Review

Health Effects of Mixed Fruit and Vegetable Concentrates: A Systematic Review of the Clinical Interventions

Amin Esfahani, MSc, Julia M.W. Wong, PhD, RD, Jennifer Truan, MSc, Christopher R. Villa, BSc, Arash Mirrahimi, BSc, Korbua Srichaikul, BSc, Cyril W.C. Kendall, PhD

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto (A.E., J.T., C.R.V., A.M., K.S., C.W.C.K.), Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital (A.E., J.T., A.M., K.S., C.W.C.K.), Toronto, Ontario, College of Pharmacy and Nutrition, University of Saskatchewan (C.W.C.K.), Saskatoon, Saskatchewan, CANADA, School of Medicine, New York Medical College (A.E.), Valhalla, New York, Division of Endocrinology, Children's Hospital Boston (J.M.W.W.), Department of Pediatrics, Harvard Medical School (J.M.W.W.), Boston, Massachusetts

Key words: fruit, vegetable, supplement, concentrate, antioxidant, oxidative stress

Diets rich in fruits and vegetables (FV) have been associated with a reduced risk of chronic disease, including cardiovascular disease. Unfortunately, public health campaigns to increase FV intake have had limited success. A number of mixed concentrated FV products have been studied, which may help certain individuals improve nutrient status. However, the possible health benefits of FV supplements have not been systematically reviewed. We, therefore, undertook a systematic search of MEDLINE and EMBASE to identify clinical interventions that examined the effect of commercially available concentrated mixed FV supplements on cardiovascular disease risk factors. Twenty-two reports, which used commercially available products, were identified. None of the studies reported any serious adverse effects. Overall, daily consumption of FV supplements significantly increased serum concentrations of the major antioxidant provitamins and vitamins found in plant foods (β-carotene, vitamins C and E) and folate. Functional changes, such as reduced serum homocysteine and markers of protein, lipid, and DNA oxidation, were also reported; in addition, the health advantages on markers of inflammation, immunity, and endothelial function are promising. Limitations of the available studies were related to the diversity of studies conducted with respect to design and study population and the variability in the measured outcomes and assays utilized. While mixed FV supplements may serve as an efficacious complement for individuals who have difficulty achieving their daily FV intake requirement, further research on additional retail preparations is warranted.

Key teaching points:

- Mixed fruit and vegetable supplements produced from plant foods may serve as an efficacious complement to the habitual diet in individuals who have suboptimal intake or variety of nutrient-dense fruits and vegetables.
- Current research indicates that fruit and vegetable concentrates significantly increase serum levels of antioxidant provitamins and vitamins (β-carotene, vitamins C and E) and folate and reduce homocysteine and markers of oxidative stress.
- Mechanistic studies and larger, randomized, placebo-controlled double-blind trials in both healthy and high-risk populations are necessary to better understand the health effects of these supplements.

Address reprint requests to: Cyril W.C. Kendall, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, M5S 3E2 CANADA. E-mail: cyril.kendall@utoronto.ca

J.T., C.R.V., A.M. contributed equally to this manuscript.

Presentations: Aspects of this manuscript were presented at the Experimental Biology Meeting (April 24–28, 2010, Anaheim, California).

Support: Amin Esfahani received a travel grant from NSA (Collierville, Tennessee) to attend the 2010 Experimental Biology Meeting. Julia Wong is a recipient of a Canadian Institutes of Health Research Fellowship Award in the area of clinical research.

Abbreviations: 8-OHdG = 8-hydroxydeoxyguanosine, FRAP = ferric reducing ability of plasma, FV = fruits and vegetables, FVB = fruit, vegetable, and berry, hsCRP = high-sensitivity C-reactive protein, MDA = malondialdehyde, ORAC = oxygen radical absorbance capacity, PC = protein carbonyls, RANTES = regulated upon activation, normal T-cell expressed and secreted, TEAC = trolox equivalent antioxidant capacity.

Journal of the American College of Nutrition, Vol. 30, No. 5, 285–294 (2011)
Published by the American College of Nutrition

INTRODUCTION

Increased consumption of fruits and vegetables (FV) has been associated with a reduced risk of many chronic diseases [1,2]. While it has been argued that the risk-reducing effects of FV stem from the displacement of unhealthy foods in the diet, ample evidence suggests that FV contain a number of bioactive components (vitamins, sterols, phenolic compounds, and fiber) that may protect against various diseases independently [3–6]. However, despite these health benefits and numerous public health campaigns to increase FV consumption, the vast majority of individuals do not meet intake levels set by national guidelines [7–9]. A variety of practical alternatives have been developed to help individuals improve their intake of FV and dietary bioactive compounds. One category includes concentrates prepared from mixed FV. These products may be effective complements to the intake of FV, as it has been argued that a well-balanced mixture of vitamins, minerals, and other bioactive compounds, rather than supplementation with one or a few, may lead to additive and synergistic interactions that result in health benefits [10,11]. A number of clinical studies have examined the effects of commercially available mixed FV products on various health outcomes. However, a systematic review of this literature has not been undertaken.

STUDY DESCRIPTION

To perform a systematic review of studies that have utilized various approaches to increase dietary bioactive intake via concentrated FV products, we searched the MEDLINE (1950–2010) and EMBASE (1980–2010) databases using the search terms "fruit" AND "vegetable" AND/OR "concentrate," "extract," "powder," "capsule," and "supplement." Search limits were set for studies in English and human interventions. Clinical dietary interventions using commercially available mixed FV supplements were the only studies included. Reviews; letters to editors; rebuttals; observational, animal, and *in vitro* analyses; and other clinical interventions that did not comply with the aforementioned inclusion criteria were excluded.

