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Health effects of 100% fruit and vegetable juices: evidence from human subject intervention studies

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Abstract

The health effects of 100% fruit and vegetable juices (FVJ) represent a controversial topic. FVJ contain notable amounts of free sugars, but also vitamins, minerals, and secondary compounds with proven biological activities like (poly)phenols and carotenoids. The review aimed to shed light on the potential impact of 100% FVJ on human subject health, comprehensively assessing the role each type of juice may have in specific health outcomes for a particular target population, as reported in dietary interventions. The effects of a wide range of FVJ (orange, grapefruit, mandarin, lemon, apple, white, red, and Concord grapes, pomegranate, cranberry, chokeberry, blueberry, other minor berries, sweet and tart cherry, plum, tomato, carrot, beetroot, and watermelon, among others) were evaluated on a series of outcomes (anthropometric parameters, body composition, blood pressure and vascular function, lipid profile, glucose homeostasis, biomarkers of inflammation and oxidative stress, cognitive function, exercise performance, gut microbiota composition and bacterial infections), providing a thorough picture of the contribution of each FVJ to a health outcome. Some juices demonstrated their ability to exert potential preventive effects on some outcomes while others on other health outcomes, emphasising how the differential composition in bioactive compounds defines juice effects. Research gaps and future prospects were discussed. Although 100% FVJ appear to have beneficial effects on some cardiometabolic health outcomes, cognition and exercise performance, or neutral effects on anthropometric parameters and body composition, further efforts are needed to better understand the impact of 100% FVJ on human subject health.

Keywords: **Juice: Nutrition: Health properties: Food bioactives: phytochemicals**

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Introduction

The health effects of 100% fruit and vegetable juices (FVJ) represent a controversial topic to date. Despite the plant origin of 100% FVJ and the role of fruit and vegetable consumption in preventing non-communicable diseases[1], scientific evidence is less robust, and the debate is focused almost exclusively on the sugar content of FVJ. Indeed, although 100% FVJ have no added sugars, they still have a total sugar content that depends on the fruit or vegetable from which they are made (approximately 16–24 g/200 ml serving size)[2]. Considering international (for example, WHO) and national recommendations, 100% FVJ should be consumed in moderate amounts. According to the WHO guidelines, total daily free sugar intake should be reduced to less than 10% of energy intake (50 g/d for a 2000 kcal/8368 kJ diet), with sugars from FVJ being classified as free sugars[3]. While the adverse effects of excess added sugars are well established, the contribution of naturally occurring sugars, such as in fruits and fruit juices, to the increased prevalence of non-communicable diseases is unclear and deserves further discussion[2,4]. Overall, limiting 100% FVJ only because of their sugar content is not a balanced but a reductionist approach that may lead to possibly unfounded evaluations.

In a recent review, Ruxton and Myers (2021)[2] showed that 100% fruit juices (FJ) have a nutritional composition closer to whole fruits than to classic sugar-sweetened beverages (SSB), primarily due to their micronutrient and phytochemical content. In terms of micronutrients, Mitchell *et al.* (2020)[6] found that 100% FJ contribute to vitamin C, folate, magnesium, and potassium intakes in the USA, UK and Brazil. These findings are supported by Brauchla *et al.* (2021)[7], who observed a dramatic decline in vitamin C intake over a 20-year period (1999–2018) in a US nationally representative survey, likely driven by a decreasing FJ consumption. Similarly, according to NHANES data, 100% FJ intake was associated with better nutrient intake and diet quality in adults[8] and improved nutrient adequacy in children and adolescents (2–18 years)[9]. Regarding phytochemicals, the HELENA study showed that FVJ were among the top three food contributors of dietary (poly)phenols in European adolescents (12·5–17·5 years)[10]. Similar results have been reported for European adults, where FJ are sources of specific phenolic compounds[11]. (Poly)phenols or phenolic compounds are phytochemicals with proven biological activity widespread in all plant products, and (poly)phenol-rich diets are associated with reduced risk of various diseases[12,13,14]. Ho *et al.* (2020)[15] reported that 100% FJ contribute to dietary (poly)phenol intake,

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making them complementary to commonly consumed (poly) phenol-rich sources (for example, some fruits, coffee, tea, cocoa, etc.), and that some FJ (dark-coloured ones) might provide many of the same benefits as whole fruits. Indeed, a recent systematic reviews and meta-analysis (SRMA) on randomised controlled trials (RCT) providing quantitative data on the (poly)phenol content in 100% FJ has demonstrated how anthocyanins, but not total (poly)phenols, may mediate the potential beneficial effects of some 100% FJ on total and LDL-cholesterol (LDL-C)[16]. The contribution of other bioactive phytochemicals available in specific FVJ, such as carotenoids (tomato; carrot; citrus; etc.) and betalains (beetroot), may also account for the potential benefits of 100% FVJ. Therefore, it is essential to address the discussion on the health effects of 100% FVJ from a comprehensive point of view, taking into account the juice as a whole, as a food product naturally containing sugars, but also other beneficial components, such as vitamins, minerals and phytochemicals.

Current dietary guidelines are primarily based on observational studies or systematic reviews/meta-analyses of observational studies. This literature is key to understanding the health prospects of FVJ, but it presents a great heterogeneity of outcomes as the classification of FVJ is often ambiguous: although some authors distinguish between 100% FVJ and other types of juices (nectars), many epidemiological studies do not consider the compositional differences among 100% FVJ, nectars and even most SSB that typically contain only small amounts of FVJ[17]. Assessing together all the FVJ-derived products may lead to misunderstandings as it is clear that the composition of sugars, micronutrients, and phytochemicals varies among these products, as does their potential contribution to human subject health[2]. On the other hand, while merging all the different 100% FVJ ('one-size-fits-all' approach) is essential to provide sound dietary recommendations for the general population, an accurate assessment of the biological effects of these juices needs certain specificity. It seems reasonable to expect that juices from different botanical species (and compositions in secondary bioactive compounds, Fig. 1) may lead to different effects on a specific health outcome, so the assessment of the contribution of 100% FVJ to human subject health should be addressed for every juice and outcome.

The aim of this review was to shed light on the potential impact on human subject health of 100% FVJ. A brief overview of the contribution of 100% FVJ to main health outcomes was provided, considering mainly epidemiological studies. The core of this literature review focused on assessing the effects of FVJ on a wide range of outcomes through intervention studies conducted in human subjects and using 100% pure juice or purées (when available). To provide a complete picture of the research question, no limit was set with regard to the botanical species and health outcomes considered, neither by population setting or publication year. Discussion is provided by juice type, addressing the most relevant publications for any FVJ and health outcome: when only a few articles for a specific juice and outcome were available, they were all reported; however, when several articles were available for a specific outcome, the most representative papers (by experimental design and sample size) were selected as examples, together with available systematic reviews on the topic. When available, the phytochemical composition was reported to better understand the potential compounds behind the observed effects. When some relevant studies were on juice drinks but not on 100% fruit juice (for example, as for many studies on berry juices), they were included by specifying that the juice was not 100% FJ. Lastly, a thorough picture of the contribution of each FVJ to a health outcome was provided, considering the evidence available and research gaps and future needs were discussed.

General evidence from 100% fruit and vegetable juices as reported in observational studies and literature reviews

Most of the studies on the effects of 100% FVJ are related to cardiometabolic health and obesity, as they are closely associated with an increased sugar intake[17]. Comparison among different beverages derived from FVJ is essential to really understand the contribution of each juice beverage to cardiometabolic health in different population settings. In this sense, in the EPIC-NL prospective cohort study with 35,000 participants (aged 20–70 years at enrolment), Scheffers *et al.* (2021)[18] found that substituting 100% FJ for SSB was associated with lower cardiometabolic risk, whereas replacing 100% FJ for fruit was not associated with differences in the risk of cardiovascular diseases (CVD), stroke, and type 2 diabetes (T2D). Authors concluded that 100% FJ did not appear to be different from whole fruit in relation to cardiometabolic risk[18]. Cross-sectional data from about 8500 participants in the US Nurses' Health Study indicated that the intake of SSBs was associated with adverse levels of multiple cardiometabolic biomarkers, whereas the association was less consistent for FJ[19]. Similar results were found for the Framingham Heart Study, as SSB consumption was associated with adverse changes in lipoprotein concentrations and increased incidence of dyslipidemia, while regular consumption of 100% FJ up to 1·5 daily servings was not linked to adverse effects on lipoproteins or dyslipidaemia[20]. Elsahoryi *et al.* (2021)[21] found that a high overall intake of fruits, vegetables and FJ was inversely associated with blood pressure (BP) in the PRIME study, a prospective study including about 10,600 men from France and Northern Ireland, while sub-type analysis did not show any effect of FJ on BP.

Previous results on cardiometabolic risk biomarkers are in line with two recent SRMA of prospective cohort studies and RCT assessing the incidence of cardiovascular diseases and showing that 100% FVJ are among the fruit and vegetable sources associated with greater cardiovascular benefits[22,23]. Indeed, researchers[22,23] indicated that 100% FVJ intake was not linked to higher CV risk and that a non-linear inverse dose-response relationship was shown between 100% FVJ consumption and CVD, especially for the risk of stroke. In the case of T2D, no association between intake of 100% FVJ and risk of T2D in Japanese adults (40–59 years), who had no previous history of diabetes, was observed[24]. These findings were in line with a SRMA of RCT that reported a neutral effect of 100% FJ on glycaemic control[25]. Since this point would benefit from a more accurate discussion, but it is not the aim of this review, the following meta-analysis on the effect of FVJ on glycaemic management are suggested: Choo *et al.* (2018)[26], D'Elia *et al.* (2020)[23] and Murphy *et al.* (2017)[25]. Lastly,

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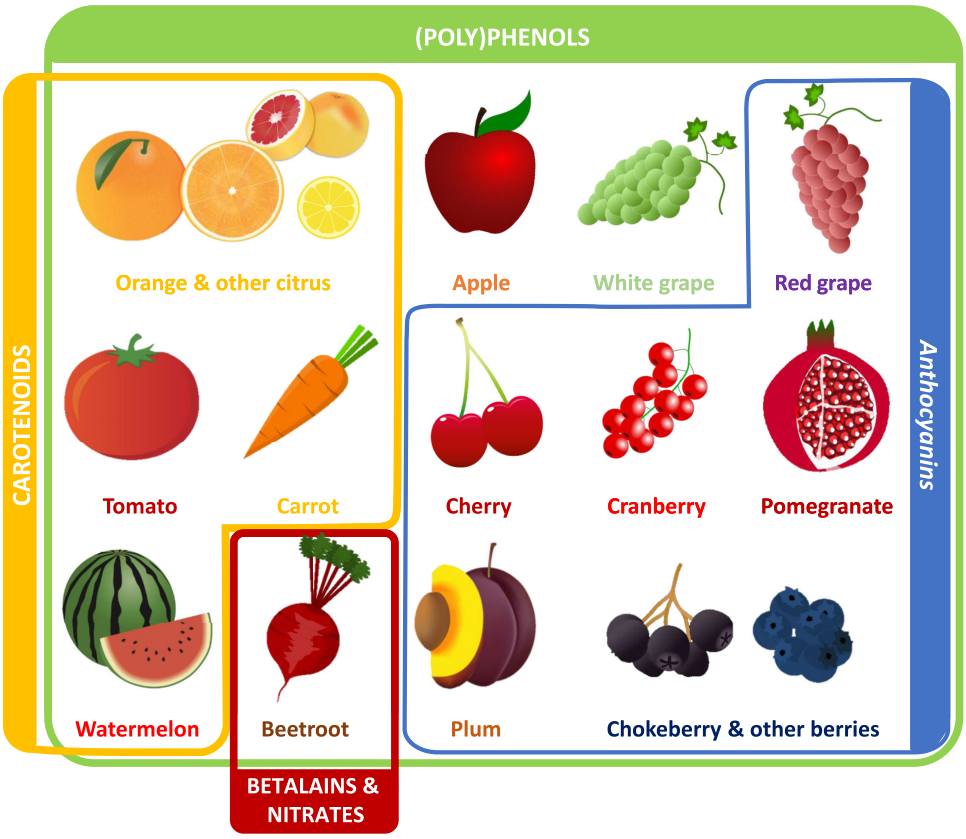

Fig. 1. Main families of non-nutrient bioactive compounds in the FVJ assessed. Anthocyanins are a class of coloured polyphenols

regarding body weight, the results of a systematic review by Crowe-White *et al.* (2016)[27] did not suggest an association between 100% FJ and weight status or adiposity in children (1–18 years) after controlling for total energy intake. Auerbach *et al.* (2017)[28], in a meta-analysis of eight prospective cohort studies, also did not find an association of 100% FJ with clinically significant weight gain in children.

In general, this information on obesity and cardiometabolic outcomes is in agreement with a recent review by Ruxton and Myers (2021)[2], who reported that moderate consumption of 100% FJ (75–224 ml/d) did not increase the risk of T2D, poor glycaemic control, obesity or CVD, and that pure juices may confer health benefits in terms of vascular function and reduced BP. Authors thus concluded that 100% FJ appear to offer more benefits than risks within a balanced diet. A similar position was also reported by Auerbach *et al.* (2018)[29], highlighting that adverse health effects are not conclusive and dietary recommendations allowing moderate consumption of 100% FVJ are supported by the available evidence. Indeed, although 100% FVJ can be a source of fructose increasing the risk of suffering from metabolic syndrome when consumed excessively, juice consumption at moderate amounts (between 75 and 150 ml/d) may show protective effects on the incident of metabolic syndrome[30].

Two other emerging research fields related to FVJ are mental health and gut microbiota. Głąbska *et al.* (2020)[31], in a recent systematic review of observational studies, reported that FVJ were among the fruit and vegetable sources associated with a possible beneficial influence on mental health. Similarly, Pontifex *et al.* (2020)[32] supported the potential beneficial effects of (poly)phenols present in citrus fruits and juices on brain health, even though more has to be investigated. On the other hand, Henning *et al.* (2017)[33], in an intervention study designed to better understand the health benefits of an FVJ-based diet, showed an alteration in the intestinal microbiota associated with weight loss among other physiological improvements. However, despite the prospects of FVJ on gut microbiota, comprehensive literature reviews on this topic are still lacking.

Evidence of the health effects of 100% fruit and vegetable juices as reported in human subject intervention studies

Citrus juices

Citrus fruits and their juices are rich in micronutrients such as vitamin C, folate, potassium and magnesium, as well as in bioactive (poly)phenols[34,35,36]. Citrus are the main dietary source of flavanones, a flavonoid subclass. Flavanones in citrus fruit occur primarily in a glycosylated form, and the dominant flavanone glycosides are hesperidin in sweet orange and tangerine, naringin and neohesperidin in sour orange, naringin in grapefruit, and hesperidin and eriocitrin in lemon and lime[37,38]. Citrus juices have been associated with different protective features, as they may have a role in reducing the risk of T2D[34] and in the inflammatory response[35]. They are among the most studied FVJ as they also represent the major group of FVJ consumed by Western populations, orange juice being the most consumed 100% juice worldwide.

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Orange juice. Most of the literature on the health effects of juices is related to orange juice, and the number of targets addressed is quite broad. Some representative studies have been presented in Table 1.

Regarding body weight, Rangel-Huerta *et al.* (2015)[39], in a randomised crossover double-blind 12-week study, investigated the effects of consuming 500 ml/d of orange juice containing either normal (589 mg/l) or high (1490 mg/l) concentrations of flavanones (normal-polyphenol juice (NPJ) and high-polyphenol juice (HPJ), respectively) in 100 non-smoking adults who were overweight or obese. In both juices, hesperidin was the main flavanone, accounting for 89% and 78% of the polyphenol content for NPJ and HPJ, respectively. Potassium (460 and 1065 mg/500 ml, in NPJ and HPJ, respectively) and vitamin C (210 and 235 mg/500 ml, in NPJ and HPJ, respectively) were the main minerals and vitamins. Results showed a reduction in body weight, BMI and waist circumference following consumption of both juices. These reductions could be explained by the decrease in energy intake during the study, but not by the flavanone content of each treatment, which did not entail differences in the urinary excretion of flavanone metabolites between treatments[39]. A similar experimental protocol (12-week intervention, 500 ml/d, 100% orange juice, 324 mg/l hesperitin), where orange juice was supplemented as part of a reduced-calorie diet, did not inhibit weight loss in seventy-eight patients with obesity, as compared with the control group (a reduced-calorie diet without orange juice)[40]. Another 12-week study showed no effect of 250 ml/d of orange juice (542 mg/l hesperidin) on body weight in men who were overweight[41]. Together, these studies showed no adverse effect of orange juice on body weight management, in agreement with two recent meta-analyses of RCT on the effect of orange juice on anthropometric measures in healthy or unhealthy/at-risk adults[42,43].

Considering vascular health, daily consumption of flavanone-rich orange juices may be able to reduce BP, while red orange juice might affect endothelial function (contrary to 'blonde' or common orange, red or 'blood' orange contains anthocyanins). Consumption of an orange juice with normal levels of flavanones (NPJ, 589 mg/l) for 12 weeks reduced both systolic and diastolic BP in adults who were overweight/obese, while the decrease after consuming a juice with higher flavanone content (HPJ, 1490 mg/l) was not significant[39]. Contrarily, an effect of the flavanone content on BP has been described in a 12-week randomised parallel double-blind placebo-controlled trial evaluating the effects of hesperidin in orange juice on BP in 129 mildly hypertensive individuals[44]. Consumption of 500 ml/d of orange juice containing 690 mg/l of hesperidin, or enriched orange juice containing 1200 mg/l of hesperidin, decreased both systolic BP and pulse pressure in a dose-dependent manner with the hesperidin content of the beverage administrated and in comparison to a control drink. Furthermore, a single dose of enriched orange juice (500 ml) but no other treatments reduced systolic BP. These functional changes were backed by changes in the plasma concentrations of hesperetin metabolites[44]. Similarly, Morand *et al.* (2011)[45] showed that lower levels of diastolic BP were reached after consumption of both orange juice, naturally rich in hesperidin, and an hesperidin-enriched control drink. Nevertheless, other authors have reported a lack of effect of orange juice on BP. Hollands *et al.* (2018) compared 4-week consumption of 500 ml/d of 'blood' orange juice (134 mg/l of hesperidin + 100 mg/l of anthocyanins) or 'blonde' orange juice (208 mg/l of hesperidin, without anthocyanins) in 41 predominantly individuals who were overweight and found no effect of any juice on BP. In a 2-week study, consumption of 400 ml/d of 'blood' orange juice (802 mg/l of hesperidin + 24 mg/l of anthocyanins) did not change BP in 15 non-smoking adults who were overweight or obese and who had baseline pressure within a healthy range[47]. The low amounts of flavanones provided[46], the intervention duration, and the baseline values in the study population[47] might be behind the lack of effect reported. The inter-individual variability in the metabolism of flavanones may also condition the effect of orange juice consumption on systolic BP[48]. On the other hand, in the case of endothelial function,[47] a favourable effect (2% increase in flow-mediated dilation (FMD)) of blood orange juice (400 ml/d for 2 weeks) was demonstrated compared with a control drink. The result correlated with a higher urinary excretion of hesperetin metabolites[47]. A similar improvement in FMD was reported following 7-d consumption of red orange juice (500 ml/d, 319 mg/l of hesperidin and 71 mg/l of anthocyanins) in 19 non-diabetic subjects with increased cardiovascular risk, while there was no effect in healthy subjects[49]. The result of the ongoing HESPER-HEALTH study, which evaluates the role of orange juice in vascular health[50], will help to better establish the effect of orange juice intake on FMD.

