanswered questions related to fruit juice and health in humans. There is a clear need for larger, well-controlled studies of longer duration with well-defined outcomes. Most studies had limited sample sizes of varied gender and ethnicity, in addition to short treatment periods and a focus on early biomarkers rather than functional endpoints, which are costly but more meaningful. Investigations included single-dose tests, 5-d studies, 4–8-wk studies (most common), and only very rarely, studies of more than a few months' duration. Very few studies controlled for variability in background diet and other confounding variables.

Additional challenges included determining accurate dietary intake and compliance with the study protocol. Differing methods of preparing juices, the variable nutrient and phytochemical content between varietals, regions, and storage conditions are inherent issues associated with the field. Furthermore, determining an appropriate dose of juice to study is a challenge; volumes ranged from 30 mL/d to 1 L in the studies reviewed. Many investigations raised important questions regarding the bioavailability and in vivo metabolism of phytochemicals in juice as well as the required exposure time and concentrations needed to be effective.

The implications of baseline health status are uncertain. Some authors observed a greater response in populations deemed less healthy but apparently more likely to benefit from dietary treatment. Recent investigations have involved "at risk" subjects, but traditionally most work has focused on healthy young adults who might be more "resistant" to treatment effects. The incorporation of subjects with existing disease or risk factors introduces variability into a study but is important given the increasing risk profile of the population.

It is notable that a number of studies did not find an association between fruit juice and adverse outcomes related to bodyweight, plasma lipids, or blood glucose in adults or children. Although weight gain has been cited as a potential concern associated with fruit juice intake, many studies in the current review imply that dietary compensation or other mechanisms associated with components in juice might account for the lack of predicted weight gain, even when juice provided additional calories.

Collectively, the data presented in this review suggest that some potential health-related and disease prevention markers associated with consuming PFJ as part of a balanced diet should not be overlooked. However, well-controlled clinical trials with adequate power to demonstrate clear outcomes are critical to advancing our understanding of the relationship between PFJ and human health.

Acknowledgments

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