Our search yielded 22 full reports [12–33] (18 trials) (Table 1). These studies examined a total of 1363 adults with observation periods ranging from 7 days to 24 months. Of the 18 trials, 12 (14 reports) were placebo-controlled [15–18,20–22,25,26,29–33]. Of these, eight (10 reports) had a parallel design [15,17,21,22,26,29–33], and the remainder were randomized crossover studies. Thirteen trials contained only healthy participants, one (two reports) included healthy elderly patients [13,14], one study used overweight but otherwise healthy subjects [18], one included prehypertensive and hypertensive patients [27], one included healthy nonsmokers and light smokers [28], and one trial (two reports) used a combination of healthy and human immunodeficiency virus (HIV)–positive participants [23,24]. In all of the trials, subjects were instructed to follow their habitual ad libitum diets. However, only about half of the trials analyzed the dietary intake of the participants [16,17,20–25,29–31,33].

Two types of mixed FV supplements were identified. The first was a FV or FVB (FV concentrate including berry concentrate) capsule (Juice Plus+; NSA, Collierville, TN), which was used in 17 trials (20 reports) [12–22,25–33]. These capsules were derived through a proprietary method and consisted of blended FV juice powder concentrate (Table 2). The dosage of this product in the identified trials ranged from two to six capsules per day (Table 1). The second product was a liquid FV concentrate (Cellagon Aurum; H.G. Berner GmbH, Altenholz, Germany), which was used in one trial (two reports) [23,24]. This product is a viscous liquid concentrate made from pressed juices from a variety of FVs (Table 2). The prescribed dosage of the FV liquid concentrate was 30 mL per day. The micronutrient composition of the supplements is summarized in Table 3.

EVALUATION OF OUTCOME MEASURES

For this systematic review, we examined the effect of FV concentrates on known and emerging health-associated risk factors, which included markers of oxidative stress, endothelial function, inflammation, and immune function. We also examined the bioavailability of these supplements by looking at their impact on serum phytonutrients, antioxidant vitamins, folate, and homocysteine concentrations.

Serum Antioxidant Concentrations

Free radical–induced oxidative damage to lipids, proteins, and DNA has been linked to a number of chronic diseases [34]. Therefore, strengthening the free radical defense system through dietary antioxidants, such as carotenoids and vitamins C and E, may be of importance. Eleven trials (13 reports) [12–14,16–19,21,22,25–27,31] published between 1996 and 2010 examined the bioavailability of antioxidants administered in the form of FV capsules (Table 4).

The FV concentrates provided significant amounts of folate, vitamins E and C, and β-carotene, and the doses used in most studies would have met the dietary reference intake (DRI) for these nutrients. As such, it is not surprising that, in the majority of studies, significant increases in serum levels of these vitamins were reported for the FV concentrate group in comparison to baseline or placebo. Significant increases in vitamin E were found in 10 of 12 reports. Significant increases in vitamin C were found in seven of nine reports, and for β-carotene, all 11 reports found significant increases. Two reports on the same cohort [21,22] showed conflicting findings for

Table 1. Description of the Studies Included in the Systematic Review

Authors (Year)	Design	Duration	Location	Sample Size[†] (m:f)	Subject Category	Control	Active Treatment(s)	Daily Dosage	Outcome Measurements: Serum Anti-oxidants	Oxidative Stress	Homocysteine and Folate	Other Outcomes
Arendt et al. (2001)[a] [23]	Postprandial NCT	300 min 16 wk	Germany	(1) 17 (9:8) (2) 20 (17:3)	H, HIV	NC	(1) FV concentrate (2) Fruit juice	(1) 30 mL (2) 1 L	✓	-	-	-
Bamonti et al. (2006) [28]	NCT	30 d	Italy	16 (8:8)	LS, H	NC	FV capsules	4	✓	✓	✓	-
Bloomer et al. (2006)[b] [21]	Parallel RCT	2 wk	USA	48 (25:23)	H	PC	(1) FVB capsules (2) Vit C & E	6	✓	✓	-	-
Goldfarb et al. (2007)[b] [22]	Parallel RCT	2 wk	USA	48 (25:23)	H	PC	(1) FVB capsules (2) Vit C & E	6	✓	✓	-	-
Goldfarb et al. (2011) [33]	Parallel RCT	28 d	USA	41 (26:15)	H	PC	FVB capsules	6	-	✓	-	-
Houston et al. (2007) [27]	NCT	24 mo	USA	51 (42:9)	PHT, HT	NC	FVB capsules	6	✓	-	Homocysteine	Coronary artery Calcium score
Inserra et al. (1999)[c] [13]	NCT	80 d	USA	53 (21:32)	H, E, ES	NC	FV capsules	4	✓	-	-	Immune function
Jin et al. (2010) [31]	Parallel RCT	60 d	USA	117 (29:88)	H	PC	(1) FV capsules (2) FVB capsules	6	✓	-	-	Inflammation
Kawashima et al. (2007) [17]	Parallel RCT	28 d	Japan	60 (39:21)	H	PC	FV capsules	4	✓	✓	✓	-
Kiefer et al. (2004) [16]	Crossover RCT (nw)	7 wk	Austria	59 (26:33)[‡]	H	PC	FV capsules	4	✓	✓	Folate	-
Lamprecht et al. (2007)[d] [29]	Parallel RCT	28 wk	Austria	41 (41:0)	H	PC	FVB capsules	6	-	✓	-	(1) Inflammation (2) Lost duty days
Lamprecht et al. (2009)[d] [30]	Parallel RCT	28 wk	Austria	41 (41:0)	H	PC	FVB capsules	6	-	✓	-	-
Leeds et al. (2000) [19]	NCT	7 d	UK	16 (8:8)	H	NC	(1) Fruit capsules (2) Veg capsules	2	✓	✓	-	-
Nantz et al. (2006) [26]	Parallel RCT	11 wk	USA	59 (23:36)	H	PC	FV capsules	4	✓	✓	-	Immune function
Panunzio et al. (2003) [20]	Crossover (4-wk wo)	4 wk	Italy	26 (12:14)	H	DC	FV capsules	4	-	-	✓	-
Plotnick et al. (2003) [15]	Parallel RCT	4 wk	USA	38 (14:24)[‡]	H	PC	(1) FV capsules (2) FVB capsules	6	-	-	Homocysteine	Endothelial function
Roll et al. (2010) [32]	Parallel RCT	8 mo	Germany	529 (105:424)	H	PC	FV capsules	4	-	-	-	Cold symptom freq and severity
Samman et al. (2003) [25]	Crossover RCT (3-wk wo)	6 wk	Australia	32 (32:0)	H	PC	FV capsules	4	✓	✓	✓	-
Smith et al. (1999)[c] [14]	NCT	80 d	USA	20 (7:13)	H, E	NC	FV capsules	4	✓	✓	-	-
Winkler et al. (2004)[a] [24]	NCT	16 wk	Germany	(1) 17 (9:8) (2) 20 (17:3)	H, HIV	NC	(1) FV concentrate (2) fruit juice	(1) 30 mL (2) 1 L	-	-	-	Immune function
Wise et al. (1996) [12]	NCT	28 d	USA	15 (5:10)	H	NC	FV capsules	4	✓	✓	-	-
Wise et al. (2009) [18]	Crossover RCT (nw)	28 d	USA	92 (24:68)	H, O	PC	FV capsules	4	✓	-	-	-