Regarding lipid profile, a recent SRMA of fifteen RCT in healthy or unhealthy at-risk adults investigated the effectiveness of orange juice intake on primary cardiometabolic markers, including lipid profile[43]. The results suggested that orange juice intake might be associated with reduced serum total cholesterol (TC) concentration. But, despite this extensive evidence, several works have failed to find an effect of orange juice consumption on lipid profile. Hollands *et al.* (2018)[46], comparing 4-week consumption of 500 ml/d of blood orange juice (containing anthocyanins) or blonde orange juice (without anthocyanins), found no effect of the orange juice pre- and post-supplementation on the lipid profile of forty-one predominantly overweight individuals. In particular, the hypothesised improvement in LDL-C with blood orange juice (because of its anthocyanin content) did not occur, nor was there any change in TC, HDL-cholesterol (HDL-C) and triacylglycerols (TG). As suggested by the authors, the study population was only minimally hyperlipidaemic (5·1 mmol/l TC), and an effect in individuals with higher TC (for example, >6·0 mmol/l) cannot be precluded. However, 12-week consumption of 250 ml/d of orange juice did not affect circulating lipids in thirty-six men with overweight and elevated fasting serum TC (5–7 mmol/l)[41]. Nevertheless, in the orange juice group, those with the highest TG concentration pre-intervention showed the greatest reduction after 12 weeks of supplementation[41]. Li *et al.* (2020)[47] also reported that the lipid profile (TC, LDL-C, HDL-C, and TGs) was unaffected by blood orange juice (400 ml/d for 2 weeks) in subjects with normal lipid levels. The same conclusions were found following either consumption of NPJ or HPJ (normal or high-polyphenol concentration orange juice, respectively), except for TG and

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Table 1. Characteristics of some representative studies investigating the health effects of 100% orange juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Orange (blood orange)	RT, CO, 21 d	*n* = 16 (F), NW, 20–27 years	600 l/d	450 mg vitamin C, 21 mg cyanidin-3-glucoside	Diet devoid of blood orange juice	No changes in PAC, MDA, 11-dehydro-TXB2, DNA damage	Riso *et al.*, 2005[57]
Orange, control drink + placebo (CDP), control drink + hesperidin (CDH)	RCT, CO, O + DB, 4-week	*n* = 24 (M), healthy, OW, 56 (SD 1) year	500 ml/d	292 mg hesperidin, 47·5 mg narirutin	CDP: isoenergetic control drink containing starch; CDH: isoenergetic control drink containing 292 mg of hesperidin	OJ and CDH: ↓ DBP and sVCAM-1, improved endothelial function; OJ: ↓ uric acid	Morand *et al.*, 2011[45]
Orange (Red orange)	RCT, SB, CO, 1-week	*n* = 31 (16 F, 19 intervention), OW/OB non-diabetic subjects with increased cardiovascular risk + healthy nonobese control subjects, 48 (SD 13) year CVR group, 35 (SD 8) year control group	500 ml/d	210 mg GAE total (poly)phenols, 160 mg hesperidin, 22 mg narirutin, 36 mg cyanidin 3-glucoside anthocyanins	Control drink made up of water, orange aroma, colourants (azorubin and tartrazine), sucrose, citric acid	↓ FMD, hs-CRP, IL-6, TNF-α; no changes in plasma protein carbonyl concentrations	Buscemi *et al.*, 2012[49]
Orange	RCT, DB, CO, 8-week	*n* = 37 (24 F), healthy, OW, 67 (SD 5) years	500 ml/d	305 mg flavanones, 275 hesperidin, 30 mg narirutin	Isoenergetic low-flavanone control drink (37 mg/500 ml)	Better global cognitive function compared with the control drink	Kean *et al.*, 2015[58]
Orange (normal or high concentrations of (poly)phenols, NPJ and HPJ, respectively)	RT, DB, CO, two 12-week periods	*n* = 100, OB, 18–65 years	500 ml/d	NPJ: 299 mg flavanones (237 mg hesperidin); HPJ: 745 mg flavanones (582 mg hesperidin)	Comparison of both interventions	Both NPJ and HPJ: ↑ glucose, urine hesperetin and naringenin metabolites; ↓ BW, BMI, WC, insulin, leptin; no changes in LDL-c, TC, HDL-c, HOMA-IR; NPJ: ↓ SBP and DBP, TAG, apoB; HPJ: ↑ Apo A-I, SOD activity	Rangel-Huerta *et al.*, 2015[39]
Orange (juice with added orange pomace fibre)	RCT, DB, CO, single-dose	*n* = 24 (M), healthy, OW/OB, 51 (SD 7) years	240 ml	272 mg flavonoids + with 5·5 g of added orange pomace fibre	Colour/flavour/energy-matched beverage without flavonoids	Acute improvements in cognitive function and subjective alertness up to 6 h post-consumption	Alharbi *et al.*, 2016[59]
Orange (without pulp (OJ), OJ with orange pomace fibre (OPF), juice made from lightly blended whole orange fruit (WOF))	RCT, DB, CO, post-prandial single-dose with four treatments	*n* = 36 (M), with ≥1 cardiometabolic risk factor, OW, 48 (SD 1) years	240 ml	OJ: 129 mg total flavonoids + 0·7 g fibre; OPF: 272 mg + 5·5 g; WOF: 453 mg + 6·3 g	Isoenergetic control drink without (poly)phenols	OPF delayed the time to reach the peak glucose concentration compared with Control and OJ, and of insulin compared with Control after breakfast	Dong *et al.*, 2016[52]
Orange	RCT, SB, parallel, 12-week	*n* = 36 M, elevated serum cholesterol, OW/OB, 49 (SD 4) years	250 ml/d	135 mg hesperidin, 15 mg narirutin	Colour/flavour/energy-matched beverage	No changes in BW, LDL-c, TC, HDL-c, TAG, HOMA-IR	Simpson *et al.*, 2016[41]
Orange consumed with a reduced-calorie diet	RCT, parallel, 12-week	*n* = 78 (54 F, 39 intervention), OB, 36 (SD 1) years	500 ml/d	162 mg hesperitin, 7·7 mg naringenin	Reduced-calorie diet without orange juice	↓ TC and LDL-c, insulin, HOMA-IR, hs-CRP	Ribeiro *et al.*, 2017[40]

Table 1. (*Continued*)

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Orange (anthocyanin-rich blood orange juice)	RCT, OL, two-arm CO, 4-week	*n* = 41 (21 F), WC men >94 cm and women >80 cm, 52 (SD 14) years	500 ml/d	50 mg anthocyanins, 67 mg of hesperidin	Blonde orange juice without anthocyanins, 104 mg/500 ml of hesperidin	No changes in LDL-c, TC, HDL-c, TAG, glucose, fructosamine, NO, hs-CRP, SBP, DBP, carotid-femoral and brachial-ankle PWV	Hollands *et al.*, 2018[46]
Orange, cvs. 'Bahia' and 'Cara Cara'	RCT, CO, 7-d	*n* = 21 (10 F), healthy, NW, 18–45 years	500 ml/d		Isoenergetic control drink containing water, sucrose, and vitamin C	Bahia and Cara Cara orange juice affected the gut microbiota composition differently	Brasili *et al.*, 2019[61]
Orange	nonRCT, temporal series intergroup design, 120-d (60-d experimental period with OJ)	*n* = 10 (F), healthy, NW/OW, 28 (SD 8) years	300 ml/d		No control	↑ SCFAs, *Lactobacillus* spp., *Bifidobacterium* spp., total anaerobic bacteria; ↓ blood glucose, insulin, HOMA-IR, TAG, TC, LDL-c	Delgado *et al.*, 2019[62]
Orange (blood orange)	RCT, SB, CO, 2-week	*n* = 15 (10 F), healthy, OW/OB, 28 (SD 6) years	400 ml/d	321 mg hesperidin, 38 mg narirutin, 10 mg anthocyanins	Sugar-matched, low-flavonoid drink	↑ FMD; no changes in BP, LDL-c, TC, HDL-c, and TAG	Li *et al.*, 2020[47]
Orange	RCT, SB, parallel, two-arm, 8-week	*n* = 40 (24 F), with depressive symptom, NW, 22 (SD 2) years	380 ml/d	600 ±5·4 mg flavonoids/380 ml	Isoenergetic flavonoid-low orange cordial (108±2·6 mg flavonoids)	↑ BDNF, folate; changed in microbiota composition potentially related to an improvement in depression	Park *et al.*, 2020[63]
Orange (without pulp (OJ), OJ with orange pomace fibre (OPF), whole orange fruit (WOF))	RCT, CO, single-dose with three treatments (both studies)	*n* = 17 (11 F), healthy, NW, 39 (SD 3) years (study 1) *n* = 45 (21 F), healthy, NW, 25 (SD 4) years (study 2)	OJ: 250 g; OPF: 257 g; WOF: 227 g		No control	In both studies: OPF significantly attenuated glucose C_{max} compared with OJ; glucose T_{max} significantly delayed in OPF compared with OJ and WOF; insulin T_{max} significantly delayed in OPF compared with OJ and WOF	Guzman *et al.*, 2021[53]
Orange, natural hesperidin content (OJ) or enriched (EOJ)	RCT, DB, parallel, 12 weeks	*n* = 129, with pre- or stage-1 hypertension, 18–65 years	500 ml/d	OJ: 345 mg hesperidin; EOJ: 600 mg hesperidin	Colour/flavour/energy-matched beverage without hesperidin	EOJ: ↓ SBP, PP; OJ and EOJ: ↓ DBP, homocysteine	Valls *et al.*, 2021[44]

Juices were 100% juice unless otherwise stated. Abbreviations: 11-dehydro-TXB2, 11-Dehydrothromboxane B2; Apo A, apolipoprotein A; Apo B, apolipoprotein B; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BP, blood pressure; BW, body weight; C_{max}, maximal glucose concentration; CDH, hesperidin control drink; CDP, placebo control drink; CO, crossover; CVR, cardiovascular risk; DB, double-blind; DBP, diastolic blood pressure; EOJ, enriched orange juice; F, female; FMD, flow-mediated dilation; GAE, gallic acid equivalent; HDL-c, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HPJ, high concentrations of (poly)phenols; hs-CRP, high-sensitivity CRP; IL-6, interleukin-6; LDL-c, LDL-cholesterol; M, male; MDA, malondialdehyde; NO, nitric oxide; NPJ, normal concentrations of (poly)phenols; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OJ, orange juice; OL, open label; OPF, orange pomace fibre; OW, overweight (BMI: 25–30 kg/m^2); PAC, A-type proanthocyanidins; PP, pulse blood pressure; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; $T_{max,}$ time to reach the maximal glucose concentration; TAG, triglycerides; TC, total cholesterol; TNF-α, tumour necrosis factor-α; WC, waist circumference; WOF, whole orange fruit; ↓, decreased level; ↑ increased level

apoB (the major component of LDL-C), which decreased significantly only after the intake of NPJ when compared with baseline[39]. Differently, when orange juice was consumed concomitantly to a reduced-energy diet for 12 weeks, it helped to reduce TC and LDL-C in individuals with obesity and a normal lipid profile compared with the control group[40]. Therefore, orange juice consumption may impact the lipid profile but only for specific target populations, particularly in subjects with high TG concentrations.

The effect of orange juice supplementation on glucose–insulin homeostasis and the prevention of T2D onset has been broadly studied. Dietary supplementation of 500 ml/d of blood or blonde orange juice for 4 weeks did not change glycaemia in subjects with overweight[46]. Similarly, orange juice, as part of a reduced-calorie diet, did not increase glucose levels over time in patients with obesity, whereas it improved insulin sensitivity[40]. The decrease in insulin levels and the reduction of homeostasis model assessment-insulin resistance (HOMA-IR) were noted only after 8 weeks of intervention[40]. However, Simpson *et al.* (2016)[41] and Rangel-Huerta *et al.* (2015)[39] found no change in HOMA-IR index after a 12-week orange juice intervention in individuals who were overweight and with elevated fasting serum cholesterol and individuals who were overweight/obese, respectively, despite the amounts of orange juice administered were different (250 ml versus 500 ml per day). On the other hand, orange juice consumption may have positive effects on reducing uric acid levels in healthy adults[45].

The SRMA of RCT by Motallaei *et al.* (2021)[43] suggested that orange juice intake might be associated with improved insulin sensitivity, although the quality of the evidence was low-to-moderate and further well-designed studies are needed to confirm this finding. Indeed, the contradictory nature of the available evidence has been highlighted and investigated by Prof. Williamson's group[34]. In a recent review of epidemiological and intervention studies on the effect of orange juice consumption on risk of developing T2D, it was stated that orange juice might improve fasting glucose, fasting insulin and insulin sensitivity after 4 to 12 weeks of orange juice consumption. Inter-individual variability in the metabolism of flavanones seems to be one of the main drivers affecting the physiological responses to chronic consumption in humans[34]. This review also concluded that the acute effect of orange juice consumption on post-prandial glycaemic response is relatively small[34], as it may depend on the hesperidin and sugar content of the juice[51]. Fibre content may also play a role in the post-prandial glycaemic response. Dong *et al.* (2016)[52] found that consuming 240 ml of orange juice added with pomace fibre (5·5 g) significantly reduced the maximal change in glucose concentrations reached after meal ingestion in men with increased cardiometabolic risk. Similar results have been recently shown by Guzman *et al.* (2021)[53].

Motallaei *et al.* (2021)[43] also investigated how orange juice intake might be associated with other cardiometabolic markers such as inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1)), although no significant associations were found. However, two recent meta-analyses have accounted for the beneficial effect of 100% orange juice and hesperidin in orange juice on inflammation[54,55]. In this sense, some works indicated positive effects of orange juice consumption on inflammatory markers[40] and genes[56]. On the other hand, markers related to oxidative stress have also been considered. Both NPJ and HPJ protected against DNA damage and lipid peroxidation and modified several antioxidant enzymes in non-smoking subjects who were overweight/obese [39]. In contrast, no change in plasma protein carbonyl concentrations, measured as a biomarker of oxidative stress, was observed following red orange juice intake in subjects with increased cardiovascular risk[49]. Similarly, consumption of 600 ml/d of blood orange juice for 21 d did not modify plasma antioxidant status and lipid peroxidation, but it improved lymphocyte DNA resistance to oxidative stress in healthy women[57]. The 600 ml portion provided approximately 450 mg of vitamin C, 21 mg of cyanidin-3-glucoside, 0·4 mg of β-cryptoxanthin, 0·12 mg of lutein, 0·11 mg of zeaxanthin and 0·1 mg of lycopene, and higher plasma concentrations of these components were recorded after juice intake[57]. The recent meta-analysis by Cara *et al.* (2022)[55] also suggested a positive effect of 100% orange juice on malondialdehyde (MDA) levels, although the results were not statistically significant.

Other health outcomes such as cognitive function have also been investigated. Kean *et al.* (2015)[58], in a randomised double-blind placebo-controlled trial in thirty-seven healthy older adults (66·7; SD 5·3 years), showed a significantly better global cognitive function after 8 weeks of 500 ml/d of high-flavanone 100% orange juice (610 mg/l flavanones, 90% hesperidin) compared with an isoenergetic low-flavanone control drink. In another study, consumption of 240 ml of orange juice with added orange pomace fibre containing 917 mg/l hesperidin and 5·5 g fibre was associated with acute improvements in cognitive function and subjective alertness up to 6 h post-consumption in healthy middle-aged males (51; SD 6·6 years), relative to an energy-matched placebo drink[59]. In young adults (18–30 years), 500 ml/d of citrus juice (mainly orange including grapefruit juice, containing 140 mg/l flavonoids, of which 84 mg/l was hesperidin) enhanced cerebral blood flow. However, the results did not show a clear association between increased cerebral blood flow and behavioural benefits[60]. Moreover, a recent review on the impact of citrus (poly)phenols, mainly from orange juice, on brain functions accounted for positive effects on reduction of depression risk and cognitive ability linked to schizophrenia[31].

Orange juice could play a role in gut microbiota modulation. In a randomised crossover 7-d study, Brasili *et al.* (2019)[61] found that 500 ml/d consumption of two different orange juices belonging to 'Bahia' or 'Cara Cara' cultivars, significantly changed the gut microbiota composition in twenty-one healthy individuals. Interestingly, the authors observed that the two juices, characterised by different vitamin C content, flavanones and carbohydrates, affected the modulation of the microbiota profile differently. Changes in metabolome were also cultivar-specific[61]. In another study carried out in ten healthy young women that consumed 300 ml of commercial pasteurised orange juice for 2 months, orange juice positively modulated the composition and metabolic activity of gut microbiota, increasing the population of *Bifidobacterium* spp. and *Lactobacillus* spp.[62]. Changes in microbiota composition following

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flavonoid-rich orange juice (600 mg flavonoids/380 ml daily dose, for 8 weeks) were also linked to a potential improvement in depression status in young adults[63].

In conclusion, orange juice shows no adverse effect on body weight and other anthropometric markers, as supported by recent meta-analyses. It could lower systolic BP and improve endothelial function, notably due to the hesperidin content. It did not adversely affect the lipid profile and may help reduce high plasma TG concentrations. Similarly, it did not modify glycaemia and insulin sensitivity, neither could it improve the latter. The role of orange juice in oxidative stress and inflammation is not clear. Last, its effect on cognitive function and microbiota modulation showed interesting prospects, although these observations are still preliminary. Further studies should investigate the potential role of hesperidin and other bioactives in orange juices. Indeed, more attention should be paid on characterisation of the carotenoid and fibre content in orange juices. For instance, it has been reported that the bioavailability of β-cryptoxanthin is greater from pasteurised orange juice than from fresh oranges, while higher fibre amounts may limit carotenoid bioavailability[64]. To draw more robust conclusions, a detailed phytochemical profiling is needed, and future research must consider the numerous confounding factors that may condition the physiological response, from the orange juice characteristics to the drivers of the inter-individual variability both in the metabolism and the response (responders/non-responders) to phytochemicals[34,54].

Grapefruit, mandarin and lemon juice. In comparison to orange juice, only a few studies have addressed the impact of grapefruit, mandarin and lemon juices on human subject health (Table 2). Some works have investigated the potential interaction of grapefruit juice with medication pharmacokinetics, particularly calcium channel blockers as antihypertensive therapy, but these were not reported as they go beyond the aim of this review.

Habauzit *et al.* (2015)[65], in a 6-month randomised controlled crossover double-blind trial in forty-eight healthy postmenopausal women, found that 340 ml/d of either blonde grapefruit juice (626 mg/l of naringenin glycosides) or isoenergetic control drink matched for the macro- and micronutrients of the juice, but without naringenin glycosides, did not affect body weight and other anthropometric measures. Considering vascular function, no effect on BP and endothelial function (for example, FMD) was observed following grapefruit juice consumption. However, grapefruit flavanones significantly lowered arterial stiffness compared with the control drink[65]. This effect has been recently attributed to the ability of grapefruit juice flavanones to modulate the expression of genes regulating inflammation, cell interactions and vascular function[66]. Considering glucose metabolism, inflammatory biomarkers and oxidative stress, they were not affected by grapefruit juice[65]. A similar lack of effect on body composition, BP and glucose homeostasis was achieved by Silver *et al.* (2011)[67] on subjects with obesity, although higher increases in serum HDL-C concentrations in the grapefruit juice group relative to the grapefruit group were observed. Anyway, the evidence on grapefruit is still limited.

There is also a scarcity of available information on the health effects of mandarin or clementine juices in human subject settings. To date, just a few studies have been published. One dealt with children with obesity[68], where mandarin juice consumption (35 mg of vitamin C, 30 mg/l of low flavanone content, and 700 μg/l of carotenoids) within a 4-week hypoenergetic diet significantly decreased fasting insulin and HOMA-IR index when compared with those who were not supplemented. Treatment reduced some markers of oxidative stress (MDA and carbonyl groups) while increasing the level of circulating antioxidants (vitamin C, α-tocopherol and glutathione)[68]. Another intervention assessed the effect of β-cryptoxanthin-rich Satsuma mandarin juice supplementation (4 mg) in comparison to a β-cryptoxanthin-deprived Satsuma mandarin juice (0 mg) on pulse wave velocity[69]. A total of 117 participants completed this 12-week parallel intervention and, although serum β-cryptoxanthin concentration increased in the treatment group, there were no differences between the treatment and control groups. Nonetheless, supplementation of both juices led to decreases in brachial ankle pulse wave velocity (PWV) and the levels of oxidative stress biomarkers, reducing the cardiovascular risk[69]. Despite the lack of effect of β-cryptoxanthin in Satsuma mandarin juice at the cardiovascular level, a previous work showed that the 8-week intake of juice fortified with β-cryptoxanthin might have stimulatory effects on bone formation and inhibitory effects on bone resorption in humans and, in particular, in post-menopausal women[70].

Unlike orange, grapefruit and mandarin, lemon juice is not consumed alone, and there are no 100% lemon juices commercially available. Nevertheless, lemon juice can be used to prepare lemon-based drinks or to acidulate some other juices to create 100% juices, being a way to increase the level of some bioactive compounds in the final beverage[71,72]. Freitas *et al.* (2021)[73], in a randomised crossover trial, investigated the effect of drinking 250 ml lemon juice (50% lemon juice, 50% spring water), black tea or spring water (control) with 100 g of bread on glycaemia and subsequent energy intake. No beverage affected the energy intake, but results showed that lemon juice significantly delayed and reduced peak postprandial blood glucose concentrations compared with water. Authors suggested that lemon juice, which lowered the pH of the meal, slowed down starch digestion through premature inhibition of salivary α-amylase[73]. Therefore, lemon juice may help to control the glycaemic response, although further research is needed to confirm this aspect. In addition, the role of lemon flavanones should be explored in the light of the evidence collected for orange flavanones. Last but not least, a recent prospective randomised controlled open trial assessed the effects of fresh lemon juice supplementation (60 ml twice per day) to a standard diet on time to stone recurrence in 203 patients with recurrent idiopathic calcium oxalate nephrolithiasis[74]. Results suggested that lemon juice supplementation might prevent stone recurrence in patients with calcium-oxalate nephrolithiasis. Nevertheless, adherence to the treatment was an issue as it also increased the frequency of gastrointestinal disorders[74].

Apple juice

Apples provide good amounts of fibre, in particular pectin, and a variety of (poly)phenols. Juice processing, specifically clarification, notably reduces the fibre and pectin content. In addition,

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Table 2. Characteristics of some representative studies investigating the health effects of grapefruit, mandarin and lemon juices

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Grapefruit	RCT, OL, parallel, three-arm, 12 weeks	*n* = 68 (22 intervention), OB, 40 (SD 8) years	Restricted diet with 127 g juice	40 mg naringin	Water	↑ HDL-c; no changes in BP, fasting glucose, insulin, HOMA, and body composition	Silver *et al.*, 2011[67]
Grapefruit	RCT, DB, CO, 6 months	*n* = 48 (F), healthy, NW/OW, 58 (SD 4) years	340 ml/d	213 mg naringenin glycosides	Drink matched for the nutrients of the juice but without naringenin glycosides	↓ PWV; no changes in BW, other anthropometric measures, BP, FMD, FG, HOMA-IR, insulin, hs-CRP, ICAM-1, IL-6, vWF, FRAP	Habauzit *et al.*, 2015[65]
Mandarin (β-cryptoxanthin–rich juice)	Non-RCT, parallel, four-arm, 56 d	*n* = 90 (71 F, 36 menopausal women), heathy, 27–65 years	200 ml/d	β-cryptoxanthin–rich Satsuma mandarin juice (1·5, 3·0, or 6·0 mg/d)	Placebo	Juice fortified with β-cryptoxanthin has stimulatory effects on bone formation and inhibitory effects on bone resorption	Yamaguchi *et al.*, 2006[70]
Mandarin	RCT, OL, longitudinal, parallel, 4 weeks	*n* = 40 (23 F, 20 intervention), OB, 12 (SD 2) years	500 ml/d	hesperidin 10 mg, naringenin 5 mg	No juice supplementation	↓ fasting insulin, HOMA-IR, MDA, carbonyl groups; ↑ vitamin C, α-tocopherol, GSH	Codoñer-Franch *et al.*, 2010[68]
Mandarin (β-cryptoxanthin–rich juice)	RCT, DB, parallel, 12 weeks	*n* = 117 (45 F, 59 intervention), NW, 41 (SD 11) years	125 ml/d	β-cryptoxanthin–rich Satsuma mandarin juice (4 mg)	β-cryptoxanthin–deprived Satsuma mandarin juice (0 mg)	No differences between interventions. Both juices on time: ↓ brachial-ankle PWV, MDA-oxidised LDL, adiponectin; ↑ BMI, BP, FG, fasting insulin, HOMA-IR, GGT	Nakamura *et al.*, 2017[69]
Lemon	RT, CO, 3d	*n* = 18 (11 F), healthy, NW, 33 (SD 10) years	250 ml (50% lemon juice)		Spring water or tea	Delayed and reduced peak post-prandial blood glucose concentration compared with water	Freitas *et al.*, 2021[73]
Lemon	RCT, SB, OL, prospective	*n* = 158, patients with recurrent idiopathic calcium oxalate nephrolithiasis, NW/OW, 45 (SD 13) years	120 ml/d		No supplementation	Fresh lemon juice supplementation to a standard diet prevents stone recurrence in patients with calcium-oxalate nephrolithiasis; ↑ frequency of gastrointestinal disorders	Ruggenenti *et al.*, 2021[74]

Juices were 100% juice unless otherwise stated. Abbreviations: BMI, body mass index; BP, blood pressure; BW, body weight; CO, crossover; DB, double-blind; FG, fasting blood glucose; FMD, flow-mediated dilation; FRAP, ferric reducing ability of plasma; GGT, &x01B4;-glutamyl transpeptidase; GSH, glutathione; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity CRP; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6; MDA, malondialdehyde; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; vWF, von Willebrand factor; ↓, decreased level; ↑ increased level

the concentration of (poly)phenols varies considerably between the peel and flesh of the apple. The compounds most found in apple peel are chlorogenic acids, flavan-3-ols (catechin, epicatechin and proanthocyanidins), phloridzin and quercetin derivatives. While quercetin derivatives are found exclusively in apple peel, the other compounds are also in the apple flesh but at much lower concentrations, except for chlorogenic acids, which are higher in the flesh than in the peel[75]. Apple pomace has been widely associated with cardiometabolic health benefits[76], while the information on apple juice is relatively scarce considering the commercial importance of apple juices. A recent review has tried to bridge this gap[77] and some relevant articles are presented in Table 3.

Barth *et al.* (2012)[78], in a randomised parallel study, investigated the effect of a (poly)phenol-rich cloudy apple juice (total phenol content: 1070 mg/l) or an isoenergetic control drink (without (poly)phenols) on obesity-associated metabolic and endocrine parameters in males with obesity. After 4 weeks at 750 ml/d, cloudy apple juice had no significant effect on BMI and waist circumference, while it significantly reduced percent body fat compared with the control drink. This effect was related to the IL-6–174 G/C polymorphism as body fat reduction was detectable only in C/C carriers but not in G/C or G/G ones[78]. Genetic polymorphisms were considered key to the better understanding of the effect of cloudy apple juice on fat reduction; although, it was not related to other obesity-related parameters. In agreement with this study, a randomised five-arm crossover study reported no changes in body weight and waist-to-hip ratio in healthy individuals who followed a 4-week restricted diet supplemented with 500 ml/d of either cloudy or clear apple juice compared with whole apples (550 g/d), apple pomace (22 g/d) and the control (diet without supplementation)[79]. The cloudy and clear apple juice contained 290 and 216 mg polyphenols per litre, respectively, where chlorogenic acid, procyanidin dimers and epicatechin were the major compounds in both juices; in addition, the cloudy juice had a pectin content of 0·94 g/l while it was almost absent in clear juice[79]. Therefore, although the literature shows promising results coming from animal studies[80], the available information through human subject interventions with apple juice do not account for improvements in anthropometric parameters and body composition, except when specific genotypic differences are considered.

Considering cardiometabolic biomarkers, BP, TC and HDL-C were not affected by cloudy or clear apple juice in healthy subjects[79]. However, cloudy apple juice showed a similar – not significant ($p = 0{\cdot}064$) – trend to the whole apple and apple pomace in lowering TC and LDL-C, while these parameters increased with clear apple juice compared with whole apple and pomace, but not to the control[79]. Similarly, Barth *et al.* (2012)[78] found no changes in blood lipids upon cloudy apple juice consumption. Results from a meta-analysis of the effects of flavan-3-ol-containing products on blood lipids and including the two previous studies indicated that intake of apple products was associated with reduced TC and LDL-C levels[81]. Therefore, as the impact of apple juice on blood lipids is still contradictory, further research would be appreciated.

In the case of glucose–insulin homeostasis, cloudy or clear apple juice did not show any effect on glucose metabolism markers (including insulin), in line with the consumption of whole apples or apple pomace[79]. On the other hand, Soriano-Maldonado *et al.* (2014)[82] conducted a randomised crossover study in healthy adults for 4 weeks comparing two cloudy apple juices: a vitamin C-rich juice (vitamin C and total polyphenol content: 60 and 510 mg/l, respectively) and a polyphenol-rich juice (22 and 993 mg/l, respectively). An increase in insulin and HOMA index was observed after polyphenol-rich cloudy apple juice consumption but not in the vitamin C-rich cloudy apple juice group. Glucose and blood lipids did not change between treatments[82].

Considering inflammatory markers, no significant changes were found in a panel of systemic and vascular inflammation markers and adipokines after cloudy apple juice consumption by individuals with obesity[78]. Apple consumption, regardless of form (whole, pomace, clear or cloudy juice), did not change high-sensitivity CRP (hs-CRP) levels in healthy volunteers[79]. The same results were reported by Soriano-Maldonado *et al.* (2014)[82], where the vitamin C-rich or polyphenol-rich cloudy apple juice did not change inflammation-related parameters compared to the baseline. Examining biomarkers of oxidative stress, clear and cloudy apple juices did not modify the antioxidant status with respect to the control in healthy individuals[79]. These results were in line with the data collected for the polyphenol-rich cloudy apple juice compared to the vitamin C-rich one, as no modifications in plasma antioxidant activity were registered[82]. On the contrary, antioxidant activity significantly increased after vitamin C-rich juice, but this increase was not related to the plasma vitamin C levels. In addition, consuming the polyphenol-rich juice reduced total glutathione levels in peripheral blood mononuclear cells[82].

A thorough acute intervention study was conducted to assess the effect of fructose from fruit sources in the increase in uric acid concentration, as it is well known that the intake of large amounts of fructose raises circulating urate[83]. Participants ingested two servings (small or large) of apple segments and apple juice, or a glucose and a fructose control beverage. Plasma uric acid levels increased after consumption of all fructose-containing treatments, without differences between apple segments and juices[83]. More attention should be paid to this point, as hyperuricemia (high levels of uric acid) represents the main risk factor for gout, the most common inflammatory form of arthritis in men[84].

Finally, no changes in microbiota composition were observed after consumption of apple juice, clear or cloudy, by healthy volunteers for 4 weeks[79]. Similar results were achieved after cloudy apple juice intake by patients with T2D for the same time period: although small decreases were found in numbers of Enterococci and Firmicutes, the overall microbiota profile did not change when compared with the isoenergetic control beverage[85].

Few high-quality studies have been conducted on apple juice despite its market share. No significant effects of apple juice on human subject health have been discovered. Apple juice only showed a moderate effect in reducing body fat depending on gene polymorphisms. This is a point worth mentioning as inter-individual variability may be key to better evaluating the beneficial effects of apple juice. Indeed, as a notable

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Table 3. Characteristics of some representative studies investigating the health effects of 100% apple juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Apple (cloudy)	RCT, blinded, parallel, 4 weeks	$n = 68$ (M, 38 intervention), OB, mean age 49 years	750 ml/d	802·5 mg total phenols	Isoenergetic control drink without (poly) phenols	↓ body fat % (in C/C variants of IL-6-174 G/C polymorphism); no changes in BMI and WC, adipokines, hs-CRP, IL-6, TNF-α, ICAM-1, VCAM-1, TC, LDL-c, and HDL-c, ↑ plasma TAG levels in both groups	Barth *et al.*, 2012[78]
Apple (cloudy (CDJ) clear (CLJ))	RT, SB, CO, 4 weeks	$n = 23$ (14 F), healthy, NW, 36 (SD 18) years	Restricted diet with 500 ml/d juice	total (poly)phenols: CDJ: 145 mg; CLJ: 108 mg	Restricted diet without supplementation	No changes in BW and WHR, BP, hs-CRP, insulin, IGF1 and IGFBP3, TAG and HDL-c; CDJ trend in lowering TC and LDL-c; CLJ trend in increasing these parameters	Ravn-Haren *et al.*, 2013[79]
Apple (vitamin C-rich (VCR) or (poly)phenol-rich (PR) cloudy apple juice)	RT, CO, 4 weeks	$n = 20$ (12 F), healthy, NW, 24 (SD 2) years	500 ml/d	PR: 11 mg vitamin C, 496·5 mg epicatechin eq.; VCR: 30 mg vitamin C, 255 mg epicatechin eq.	Comparison of both interventions	No changes in inflammation-related parameters; PR: ↑ insulin and HOMA, ↓ GSH levels in PBMCs; VCR: ↑ FRAP, ↓ trend in ICAM-1 and TC	Soriano-Maldonado *et al.*, 2014[82]
Apple (cloudy)	RCT, DB, parallel, 4 weeks	$n = 10$ (M, 5 intervention), patients with T2D, NW, 57–71 years	750 ml/d		Isoenergetic control drink without (poly) phenols	↓ Enterococci and Firmicutes, the overall microbiota profile did not change with respect to the control	Cho *et al.*, 2015[85]
Apple	RCT, CO, single-dose	$n = 51$ (15 control, 19 apple, 17 apple juice), healthy, NW/OW, 18–65 years	small (170 ml) and large (340 ml) servings		Positive control (fructose beverage), negative control (glucose beverage) and apple segments	↑ plasma uric acid after consumption of all fructose-containing treatments	White *et al.*, 2018[83]

Juices were 100% juice unless otherwise stated. Abbreviations: BP, blood pressure; BMI, body mass index; BW, body weight; CLJ, clear apple juice; CO, crossover; DB, double-blind; F, female; FRAP, ferric reducing ability of plasma; GSH, glutathione; hs-CRP, high-sensitivity CRP; ICAM-1, intercellular adhesion molecule 1; IGF1, insuline-like growth factor; IGFBC3, Insulin-like growth factor-binding protein 3; IL-6, interleukin-6; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; M, male; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); PBMCs, peripheral blood mononuclear cell; PR, (poly)phenol-rich juice; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; T2D, type 2 diabetes; TAG, triglycerides; TC, total cholesterol; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule; VCR, vitamin C-rich juice; WC, waist circumference; WHR, waist-to-hip ratio; ↓, decreased level; ↑ increased level

inter-individual variability has been reported in the metabolism of apple flavan-3-ols[86], leading to different profiles of biologically active metabolites, individual profiles of phenolic metabolites, as well as genotypic differences, should be investigated in further interventions studies with apple juice. Further efforts to assess the impact of compositional differences would favour further mechanistic research.

Grape juice

Red (or purple) and white grape juices from *Vitis vinifera* cultivars are predominant in the market, and most of the scientific literature on the health properties of grape juices is related to these two juices. Nevertheless, other purple grape juices made from Concord (*V. labrusca*) and Muscadine (*V. rotundifolia*) cultivars have received much attention in recent years. Grapes are typically good sources of (poly)phenols, being rich in flavan-3-ols (both catechins and proanthocyanidins), flavonols, phenolic acids, stilbenes and, in the case of red/purple cultivars, anthocyanins. The cultivar used for juice production substantially influences the phenolic profile and content, as well as environmental factors and cultivation methods[87]. As a general indication, white grape juice shows higher contents in phenolic acids and resveratrol and lower contents in flavan-3-ols, flavonols, and anthocyanins[88]. Although their health effects may change notably due to the grape type (Table 4), all the grape juices are discussed together to provide a global overview and since the evidence in humans is not so broad as for grape wines.

Zuanazzi *et al.* (2019)[89] investigated the health effects of 100% white grape juice from *V. labrusca*, characterised by a total phenolic content of 267·9 mg/l, where caffeic acid (13·9 mg/l) and (+)-catechin (11·3 mg/l) were the most abundant compounds. Over a 30-d intervention at 7 ml/kg/d (490 ml/d for a 70-kg woman), white grape juice supplementation to twenty-five non-smoking women (eleven eutrophic and fourteen who were overweight or obese) reduced BMI and waist and abdominal circumference. Nevertheless, the lack of a control arm precludes solid conclusions. Indeed, in contrast to this work, Dohadwala *et al.* (2010)[90] reported no change in body weight following consumption of 7 ml/kg/d of 100% Concord grape juice (total phenols: 1970 mg/l) or placebo beverage for 8 weeks in sixty-four otherwise healthy patients (with prehypertension and with stage one hypertension, but taking no anti-hypertensive medications).

Considering vascular function, BP did not change after consumption of white (Zuanazzi *et al.* 2019)[89] or Concord grape juice[90]. Similarly, no effect on BP was observed after 12-week daily consumption of 355 ml Concord grape juice (total phenols: 2188 mg/l, 21% anthocyanins and 43% proanthocyanidins) in healthy middle-aged working mothers compared with a placebo[91]. Nevertheless, some works have reported a positive effect of grape juice consumption on both systolic and diastolic BP in healthy individuals (Concord grape juice, 5·5 ml/kg/d, 8 weeks)[92], hypertensive men (Concord grape juice, 5·5 ml/kg/d, 8 weeks)[93] and hypercholesterolemic patients (purple grape juice, 500 ml/d, 2 weeks)[94], so that a beneficial effect of grape juice on BP cannot be ruled out. While BP effects are contradictory, the evidence on arterial function assessed using FMD seems more promising. Coimbra *et al.* (hypercholesteraemic patients)[94], Stein *et al.* (coronary patients, Concord grape juice, 8 ml/kg/d, 2 weeks)[95], Chou *et al.* (coronary patients, Concord grape juice, 4 and 8 ml/kg/d, 8 weeks)[96], and Siasos *et al.* (healthy smokers, Concord grape juice, 7 ml/kg/d, 2 weeks; juice phenolics: flavan-3-ols 434 μmol/l, anthocyanins 296 μmol/l, hydroxycinnamates 162 μmol/l, and flavonols 76 μmol/l)[97] demonstrated that short-term ingestion of purple/Concord grape juice could improve FMD in different population settings.

Regarding lipid profile, white[89], purple[94], and Concord[96] grape juice did not affect blood lipids, except for a 16% increase in HDL-C in women consuming white grape juice for 30 d[89]. In the case of glucose metabolism, grape juice supplementation did not modify glycaemia or insulin levels[89,90], unless for a minimal but significant reduction in glucose levels after 8-week Concord grape juice consumption[90]. Taking into account other cardiometabolic biomarkers, no major changes in blood markers of inflammation and platelet activity are reported in the literature.

Examining biomarkers of oxidative stress, Zuanazzi *et al.* (2019)[89] reported no change in nitric oxide levels or markers of oxidative damage following consumption of white grape juice in women. No change in lipid peroxidation was observed following a single dose of 10 ml/kg of 100% purple grape juice in recreational runners[98]. Differently, O'Byrne *et al.* (2002)[99] found that consumption of 10 ml/kg/d 100% Concord grape juice for 2 weeks increased serum antioxidant capacity and protected LDL against oxidation in thirty-two healthy adults, to an extent similar to that obtained with 268 mg/d α-tocopherol, while decreased native plasma protein oxidation significantly more than α-tocopherol. A reduction in LDL susceptibility to oxidation was also reported by Stein *et al.*[95]. Last, protective effects on lymphocyte DNA damage have also been reported[92].

The association between grape juice and cognitive function has been widely studied. A recent critical review of epidemiological and randomised-controlled human subject trials regarding the role of grapes and their derivatives in modulating cognitive decline was conducted by Restani *et al.* (2021)[100]. All reviewed studies investigating the effect of grape juice consumption reported improved cognitive function in the intervention group versus the control group after both single dose and long-term (up to 6 months) supplementation. Remarkably, the most encouraging results included reaction times, verbal skills, degree of orientation, learning, and memory. Cognitive improvement was observed in both healthy young adults (21·05 ± 0·89 years)[101], healthy middle-aged women (40–50 years)[91], and older adults with mild cognitive decline (78·2; SD 5·0 years)[102]. Restani *et al.* (2021)[100] concluded that Concord and purple grape juice consumption (200–500 ml/d) was generally associated with improved cognitive performance. Similar conclusions have been presented in a recent systematic review on the topic[103].

Grape juice is considered a potentially ergogenic food for sports performance. De Lima Tavares Toscano *et al.* (2020)[104] demonstrated that drinking a single dose of 100% purple grape juice (10 ml/kg, total phenols: 3106 mg/l) increased run time to exhaustion by almost 19% in fourteen male recreational runners. In a previous study, Toscano *et al.* (2015)[105] also found a 15% increased physical performance following 28-d supplementation with a similar juice (10 ml/kg/d, same grape cultivar).