Studies sharing the same superscript letters represent analysis of different outcomes from the same study.

NCT = uncontrolled trial, RCT = randomized controlled trial, NC = not controlled, PC = placebo capsules, DC = diet controlled, FV = fruit and vegetable, FVB = fruit, vegetable, and berry, nw = no washout, wo = washout, - = not applicable; H = healthy, LS = light smokers, HIV = HIV-positive, E = elderly, ES = elderly smokers, O = overweight, PHT = prehypertensive, HT = hypertensive.

[†] Number of participants analyzed unless otherwise stated.

[‡] Number of participants randomized.

Table 2. Fruit and Vegetable Composition of the Products

	Capsules[†]	Liquids[‡§]
Fruit	Apple	Acerola cherry
	Acerola cherry	Bilberry
	Cranberry	Currant
	Orange	Elderberry
	Papaya	Hawthorn
	Peach	Lemon
	Pineapple	Orange
		Passion fruit
		Schizandra fruit
Vegetable	Beet	Artichoke
	Broccoli	Beet
	Cabbage	Broccoli
	Carrot	Carrots
	Kale	Celery
	Parsley	Jerusalem artichoke
	Spinach	Kale
	Tomato	Onion
	Oat bran	Pumpkin
	Rice bran	Tomato
Berry	Bilberry	
	Blackberry	
	Blueberry	
	Cranberry	
	Elderberry	
	Raspberry	
	Red currant	
	Black currant	
	Concord grape	

[†] Juice Plus+ (NSA, Collierville, TN); list extracted from www.juiceplus.com.
[‡] Cellagon Aurum (H.G. Berner GmbH, Altenholz, Germany); values extracted from Winkler et al. [24].
[§] In addition to fruits and vegetables, these products contained herbs, plant oils, and vitamins.

vitamins C and E. Whereas Bloomer et al. [21] reported no improvements in levels of vitamins C and E compared to baseline, Goldfarb et al. [22], who separated the data based on gender and measured between-treatment effects, showed that the FV capsules increased serum vitamin C levels in comparison to placebo and improved serum vitamin E levels in men but not in women. The study of Smith et al., which also reported no improvements in vitamin E levels [14], included a subgroup (n = 20) from the study by Inserra et al. (n = 53) [13]. The lack of effect may, therefore, be a result of insufficient statistical power to detect a change. Finally, the study by Houston et al. [27] showed a nonsignificant increase in vitamin C levels ($p = 0.097$). However, since the prehypertensive subjects had much higher serum vitamin C levels in comparison to the hypertensive subjects at baseline (776 ± 216 μmol/L versus 640 ± 177 μmol/L), the pooling of results may have confounded the overall impact of the capsules on vitamin C status.

In addition to their beneficial effect on serum concentrations of vitamins E and C and β-carotene, in comparison to baseline or placebo, the FV capsules significantly increased serum retinol in two of three reports and lycopene in four of five reports (Table 4). Furthermore, when the data from the three placebo-controlled trials that assessed serum lycopene [17,25,26] were pooled using Review Manager (RevMan), a trend toward increased serum lycopene concentrations with an effect size of 0.34 (95% confidence interval −0.05 to 0.72; $p = 0.09$) was found [35]. It is worth noting that the studies did not control for lycopene intake in the background diet, which may explain the nonsignificant increase.

The effect of the FV capsules on serum concentrations of other carotenoids, including α-carotene, β-cryptoxanthin, lutein, and zeaxanthin, was also assessed in some trials (Table 4). The FV capsules were found to increase serum concentrations of α-carotene in three of five reports and to increase lutein/zeaxanthin concentrations in three of the six reports in which these carotenoids were measured. None of the four reports in which it was assessed found a significant increase in β-cryptoxanthin.

A number of assays have been developed to assess the antioxidant potential of plasma, including total plasma antioxidant capacity, trolox-equivalent antioxidant capacity (TEAC), oxygen radical absorbance capacity (ORAC), and ferric-reducing ability of plasma (FRAP). Four trials [23,25,26,28] assessed the effect of FV concentrates on at least one of these markers (Table 4). Nantz et al. [26] found that FV concentrates significantly increased plasma ORAC after both 35 and 77 days of supplementation. Arendt et al. [23] found that the liquid FV concentrate significantly increased

Table 3. Declared Micronutrient Composition of the Supplements

	Capsule[†]				
Nutrient	Fruit	Vegetable	Berry	FV Liquid[‡]	DRI[§]
Vitamin E (mg)	7 (47)	8 (53)	21 (140)	16 (107)	15
Vitamin C (mg)	96 (106)	21 (23)	21 (23)	150 (167)	90
Folate (μg)	70 (17.5)	140 (35)	180 (45)	-	400
β-carotene (mg)	1.65 (15)	2.1 (19)	-	5 (46)	10.8

Values in parentheses represent the percentage of Dietary Reference Intake (DRI).
[†] Juice Plus+ (NSA; Collierville, TN, USA); values represent amount per capsule and have been modified from Jin et al. [31].
[‡] Cellagon Aurum (H.G. Berner GmbH, Altenholz, Germany); values represent amount per 15 mL of the concentrate and have been modified from Winkler et al. [24].
[§] DRI for adult men (generally for the 19–50 age group). Taken from the National Academies Press report on DRI at http://www.nap.edu/.

Table 4. The Effects of Supplements on Serum Antioxidant Levels

Authors (Year)	Vitamin E	Vitamin C	Carotenoids					Retinol	Antioxidant Capacity
			α-Carotene	β-Carotene	Lycopene	β-Crypto-xanthin	Lutein/ Zeaxanthin		
Arendt et al. (2001) [23]	-	-	-	-	-	-	-	-	↑**
Bamonti et al. (2006) [28]	-	-	-	-	-	-	-	-	↔
Bloomer et al. (2006)[a] [21]	↔	↔	-	-	-	-	-	-	-
Goldfarb et al. (2007)[a] [22]	↑	↑	-	-	-	-	-	-	-
Houston et al. (2007) [27]	↑	↔	-	↑	-	-	-	-	-
Inserra et al. (1999)[b] [13]	↑	-	↑	↑	↑	↔	↑	-	-
Jin et al. (2010) [31]	↑	↑	-	↑	-	-	-	-	-
Kawashima et al. (2007) [17]	↑	↑	↔	↑	↑	↔	↔	↑*	-
Kiefer et al. (2004) [16]	↑	↑	-	↑	-	-	-	-	-
Leeds et al. (2000) [19]	↑†	↑	-	↑	-	-	-	-	-
Nantz et al. (2006) [26]	-	↑	↔	↑	↑	↔	↑‡	-	↑
Samman et al. (2003) [25]	↑	↑	-	↑	↔	-	↔	↑	↔
Smith et al. (1999)[b] [14]	↔	-	↑	↑	↔	↔	↔	-	-
Wise et al. (1996) [12]	↑	-	↑	↑	↑	-	↑	↔	-
Wise et al. (2009) [18]	↑	-	-	↑	-	-	-	-	-

Studies sharing the same superscript represent analysis of different outcomes from the same study.

↑ Indicates significant increase in serum concentrations of that vitamin in comparison to the control or baseline ($p < 0.05$).

↔ Indicates no difference in comparison to the control or baseline ($p > 0.05$).

* Retinol levels increased in both placebo and FV groups.

† Vitamin E levels increased significantly with the fruit capsules but not the vegetable capsules.

‡ Significant increases were obtained in serum lutein levels but not zeaxanthin with FV capsules.

** Trolox equivalent antioxidant capacity increased in HIV-seropositive subjects but not in seronegative subjects in both juice and concentrate groups.

Table 5. Effects of Capsules on Markers of Oxidative Stress

Authors (Year)	Control	Treatment(s)	Treatment Dosage	Protein Oxidation§	Lipid Oxidation	DNA Oxidation
Bamonti et al. (2006)* [28]	NC	FV capsules	4 capsules/day	↔	↓	-
Bloomer et al. (2006)[b] [21]	PC	(1) FVB capsules (2) Vit C & E capsules	6 capsules/day	↓	↔	↔
Goldfarb et al. (2007)[b] [22]	PC	(1) FVB capsules (2) Vit C & E capsules	6 capsules/day	↓	↓	↔
Goldfarb et al. (2011)*** [33]	PC	FVB capsules	6 capsules/day	↓	↓	-
Kawashima et al. (2007)** [17]	PC	FV capsules	4 capsules/day	-	↓	↓
Kiefer et al. (2004)** [16]	PC	FV capsules	4 capsules/day	-	-	↓
Lamprecht et al. (2007)[d] [29]	PC	FVB capsules	6 capsules/day	↓	-	-
Lamprecht et al. (2009)[d] [30]	PC	FVB capsules	6 capsules/day	↓	-	-
Leeds et al. (2000) [19]	NC	(1) Fruit capsules (2) Veg capsules	2 capsules/day	-	↓	-
Nantz et al. (2006) [26]	PC	FV capsules	4 capsules/day	-	-	↓
Samman et al. (2003) [25]	PC	FV capsules	4 capsules/day	-	↔	-
Smith et al. (1999)** [14]	NC	FV capsules	4 capsules/day	-	-	↓
Wise et al. (1996) [12]	NC	FV capsules	4 capsules/day	-	↓	-

Studies sharing the same superscript letters represent analysis of different outcomes from the same study.

NC = not controlled, PC = placebo capsules, FV = fruit and vegetable, FVB = fruit, vegetable, and berry.

§ Protein oxidation assessed as protein carbonyl groups or protein thiols.

- Not assessed.

↔ No significant effects found.

↓ Significant reduction compared to placebo or baseline for at least one parameter assessed.

* Significant reduction was found only for free malondialdehyde in light smokers.

** Significant reduction compared to baseline but not to placebo.

*** Significant reduction compared to placebo but not baseline.

serum TEAC levels in HIV-seropositive subjects but not in HIV-seronegative subjects [23]. Samman et al. [25] found that FV concentrates increased FRAP compared to the placebo but not significantly ($p = 0.065$) [25]. However, the study by Bamonti et al. [28], which included smokers and nonsmokers, found no improvement in total antioxidant capacity.

Overall, the majority of the studies demonstrated that FV capsules have high bioavailability and as such are capable of improving serum concentrations of the major antioxidant vitamins (C and E) and carotenoids.

Oxidative Stress

Eleven trials (13 reports) [12,14,16,17,19,21,22,25,26,28–30,33] examined the effect of FV capsules on various markers of oxidative stress related to protein, lipid, or DNA oxidation (Table 5).