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Table 4. Characteristics of some representative studies investigating the health effects of 100% grape (white, red/purple and Concord) juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Grape (Concord grape)	RT, prospective single-centre, 2 weeks	$n = 15$ (3 F), CAD patients, 63 (SD 13) years	8 ml/kg/d		No control nor placebo	↓ LDL susceptibility to oxidation; improved FMD	Stein *et al.*, 1999[95]
Grape (Concord grape)	RT, prospective single-centre, 4 weeks	$n = 22$ (4 F, 11 high GJ dose, 11 low GJ dose), with CAD, 64 (SD 10) years	4 ml/kg/d and 8 ml/kg/twice daily		Comparison of both interventions	↑ FMD; no changes in blood lipids, glucose, insulin levels	Chou *et al.*, 2001[96]
Grape (Concord grape or capsules of α-tocopherol)	RT, blinded, 2 weeks	$n = 32$ (19 F, 15 intervention), healthy, NW/OW/OB, 28 (SD 5) years	10 ml/kg/d	560 mg phenolic equivalents per litre of flavonoid content	Comparison of both interventions	↑ serum antioxidant capacity and protected LDL against oxidation, ↓ native plasma protein oxidation	O'Byrne *et al.*, 2002[99]
Grape (Concord grape)	RCT, DB, 8 weeks	$n = 40$ (M, 21 intervention with GJ), hypertensive not treated, OW, 45 (SD 2) years (GJ)	5·5 ml/kg/d	2109 mg/l phenol content	Placebo drink without (poly) phenols	↓ SBP and DBP	Park *et al.*, 2004[93]
Grape (purple grape)	RCT, CO, 2 weeks	$n = 16$ (8 F) + 24 external controls, hypercholesterolemic individuals, NW/OW, 52 (SD 8) years	500 ml/d		Red wine 250 ml/d	↓ ICAM-1; ↑ FMD; no changes in BA diameter, NTGD, Lp(a), Apo A, Apo B, VCAM-1	Coimbra *et al.*, 2005[94]
Grape (Concord grape)	RCT, DB, 8 weeks	$n = 40$ (M, 21 intervention with GJ), not-treated mild-hypertensive men, OW, 45 (SD 2) years (GJ)	5·5 ml/kg/d	2108 mg/l phenol content	Placebo drink without (poly) phenols	↓ SBP and DBP, lymphocyte DNA damage; no effects on plasma lipids and TRAP	Park *et al.*, 2009[92]
Grape (Concord grape)	RCT, DB, CO, 8 weeks	$n = 64$ (20 F), with prehypertension and stage 1 hypertension taking no medication, OW, 43 (SD 12) years	7 ml/kg/d	473 mg/8 oz total (poly)phenols	Colour/flavour/energy-matched beverage without (poly)phenolics	↓ glycaemia; no changes in BW, BP, blood markers of inflammation and platelet activity, HDL-c, TC, LDL-c, TAG, insulin	Dohadwala *et al.*, 2010[90]
Grape (Concord grape)	RT, DB, 16 weeks	$n = 21$ (10 F), with mild age-related cognitive impairment, OW/OB, 77 (SD 6) years	6·3–7·8 ml/kg/d	2091 mg GAE/l total (poly)phenolics, 425 mg/l anthocyanin, 888 mg/l proanthocyanidins	Colour/flavour/energy-matched beverage without (poly)phenolic compounds	Improved cognitive function	Krikorian *et al.*, 2012[102]
Grape (Concord grape)	RCT, DB, CO, 2 weeks	$n = 26$ (16 F), healthy smokers, NW/OW, 26 (SD 5) years	7 ml/kg/d	473 mg/240 ml total (poly)phenols, flavan-3-ols 434 μmol/l, anthocyanins 296 μmol/l, hydroxycinnamates 162 μmol/l, and flavonols 76 μmol/l	Grapefruit juice without (poly) phenol	Improved FMD and PWV; no changes in body weight, total cholesterol, triglycerides, LDL-c, serum glucose, and SBP, DBP	Siasos *et al.*, 2014[97]
Grape (purple grape)	RT, 28 d	$n = 28$ (6 F, 15 intervention), NW/OW, 40 (SD 8) years	10 ml/kg/d		Isoenergetic, isoglycemic beverage (artificial grape flavour)	↑ run time to exhaustion (15% increase)	Toscano *et al.*, 2015[105]

Table 4. (*Continued*)

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Grape (Concord grape)	RCT, DB, CO, 12 weeks	*n* = 25 (F, 25 completed the first arm, 19 completed both arms, 10 completed driving performance task), healthy, NW/OW, 43 (SD 1) years	355 ml/d	777 mg GAE total (poly) phenolics	Colour/flavour/energy-matched beverage, without (poly)phenolic compounds	No effect on BP; improvement in cognitive function, better immediate spatial memory and driving performance	Lamport *et al.*, 2016[91]
Grape (purple grape)	RCT, DB, counterbalanced-CO, single-dose	*n* = 20 (13 F), healthy, 21 (SD 1) years	230 ml (200 ml purple grape juice plus 30 ml of Schweppes™ blackcurrant flavour cordial)	1504 ug GAE/ml total phenolics, 138 mg/l anthocyanin content	Beverage with 200 ml white grape juice plus 10 ml blackcurrant flavour cordial and 20 ml cold water, only a small concentration of phenolic compounds	Improved cognitive function	Haskell-Ramsay *et al.*, 2017[101]
Grape	RCT, DB, parallel, 4 weeks	*n* = 26 (17 F, 14 intervention), hypertensive, NW/OW, 53 (SD 2) years	150 ml for men, 100 ml for women		Control drink	↓ BP at rest; improved PEH	Neto *et al.*, 2017[107]
Grape (JG, exercise group and juice + exercise group)	RT, prospective, parallel, 12 weeks	*n* = 45 (12 JG), hypertensive, NW/OW, 69 (SD 5) years	200 ml/d		Control drink	↓ SBP, DBP and HR	Leal *et al.*, 2019[106]
Grape (white grape)	30 d	*n* = 25 (F), NW/OW/OB, 50–67 years	7 ml/kg/d	267·9 mg GAE/l total phenolic, 13·9 mg/l caffeic acid, 11·3 mg/l (+) catechin	No control	↓ BMI, WC and AC; ↑ HDL-c; no changes in BP, TC, LDL-c, TAG, glycemia, insulin, NO, SOD	Zuanazzi *et al.*, 2019[89]
Grape (purple grape)	RCT, DB, CO, single-dose	*n* = 14 (M), recreational runners, NW/OW, 39 (SD 9) years	10 ml/kg/d	3107 mg/l total phenolics, 84 mg/l phenolic acids	Colour/flavour/energy-matched beverage, total (poly)phenol content: 940 mg/l	No change in lipid peroxidation; ↑ run time to exhaustion (18·7% increase)	de Lima Tavares Toscano *et al.*, 2020[98]

Juices were 100% juice unless otherwise stated. Abbreviations: AC, abdominal circumference; Apo A, apolipoprotein A; Apo B, apolipoprotein B; BA, brachial artery; BP, blood pressure; CAD, coronary artery disease; CO, crossover; DB, double-blind; DBP, diastolic blood pressure; F, female; FMD, flow-mediated dilation; GAE, gallic acid equivalent; GJ, grape juice; HDL-c, HDL-cholesterol; HR, heart rate; ICAM-1, intercellular adhesion molecule 1; JG, juice group; LDL-c, LDL-cholesterol; Lp(a), lipoprotein (a); M, male; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); NO, nitric oxide; NTGD, nitroglycerin-mediated vasodilation; PEH, post-exercise hypotension; PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; SOD, superoxide dismutase; TAG, triglycerides; TC, total cholesterol; TRAP, plasma total radical-trapping antioxidant potential; VCAM-1, vascular cell adhesion molecule; WC, waist circumference; ↓, decreased level; ↑ increased level

Authors also reported some benefits in inflammatory markers in these runners. Last, contrary to the evidence on BP upon chronic consumption of grape juice by non-sport individuals, grape juice supplementation may also help BP management after aerobic exercise[110, 111].

In conclusion, homogeneous results were observed for vascular and cognitive function, showing moderate improvements after red or Concord grape juice consumption. Some benefits in specific markers of oxidative stress are also well documented. The benefits on exercise conditions are of interest, but they cannot be extrapolated to all physical activity contexts. More discordant results for other outcomes were achieved. In general, the evidence to date is quite limited, considering the importance of this juice at the market level. Although some health benefits might be similar to those investigated for grape wines[108], further high-quality intervention studies are needed. In addition, emphasis should also be paid to white grape juice, as the evidence is quite limited. Comparisons among different classes of grape juice (white, red or Concord) may help to better understand the potential role of grape juices in disease prevention and what are the responsible compounds backing the physiological effects observed.

Pomegranate juice

Regarding main bioactive compounds, pomegranate juice contains anthocyanins, ellagitannins and ellagic acid derivatives, among other phenolics[109]. Although the edible part of pomegranate (arils) contains almost exclusively anthocyanins, commercial pomegranate juices also present high amounts of ellagitannins and ellagic acid coming from the peel and inner parts (mesocarp) as a consequence of the juicing process[110]. In addition, besides cultivars, agronomical and harvest conditions, processing may pretty much alter the phytochemical composition of pomegranate juices[72,111,112,113]. Several works have reviewed the evidence behind the potential health benefits of pomegranate juice[112,113,114,115,116], so here only a brief overview is presented. Of note, many studies have focused on the role of pomegranate juice in patients rather than in the general population (Table 5).

Moazzen & Alizadeh (2017)[118], in a double-blinded randomised crossover controlled trial, investigated the effects of 1-week supplementation with 500 ml/d of pomegranate juice on cardiovascular risk factors in thirty patients with metabolic syndrome. The juice contained 100 mg/l of anthocyanins, while the composition in ellagitannins was not reported. Results showed a reduction in systolic and diastolic BP in the intervention group compared with placebo[117]. Similarly, after 6 weeks at 200 ml/d of pomegranate juice (total polyphenols: 2125 mg/l), a significantly reduced systolic and diastolic BP was observed in sixty patients with T2D in comparison with the control group (no juice supplementation)[119]. In another double-blind randomised controlled study in 101 haemodialysis patients, Shema-Didi *et al.* (2014)[120] found that systolic BP decreased with respect to placebo after one year of consuming 100 ml pomegranate juice (total polyphenols: about 1190 mg/l) three times per week. However, improvements in BP or PWV were not observed in fifty-one healthy subjects (middle-aged normotensive adults) consuming 330 ml/d of pomegranate juice (total polyphenols: 3162 mg/l; potassium: 1711 mg/l) for 4 weeks[121]. Cumulative evidence indicates that pomegranate juice consumption may lead to consistent benefits on BP, as stated by a SRMA of eight RCT[122]. Nevertheless, these BP improvements happen mainly in hypertensive patients, regardless of the presence/absence of antihypertensive medication, that may also suffer from other cardiometabolic diseases. Further information on healthy subjects or individuals at risk of hypertension may help to draw preventive strategies taking pomegranate juice into account.

Evaluating the effect of pomegranate juice on lipid profile, 500 ml/d supplementation for 1-week increased blood TG and very low-density lipoprotein cholesterol (VLDL-C) levels in individuals with metabolic syndrome, as opposed to the placebo, whereas TC, HDL-C, and LDL-C did not change[117]. Authors hypothesised that this negative effect could disappear in a long-term supplementation so, rather than as a negative outcome, this data should be regarded as part of the inconclusive evidence on the role of pomegranate juice in the lipid profile. For instance, contrary to the previous work, TC, LDL-C, HDL-C and TG concentrations were not different compared with the control group after 6-week pomegranate juice consumption in patients with T2D[119]. Shema-Didi *et al.* (2014)[120] found that 1-year pomegranate juice consumption, compared with the placebo, improved TG and HDL-C levels in haemodialysis patients, with a greater effect in subjects with hypertension, low HDL-C and high blood TGs (higher cardiovascular risk)[120]. Overall, it seems that pomegranate juice is not able to modify the lipid profile consistently. Differences may be due to the heterogeneous evidence available, as well as due to the different physiological responses of individuals metabolising differently pomegranate ellagitannins[115].

In the case of glucose–insulin metabolism, pomegranate juice did not change fasting blood glucose, insulin and HOMA-IR in patients with metabolic syndrome on 1 week of consumption[117]. Similarly, no adverse effect on fasting blood glucose level was found after 6 weeks at 200 ml/d[123] and 12 weeks at 250 ml/d[124] in T2D patients. In the case of acute responses, Kerimi *et al.* (2017)[125] found that 200 ml pomegranate juice (71·5 mg punicalin, 12·4 mg punicalagin, 4·8 mg ellagic acid and 2·8 mg ellagic acid hexose), consumed with approximately 109 g of white bread (50 g available carbohydrate), significantly attenuated the post-prandial glycaemic response in healthy subjects, compared with a control solution containing the equivalent amount of sugars. These authors proposed that the effect was primarily due to the ability of punicalagin to inhibit human subject salivary α-amylase, whereas microbial metabolites of pomegranate ellagitannins (namely urolithins) may also modulate glucose metabolism after the acute post-prandial period. Interestingly, a pomegranate polyphenol-rich extract was ineffective on glycaemic response, and the beneficial effects were only observed after juice intake. So, while pomegranate juice does not seem able to modify glucose metabolism in chronic conditions, it may be able to reduce acute post-prandial glycemic response in healthy subjects[125].

In the context of inflammation, Moazzen and Alizadeh (2017)[118] found that pomegranate juice (500 ml/d, 1 week), but not the placebo, decreased hs-CRP levels in patients with

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Table 5. Characteristics of some representative studies investigating the health effects of 100% pomegranate juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Pomegranate	RCT, OL, parallel, 4 weeks	$n = 48$ (32 F, 24 intervention group), healthy, OW, 38 (SD 1) years	330 ml/d	6·14 mmol total phenol	Commercial lemonade drink matched for energy and carbohydrate content	↓ SBP and DBP; no effect on PWV	Lynn *et al.*, 2012[121]
Pomegranate	RCT, DB, 1 year (3 times per week)	$n = 101$ (66 intervention), chronic hemodialysis patients, 66 (SD 12) years	100 ml/time	0·7 mmol (poly)phenols	Colour/flavour-matched juice without (poly) phenols	↓ SBP, PP, TAG; ↑ HDL-c; no changes in TC, LDL-c, DBP	Shema-Didi *et al.*, 2014[120]
Pomegranate	RCT, DB, 12 weeks	$n = 44$ (21 F, 22 intervention), with T2D, OW/OB, 56 (SD 7) years	250 ml/d	486 mg GAE total phenol, 86 mg total flavonoid	Colour/flavour/energy-matched beverage without (poly)phenols	↑ TAC; ↓ MDA; no effect on FG, pentosidine and CML	Sohrab *et al.*, 2015[124]
Pomegranate	RCT, DB, CO, acute, six-arm	$n = 16$, healthy, NW/OW, 31 (SD 5) years	200 ml	71·5 mg punicalin, 12·4 mg punicalagin, 4·8 mg ellagic acid, 2·8 mg ellagic acid hexose	Water with balancing sugars	Attenuated the post-prandial glycemic response due to the consumption of bread	Kerimi *et al.*, 2017[125]
Pomegranate	RCT, DB, CO, 1 week	$n = 30$ patients with MetS, (60% female), 52 (SD 10) years	500 ml/d	50 mg anthocyanins, 142 mg total flavonoids	Isoenergetic control drink	↓ SBP and DBP, hs-CRP; ↑ TAG and VLDL; no changes in TC, HDL-c, and LDL-c, FG, insulin, HOMA-IR	Moazzen & Alizadeh, 2017[117]
Pomegranate	RT, SB, 6 weeks	$n = 60$ (30 F, 30 intervention), with T2D, NW/OW/OB, 55 (SD 8) years	200 ml/d	425 mg (poly)phenols and 77 mg flavonoids	No intervention	↓ ox-LDL-c and anti-oxidised LDL antibodies; ↑ TAC and PON1; no adverse effect on FG level	Sohrab *et al.*, 2017[123]
Pomegranate	RT, SB, 6 weeks	$n = 60$ (30 F, 30 intervention), with T2D, NW/OW/OB, 55 (SD 8) years	200 ml/d	425 mg (poly)phenol	No intervention	↓ SBP and DBP; no changes in TC, TAG, LDL-c and HDL-c	Sohrab *et al.*, 2019[119]
Pomegranate	RCT, DB, parallel, 12 months	$n = 200$ (98 intervention group), with mild cognitive impairment, NW/OW/OB, 61 (SD 7) years	236·5 ml/d	368 mg punicalagins, 93 mg anthocyanins, 29 mg ellagic acid, 98 mg other tannins	Colour/flavour/energy-matched beverage without pomegranate (poly)phenols	No change in the ability to learn visual information	Siddarth *et al.*, 2020[128]

Juices were 100% juice unless otherwise stated. Abbreviations: CML, carboxy methyl lysine; CO, crossover; DB, double-blind; DBP, diastolic blood pressure; F, female; FG, fasting blood glucose; HDL-c, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity CRP; LDL-c, LDL-cholesterol; M, male; MDA, malondialdehyde; MetS, metabolic syndrome; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); ox-LDL, oxidised-LDL; PON1, paraoxonase-1; PP, pulse blood pressure; PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; T2D, type 2 diabetes; TAC, total antioxidant capacity; TAG, triglycerides; TC, total cholesterol; VLDL, very low density lipoproteins; ↓, decreased level; ↑ increased level

metabolic syndrome. However, when pooling evidence, a meta-analysis of five RCT did not indicate a significant effect of pomegranate juice in lowering plasma CRP levels[126]. Similarly, a recent SRMA of six RCT showed no significant effect of pomegranate juice on vascular adhesion factors, intercellular adhesion molecule 1 (ICAM-1), VCAM-1 and E-selectin compared with the control group, but a significant effect in reduction of IL-6[127].

Examining biomarkers of oxidative stress, the information is not so robust, but still promising. For instance, Sohrab *et al.* (2017)[123] found that consumption of 200 ml/d of pomegranate juice for 6 weeks significantly decreased oxidised LDL (ox-LDL) and anti-oxidised LDL antibodies, as well as increased total serum antioxidant capacity and arylesterase activity of paraoxonase-1 (PON-1) in T2D patients in comparison with the control group. An increase in total antioxidant capacity in diabetic patients had already been observed in a previous study[124]; however, reductions in any biomarkers of oxidative stress were not reported. Detailed information on the potential antioxidant effects of pomegranate juice, particularly in the context of LDL oxidation, is broadly discussed in some comprehensive reviews[112,115,116].

Taking into account health outcomes beyond cardiometabolic diseases, some information has been published with regard to memory and exercise performance. In a recent randomised double-blind placebo-controlled study, Siddarth *et al.* (2020)[128] investigated the memory effects of pomegranate juice in non-demented middle-aged and older adults. The intervention group did not show any change in the ability to learn visual information after daily consumption of 236 ml (8 oz.) of pomegranate juice (368 mg punicalagin, 93 mg anthocyanins, 29 mg ellagic acid and 98 mg other tannins) for 12 months, whereas the placebo group showed a significant decline. Other visual and verbal memory measures were not significantly different between groups. On the other hand, pomegranate juice has also been evaluated for its effect on exercise performance and post-exercise recovery. Ammar *et al.* (2018)[129], in a systematic review of eleven studies, nine on pomegranate juice and two on pomegranate extract, concluded that pomegranate could enhance exercise performance and expedite recovery from intensive exercise in healthy adults. However, positive effects were more likely when pomegranate juice contained >1·4 g/l total (poly)phenols, when it was consumed at least 60 min before exercise, and when large muscle mass exercise was engaged.

In conclusion, pomegranate juice may significantly improve BP and, to a limited extent, post-prandial glycaemic response, markers of oxidative stress, some cognitive markers and exercise performance. Further well-designed experiments are needed to confirm these insights[115]. Attention should be paid to the accurate characterisation of the phytochemical profile (most of the studies present a scarce characterisation of the juice bioactives) and the inter-individual variability in the metabolism of their bioactive compounds (the existence of diverse metabolic phenotypes in the metabolism of ellagitannins is well-known). Of note, while ellagitannins, in particular punicalagins, have attracted much attention in nutrition research, the amount of anthocyanins in some pomegranate juices may also play a role in their beneficial effect, and they should be considered[112,116].

Berry juices

Berries are a broad family of species including cranberries, blueberries, strawberries, raspberries, blackberries, chokeberries, blackcurrants, elderberries and bilberries, among others. They have attracted considerable attention owing to their potential benefits to human subject health[130]. Besides vitamins, minerals, and fibre, they present high amounts of different bioactives, in particular (poly)phenols. Berries are rich in flavonoids, such as coloured anthocyanins, flavonols, and flavan-3-ols (both catechins and proanthocyanidins), phenolic acids (both hydroxybenzoic and hydroxycinnamic acids) and hydrolysable tannins such as ellagitannins. Their phenolic composition depends on the botanical species, cultivar, growing location, environmental and growing conditions, ripeness stage, time of harvest, and subsequent storage conditions and processing methods[131]. To date, most of the evidence on the health effects of berries comes from dietary interventions considering whole fruits or extracts, while the insights derived from dietary interventions with berry juices are scarce. This review will focus on major berry juices such as cranberry and chokeberry, but will also consider other interesting outcomes associated with other berry juices.

Cranberry juice. Cranberries (*Vaccinium macrocarpon*) have been widely associated with the prevention of urinary tract infections and cardiometabolic diseases. Their beneficial effects have been associated with their unique phenolic profile, rich in anthocyanins, proanthocyanidins (both A- and B-type), flavonols and hydroxycinnamic acids. However, evidence is inconclusive and further research is needed[132]. The following lines will provide an overview of the state-of-the-art, taking into account, when possible, 100% cranberry juices, although most of the evidence is provided for beverages prepared with cranberry juice concentrate (Table 6). Cranberry beverages prepared with powders/extracts were not considered.

Regarding anthropometric parameters, the information available is quite limited. Javid *et al.* (2017)[133] indicated that daily supplementation of 400 ml cranberry juice (230 mg/l vitamin C, 40 mg/l anthocyanins and 535 mg/l proanthocyanidins, 13 g/l fructose, 4 g/l glucose and 2 g/l sucrose) for 8 weeks in diabetic patients with periodontal disease did not condition BMI or waist circumference. Similarly, 480 ml/d of low-calorie cranberry beverage (27% cranberry juice, 250 mg/l vitamin C, 52 mg/l anthocyanins, 496 mg/l proanthocyanidins, 20 g/l fructose, 8 g/l glucose, 0·4 g/l sucrose) for 8 weeks did not significantly affect waist circumference in women with metabolic syndrome[135].

The former study also assessed the effect of juice supplementation on BP, but no significant improvements following cranberry or placebo beverage were observed[135]. Conversely, Novotny *et al.* (2015)[136] found a reduction in diastolic BP in healthy adults (predominantly subjects who were overweight/obese) after 8 weeks at 480 ml/d of low-calorie cranberry juice (its composition was almost identical to that previously reported for Basu *et al.*, 2011, also for sugar content)[135] compared with the placebo beverage. Nevertheless, pooled evidence from a recent meta-analysis indicated that cranberry juice could not

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Table 6. Characteristics of some representative studies investigating the health effects of cranberry juices

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Cranberry (low-calorie beverage)	RCT, DB, 8 weeks	$n=31$ (F, 15 intervention), with features of MetS, OB, 52 (SD 8) years	480 ml/d	458 mg phenolic compounds, 238 mg proanthocyanidins, 25 mg anthocyanins	Cranberry-flavoured beverage without (poly)phenol	No changes in WC, BP, hs-CRP, IL-6, TAG, TC, LDL-c, VLDL, HDL-c, glucose; ↑ plasma antioxidant capacity; ↓ ox-LDL and MDA	Basu *et al.*, 2011[135]
Cranberry (54% cranberry juice)	RCT, DB, CO, 4 weeks	$n=44$, patients with stable coronary artery disease, OW/OB, 61 (SD 11) years	480 ml/d	835 mg total phenolics, 94 mg anthocyanins	Isoenergetic control drink without (poly) phenols	↓ PWV	Dohadwala *et al.*, 2011[142]
Cranberry (27% cranberry juice)	Multi-centre, RCT, DB, three-arm, median of 168 d	$n=176$ (F, 120 intervention), with a history of ≥1 UTI in the previous year, 26 (SD 7) years	4 oz/d–8 oz/d		Isoenergetic control drink without (poly) phenols	No reduction in UTI risk	Stapleton *et al.*, 2012[148]
Cranberry (low-calorie beverage)	RCT, two-arm, 2 months	$n=56$ (42 F, 20 intervention) with the MetS, OW/OB, median age 51 years	700 ml/d	104 mg total phenolics, 66 mg proanthocyanidins	No drink	↑ adiponectin and folic acid, ↓ homocysteine, lipoperoxidation and protein oxidation levels	Simão *et al.*, 2013[145]
Cranberry (low-calorie beverage)	RCT, DB, CO, single-dose	$n=12$ (6 F), NW, 28 (SD 1) years	16 oz	LCJC 338 mg total phenolics, 17·4 mg total anthocyanins, 192 mg proanthocyanidins	Placebo (19 mg total phenolics) and cranberry leaf extract beverage (111 mg)	↑ GSH, SOD activity; ↓ IL-4, plasma NO concentrations; no changes in CRP, creatinine excretion	Mathison *et al.*, 2014[144]
Cranberry (low-calorie beverage)	RCT, DB, parallel, 8 weeks	$n=56$ (30 F, 29 intervention), healthy, NW/OW/OB, 51 (SD 11) years	480 ml/d	346 mg phenolic compounds, 236 mg proanthocyanidins, 21 mg anthocyanins	Colour/flavour/energy-matched beverage, 124 mg phenolic compounds	↓ DBP, hs-CRP, HOMA-IR, fasting serum TAG, FG; no changes in SBP, IL-6, IL-10, IL-1β, and TNF-α, ICAM-1, VCAM-1, TC, LDL-c, and HDL-c, fasting serum insulin	Novotny *et al.*, 2015[136]
Cranberry (27% cranberry juice)	Multicentre, RCT, DB, 24-week	$n=322$ (F, 160 intervention), with a history of ≥2 UTI in the previous year, OW, 41 (SD 1) years	240 ml/d	135 (SD 31) mg total phenolics	Isoenergetic control drink with 17±5 mg total phenolics/240 ml	↓ number of UTI episodes	Maki *et al.*, 2016[147]
Cranberry (25, 48, 76, 94, and 117%, doses of concentrated cranberry juice)	RCT, DB, CO, 6 da	$n=10$ (M), NW/OW, 24 (SD 2) years	450 ml/d	409, 787, 1238, 1534, and 1910 mg total (poly) phenols	Isoenergetic control drink without (poly) phenols	↑ FMD in a dose-dependent way	Rodriguez-Mateos *et al.*, 2016[139]
Cranberry (low-calorie beverage)	RCT, parallel, 8 weeks	$n=41$ (27 F; 9 CJ), diabetic patients with periodontal disease, NW/OW/OB, 56 (SD 7) years	400 ml/d	390 mg total phenolics, 16 mg anthocyanins, 214 mg proanthocyanidins	Control, omega-3, cranberry juice+omega-3	No changes in BMI, WC, FG, TAG, TC, LDL-C, HDL-C, HbA1c and PD	Javid *et al.*, 2017[133]
Cranberry (27% cranberry juice)	RCT, DB, 2 × CO, 8 weeks	$n=40$, with elevated brachial blood pressure, OW/OB, 47 (SD 12) years	500 ml/d		Isoenergetic control drink without (poly) phenols	↓ 24-h ambulatory DBP and the lipoprotein profile; no effects for central or brachial diastolic pressure or other measures of vascular function, glucose/insulin, lipids, markers of oxidative stress	Richter *et al.*, 2021[138]
Cranberry (35% cranberry juices)	RCT, DB, 8 weeks	$n=470$, Helicobacter pylori-positive adults, 47 (SD 11) years	480 ml/d	88 mg A-type proanthocyanidin/480 ml	Cranberry-flavoured beverage without A-type proanthocyanidins	↓ *H. pylori* infection rate (20%), as compared with other dosages (23 and 44 mg A-type proanthocyanidin/d) and placebo	Li *et al.*, 2021[155]

Juices were 100% juice unless otherwise stated. Abbreviations: BMI, body mass index; BP, blood pressure; CO, crossover; DB, double-blind; DBP, diastolic blood pressure; F, female; FG, fasting blood glucose; FMD, flow-mediated dilation; GSH, glutathione; HbA1c, hemoglobin A1c; HDL-c, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity CRP; ICAM-1, intercellular adhesion molecule 1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; LDL-c, LDL-cholesterol; M, male; MDA, malondialdehyde; MetS, metabolic syndrome; NO, nitric oxide; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); ox-LDL, oxidised-LDL; PD, pocket depth; PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SOD, superoxide dismutase; TAG, triglycerides; TC, total cholesterol; TNF-α, tumour necrosis factor-α; UTI, urinary tract infection; VCAM-1, vascular cell adhesion molecule; VLDL, very low density lipoproteins; WC, waist circumference; ↓, decreased level; ↑ increased level

reduce systolic or diastolic BP, while cranberry products as a whole may favour physiologically relevant decreases in systolic BP[137]. A recent work carried out in middle-aged adults with overweight/obesity and elevated brachial blood pressure also accounted for a lack of effect of cranberry juice (8 weeks, 500 ml/d, 27% cranberry juice; 27 g/l of total sugars of which 19 g/l are added sugars) on BP[138]. In the case of acute studies on vascular function, the work by Rodriguez-Mateos *et al.* (2016)[139] is worth mentioning as it assessed whether cranberry juice consumption in a dose-dependent manner could improve vascular function in healthy men. The different doses (450 ml) were equivalent to 25, 48, 76, 94 and 117% of concentrated cranberry juice, having a total sugar-content of 78 g/l. Juice supplementation increased FMD in a dose-dependent way and the effect was correlated to a series of phenolic metabolites belonging to different classes of (poly)phenols[139]. Interestingly, cranberry juice consumption also increased the production of phenyl-γ-valerolactones in a dose-dependent way[140], which are the main gut microbial metabolites derived from flavan-3-ols that may be behind some beneficial effects attributed to flavan-3-ol-rich sources such as cranberry juice[141]. Improvements in vascular function (PWV) have also been reported upon chronic consumption of cranberry juice (54% juice, 835 mg total polyphenols and 94 mg anthocyanins; 3% glucose and 1% fructose) for 4 weeks in comparison with placebo[142].

Regarding biochemical parameters associated with cardiometabolic risk, a recent SRMA concluded that neither cranberry products nor cranberry juice specifically improve TC, LDL-C, HDL-C, TG, fasting glucose, fasting insulin and HOMA-IR[138]. Some controversy has been observed for fasting serum TG levels, as they decreased after 8-week cranberry juice consumption in the work by Novotny *et al.* (2015)[136], while they increased significantly in the study conducted by Basu *et al.* (2011)[135] in women with metabolic syndrome. The recent paper by Richter *et al.* (2021)[138] confirmed the lack of effect in blood lipids of cranberry juice after 8 weeks at 500 ml/d in subjects at risk of CVD, while it reported an interesting shift in the lipoprotein profile.

Considering inflammation biomarkers, CRP did not change after cranberry juice consumption[137], and a lack of effect on other biomarkers (IL-6, IL-10, IL-1β, tumour necrosis factor-alpha or TNF-α, soluble ICAM or sICAM, and soluble VCAM or sVCAM) has also been reported[136]. Cranberry juice significantly increased plasma antioxidant capacity and decreased ox-LDL and MDA at 8 weeks versus placebo[135]. In agreement with these findings, other works have also reported improvements in the endogenous antioxidant status[144] and oxidative stress measurements[145].

Many studies have investigated the effect of cranberry juice on the prevention of recurrent urinary tract infections (UTI)[146]. To date, the results are contradictory. Maki *et al.* (2016)[147] reported that consumption of a cranberry juice beverage (27% juice, 240 ml/d, 5 mg/l anthocyanins, 496 mg/l proanthocyanidins, 25 g/l sugars) for 24 weeks significantly reduced the number of UTI episodes in women (40·9 SD 1·1 years) with a history of ≥2 UTI in the previous year. Conversely, Stapleton *et al.* (2012) [148] did not observe a significant reduction in UTI risk after juice consumption juice (27% juice and sucralose, 120 or 240 ml/d) compared with placebo in premenopausal women with a history of ≥1 UTI in the previous year. To comprehensively assess the effect of cranberry on the risk of UTI recurrence in otherwise healthy women, Fu *et al.* (2017)[149] conducted a SRMA of seven randomised controlled trials. The meta-analysis revealed that cranberry products could effectively prevent UTI recurrence, but this protective effect was not significant when only juice-related studies were taken into account. Similar insights (protective effect of cranberry products, but not cranberry juice by itself) were reported for another, more updated meta-analysis for women and UTI[150]. Nevertheless, the last meta-analysis published in this field, taking into account not only women with recurrent UTI but also children and patients using indwelling catheters, for a total of almost 4000 participants, concluded that cranberry juice could be considered an adjuvant therapy for preventing UTI in susceptible populations[151]. Of note, all the authors of these meta-analyses emphasised the need for larger, high-quality studies to confirm these results. A call for caution in the design of new studies is thus needed as one of the reasons behind this inconsistent evidence may be related to the high inter-individual variability associated with the metabolism of cranberry phenolics[139,140]. Some phenolic metabolites, in particular phenyl-γ-valerolactones, have demonstrated to exert a high anti-adhesive activity against uropathogenic *Escherichia coli* in bladder epithelial cells at concentrations achievable upon consumption of reasonable amounts of cranberry juice[152,153]. Consequently, they may be the responsible compounds behind the preventive features of cranberry juice on UTI. However, not everybody metabolises these compounds equally[139,140] and some individuals may benefit more from a dietary intervention with cranberry juice. Keeping in mind the existence of different metabolic phenotypes in the production of phenyl-γ-valerolactones and phenylpropanoic acids after cranberry intake[154] might be a winning strategy to demonstrate the effectiveness of this juice in UTI prevention.

The antimicrobial activity of cranberry juice components has also been investigated for *Helicobacter pylori*. *H. pylori* infection can induce peptic ulcers and increase the risk of developing gastric cancer. In a recent double-blind randomised placebo-controlled study, Li *et al.* (2021)[155] evaluated the effects of cranberry juice in 522 *H. pylori*-infected adults. Consumption of 240 ml of a beverage containing 35% cranberry juice (4·6% cranberry concentrate, 11·8% beet sugar and 83·6% water, 183 mg/l A-type proanthocyanidins) twice daily for 8 weeks (high-proanthocyanidin cranberry juice) decreased infection rate by 20% as compared with other dosages (low- and medium-proanthocyanidin cranberry juices) and placebo. Furthermore, an increase in the percentage of *H. pylori*-negative participants was observed. Contrary to juice, encapsulated cranberry powders were not significantly effective.

Overall, cranberry juice showed no effect on body weight, BP, blood lipids, glycaemic control and biomarkers of inflammation. Nevertheless, promising insights have been reported about the role of cranberry juice on vascular function (FMD), redox status, prevention of UTI recurrence in susceptible populations and suppression of *H. pylori* infection. Although most of the publications were conducted with juice made from concentrates and presenting low/medium (27–56%) amounts of juice, the evidence behind this juice is encouraging and may boost the development of 100% cranberry juices acceptable from a sensory

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point of view. Cranberry juices are preferably blended with other fruit juices or added with sweeteners to improve palatability affected by the tart taste. In any case, the amount of phenolic compounds provided by these diluted juices is high compared with other FVJ and this may, in fact, back the beneficial effects observed. To better understand cranberry juice effects, further research should consider the high inter-individual variability in the metabolism of cranberry phenolics.

Black chokeberry juice. Black chokeberry or aronia (*Aronia melanocarpa*) is known for its high content in anthocyanins and intense red/black colour, but it also contains high amounts of hydroxycinnamic acids and proanthocyanidins. This significant amount of (poly)phenols has been related to the potential benefits on human subject health[156]. Nevertheless, the evidence of chokeberry juice in humans is limited as only a few studies have been conducted (Table 7). Most of the biological properties of aronia have been tested in human subject interventions with extracts or animal models, as recently reviewed[156].

In a randomised controlled double-blind study, Pokimica *et al.* (2019)[157] found no significant change in BMI after a 4-week intervention with 100 ml/d of high- or low-dose polyphenol chokeberry juice (or a polyphenol-free placebo drink) in individuals with cardiovascular risk. The high-polyphenol juice consisted of a 100% chokeberry juice containing almost 12000 mg/l total phenols and 1100 mg/l anthocyanins; the low polyphenol dose was prepared by dilution (1:3) of the juice into the placebo drink. Similarly, in an 8-week intervention study in subjects with untreated mild hypertension, body weight remained unchanged after 300 ml/d of a 100% chokeberry hybrid juice mixed with chokeberry powder (3 g)[158]. Chokeberry juice mixed with the powder provided a total of 7313 mg of polyphenols per litre, anthocyanins (3413 mg/l) and proanthocyanidins (2483 mg/l) being the most abundant compounds.

Considering cardiometabolic biomarkers, Pokimica *et al.* (2019)[157] concluded that a 4-week intake of 100 ml/d of chokeberry juice could not be linked with a reduction in systolic and diastolic BP in individuals at cardiovascular risk. An acute study investigating the effect of chokeberry juice (three portions consumed at 1-h intervals, for a total of 600 ml) on BP did not yield significant improvements in young adults[159]. Differently, Loo *et al.* (2016)[160] found that 8-week consumption of 300 ml/d of chokeberry juice mixed with chokeberry powder decreased daytime ambulatory diastolic BP in patients with untreated mild hypertension. No conclusive results can be drawn from this information.

In the case of the lipid profile, chokeberry juice containing either low or high doses of polyphenols did not significantly change TC and LDL-C compared with the placebo drink[157]. Similarly, Loo *et al.* (2016)[160] reported no effect of chokeberry juice on lipoproteins and TG. Indeed, although some positive effects on HDL-C have been reported for aronia products, benefits occurred in works carried out with supplements[161]. No significant impacts of chokeberry consumption on serum glucose concentration have been reported[157,159,160].

A reduction in the concentration of the inflammation biomarkers IL-10 and TNF-α and a downward trend for IL-4 and IL-5 have been reported[158]. However, no significant effects on the serum levels of the other cytokines (IL-6, IL-7, IL-8, IL-13) and hs-CRP levels were observed in this study[158]. In general, the meta-analysis by Rahmani *et al.* (2019)[161] did not show beneficial effects of aronia products on inflammatory markers.

In conclusion, chokeberry juice showed only limited benefits on HDL-C and systolic BP. Further studies are fully needed to increase the limited body of evidence available to date.

Other berries juices: blueberry, bayberry, bilberry, barberry, blackcurrant, sea buckthorn, açaí, juçara and noni. Huma subject interventions have been conducted for many other berry juices, but the information available for them is scarce, and many targets have not been investigated. Here, a selection of some interesting articles for specific juices is presented to provide some insights on the overall prospects of 100% berry juice consumption on human subject health (Table 7).

Regarding wild (lowbush) blueberry (*Vaccinium angustifolium*), 240 ml/d of 100% blueberry juice (total phenols and anthocyanins: 8900 and 1300 mg/l, respectively) in adults at risk for T2D for 7 d did not change body weight, anthropometric parameters, endothelial function, glucose, insulin, insulin sensitivity (HOMA-IR), TG, and inflammatory and oxidative stress markers in a single-blind placebo-controlled randomised crossover trial[162]. The only benefit was an increase in nitric oxide production that could be related to a non-significant, marginal decrease in systolic BP[162]. A lack of effect of blueberry juice from concentrate (30 ml twice daily; 774 mg anthocyanins) on anthropometric parameters and BP has been recently reported in healthy adults after 20-d juice supplementation[163]. Of note, while a reduction of LDL-C levels compared with placebo was found, fasting glucose increased slightly[163]. On the contrary, a trend for lower glucose levels was found when providing 100% blueberry juice (6–9 ml/kg body weight, 428–598 mg anthocyanins) to older adults for 12 weeks[163], emphasising the need for further studies in this topic. Improvements in memory tests were observed, although the sample size was quite limited[164].

Guo *et al.* (2014)[165], in a randomised double-blind crossover study, supplemented 250 ml of 100% Chinese bayberry (*Myrica rubra*) juice, twice per day, for 4 weeks to young individuals with features of non-alcoholic fatty liver disease (NAFLD). The juice contained 896 mg/l vitamin C, 2702 mg/l total phenols and 835 mg/l anthocyanins, and the placebo was matched for vitamin C content. The treatment did not affect body weight, BMI and other anthropometric parameters, blood lipids, glucose, insulin and insulin sensitivity. Bayberry juice significantly decreased plasma levels of TNF-α, IL-8 and protein carbonyl groups, whereas no significant alterations in plasma levels of hs-CRP or apoptotic markers were observed[165].

Bilberry (*Vaccinium myrtillus*) juice consumption has also been assessed in subjects at increased risk of CVD[166]. Consumption of 330 ml 100% bilberry juice/d (diluted to 1 litre using tap water) for 4 weeks, compared with placebo (1 litre of water per day), did not modify body weight and blood lipids. A significant decrease in plasma concentrations of CRP, IL-6, IL-15, and monokine induced by interferon-γ was reported, but, surprisingly, TNF-α increased in the bilberry group. No changes in antioxidant status and oxidative stress biomarkers occurred[166].

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Table 7. Characteristics of some representative studies investigating the health effects of some berries (chokeberry, blueberry, bayberry, bilberry, barberry, blackcurrant, sea buckthorn, açaí, juçara and noni) juices

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Chokeberry hydrid mixed with chokeberry powder (3 g/d)	RCT, SB, CO, two 8 weeks periods	$n = 37$, untreated mild hypertensive, NW/OW, 40–70 years	300 ml/d	2194 mg total (poly)phenols, 1024 mg anthocyanins, 745 mg proanthocyanidins	Isoenergetic placebo juice	↓ daytime ambulatory DBP, the true awake SBP and DBP (measured on awakening), IL-10 and TNF-α; no changes in BW, IL-6, IL-7, IL-8, IL-13, hs-CRP, TC, HDL-c, TAG, serum glucose	Loo *et al.*, 2016[158]
Chokeberry	RT, parallel, four-arm, single-dose	$n = 88$ (49 F, 22 intervention), NW/OW, 25 (SD 6) years	3 × 200 ml/d	6393 mg GAE total (poly) phenol	Noni juice, energy drink, water	No changes in SBP, DBP, HR, BG	Nowak *et al.*, 2019[159]
Chokeberry	RCT, DB, parallel, 4 weeks	$n = 84$ (52 F), at cardiovascular risk, NW/OW/OB, 41 (SD 7) years	100 ml/d	High (1177 mg GAE) or low dose (294 mg GAE) (poly)phenol, 113 mg and 28 mg total cyanidin-3-glucoside equivalents, respectively	Isoenergetic control drink without (poly) phenols	No change in BMI, SBP, DBP, TC, LDL-c, blood glucose; ↑ saturated fatty acids; ↓ *n*-6 polyunsaturated fatty acids	Pokimica *et al.*, 2019[157]
Wild blueberry	RCT, SB, CO, 7 d	$n = 19$ (F), at risk for T2D, 53 (SD 6) years	240 ml/d	2138 GAE mg total phenolics, 314 mg anthocyanins	Colour/flavour/energy-matched juice but without (poly)phenols	No changes in BW, anthropometric parameters, SBP, DBP, endothelial function, IL-6, IL-10, hs-CRP, TNF-α, serum amyloid A, ICAM-1, VCAM-1, TAG, glucose, insulin, HOMA-IR, oxidative stress; downward trend for SBP	Stote *et al.*, 2017[162]
Blueberry	RCT, SB, parallel, three-arm, 20 d	$n = 44$ (20 F), healthy, NW/OW, 34 (SD 13) years	60 ml/d (diluted in 200 ml of water)	774 mg anthocyanins	Isoenergetic placebo juice	No changes in anthropometric parameters and SBP; ↓ TC, LDL-c; ↑ glucose; improved psychological wellbeing indices	Sinclair *et al.*, 2022[163]
Bayberry	RCT, DB, 2 × 2 CO, 4 weeks	$n = 44$ (32 F), OW, 21 (SD 1) years	500 ml/d	1351 mg total (poly)phenol, 417 mg anthocyanin	Isoenergetic control drink without (poly) phenols	↓ TNF-α, IL-8, PCG; no changes in BW, hs-CRP, TAG, TC, LDL-c, glucose, insulin and HOMA-IR	Guo *et al.*, 2014[165]
Bilberry	RCT, parallel, 4 weeks	$n = 62$ (17 F, 31 intervention), at-risk of CVD, OW, mean age 53 years	330 ml/d (diluted to 1 litre using tap water)		Water	↓ hs-CRP, IL-6, IL-15, and MIG; ↑ TNF-α; no changes in oxidative stress, blood lipids, and BW	Karlsen *et al.*, 2010[166]
Barberry	RCT, parallel, 8 weeks	$n = 42$ (27 F, 21 intervention), patients with T2D, OW/OB, 57 (SD 8) years	200 ml/d	481 mg GAE total (poly) phenols	No intervention	↓ SBP and DBP, fasting glucose, TC and TG, ↑ PON-1	Lazavi *et al.*, 2018[167]
Blackcurrant 20%	RCT, DB, CO, single-dose	$n = 20$ (11 F), NW/OW, 45 (SD 13) years	250 ml/d		Isoenergetic control drink without (poly) phenols	↑ plasma vitamin C, insulin and urinary anthocyanins; trend for an increase in plasma phenolic acids; no effect on vascular reactivity or biomarkers of endothelial function	Jin *et al.*, 2011[170]