Excessive protein oxidation has been linked to a number of chronic diseases [36]. Three trials (five reports) [21,22,29,30,33] assessed the effect of FVB capsules on protein carbonyl (PC) concentrations, a stable marker of protein oxidation [37] (Table 5). All studies reported a significant improvement in this marker, i.e., a decrease in oxidative stress with FVB capsule supplementation that attenuated the rise in PC concentrations induced by aerobic exercise [21,22,29,30,33]. However, in another study [28], FV capsules did not improve another marker of protein oxidation (thiol groups), which may be a result of their rapid regeneration.

Lipid oxidation was examined in six trials (eight reports) [12,17,19,21,22,25,28,33] (Table 5). Of these, four studies (five reports) reported on malondialdehyde (MDA) levels. Leeds et al. found that supplementation with either fruit or vegetable capsules significantly reduced plasma MDA concentrations (by approximately 40%) [19]. The studies by Goldfarb et al. and Bloomer et al. found that FVB concentrates decreased MDA in comparison to placebo but not baseline [21,22,33]. The study by Bamonti et al. [28] examined all MDA fractions (total, free, and bound) and found that, whereas t-MDA did not change, f-MDA decreased significantly by predominantly converting to b-MDA in light smokers. No differences were observed in healthy subjects. Based on these findings, future studies could provide a more complete understanding of the potential benefits of FV supplements by measuring both bound and free fractions of MDA. Conflicting findings were reported with other markers of lipid oxidation. Three studies assessed the effect of FV concentrates on lipid peroxides. The 1996 study of Wise et al. showed a significant reduction in lipid peroxides [12]. The study of Kawashima et al. demonstrated a significant reduction compared to baseline but not the placebo in Japanese adults [17]. The 2011 study of Goldfarb et al. [33] found no effect of FVB concentrates versus placebo in altering lipid peroxide levels in response to an acute bout of eccentric exercise. The study of Samman et al. [25] found that FV concentrates did not increase the resistance of low-density lipoprotein to oxidative modification, as assessed by the lag-phase technique, and had no effect on conjugated dienes in young Australian men.

A total of five studies (six reports) assessed the effect of FV concentrates on DNA oxidation. Three studies (four reports) [16,17,21,22] measured serum or urinary concentrations of 8-hydroxydeoxyguanosine (8-OHdG) [38]. The studies by Kiefer et al. and Kawashima et al. found a significant reduction in urinary concentration of 8-OHdG after FV concentrate supplementation compared to baseline values [16,17]. The reports by Bloomer et al. and Goldfarb et al. found no effect of FV concentrates on serum levels of 8-OHdG [21,22]. Smith et al. [14] assessed the effect of FV concentrates on DNA damage in peripheral lymphocytes using the Comet assay. They found a highly significant ($p < 0.0001$) decrease in measured DNA damage between pre- and posttreatment. Nantz et al. [26] assessed lymphocyte DNA strand breaks and found that FV concentrates significantly reduced DNA damage in comparison to baseline. However, the treatment difference compared to the placebo did not reach statistical significance ($p = 0.055$). The lack of statistical significance may have been a result, in part, of the significantly lower baseline values for the placebo group in comparison to the FV test group [26].

Overall, the evidence indicates that FV concentrates have a positive impact on reducing oxidative stress. In the majority of studies, FV concentrates were associated with significant reductions in the oxidation of protein, lipids, and DNA.

Serum Homocysteine

Elevated serum homocysteine levels have been found to be an independent risk factor for cardiovascular disease [39] and a predictor of all-cause mortality in adults [40,41]. However, the association between homocysteine and cardiovascular disease appears to be less clear, given the results of a recent meta-analysis [42] and other studies [43]. Hyperhomocysteinemia can result from dietary deficiencies in B vitamins, including B_6, B_{12}, and folate. Serum folate levels have been inversely associated with serum homocysteine levels [44]. FV concentrates are a rich source of folate, with FV and FVB capsules providing approximately 100%–200% of the adult DRI per day, based on the studied dosages (Table 3). Seven trials [15–17,20,25,27,28] examined the effect of these capsules on serum folate and/or homocysteine concentrations (Table 6). Of these, four of six studies reported significant increases in serum folate in comparison to baseline levels [16,17,20,27]. All three studies that used a placebo control found a significant increase in serum folate compared to the control [16,17,25]. In addition, four of six studies found significant reductions in homocysteine levels in comparison to baseline or the control [17,20,25,27]. Plotnick et al. [15] and Bamonti et al. [28] did not report a reduction in serum homocysteine. The lack of effect in the study by Plotnick et al. may be a result of the relatively low and

Table 6. The Impact of Capsules on Serum Folate and Homocysteine Levels

	Serum Folate (nmol/L)				Serum Homocysteine (μmol/L)			
	Active		Placebo (Control)		Active		Placebo (Control)	
Authors (Year)	Baseline	End Study	Baseline	End Study	Baseline	End Study	Baseline	End Study
Bamonti et al. (2006)[¥] [28]	11.7 (5.2–20.6) 17.9 (11.3–30.8)	25.1 (22.0–28.5) 33.6 (28.5–34.2)	- -	- -	9.0 (7.9–11.3) 8.7 (7.1–9.3)	9.1 (7.1–11.2) 8.2 (6.6–8.8)	- -	- -
Houston et al. (2007)[€] [27]	25.0 ± 8.0	(+3.2 ± 3.4)*	-	-	10.4 ± 2.3	(−2.6 ± 0.8)*	-	-
Kawashima et al. (2007)[‡] [17]	8.2 ± 0.5	22.4 ± 1.3*[†]	8.7 ± 0.5	7.7 ± 0.1	10.2 ± 0.5	8.1 ± 0.4*[†]	9.9 ± 0.5	9.6 ± 0.5
Kiefer et al. (2004) [16]	8.7 ± 3.1	15.6 ± 5.2*[†]	8.7 ± 3.1	7.6 ± 2.9	-	-	-	-
Panunzio et al. (2003) [20]	4.1 ± 0.5	11.0 ± 0.9*	-	-	12.5 ± 3.3	8.0 ± 1.7*[†]	12.5 ± 3.8	12.7 ± 3.2
Plotnick et al. (2003)[‡‡] [15]	-	-	-	-	7.5 ± 1.5	7.3 ± 1.8	6.2 ± 1.1	5.9 ± 0.7
Samman et al. (2003)[§] [25]	25 ± 12	45 ± 25[†]	25 ± 13	23 ± 10	8.3 ± 1.6	7.5 ± 0.9[†]	8.3 ± 1.6	8.2 ± 1.7

All values are mean ± SD unless indicated otherwise.