Table 7. (*Continued*)

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Blackcurrant 20%	RCT, DB, three-arm, parallel, 6 weeks	*n* = 64 (21 F, 22 low BJ, 21 high BJ), healthy subjects with habitually low intake of fruit and vegetables, OW, mean age 53 years	1 litre/d	High BJ (20% juice; 815 mg total (poly)phenols, 143 mg anthocyanins)	Low BJ (6·4% juice; final diluted concentration: 273 mg total (poly)phenols, 40 mg anthocyanins); flavoured water	↑ FMD and plasma vitamin C; ↓ F2-isoprostanes marker of oxidative stress	Khan *et al.*, 2014[169]
Blackcurrant	RCT, DB, CO, pilot, single-dose	*n* = 9 (6 F), healthy, NW, mean age 23 years	100 ml/d	516 mg total (poly)phenols, 119 anthocyanins	Isoenergetic control drink without (poly) phenols	↑ mood and attention; no changes for any outcome	Watson *et al.*, 2019[168]
Sea buckthorn fruit puree (95·7%)	RCT, DB, CO, two-stage, 35 d	*n* = 38 (30 F), subjects with impaired glucose regulation, 59·1 (SD 4·8) years	90 ml/d	84 mg total flavonoids	Colour/flavour-matched juice without (poly) phenols	Trend in ↓ FG; no effect on 2h post-prandial plasma glucose or glycated serum protein; no change in BP or BMI	Ren *et al.*, 2021[171]
Açaí (AJ) and Juçara (JJ)	RT, SB, CO, 4 weeks	*n* = 30 (22 F), healthy, NW, 28 (SD 7) years	200 ml/d	cyanidin derivatives: Açaí: 222 mg GAE; Juçara: 330 mg GAE	Comparison of both interventions	AJ and JJ ↑ HDL-c; no changes in TC, LDL-c, TAG; AJ ↑ FG, TAC and activities of catalase and glutathione peroxidase, ↓ OSI; JJ ↑catalase	de Liz *et al.*, 2020[172]
Noni	RT, parallel, four-arm, single-dose	*n* = 88 (49 F, 22 intervention), NW/OW, 25 (SD 6) years	90 ml/d	318 mg GAE total (poly) phenol	Chokeberry juice, energy drink, water	↓ SBP, DBP, HR, BG	Nowak *et al.*, 2019[159]

Juices were 100% juice unless otherwise stated. Abbreviations: AJ, Açaí juice; BG, blood glucose; BJ, blackcurrant juice drink; BMI, body mass index; BW, body weight; CO, crossover; CVD, cardiovascular disease; DB, double-blind; DBP, diastolic blood pressure; F, female; GAE, gallic acid equivalent; HDL-c, HDL-cholesterol; HR, heart rate; hs-CRP, high-sensitivity CRP; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6; IL-7, interleukin-7; IL-8, interleukin-8; IL-10, interleukin-10; IL-13, interleukin-13; IL-15, interleukin-15; JJ, Juçara juice; LDL-c, LDL-cholesterol; M, male; MIG, monokine induce by INF-γ; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OSI, oxidative stress index; OW, overweight (BMI: 25–30 kg/m^2); PCG, protein carbonyl groups; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; T2D, type 2 diabetes; TAC, total antioxidant capacity; TAG, triglycerides; TC, total cholesterol; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule; ↓, decreased level; ↑ increased level

Barberry (*Berberis vulgaris*) juice consumption (100% from concentrate, 200 ml/d, 8 weeks, 2403 mg/l total phenols) by patients with T2D led to significant decreases in systolic and diastolic BP, fasting glucose and TC and an increase in PON-1[167]. The amount of the alkaloid berberine, which may have some protective cardiometabolic effects, was not indicated.

Blackcurrant (*Ribes nigrum*) juice has been tested in different contexts and promising effects have been reported. Briefly, 100% anthocyanin-rich blackcurrant juice (about 100 ml, 500 mg polyphenols per serving) improved mood and attention in young health volunteers[168], while 20% blackcurrant juice has demonstrated improvements in FMD in healthy subjects with habitually low intake of fruit and vegetables[169] and vascular reactivity in acute conditions[170].

Sea buckthorn (*Hippophae rhamnoides*) berries contain flavonols such as quercetin, isorhamnetin, kaempferol and myricetin[171]. Sea buckthorn fruit puree(95·7% fruit, 90 ml/d) consumption for 35 d led to a slight downward trend in fasting plasma glucose in subjects with impaired glucose regulation, but it did not affect the 2 h post-prandial plasma glucose or glycated serum protein, compared with a placebo[171]. Juice supplementation did not change BP or BMI. The juice contained 930 mg/l of total flavonoids, with isorhamnetin glycosides being the main flavonols[171].

Açaí (*Euterpe oleracea*) and juçara (*E. edulis*) berries are characterised by a high anthocyanin content[172]. In a randomised crossover study, de Liz *et al.* (2020)[172] found that consumption of 200 ml/d of açaí or juçara juice (1105 and 1645 mg/l cyanidin derivatives, respectively) for 4 weeks promoted a significant increase in HDL-C compared with the respective baseline values in thirty healthy adults, with greater increase observed after juçara juice consumption. Conversely, TC, LDL-C and TG were not affected by the interventions. A significant increase was also observed for fasting glucose levels only after açaí juice consumption; nonetheless, the results were within the reference range. Concerning biomarkers of oxidative stress, açaí juice was more effective, leading to increases in the activity of antioxidant enzymes (catalase and glutathione peroxidase) and total antioxidant capacity, also decreasing an oxidative stress index (the ratio of total oxidant status to total antioxidant capacity); juçara juice increased only catalase[172]. The lack of a control juice hindered the understanding of the true relevance of these insights but did not preclude the collection of encouraging results with regard to the preventive features of these anthocyanin-rich berry juices.

Noni (*Morinda citrifolia*) fruits show a particular phytochemical profile, including flavonols such as quercetin and rutin, hydroxycoumarin such as scopoletin, and anthraquinone 5,15-dimethylmorindol[173]. Despite some controversial hepatotoxic events related to products labelled as noni products, but lacking noni, noni has been recognised as safe[174]. West *et al.* (2018)[174] conducted a review of human subject intervention studies to evaluate the potential health benefits of noni juice. Potential health benefits included protection against tobacco smoke toxicity, joint pain and mobility improvement, bone health, control of BP and antioxidant activity, among others. Nevertheless, all the studies reviewed regarded mixed noni juice beverages, so the evidence on pure noni juice is limited. A recent study conducted with pure noni juice evaluated the acute effects on BP and glucose of noni juice, chokeberry juice and an energy drink and water (placebo) in eighty-eight young adults[159]. Acute intake of three portions of noni juice at 1-h intervals (30 ml/portion) led to a significant reduction in BP and a mild, borderline reduction in blood glucose[159].

In conclusion, the evidence for minor berry juices showed some beneficial effects of 100% juice consumption on subjects at risk for disease or with pre-existing diseases. However, the number of studies for each berry juice is quite limited, so no major conclusions should be drawn from them. Further studies are fully needed, and they should take into account also other population settings to really address the preventive effects of these berry juices for the general population. Of note, some important studies on the health properties of commercially relevant berry juices, such as blueberry[175] or strawberry[176], were performed with reconstituted freeze-dried powders. Although they provided significant outcomes on the bioactivity of these fruits, similar works should be carried out with 100% juices to endow them with robust insights and increase the body of evidence for berry juices.

Cherry juice

Cherries can be classified into sweet cherries (*Prunus avium* L.) and tart cherries (*Prunus cerasus* L.). They are rich in vitamin C, potassium and phenolic compounds, and especially rich in anthocyanins such as cyanidin and peonidin derivatives, with notable amounts of hydroxycinnamic acids and flavan-3-ols. Generally, tart cherries show higher concentrations of phenolics than sweet cherries[177] and evidence of the health effects of cherry juices comes predominantly from tart cherries. Many studies used tart cherry juice from the 'Montmorency' cultivar, which shows high amounts of anthocyanins[178]. Melatonin is also present in cherries, and some sleep regulation-related biological activities have been attributed to this compound[177]. Here, the available literature on cherry juice is discussed even when no 100% chery juices, but only diluted ones, were provided to volunteers, as the number of intervention studies providing pure cherry juice is quite scarce, and the amounts of (poly)phenols provided by these diluted ones are quite high and might lead to potential beneficial effects (Table 8).

Chai *et al.* (2019)[180], in a randomised controlled trial, showed no change in body weight or BMI after 12-week supplementation of either 480 ml/d of Montmorency tart cherry juice (68 ml juice concentrate diluted in water, total phenols: 937 mg/l, potassium: 740 mg/l) or control drink in 34 older adults who were overweight. In this line, Johnson *et al.*[181] claimed that 480 ml/d of tart cherry juice for 12 weeks in metabolic syndrome patients did not affect body weight or composition. A lack of effect of Montmorency tart cherry juice from concentrate on anthropometric parameters has also been reported recently by two studies in healthy adults[175,197]. No effect on BP was also noted in these studies[175,197], contrary to previous evidence in at-risk/diseased subjects. Indeed, in a randomised single-blind crossover trial, Desai *et al.* (2021)[183] investigated the effects of 130 ml/d consumption of Montmorency tart cherry juice (30 ml juice concentrate diluted in water, 2076 mg/l anthocyanins) on

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Table 8. Characteristics of some representative studies investigating the health effects of cherry (sweet and tart) juices

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Montmorency tart cherry	RCT, OL, parallel, 6 weeks	$n = 46$ (29 F), healthy, NW/OW, 38 (SD 6) years	250 ml/d (30 ml juice concentrate diluted)	273 mg total anthocyanin	Commercial lemonade	↑ FRAP; no changes in PWV, SBP, DBP, TC, HDL-c, CRP, arterial stiffness	Lynn *et al.*, 2014[188]
Montmorency tart cherry	RCT, blinded, LS, CO, single-dose	$n = 15$ (M), nonsmoking, hypertensive, OW, 31 (SD 9) years	160 ml (60 ml juice concentrate diluted)		Isoenergetic control drink without (poly) phenols	↓ SBP; no changes in PWV, microvascular vasodilation	Keane *et al.*, 2016[186]
Bing sweet cherry	RCT, parallel, 12 weeks	$n = 42$ (21 intervention), with mild-to-moderate Alzheimer's type dementia, NW/OW, 81 (SD 7) years	200 ml/d	138 mg anthocyanin	Commercially apple juice with negligible anthocyanin content	↓ SBP, trend in reducing DBP; ↑ verbal fluency, short- and long-term memory	Kent *et al.*, 2017[185]
Montmorency tart cherry	RCT, parallel, 12 weeks	$n = 34$ (17 intervention), consuming ≤5 servings of fruits and vegetables per day, OW, 70 (SD 4) years	480 ml/d (68 ml juice concentrate diluted in water)	451 mg total phenolics, 96 mg tannins	Isoenergetic control drink without (poly) phenols	↓ SBP, LDL-c; ↑ glucose levels; no change in BW, DBP, HDL-c, insulin and HOMA-IR	Chai *et al.*, 2018[184]
Tart Cherry	RCT, 2 × 2 CO, pilot, 4 weeks	$n = 10$ (8 F), OW/OB, 38 (SD 12) years	240 ml/d	438 GAE total (poly) phenol	Isoenergetic control drink without (poly) phenols	No change in hs-CRP levels, IL-6 or IL-10 levels; ↓ proinflammatory MCP-1; trend for reducing TNF-α levels	Martin *et al.*, 2018[191]
Tart Cherry	RCT, parallel, 12 weeks	$n = 34$ (20 intervention), NW/OW/OB, 70 (SD 4) years	480 ml/d (68 ml juice concentrate diluted)	451 GAE total phenolics, 95·9 mg tannins	Isoenergetic control drink without (poly) phenols	↑ cognitive abilities, subjective memory in the domain of contentment with memory by 5% and reduced movement time by 4%; ↓ errors in episodic visual memory by 23%	Chai *et al.*, 2019[180]
Tart Cherry	RCT, parallel, 12-week	$n = 34$ (20 intervention), NW/OW/OB, 70 (SD 4) years	480 ml/d (68 ml juice concentrate diluted)	451 GAE total phenolics, 95·9 mg tannins	Isoenergetic control drink without (poly) phenols	↓ CRP, MDA, and ox-LDL; ↑ DNA repair activity of 8-oxoguanine glycosylase; TNF-α, 4HNE, 8-OHdG	Chai *et al.*, 2019b[179]
Montmorency tart cherry	RCT, SB, CO, pilot, 6 h	$n = 11$ (5 F), with MetS, OB, 49 (SD 12) years	130 ml (30 ml juice concentrate diluted)	270 mg anthocyanin	Commercially available fruit-flavoured cordial mixed with water	↓ SBP, insulin; no changes TAG and HDL-c	Desai *et al.*, 2019[190]
Tart Cherry	RCT, DB, parallel, 9 d	$n = 36$ (M) non-resistance trained men) NW/OW, 24 years	500 ml/d (30 ml concentrate juice diluted twice daily)	600 mg total phenolics	Energy-matched blackcurrant-flavoured maltodextrin sports drink	TCJ did not enhance recovery from high-force eccentric exercise of the elbow flexors	Lamb *et al.*, 2019[196]
Tart Cherry	RCT, DB, CO, 3 d	$n = 10$ (M), soccer players, 19 (SD 1) years	250 ml/d (30 ml juice concentrate diluted)		Isoenergetic cherry-flavoured control drink (CON)	No differences in CMJ, RSI and MS between groups	Abbott *et al.*, 2020[198]
Montmorency tart cherry	RCT, SB, parallel, pilot, 12 weeks	$n = 19$ (9 F, 9 intervention), MetS patients, mean age 37 years	480 ml/d	2140 mg total phenolics, 176 mg total anthocyanins	Isoenergetic control drink without (poly) phenols	↓ ox-LDL, VCAM-1, TC; ↑ HOMA-B%, WHR; no changes in BW or composition, PWV	Johnson *et al.*, 2020[181]

Table 8. (*Continued*)

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Montmorency tart cherry	RCT, SB, CO, 2 weeks	*n* = 11 (M, 6 intervention), rugby players, 18 (SD 1) years	260 ml/d (60 ml juice concentrate diluted)	anthocyanins 640 mg/60 ml	Isoenergetic control drink without (poly) phenols	No effects on markers of muscle soreness, function and inflammation	Morehen *et al.*, 2020[197]
Tart Cherry	RCT, 4-week	*n* = 50 (5 F), with gout and SU >0·36 mmol/l, OW/OB, mean age 59 years	four different CJ groups: 7·5, 15, 22·5, 30 ml (all consumed twice daily in 250 ml water)		Two drops of tart cherry juice	No effect in reducing serum urate levels and gout flares	Stamp *et al.*, 2020[193]
Montmorency tart cherry	RCT, SB, CO, 7 d	*n* = 12 (6 F), with MetS, OW/OB, 50 (SD 10) years	130 ml (30 ml juice concentrate diluted)	270 mg anthocyanins/130 ml	Isoenergetic control drink without (poly) phenols	↓ 24-h ambulatory SBP, DBP, mean arterial pressure, TC, LDL-c, TC:HDL-c ratio, FG; no changes in TAG	Desai *et al.*, 2021[183]
Montmorency tart cherry	RT, 90 da	*n* = 27 (F), healthy, largely osteopenic (82%), NW/OW, 71 (SD 4) years	240 ml once (TC1X) or twice (TC2X) daily (30 ml juice concentrate diluted)	225 mg GAE/30 ml total phenolics	Comparison of both interventions	No alterations in biomarkers of bone formation, bone turnover or bone resorption in response to TC1X; TC2X ↓ TRAcP 5b	Dodier *et al.*, 2021[195]
Montmorency tart cherry	RCT, DB, parallel, 30 d	*n* = 44, healthy, NW/OW, 28 (SD 7) years	480 ml/d	1586 mg total phenolics, 454 mg total anthocyanins	Placebo	No changes in anthropometric parameters, BP, sleep time and quality	Hillman *et al.*, 2022[182]
Montmorency tart cherry	RCT, SB, parallel, three-arm, 20 d	*n* = 44 (20 F), healthy, NW/OW, 34 (SD 13) years	60 ml/d (diluted in 200 ml of water)	640 mg anthocyanins	Isoenergetic placebo juice	No changes in anthropometric parameters and SBP; ↓ glucose	Sinclair *et al.*, 2022[163]

Juices were 100% juice unless otherwise stated. Abbreviations: 4HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxydeoxyguanosine; BP, blood pressure; BW, body weight; CMJ, countermovement jump-height; CO, crossover; CRP, C-reactive protein; DB, double-blind; DBP, diastolic blood pressure; F, female; FG, fasting blood glucose; FRAP, ferric reducing ability of plasma; HDL-c, HDL-cholesterol; HOMA-B%, homeostasis model assessment-beta cell function; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity CRP; IL-6, interleukin-6; IL-10, interleukin-10; LDL-c, LDL-cholesterol; M, male; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MetS, metabolic syndrome; MS, muscle soreness; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); ox-LDL, oxidised-LDL; PWV, pulse wave velocity; RCT, randomised controlled trial; RSI, reactive strength index; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; TAG, triglycerides; TC, total cholesterol; TCJ, tart cherry juice; TNF-α, tumour necrosis factor-α; TRAcP 5b, tartrate-resistant acid phosphatase type 5b; VCAM-1, vascular cell adhesion molecule; WHR, waist-to-hip ratio; ↓, decreased level; ↑ increased level

BP in twelve metabolic syndrome patients, showing that 24-h ambulatory systolic, diastolic BP and mean arterial pressure were significantly lower than placebo after 7-d cherry juice consumption. Chai *et al.* (2018)[184] reported a reduction in systolic BP (by 4·1 mmHg), but not in diastolic BP, after 12-week consumption of 480 ml/d of Montmorency tart cherry juice in older adults who were overweight. A significant reduction in systolic BP and only a trend (not significant) for diastolic BP reduction was also observed in older adults with dementia, following 12-weeks at 200 ml/d of anthocyanin-rich Bing sweet cherry juice (690 mg/l anthocyanins)[185]. Variations in BP upon acute conditions have also been assessed: a single dose of 160 ml of Montmorency tart cherry juice (60 ml juice concentrate diluted in water) significantly lowered systolic BP over a period of 3 h compared with a placebo drink in fifteen men with early hypertension[186]. Similar results were found when 300 ml of the aforementioned anthocyanin-rich cherry juice was supplied to healthy volunteers[187]. Functional improvements in both studies were related to the increase in circulating phenolic metabolites. Conversely, no significant differences in PWV, measured as a predictor of arterial stiffness, were observed in three different interventions[186,188,189].

Considering other cardiometabolic markers, TC, LDL-C and TC:HDL-C ratio were significantly lower following 7-d consumption of 130 ml/d of Montmorency tart cherry juice compared with the placebo in twelve participants with metabolic syndrome, without changes in TG concentration[183]. Nevertheless, an acute study by the same authors in the same population setting did not account for changes in blood lipids[190], in line with two studies, one conducted in forty-seven healthy adults (30–50 years) with tart cherry juice for 6 weeks[188] and another in metabolic syndrome patients for 12 weeks[181]. On the contrary, Chai *et al.* (2018)[184] reported that, after the 12-week intervention at 480 ml/d, older adults in the tart cherry juice group had lower LDL-C than the control group. Neither tart cherry juice nor control altered HDL-C concentrations. Data available to date in the case of glucose metabolism is also contradictory. Some authors observed that tart cherry juice did not affect insulin and HOMA-IR levels, while significantly increasing glucose levels in older adults (65–80 years) who were overweight[184]. Conversely, after 7-d consumption of Montmorency tart cherry juice (130 ml/d) by metabolic syndrome patients, fasting glucose concentrations decreased significantly without major changes in insulin levels[183], while only insulin changed when supplementing the same juice in acute conditions to these patients[190].