[¥] The values represent results from light smokers and nonsmokers, respectively; median data are presented (interquartile ranges).

[€] FVB capsules; the "end study" values are 24-month annualized mean changes from baseline.

[‡] Values are mean ± SE.

[‡‡] Results of FV and FVB capsules were pooled for this review.

[§] The values were estimated based on graphical representations.

* Statistically different from baseline ($p \leq 0.05$).

[†] Statistically different from placebo/control ($p \leq 0.05$).

unadjusted baseline homocysteine levels (6.2, 6.8, and 8.1 μmol/L for the placebo and the two treatment groups, respectively) [15]. Bamonti et al. [28] attributed the lack of effect in their study to the relatively healthy Italian diet of the participants, whose serum folate and B_{12} levels were within the normal range. However, the baseline serum folate and homocysteine levels, in addition to the length of study and capsule dosages, were comparable to those seen the studies in which improvements were reported (Table 6).

Overall, the majority of studies indicated that the folate in FV and FVB capsules is highly bioavailable and that these supplements are effective in increasing serum folate levels and decreasing serum homocysteine concentrations. The studies are also supportive of the current evidence showing an inverse relationship between serum folate and homocysteine [44].

Other Outcomes

A total of nine studies assessed other markers of health, including inflammatory biomarkers, immune function, cold symptom frequency and severity, muscle function, endothelial function, blood lipids, and coronary artery calcium score.

Six studies assessed the effect of FV or FVB concentrates on inflammatory biomarkers [29,31], sick days [29] or symptoms [26,32], and immune function [24,26,31]. Jin et al. [31] randomly assigned 117 subjects to receive either placebo, FV capsules, or FVB capsules for 60 days. They found that the FV and FVB capsules significantly reduced the inflammatory biomarkers monocyte chemotactic protein-1, macrophage inflammatory protein 1-β, and regulated upon activation normal T-cell expressed and secreted (RANTES), but not high-sensitivity C-reactive protein (hsCRP), compared to the control. Lamprecht et al. [11] found that FV concentrates taken over a 28-week period significantly reduced tumor necrosis factor-alpha levels compared to the placebo ($p < 0.001$). During the final 20 weeks of that study, the FVB concentrate group tended to have fewer days lost because of illness compared to the placebo, although this did not reach statistical significance ($p = 0.068$). Roll et al. [32] assessed the effect of FV concentrate capsules versus placebo on cold symptom frequency and severity during winter in Berlin, Germany, in 529 healthy healthcare professionals. They reported that intake of the FV capsules was associated with a significant 20% reduction in reported days with moderate or severe common cold symptoms, compared with the placebo ($p = 0.023$). However, the mean number of total days with any common cold symptoms was similar between the FV capsules and placebo. Nantz et al. [26] provided FV or placebo capsules to 59 healthy students for 77 days in Florida. They found improved immune function with the FV capsules, as determined by increased circulating γδ-T cells. However, there were no differences in circulating δβ-T cells or cytokines. Interestingly, the recorded log of illnesses indicated that the FV concentrate group tended to have fewer total symptoms than the placebo group ($p = 0.076$). Two other studies looked specifically at immune function. The study of Inserra et al. [13]

found that supplementation with FV concentrates for 40 days significantly improved cell-mediated immunity, as evidenced by a twofold increase in interleukin-2 levels in elderly smokers and nonsmokers. Other markers of improved immune function were also noted, including increased spontaneous proliferation of peripheral blood mononuclear cells and increased natural killer cell cytotoxicity. However, Winkler et al. [24] reported that the liquid FV concentrate did not alter markers of immunity (i.e., T-lymphocyte proliferation and apoptosis) in healthy or HIV-positive patients [24].

Two studies assessed the effect of FV concentrates on blood lipids as secondary endpoints. Plotnick et al. [15] gave FV, FVB, or placebo capsules to 38 healthy subjects for a 4-week period. They found significant reductions in total and low-density lipoprotein cholesterol with the FV capsules but not with the FVB capsules. Houston et al. [27] provided FVB capsules to 51 subjects for 2 years and showed a small (–0.03 mmol/L) but statistically significant ($p = 0.025$) decrease in serum HDL cholesterol, with no change in other serum lipid fractions. Plotnick et al. [15] also assessed the effect of the FV and FVB capsules on endothelial function (flow-mediated vasodilation). They found that both the FV and FVB capsules significantly blunted the detrimental impact of a single high-fat test meal on endothelial function ($p < 0.05$ and $p < 0.02$, respectively). They also noted an increase in serum nitrate/nitrite levels in both the FV and FVB groups, suggesting that endothelial nitric oxide synthase activity may be enhanced with the FV and FVB capsules. Houston et al. [27] also assessed the effect of FV concentrates on blood pressure and coronary artery calcium score. They found that consumption of the FV concentrates over 24 months produced modest but significant reductions in systolic (-2.4 ± 1.0 mmHg, $p < 0.05$) and diastolic (-2.2 ± 0.6 mm Hg) blood pressure and significantly improved large artery compliance ($p < 0.01$). Furthermore, the progression of coronary artery calcium score was less than expected compared with an historical database ($p < 0.001$).

FUTURE DIRECTION AND CONCLUSIONS

The current systematic review identified two commercially available mixed FV concentrate supplements, the health effects of which have been assessed in clinical studies. From the 22 reports identified, there is clear evidence to indicate that FV concentrate supplementation significantly increases serum concentrations of antioxidants (β-carotene and vitamins C and E) and folate and significantly reduces markers of oxidative stress, particularly protein and lipid oxidation. The evidence for their health effects on markers of inflammation and endothelial and immune function is promising, but further investigations are required. Further trials are warranted, particularly those utilizing a randomized, double blind, placebo-controlled design. Trials utilizing diverse FV concentrate supplements are also warranted, as the vast majority of the published research relates to relatively few consumer products. It would be helpful if more studies included dietary records, including FV intake and the overall macronutrient and micronutrient profiles of the diet. Furthermore, to clarify the potential benefit of FV supplements in a real-world setting, studies using larger numbers of subjects and longer intervention periods should be undertaken.

Overall, the studies conducted to date indicate that the FV concentrates are effective in significantly improving circulating concentrations of antioxidant vitamins, provitamins, and folate and decreasing markers of oxidative stress. There are also data indicating that FV concentrates may decrease inflammatory biomarkers and improve immune function. While these supplements are not meant to replace a healthy and well-balanced diet rich in fruits and vegetables, they may provide a useful means by which individuals can improve intake of FV bioactives. These FV concentrates have been shown to be well tolerated for up to 2 years and easy to comply with in "free living" settings [27], making them a practical choice, particularly for individuals who may have difficulty meeting the current recommendations.

ACKNOWLEDGMENT

We would like to thank Ms Shahad Abdulnour for helping with data extraction.

REFERENCES

1. Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC: Fruit and vegetable intake and risk of major chronic disease. J Natl Cancer Inst 96:1577–1584, 2004.
2. Block G, Patterson B, Subar A: Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 18:1–29, 1992.
3. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E, Lapsley KG, Trautwein EA, Josse RG, Leiter LA, Connelly PW: Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. JAMA 290:502–510, 2003.
4. Strain JJ, Elwood PC, Davis A, Kennedy O, Coulter J, Fehily A, Mulholland CW, Robson PJ, Thurnham DI: Frequency of fruit and vegetable consumption and blood antioxidants in the Caerphilly cohort of older men. Eur J Clin Nutr 54:828–833, 2000.
5. Brown L, Rosner B, Willett WW, Sacks FM: Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 69:30–42, 1999.
6. Jenkins DJ, Nguyen TH, Kendall CW, Faulkner DA, Bashyam B, Kim IJ, Ireland C, Patel D, Vidgen E, Josse AR, Sesso HD, Burton-Freeman B, Josse RG, Leiter LA, Singer W: The effect of