Regarding inflammation, after 12 weeks at 480 ml/d, tart cherry juice significantly lowered CRP levels but not TNF-α levels compared with the control drink in older adults[179]. Conversely, Martin *et al.* (2018)[191], in a randomised crossover study, showed no change in hs-CRP, IL-6, IL-10 and TNF-α levels after 4-week consumption of either 240 ml/d 100% tart cherry juice (total polyphenols: 1827 mg/l) or placebo in ten adults who were overweight/obese. Nevertheless, there was a significant decrease in pro-inflammatory monocyte chemoattractant protein 1 (MCP-1) compared with the placebo group[191]. Examining biomarkers of oxidative stress, Chai *et al.* (2019)[180] showed that tart cherry juice significantly increased the DNA repair activity of 8-oxoguanine glycosylase compared with the control drink. In addition, plasma levels of MDA slightly decreased after 12 weeks of tart cherry juice consumption compared with the control drink. Other biomarkers such as 4-hydroxynonenal and 8-hydroxydeoxyguanosine were not affected by either tart cherry or control juice[179]. Tart cherry juice supplementation twice daily for 12 weeks reduced ox-LDL and VCAM-1, but not ICAM-1, in adults with metabolic syndrome[181]. Interestingly, serum uric acid, a marker not so commonly assessed in studies evaluating the health properties of fruit juices, has been broadly studied in interventions with cherry juices. Evidence indicates that serum urate decreases consuming tart cherry juice, which may be beneficial for gout patients[192], but further studies are needed as recent data from a dose-dependent study in people with gout has pointed to a lack of effect of tart cherry juice in reducing serum urate levels and gout flares[193].

The potential beneficial effect of cherry juice on cognitive function has also been evaluated. In a randomised controlled trial, Kent *et al.* (2017)[194] investigated the effect of 200 ml/d of anthocyanin-rich Bing sweet cherry juice in older adults with dementia. After 12 weeks of intervention, improvements in verbal fluency, and short- and long-term memory were found only in the cherry juice group. Improvements in cognitive abilities have also been shown upon consumption of tart cherry juice by older adults (65–80 years)[180]. Overall, cherry juice supplementation might improve psychomotor speed, as assessed in a recent meta-analysis[103]. Interestingly, the elderly population has also been addressed with regard to testing the effect of Montmorency tart cherry juice on bone metabolism, but no major benefits were observed in post-menopausal women, who were largely osteopenic at baseline (82%), after 90-d juice consumption[195].

In the case of exercise performance/recovery, most studies have not found ergogenic effects. Lamb *et al.* (2019)[196] showed that 500 ml/d of tart cherry juice for 9 d did not enhance recovery in non-resistance trained men after high-force eccentric exercise of the elbow flexors. A lack of effect of cherry juice has also been described for rugby and soccer players[197,198]. Cherry juice had no effect on the sleep quality of rugby players[197,198] or healthy adults[182] despite the presence of melatonin in cherry juice.

In conclusion, tart cherry juice has attracted much more attention than sweet cherry juice. Cherry juice, in particular tart cherry juice, seems to improve BP and cognitive function, while it may also lead to some benefits at inflammation and oxidative stress level. Some studies have investigated the role of these juices in bone metabolism, exercise performance and gout, with no significant beneficial effects seen. In addition, most of the studies available were carried out using reconstituted concentrate juices, so human subject interventions with 100% juices would be helpful to increase the evidence behind cherry juice.

Plum juice

The term plum refers to a series of *Prunus* species, namely *P. domestica* (European plum), *P. cerasifera* (myrobalan or cherry plum) and *P. salicina* (Japanese plum). Plums provide phenolic compounds such as chlorogenic acids and other hydroxycinnamates, benzoates, anthocyanins, flavan-3-ol monomers and proanthocyanidins, flavonols, and coumarins.

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Among thirty-three plum varieties analysed, chlorogenic acids and proanthocyanidins were the major phenolics present in plums, but the qualitative and quantitative phenolic profiles showed high diversity even among closely related cultivars[199]. Regarding the health effects of plums (reviewed by Igwe and Charlton, 2016; including fresh, dried plums and juice)[200], most studies used Queen Garnet (QG) plum, an anthocyanin-rich Japanese plum cultivar developed in Australia[201] (Table 9). Evidence on plum juice is provided below.

In a randomised double-blinded placebo-controlled trial, Bhaswant *et al.* (2019)[202] found that 250 ml/d of QG plum juice for 12 weeks (1020 mg/l anthocyanins – mainly cyanidin-3-glucoside; 360 mg/l quercetin derivatives) did not change body weight, waist-to-hip ratio and body composition measurements in twenty-nine mildly hypertensive subjects who were overweight or obese. A lack of effect on BMI has also been reported for two QG plum juices containing different anthocyanins levels (48 and 201 mg daily) after supplementation of 250 ml for 8 weeks in older adults with mild cognitive impairment[203]. Considering BP, QG plum juice 12-week treatment decreased systolic and diastolic BP compared to baseline values and placebo drink (without flavonoids)[202], while do Rosario *et al.* (2021)[203] did not find any effect on BP for any QG plum juice regardless of the anthocyanin amount in older adults after 8 weeks. Under acute conditions, a BP reduction effect was reported for an anthocyanin-rich QG plum juice in both young and older adults[204], while 250 ml of QG plum juice, providing 200 mg anthocyanins and consumed in conjunction with a high fat-high energy meal, did not change the increased post-prandial BP compared with an apricot juice (control juice, no anthocyanins) in sixteen older adults who were overweight[205]. However, the authors observed that 2-h post-prandial FMD and some parameters of microvascular function were better in the QG plum juice than the apricot juice group.

Modifications of lipid profile and glucose metabolism by plum juice consumption have been scarcely investigated. QG plum juice for 12 weeks decreased fasting plasma LDL-C, but not HDL-C, TC and TG concentration, in mildly hypertensive subjects who were overweight or obese[202]. A three-arm randomised double-blind crossover trial conducted with 200 ml anthocyanin-rich QG plum juice (1010 mg/l anthocyanins: 760 mg/l cyanidin-3-glucoside, 250 mg/l cyanidin-3-rutinoside; 437 mg/l quercetin derivatives), prune juice (no anthocyanins neither quercetin derivatives) and a control drink (matched for energy and macronutrients) for 4 weeks in twenty-one healthy adults did not lead to changes in blood lipids after consumption of any of the juices, which may be related to the adequate physiological conditions of the study population[201]. Similarly, the post-prandial increases in TC and TGs due to a high fat-high energy meal were not altered by either QG plum juice or control juice[205]. Interestingly, Bhaswant *et al.* (2019)[202] reported that QG plum juice decreased fasting plasma glucose and insulin compared with baseline and placebo. This effect was not observed when plum juice was tested in healthy adults[201]. Platelet aggregation has also been considered in plum juice research: Santhakumar *et al.* (2015)[206] indicated that QG plum juice but not prune juice had a significant effect on different markers of thrombosis, reducing platelet activation and hypercoagulability.

In relation to inflammatory markers, Bhaswant *et al.* (2019)[202] found a reduction in TNF-α and plasma interleukins such as IL-6 and IL-13 after QG plum juice in mildly hypertensive subjects who were overweight or obesity. Decreased concentrations of TNF-α were also observed in older adults after 8-week QG consumption[203]. Conversely, in healthy adults, Santhakumar *et al.* (2015)[206] reported that there were no significant changes in inflammatory markers regardless of the treatment (QG plum juice, prune juice or control). Under acute post-prandial conditions, anthocyanin-rich QG plum juice decreased hs-CRP levels compared with the apricot juice[205]. Do Rosario *et al.* (2021)[205] also observed a downtrend for IL-6 while no treatment altered TNF-α and IL-1β. Examining biomarkers of oxidative stress, 200 ml/d QG plum juice for 4 weeks decreased plasma MDA levels, while prune juice did not[201]. A lack of effect of QG plum juice on oxidative stress status under acute conditions has also been reported[205]. A single dose of QG plum juice did not improve cognitive function in younger or older adults[204].

Few studies have assessed the health effects of plum juice, in particular in the case of common European plum juices. Anthocyanin-rich QG plum juice has attracted almost all the attention in terms of plum juice research, and it might be able to have positive moderate effects on vascular function, LDL-C and inflammatory status. Its ability to attenuate some biomarkers related to cardiovascular risk was seen mainly in subjects at risk of disease, but not in healthy ones. On the other hand, the choice of apricot or prune juices as control drinks[201,205] could bias the results as both drupe juices share some bioactive compounds with plum juice. Although these juices can be good choices to exclude the role of anthocyanins, they did not allow a complete assessment of the effect of plum juice on health outcomes. Further research on these drupe juices may also be needed.

Tomato juice

Tomato is one of the most popular vegetables worldwide, and its juice is likely the predominant vegetable juice on the market. Lycopene is the main carotenoid in tomatoes and tomato-based products and, among phenolic compounds, quercetin, kaempferol, naringenin, luteolin and caffeic acid derivatives are the most common[207]. Tomato has been typically investigated for its lycopene content and has been related epidemiologically to cancer prevention, specifically for prostate cancer[208]. However, the only meta-analysis that considered tomato juice for subgroup analysis did not find any significant association between juice consumption and the risk of prostate cancer, so further studies would be needed to clarify the potential chemopreventive effects of tomato juice[209]. Epidemiological studies have also emphasised the potential cardiometabolic benefits associated with tomato consumption, while the contribution of tomato juice is unknown[210]. The results from key intervention studies with 100% tomato juice are discussed below and are focused mainly on blood lipids, inflammatory markers and oxidative stress status (Table 10).

Michaličková *et al.* (2019)[211] assessed the effects of daily ingestion of tomato juice enriched in polyphenols using a tomato extract against a standard tomato juice on BP in subjects with

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Table 9. Characteristics of some representative studies investigating the health effects of plum juices

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Queen Garnet plum	RCT, DB, CO, three-arm, 4 weeks	$n = 20$ (10 F), healthy, NW, 33 (SD 12) years	200 ml/d	202 mg anthocyanins; 87 mg quercetin derivatives	Prune juice without anthocyanins or quercetins; placebo drink: diluted raspberry cordial	Inhibited platelet aggregation; ↓ plasma-fibrinogen, MDA; no changes in blood lipids	Santhakumar *et al.*, 2015[201]
Queen Garnet plum	Pilot, CO, acute	$n = 12$ (9 F), OW, 77 (SD 6) years; $n = 12$ (8 F), NW, 31 (SD 8) years	300 ml single dose or 3 × 100 ml over 3 h	369 mg total anthocyanins	No control	↓ BP (anthocyanin-rich QG plum juice group)	Igwe *et al.*, 2017[204]
Queen Garnet plum	RCT, DB, 12 weeks	$n = 29$ (14 F, 15 intervention), mild hypertensive with no medication, OW/OB, 43 (SD 13) years	250 ml/d	255 mg cyanidin-3-glucoside eq. anthocyanins, 90 mg quercetin glycosides	Commercial raspberry cordial-flavoured without flavonoids	↓ SBP, DBP, IL-6, IL-13, TNF-α, FG, insulin, LDL-c; no changes in BW, WHR, body composition measurements, HDL-c, TC, TAG	Bhaswant *et al.*, 2019[202]
Queen Garnet plum	RCT, DB, CO, single-dose	$n = 16$ (13 F), OW/OB, 66 (SD 6) years	250 ml/d (220 g plum puree added with 30 ml water) + HFHE meal	200 mg anthocyanins	Apricot juice with no anthocyanins	no changes in post-prandial BP, TNF-α, IL-1β, TC, TAG, DROM; ↑ post-prandial FMD; ↓ post-prandial hs-CRP	do Rosario *et al.*, 2021a[205]
Queen Garnet plum	RCT, DB, three-arm, 8 weeks	$n = 31$ (19 F), with MCI, OW, 75 (SD 7) years	250 ml/d	48 mg anthocyanins (low dose), 201 mg anthocyanins (high dose)	Apricot juice	no changes in BP, IL-6, IL-1 β, CRP, and parameters of microvascular function; ↓ TNF-a (high-dose anthocyanins group)	do Rosario *et al.*, 2021b[203]

Juices were 100% juice unless otherwise stated. Abbreviations: BP, blood pressure; BW, body weight; CO, crossover; CRP, C-reactive protein; DB, double-blind; DBP, diastolic blood pressure; DROM, derivatives of reactive oxidative metabolites; F, female; FG, fasting blood glucose; FMD, flow-mediated dilation; HDL-c, HDL-cholesterol; HFHE, high fat high energy; hs-CRP, high-sensitivity CRP; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-13, interleukin-13; LDL-c, LDL-cholesterol; M, male; MCI, mild cognitive impairment; MDA, malondialdehyde; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); QG, Queen Garnet; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; SBP, systolic blood pressure; TAG, triglycerides; TC, total cholesterol; TNF-α, tumour necrosis factor-α; WHR, waist-to-hip ratio; ↓, decreased level; ↑ increased level

Table 10. Characteristics of some representative studies investigating the health effects of tomato juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Tomato	RCT, parallel, four-arm, 4 weeks	$n = 52$ (20 F, 15 intervention), with T2D, 59 (SD 9) years	500 ml/d		Placebo gelatin capsule containing pharmaceutical starch	No changes in CRP, ICAM-1 and VCAM-1; ↑ resistance of LDL to oxidation induced by copper ions	Upritchard *et al.*, 2000[221]
Tomato	RT, 8-week	$n = 50$ (32 F, 29 intervention), healthy, OW/OB, 70 (SD 6) years	330 ml/d	47·1 mg lycopene, 1·7 mg β-carotene	Mineral water	↓ LDL-oxidation in R-allele carriers (QR/RR) but not in the QQ wild-type (PON1-192 polymorphism)	Bub *et al.*, 2002[224]
Tomato	RT, CO, 2 weeks	$n = 22$ (M), healthy, non-smoking, in a low-carotenoid diet	330 ml/d	37 mg lycopene, 1·6 mg β-carotene	Carrot juice (27 mg β-carotene, 13 mg α-carotene)	No changes in MDA in plasma and faeces; ↑ lag time during *ex vivo* LDL oxidisation	Briviba *et al.*, 2004[223]
Tomato	RT, 3 weeks	$n = 21$ (16 F), healthy, NW/OW, mean 30 years	400 ml/d tomato juice and 30 g/d ketchup	27 mg lycopene/d (23·6 mg from juice and 3·7 mg from ketchup)	Low tomato diet (no tomato products, or fruit and vegetables containing lycopene).	↓ TC and LDL-c compared to the LTD; HTD ↑ LDL-c resistance to copper-ion induced oxidation	Silaste *et al.*, 2007[214]
Tomato	RCT, 20 d	$n = 104$ (F, 53 intervention), OW/OB, 23 (SD 1) years	330 ml/d	37 mg lycopene	Water	↓ IL-8 and TNF-α in OW subjects, IL-6 in OB subjects	Ghavipour *et al.*, 2013[220]
Tomato	RCT, 20 d	$n = 60$ (F, 32 intervention), OW, 25 (SD 1) years	330 ml/d	37 mg lycopene	Water	↑ plasma TAC and erythrocyte antioxidant enzymes; ↓ MDA	Ghavipour *et al.*, 2015[222]
Tomato	RCT, CO, 4 weeks	$n = 28$, with high risk of developing CVD, OW/OB, 70 (SD 3) years	200 ml/d or 400 ml/d (both with 5% olive oil)	80 mg, trans-lycopene (48·1%) and β-carotene (47·4%)	Water	↓ ICAM-1 and VCAM-1; downward trend in IL-8; no changes in CRP, eotaxin, IFN-γ, CXCL10	Colmán-Martínez *et al.*, 2017[219]
Tomato (juice enriched in (poly)phenols)	RCT, SB, parallel, 4 weeks	$n = 26$ (19 F, 13 intervention), subjects with stage one hypertension, NW/OW, 46 (SD 6) years	200 g + 1g of ethanolic extract of whole tomato fruit	144 mg GAE/200 g phenolic content, 3 mg/200 g lycopene	Standard tomato juice (97 mg GAE/200 g phenolic content)	No changes in BP, FG, PT; TC and LDL-c ↓ in the control group	Michaličková *et al.* (2019)[211]
Tomato	RCT, CO, 3 d	$n = 25$ (F), healthy, NW, 22 (SD 4) years	200 g		Tomato fruits, water	Improved post-prandial glucose response	Saito *et al.*, 2020[216]

Juices were 100% juice unless otherwise stated. Abbreviations: BP, blood pressure; CO, crossover; CRP, C-reactive protein; CVD, cardiovascular disease; CXCL10, CXC motif chemokine 10; DB, double-blind; F, female; FG, fasting blood glucose; GAE, gallic acid equivalent; HTD, high tomato diet; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IL-6, interleukin-6; IL-8, interleukin-8; LDL-c, LDL-cholesterol; LTD, low tomato diet; M, male; MDA, malondialdehyde; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); PON1, paraoxonase-1; PT, prothrombin time; RCT, randomised controlled trial; RT, randomised trial; SB, single-blind; T2D, type 2 diabetes; TAC, total antioxidant capacity; TC, total cholesterol; VCAM-1, vascular cell adhesion molecule; ↓, decreased level; ↑ increased level

stage one hypertension. Juice composition was similar in both products (16 mg/l lycopene) except for the phenolic content (486 versus 721 mg/l for the control juice and the enriched one, respectively). BP did not change significantly for any treatment after 4 weeks, although 5–10 mmHg reductions were reported as a consequence of both treatments. Although pooled data from a meta-analysis have demonstrated similar outcomes for tomato products[212], the limited evidence of tomato juice effects on BP precludes from drawing robust conclusions. Nevertheless, a 5-mmHg lowering in BP could represent a reduction in the risk of cardiovascular events by about 10%, so this topic should be better explored[213].

Considering the lipid profile, Silaste *et al.* (2007)[214] observed a reduction in TC and LDL-C concentrations in healthy, normocholesterolaemic adults after a 3-week high-tomato diet (400 of ml/d tomato juice and 30 mg/d of tomato ketchup) compared with the 3-week low-tomato diet (no tomato products, or fruit and vegetables containing lycopene). The high-tomato diet provided approximately 27 mg lycopene/d, of which 23·6 mg lycopene per 400 ml was from juice and 3·7 mg lycopene per 30 mg was from ketchup, and blood lipid improvements were correlated to changes in serum concentrations of lycopene, β-carotene and γ-carotene. TC and LDL-C also decreased in the work by Michaličková *et al.* (2019)[211], but only in the control group (tomato juice with no added polyphenols). In the case of glucose metabolism, this last work did not record differences between groups for fasting glucose after 3 weeks[211], in line with pooled data for tomato products[215]. However, under acute conditions, consuming 200 g of tomato juice 30 min before a carbohydrate-rich challenge ameliorated the post-prandial glucose response[216].

Platelet hyperaggregability is among the factors associated with CVD risk. A recent review of human subject intervention studies by Cámara *et al.* (2020)[217] concluded that consuming tomatoes and tomato products is a promising nutritional strategy for the prevention of platelet aggregation. Indeed, the European Food Safety Authority (EFSA) has assessed positively the beneficial effects of a water-soluble tomato concentrate in platelet aggregation[218]. Nevertheless, the information related to tomato juice is scarce and, for instance, Michaličková *et al.* (2019)[211] did not observe differences in prothrombin time between treatments.

In a randomised controlled crossover trial, Colmán-Martínez *et al.* (2017)[219] found that, in subjects at high cardiovascular risk after 4-week consumption of tomato juice at 200 ml/d or 400 ml/d (401 μmol/l of carotenoids, *trans*-lycopene and β-carotene accounting for about 48% and 47% of the total carotenoids, respectively; both juices contained 5% olive oil), the concentration of adhesion molecules ICAM-1 and VCAM-1 was significantly lower compared with the control group (water). Other inflammatory biomarkers (IL-8, CRP, eotaxin, interferon-γ, and CXC motif chemokine 10 -CXCL10-) were not significantly different in the intervention group compared with the control group. The lowering effect in inflammatory biomarkers was correlated with the *trans*-lycopene in circulation, while the other carotenoids in tomato juice showed a minor or no association[219]. In another study, using IL-6, IL-8, hs-CRP and TNF-α as biomarkers of inflammation, Ghavipour *et al.* (2013)[220] found that 330 ml/d of tomato juice (112 mg lycopene/l) for 20 d significantly decreased serum concentrations of IL-8 and TNF-α in subjects who were overweight, while, among subjects with obesity, only serum IL-6 concentration decreased in the intervention group. Conversely, after 4-week consumption of 500 ml/d of tomato juice, no changes in inflammatory biomarkers (CRP, ICAM-1, and VCAM-1) in patients with T2D were observed[221].

Many studies have investigated the effect of tomato juice on biomarkers of oxidative stress. Ghavipour *et al.* (2015)[222], in a randomised controlled trial in females who were overweight, found that 330 ml/d of tomato juice for 20 d increased plasma total antioxidant capacity and erythrocyte antioxidant enzymes and decreased serum MDA levels compared with both baseline and the control group. No improvement was observed in subjects with obesity and, as hypothesised by the authors, this may be due to the need for a greater amount of lycopene or a longer duration of lycopene supplementation[222]. Upritchard *et al.* (2000)[221] reported that consumption of 500 ml/d of tomato juice for 4 weeks by T2D patients increased both plasma lycopene levels and the resistance of LDL to oxidation, almost as effectively as supplementation with a high dose of vitamin E (537 mg/d). Increased LDL resistance to oxidation was also observed by Silaste *et al.*[214] after 3 weeks of a high-tomato diet in healthy adults (27 mg lycopene/d). Conversely, in the study by Briviba *et al.* (2004)[223], MDA levels in plasma and faeces and *ex vivo* LDL oxidation were not affected in healthy men by supplementation for 2 weeks of 330 ml/d of tomato juice (112 and 5 mg/l of lycopene and β-carotene, respectively) in comparison to carrot juice[223]. Nonetheless, most studies have found improvements in biomarkers of oxidative stress. In addition, Bub *et al.* (2002)[224] found that the changes in antioxidant status after tomato juice consumption could be genotype-dependent, precisely related to the PON-1-192 polymorphism. Indeed, their results showed that consumption of 330 ml/d of tomato juice for 8 weeks reduced LDL-oxidation in healthy elderly who were R-allele carriers (QR/RR) but not in the QQ wildtype[224].