strawberries in a cholesterol-lowering dietary portfolio. Metabolism 57:1636–1644, 2008.
7. Casagrande SS, Wang Y, Anderson C, Gary TL: Have Americans increased their fruit and vegetable intake? The trends between 1988 and 2002. Am J Prev Med 32:257–263, 2007.
8. Naska A, Vasdekis VG, Trichopoulou A, Friel S, Leonhauser IU, Moreiras O, Nelson M, Remaut AM, Schmitt A, Sekula W, Trygg KU, Zajkas G: Fruit and vegetable availability among ten European countries: how does it compare with the 'five-a-day' recommendation? DAFNE I and II projects of the European Commission. Br J Nutr 84:549–556, 2000.
9. Billson H, Pryer JA, Nichols R: Variation in fruit and vegetable consumption among adults in Britain. An analysis from the dietary and nutritional survey of British adults. Eur J Clin Nutr 53:946–952, 1999.
10. Liu RH: Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 78:517S–520S, 2003.
11. Oude Griep LM, Geleijnse JM, Kromhout D, Ocké MC, Verschuren WM. Raw and processed fruit and vegetable consumption and 10-year coronary heart disease incidence in a population-based cohort study in the Netherlands. PLoS One 5:e13609, 2010.
12. Wise J, Morin RJ, Sanderson R, Blum K: Changes in plasma carotenoid, alpha-tocopherol, and lipid peroxide levels in response to supplementation with concentrated fruit and vegetable extracts: a pilot study. Curr Ther Res Clin Exp 57:445–461, 1996.
13. Inserra PF, Jiang S, Solkoff D, Lee J, Zhang Z, Xu M, Hesslink R Jr, Wise J, Watson RR: Immune function in elderly smokers and nonsmokers improves during supplementation with fruit and vegetable extracts. Int Med 2:3–10, 1999.
14. Smith MJ, Inserra PF, Watson RR, Wise J, O'Neil KL: Supplementation with fruit and vegetable extracts may decrease DNA damage in the peripheral lymphocytes of an elderly population. Nutr Res 19:1507–1518, 1999.
15. Plotnick GD, Corretti MC, Vogel RA, Hesslink R Jr, Wise JA: Effect of supplemental phytonutrients on impairment of the flow-mediated brachial artery vasoactivity after a single high-fat meal. J Am Coll Cardiol 41:1744–1749, 2003.
16. Kiefer I, Prock P, Lawrence C, Wise J, Bieger W, Bayer P, Rathmanner T, Kunze M, Rieder A: Supplementation with mixed fruit and vegetable juice concentrates increased serum antioxidants and folate in healthy adults. J Am Coll Nutr 23:205–211, 2004.
17. Kawashima A, Madarame T, Koike H, Komatsu Y, Wise JA: Four week supplementation with mixed fruit and vegetable juice concentrates increased protective serum antioxidants and folate and decreased plasma homocysteine in Japanese subjects. Asia Pac J Clin Nutr 16:411–421, 2007.
18. Wise JA, Kaats GR, Preuss HG, Morin RJ: Beta-carotene and alpha-tocopherol in healthy overweight adults; depletion kinetics are correlated with adiposity. Int J Food Sci Nutr 60(suppl 3):65–75, 2009.
19. Leeds AR, Ferris EAE, Staley R, Ayesh R, Ross F: Availability of micronutrients from dried, encapsulated fruit and vegetable preparations: a study in healthy volunteers. J Hum Nutr Dietet 13:21–27, 2000.
20. Panunzio MF, Pisano A, Antoniciello A, Di Martino V, Frisoli L, Cipriani V, Mongelli MA, Bronzetti G: Supplementation with fruit and vegetable concentrate decreases plasma homocysteine levels in a dietary controlled trial. Nutr Res 23:1221–1228, 2003.
21. Bloomer RJ, Goldfarb AH, McKenzie MJ: Oxidative stress response to aerobic exercise: comparison of antioxidant supplements. Med Sci Sports Exerc 38:1098–1105, 2006.
22. Goldfarb AH, McKenzie MJ, Bloomer RJ: Gender comparisons of exercise-induced oxidative stress: influence of antioxidant supplementation. Appl Physiol Nutr Metab 32:1124–1131, 2007.
23. Arendt BM, Boetzer AM, Lemoch H, Winkler P, Rockstroh JK, Berthold HK, Spengler U, Goerlich R: Plasma antioxidant capacity of HIV-seropositive and healthy subjects during long-term ingestion of fruit juices or a fruit-vegetable-concentrate containing antioxidant polyphenols. Eur J Clin Nutr 55:786–792, 2001.
24. Winkler P, Ellinger S, Boetzer AM, Arendt BM, Berthold HK, Rockstroh JK, Spengler U, Goerlich R: Lymphocyte proliferation and apoptosis in HIV-seropositive and healthy subjects during long-term ingestion of fruit juices or a fruit-vegetable-concentrate rich in polyphenols and antioxidant vitamins. Eur J Clin Nutr 58:317–325, 2004.
25. Samman S, Sivarajah G, Man JC, Ahmad ZI, Petocz P, Caterson ID: A mixed fruit and vegetable concentrate increases plasma antioxidant vitamins and folate and lowers plasma homocysteine in men. J Nutr 133:2188–2193, 2003.
26. Nantz MP, Rowe CA, Nieves C Jr, Percival SS: Immunity and antioxidant capacity in humans is enhanced by consumption of a dried, encapsulated fruit and vegetable juice concentrate. J Nutr 136:2606–2610, 2006.
27. Houston MC, Cooil B, Olafsson BJ, Raggi P: Juice powder concentrate and systemic blood pressure, progression of coronary artery calcium and antioxidant status in hypertensive subjects: A pilot study. Evid Based Complement Alternat Med 4:455–462, 2007.
28. Bamonti F, Novembrino C, Ippolito S, Soresi E, Ciani A, Lonati S, Scurati-Manzoni E, Cighetti G: Increased free malondialdehyde concentrations in smokers normalise with a mixed fruit and vegetable juice concentrate: a pilot study. Clin Chem Lab Med 44:391–395, 2006.
29. Lamprecht M, Oettl K, Schwaberger G, Hofmann P, Greilberger JF: Several indicators of oxidative stress, immunity, and illness improved in trained men consuming an encapsulated juice powder concentrate for 28 weeks. J Nutr 137:2737–2741, 2007.
30. Lamprecht M, Oettl K, Schwaberger G, Hofmann P, Greilberger JF: Protein modification responds to exercise intensity and antioxidant supplementation. Med Sci Sports Exerc 41:155–163, 2009.
31. Jin Y, Cui X, Singh U, Chumanevich A, Harmon B, Cavicchia P, Hofseth A, Kotakadi V, Stroud B, Volate S, Hurley T, Herbert J, Hofseth L: Systematic inflammatory load in humans is suppressed by consumption of two formulations of dried, encapsulated juice concentrate. Mol Nutr Food Res 54:1506–1514, 2010.
32. Roll S, Nocon M, Willich SN: Reduction of common cold symptoms by encapsulated juice powder concentrate of fruits and vegetables: a randomised, double-blind, placebo-controlled trial. Br J Nutr 105:118–122, 2011.
33. Goldfarb AH, Garten RS, Cho C, Chee PD, Chambers LA: Effects of a fruit/berry/vegetable supplement on muscle function and oxidative stress. Med Sci Sports Exerc, 43:501–508, 2011.

34. Halliwell B: Oxidative stress and cancer: have we moved forward? Biochem J 401:1–11, 2007.
35. Higgins JP, Green S: "Cochrane Handbook for Systematic Reviews of Interventions," version 5.0.0 updated. [Location]: The Cochrane Collaboration, 2008.
36. Chevion M, Berenshtein E, Stadtman ER: Human studies related to protein oxidation: protein carbonyl content as a marker of damage. Free Radic Res 33(suppl):S99–108, 2000.
37. Dalle-Donne I, Rossi R, Giustarini D, Milzani A, Colombo R: Protein carbonyl groups as biomarkers of oxidative stress. Clin Chim Acta 329:23–38, 2003.
38. Lee SH, Blair IA: Oxidative DNA damage and cardiovascular disease. Trends Cardiovasc Med 11:148–155, 2001.
39. Herrmann W: The importance of hyperhomocysteinemia as a risk factor for diseases: an overview. Clin Chem Lab Med 39:666–674, 2001.
40. Herrmann W, Knapp JP: Hyperhomocysteinemia: a new risk factor for degenerative diseases. Clin Lab 48:471–481, 2002.
41. Malinow MR: Plasma concentrations of total homocysteine predict mortality risk. Am J Clin Nutr 74:3, 2001.
42. Marti-Carvajal AJ, Sola I, Lathyris D, Salanti G: Homocysteine lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev CD006612, 2009.
43. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, Humphrey LL: Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 151:496–507, 2009.
44. Dary O: Nutritional interpretation of folic acid interventions. Nutr Rev 67:235–244, 2009.

Received May 10, 2011; revision accepted June 24, 2011.