In conclusion, tomato juice may have favourable effects on lipid metabolism and glucose post-prandial response and could improve biomarkers of inflammation and oxidative stress. However, further studies are needed to demonstrate the effect of tomato juice on CVD risk factors and establish dose-response effects taking into account the responsible bioactive compounds. Although most of the evidence points to lycopene, the role of phenolic compounds on the health benefits of 100% tomato juice should not be neglected. Genotypic differences should also be considered.

Carrot juice

Carrot (*Daucus carota*) is a popular root vegetable and an important source of dietary carotenoids. Besides vitamins and minerals, carrot juice is rich in α- and β-carotene[225]. Both carotenes are vitamin A precursors (the pro-vitamin A activity of α- and β-carotene is 50% and 100%, respectively), and β-carotene has attracted much attention during the last decades due to its preventive features in different pathophysiological scenarios.

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Moreover, carrot juice is rich in caffeic acid, among other (poly) phenols, while black carrot juice may also present a high amount of anthocyanins[225]. Carrot juice and blends are important vegetable juices from a market point of view, while the level of evidence on their health properties is low due to the limited number of works published (Table 11).

Potter *et al.* (2011)[226] evaluated the effect of carrot juice on different cardiometabolic risk markers in seventeen individuals with elevated plasma cholesterol and TG levels. Treatment consisted of 470 ml (16 oz) of freshly squeezed carrot juice for 3 months without a control group. Carrot juice did not alter anthropometric parameters, body fat percentage, BP, lipid profile, glucose metabolism markers, and inflammatory markers, while it led to an increase in plasma antioxidant status and a decrease in MDA[226]. Contrary to these benefits in the oxidative stress balance, Briviba *et al.* (2004)[223] studied lipid peroxidation in plasma and faeces of healthy men consuming a diet low in carotenoids supplemented with 330 ml/d of tomato juice, as previously reported, or carrot juice (82 and 39 mg/l of β-carotene and α-carotene, respectively) for 2 weeks. Carrot juice consumption raised the plasma levels of α- and β-carotene, but this did not lead to improvements in biomarkers of lipid peroxidation[223]. In addition, carrot juice did not modulate immune functions in comparison to tomato juice[227].

Ramezani *et al.* (2010) conducted a randomised controlled double-blind study with 200 ml/d β-carotene-enriched carrot juice (active group) and carrot juice (placebo) for 8 weeks in forty-four patients with T2D[228]. Although serum levels of β-carotene increased, both treatments had no effect on markers of glycaemic homeostasis (glucose and insulin)[228] or inflammation (CRP and IL-6)[229].

Overall, despite the content of β-carotene and other bioactives, carrot juice does not seem to exert any significant effects on human subject health.

Beetroot juice

Beetroot (*Beta vulgaris*) juice has been primarily investigated for its high concentration of dietary nitrate (NO_3^-), which is partially converted to NO after consumption and may exert vasodilation-related benefits associated with vascular function, cardiorespiratory endurance and exercise performance. Zamani *et al.* (2021)[230] recently conducted a systematic review of the benefits and risks of beetroot juice consumption in healthy subjects, and it can be useful to deepen the knowledge on beetroot juice (Table 12).

Beetroot juice could help lower systolic and diastolic BP in healthy young adults, likely due to the vasodilatory effects of NO, whereas results in the elderly were inconclusive[230]. Several studies have reported a reduction in BP within 3 h after a single dose of beetroot juice, the effect lasting for several hours. For instance, Vanhatalo *et al.* (2010)[231] observed that 500 ml/d of beetroot juice for 15 d (10·4 mmol nitrate per litre) reduced both systolic and diastolic BP at different time points between 2·5 h and 15 d, suggesting that the effect of dietary nitrate may be maintained over time if supplementation continues. However, further studies investigating the beneficial effect of long-term beetroot juice in healthy people are needed. Regarding otherwise healthy populations, Kapil *et al.* (2015)[232] demonstrated that consumption of dietary nitrate from 250 ml/d of beetroot juice (~25·6 mmol nitrate per litre) for 4 weeks significantly reduced BP in hypertensive patients with hypertension at trial inception, with no evidence of tachyphylaxis over the 4 weeks, in comparison to a nitrate-free beetroot juice (control). BP was measured as clinic BP, 24-h ambulatory BP and home BP and significant reductions in both systolic and diastolic BP were shown[232]. Conversely, despite increased plasma, salivary, and urinary nitrite and nitrate, Bondonno *et al.* (2015)[233] observed no differences in home BP or 24-h ambulatory BP after 1 week of 70 ml of concentrated beetroot juice twice daily (~50 mmol nitrate per litre) compared with the placebo (nitrate-depleted beetroot juice) in treated hypertensive individuals. Similarly, 250 ml/d of beetroot juice (30 mmol nitrate per litre) for 2 weeks led to an increase in plasma nitrite and nitrate concentration but did not reduce 24-h mean ambulatory BP in T2D patients with antihypertensive therapy, compared with placebo (nitrate-depleted beetroot juice)[234]. It has been hypothesised that antihypertensive medication may limit the potential benefits of the dietary nitrates present in beetroot[235], explaining the absence of significant results in the two previous studies. Nevertheless, pooled evidence accounts for the beneficial effect of beetroot juice on BP reduction, and a greater reduction in both systolic and diastolic BP has been reported after beetroot juice supplementation in at-risk subjects compared with healthy participants[251,252].

In a randomised double-blind placebo-controlled 6-week study, Velmurugan *et al.* (2016)[238] reported that consumption of 250 ml/d of beetroot juice (~24 mmol nitrate per litre) significantly increased the FMD response in untreated hypercholesterolemic individuals, with a worsening in the placebo group (nitrate-depleted beetroot juice). Dietary nitrates were thus associated with an improvement in vascular function. Nitrate-rich beetroot juice also led to a small but significant reduction in platelet–monocyte aggregates (a marker of platelet activation) as well as a reduction in P-selectin expression[238]. The authors also observed a modest improvement in measures of arterial stiffness (aortic PWV and augmentation index) compared with the control group. In line with these results, Kapil *et al.* (2015)[232] reported an improvement in endothelial function and a reduction in arterial stiffness in hypertensive patients who consumed beetroot juice, with no change after control treatment. However, dietary nitrate from beetroot juice did not improve endothelial function in patients with T2D[234].

Many studies have evaluated the effects of beetroot juice on exercise and sport performance in healthy subjects[230]. Beetroot juice could improve sport performance through several mechanisms, such as reducing oxygen consumption in skeletal muscle and accelerating the transition between anaerobic and aerobic metabolism in muscle cells. In the latter case, the reduced accumulation of metabolites produced during anaerobic respiration (such as lactate) can delay the onset of fatigue and increase power output and force. In addition, due to the vasodilatory effect of NO, beetroot juice could increase muscle and cerebral blood flow[230]. Consumption of a single dose of beetroot juice has led to inconclusive results on training performance, although most of the studies in recreationally active or well-trained women suggested positive effects. Short-

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Table 11. Characteristics of some representative studies investigating the health effects of 100% carrot juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Carrot	RT, CO, 2 weeks	$n = 22$ (M), healthy, non-smoking, in a low-carotenoid diet	330 ml/d	27 mg β-carotene, 13 mg α-carotene	Tomato juice (37 mg lycopene, 1·6 mg β-carotene)	No modulation of immune functions in comparison to tomato juice No changes in MDA in plasma and faeces; ↑ lag time during *ex vivo* LDL oxidisation	Watzl *et al.*, 2003[227] Briviba *et al.*, 2004[223]
Carrot	RCT, DB, two-arm, parallel, 8 weeks	$n = 44$ (22 F, 22 β-carotene-enriched carrot juice (active group), 22 carrot juice), patients with T2D, NW/OW/OB, 55 (SD 6) years	200 ml/d		Comparison of both interventions	no changes in glucose and insulin	Ramezani *et al.*, 2010[228]
Carrot	RT, 3-month	$n = 17$ (9 F), with high levels of plasma cholesterol and triglycerols, OW/OB	470 ml/d (16 fl oz)		No control	↑ plasma antioxidant status; ↓ MDA and SBP; no changes in anthropometry, DBP, TC, LDL, HDL, TAG, Apo A, Apo B, body fat %, insulin, leptin, IL-1α, CRP	Potter *et al.* (2011)[226]
Carrot	RCT, DB, two-arm, parallel, 8 weeks	$n = 44$ (22 F, 22 β-carotene-enriched carrot juice (active group), 22 carrot juice), patients with T2D, NW/OW/OB, 55 (SD 6) years	200 ml/d		Comparison of both interventions	↑ β-carotene levels in active group; no changes in CRP and IL-6	Ramezani *et al.*, 2014[229]

Juices were 100% juice unless otherwise stated. Abbreviations: Apo A, apolipoprotein A; Apo B, apolipoprotein B; CO, crossover; CRP, C-reactive protein; DB, double-blind; DBP, diastolic blood pressure; F, female; HDL-c, HDL-cholesterol; IL-1α, interleukin-1α; IL-6, interleukin-6; LDL-c, LDL-cholesterol; M, male; MDA, malondialdehyde; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); RCT, randomised controlled trial; RT, randomised trial; SBP, systolic blood pressure; T2D, type 2 diabetes; TAG, triglycerides; TC, total cholesterol; ↓, decreased level; ↑ increased level

Table 12. Characteristics of some representative studies investigating the health effects of 100% beetroot juice

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bio-active compounds	Control/Placebo group	Main findings	Reference
Beetroot	RT, CO, 15 d	*n* = 8 (3 F), healthy, 29 (SD 6) years	500 ml/d	10·4 mmol nitrate per litre	Low-calorie blackcurrant juice cordial (no nitrate)	↓ SBP and DBP	Vanhatalo *et al.*, 2010[231]
Beetroot	RCT, DB, CO, 2 weeks	*n* = 27 (9 F), patients with >5-year T2D, hypertensive, OB, 67 (SD 5) years	250 ml/d	30 mmol nitrate per litre	Nitrate-depleted beetroot juice	No changes in 24-h mean ambulatory BP and endothelial function	Gilchrist *et al.*, 2013[234]
Beetroot	RCT, DB, CO, 1 week	*n* = 27 (17 F), hypertensive medicated subjects, NW/OW, 63 (SD 4) years	140 ml/d	~50 mmol nitrate per litre	Nitrate-depleted beetroot juice	No changes in home BP and 24-h ambulatory BP	Bondonno *et al.*, 2015[233]
Beetroot	RCT, DB, 4 weeks	*n* = 64 (38 F, 32 intervention group), hypertensive patients, OW/OB, 56 (SD 16) years	250 ml/d	~25·6 mmol nitrate per litre	Nitrate-depleted beetroot juice	↓ SBP, DBP and arterial stiffness; improvement in endothelial function	Kapil *et al.*, 2015[232]
Beetroot	RCT, DB, CO, 4 d	*n* = 48 (13 F), patients with >5 years T2D, OW/OB, 63 (SD 7) years	70 ml/d	92 mmol nitrate per litre	Nitrate-depleted beetroot juice	No change in the O_2 cost of walking test and distance covered in the 6-min walk test	Shepherd, Gilchrist *et al.*, 2015[239]
Beetroot	RCT, DB, CO, 2·5 d with the final supplement ~3 h before testing	*n* = 13, with mild–moderate COPD, OW, 65 (SD 8) years	140 ml/d	97 mmol nitrate per litre (6·77 mmol/d)	Nitrate-depleted beetroot juice	↑ plasma nitrite and nitrate concentration; no reduction in the O_2 cost of cycling test nor in SBP and DBP	Shepherd, Wilkerson *et al.*, 2015[240]
Beetroot	RCT, DB, parallel, 6 weeks	*n* = 65 (33 intervention), healthy hypercholesterolemic, NW/OW/OB, 53 (SD 12) years	250 ml/d	~24 mmol nitrate per litre	Nitrate-depleted beetroot juice	↑ FMD, aortic PWV and augmentation index; ↓ platelet-monocyte aggregates, P-selectin expression; no differences in ox-LDL; ↑ microbial species capable of nitrate reduction in salivary microbiome	Velmurugan *et al.*, 2016[238]

Juices were 100% juice unless otherwise stated. Abbreviations: BP, blood pressure; CO, crossover; COPD, chronic obstructive pulmonary disease; DB, double-blind; DBP, diastolic blood pressure; F, female; FMD, flow-mediated dilation; M, male; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); ox-LDL, oxidised-LDL; PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SBP, systolic blood pressure; T2D, type 2 diabetes; ↓, decreased level; ↑ increased level

term beetroot juice consumption (more than one dose daily or multiple days) showed positive effects in recreationally active men (for example, by improving time to exhaustion or recovery), whereas results for well-trained men were inconclusive[230]. When taking into consideration subjects with underlying health conditions, Shepherd *et al.* (2015)[239] found that 4-d 70 ml/d beetroot juice (92 mmol nitrate per litre) did not reduce the O_2 cost of walking in individuals with T2D nor increase the distance covered in the 6-min walk test compared with the control juice (nitrate-depleted), despite plasma nitrate and nitrite concentration increased. The same results were obtained in individuals with chronic obstructive pulmonary disease consuming the same juice (70 ml/d, 97 mmol nitrateper litre) twice a day for 2·5 d, with the final serving 3 h before the activity; in this case, the O_2 cost was measured by a moderate intensity cycling[240]. Nevertheless, the research on this topic is continuously evolving, and a more in-depth analysis would be needed to better understand the role of beetroot juice on exercise and sport performance.

Examining biomarkers of oxidative stress, Velmurugan *et al.* (2016)[238] did not find differences in ox-LDL in untreated hypercholesterolemic subjects who consumed 250 ml/d of nitrate-rich beetroot or a control nitrate-depleted beetroot juice. These authors also indicated that beetroot juice could influence microbiota composition. The salivary microbiome was altered after beetroot juice but not after the control, and the shift in the oral microbiome was in favour of organisms capable of nitrate reduction[238]. In fact, the effect of beetroot juice on exercise performance may be mediated by oral microbiota[241], a topic that deserves further research.

Besides beneficial effects, Zamani *et al.* (2021)[230] also considered the potential risks of consuming beetroot juice. As a source of nitrate, beetroot juice could lead to the formation of potentially carcinogenic *N*-nitroso compounds. For example, Berends *et al.* (2019)[242] found a significant increase in urinary apparent total *N*-nitroso compounds after a 70 ml dose of beetroot juice (~92 mmol nitrate per litre) and a further increase after seven consecutive doses. Thus, although beetroot juice has shown several beneficial effects, further studies should also investigate the link between its intake and the formation of *N*-nitroso compounds.

In conclusion, dietary nitrate from beetroot juice has been shown to improve BP in healthy individuals or untreated hypertensive subjects, but not in treated hypertensive patients or T2D patients. Improvements in vascular function have also been reported for untreated hypercholesterolemic and hypertensive patients, but not for patients with T2D. In general, pooled results from meta-analyses point to the beneficial effects of beetroot juice on BP and vascular function, whereas the baseline characteristics of the populations seem to be critical to benefit from juice consumption[236]. The benefits of beetroot juice on exercise performance were seen in some populations, but they depended very much on the dose and type of exercise, among other factors. The effect of beetroot juice on other common cardiometabolic risk factors beyond cardiovascular function has been scarcely investigated and deserves further research. Last, attention has been paid to nitrate, but other beetroot bioactives such as betalains may also play a role and, once again, additional research is needed.

Other juices

Watermelon juice. Watermelon (*Citrullus lanatus*) is a rich source of the non-essential amino acid L-citrulline, a precursor of L-arginine, which is a substrate for nitric oxide (NO) synthase. Additionally, it is a source of lycopene and other carotenoids[243]. As previously stated, NO is a vasodilator molecule, and it is key to vascular endothelial function. In exercise/sport physiology, NO has received much interest because of its ergogenic effect and, indeed, watermelon juice has been studied primarily related to sport activity.

Shanely *et al.* (2020)[243] observed that 6-week supplementation of 710 ml/d of 100% watermelon puree (1·87 g L-citrulline per litre, 0·39 g L-arginine per litre, 45 mg lycopene per litre) improved sVCAM-1 levels, a marker connected to atherogenesis, in post-menopausal women who were overweight/obese, whereas fasting blood glucose, insulin and HOMA-IR did not change (Table 13). In another study conducted on post-menopausal women, two daily 360 ml servings of 100% watermelon juice for 4 weeks did not affect BP or arterial stiffness despite an increase in circulating lycopene being recorded[244]. No effect on inflammation and oxidative stress markers was observed[245], while fasting blood glucose slightly increased although changes in glucose homeostasis lacked clinical relevance[244]. Some post-prandial beneficial effects of watermelon juice have recently been observed in healthy adults[246].

Regarding the role of watermelon juice on exercise, Blohm *et al.* (2020)[247] found that a single dose pre-exercise of 355 ml of watermelon juice (2·2 g L-citrullineper litre; 3·1 g potassium per litre) prevented increased post-exercise systolic and diastolic BP in fourteen healthy non-athletic females, but not in thirteen males. It was thus suggested to examine the effect of sex when assessing the efficacy of watermelon juice on BP. Authors found no effect on post-exercise muscle soreness, blood lactate levels or exercise performance[247]. A lack of effect of watermelon juice on exercise performance in comparison with a placebo carbohydrate beverage was reported when twenty trained cyclists consumed 980 ml/d of watermelon puree for 2 weeks and during 75 km cycling time trials, despite watermelon increased plasma L-citrulline and L-arginine concentrations and total nitrates[248]. In another randomised crossover study, Martínez-Sánchez *et al.* (2017)[249] reported a lower muscle soreness perception from 24 to 72 h after a half marathon race and lower plasma lactate concentrations in amateur runners who consumed 500 ml L-citrulline-enriched watermelon juice (6·91 g L-citrulline per litre; 13·98 mg lycopene per litre) 2 h before the marathon race compared to runners in the placebo group (no L-citrulline and lycopene).

Few studies were available on watermelon juice to draw major conclusions. The effect of 100% watermelon juice consumption at cardiometabolic level has been studied mainly in post-menopausal women, and no relevant benefits were reported. Although it has been hypothesised that watermelon juice may have a significant effect on exercise performance, no

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Table 13. Characteristics of some representative studies investigating the health effects of other 100% juices like watermelon, wild passionfruit and cashew apple

Intervention juice	Study design	Study participants	Juice amount	Daily dose of bioactive compounds	Control/Placebo group	Main findings	Reference
Watermelon	RCT, DB, CO, single-dose 2h pre-marathon	*n* = 21 (M), healthy, amateur runners male, 35 (SD 11) years	500 ml	6·91 g L-citrulline per litre; 13·98 mg lycopene per litre	Beverage without L-citrulline	↓ plasma lactate and muscle soreness perception from 24 to 72 h after the half-marathon race	Martínez-Sánchez *et al.*, 2017[249]
Watermelon	RCT, CO, single-dose pre-exercise	*n* = 27 (14 F), healthy, NW, 25 (SD 1) years	355 ml	2·2 g L-citrulline per litre; 3·1 g potassium per litre	Bottled water, sugar water, Gatorade	No increased post-exercise SBP and DBP in females, not in males; no effect on post-exercise muscle soreness, blood lactate levels or exercise performance	Blohm *et al.*, 2020[247]
Watermelon puree	RCT, 2-arm, 6 weeks	*n* = 45 (F, 26 intervention), OW/OB post-menopausal, 60 (SD 1) years	710 ml/d	1·87 g L-citrulline per litre, 0·39 g L-arginine per litre, 45 mg lycopene per litre	No intervention	↓ VCAM-1 levels; no change in FG, insulin, and HOMA-IR	Shanely *et al.*, 2020[243]
Watermelon	RCT, DB, CO, 4 weeks	*n* = 21 (F), post-menopausal, 60 (SD 4) years	360 ml twice/d	2·26 g citrulline/l, 1·60 g arginine/l, 20 mg lycopene/l	Isoenergetic placebo matched for sugar content	No effect on inflammatory markers, oxidative stress and cognitive tests ↑ FG, no change in insulin, HOMA-IR, BP, PWV, FMD, BMI, fat %	Crowe-White *et al.* 2021[245] Ellis *et al.* 2021[244]
Wild passionfruit juice (*Passiflora setacea*)	RCT, DB, two-phase, single-dose	*n* = 12 (M), OW/OB, 49 (SD 7) years	250 ml		Isoenergetic placebo drink: 100 ml of a passionfruit-flavoured isotonic drink with 150 ml of water	↑ HDL-c; ↓ insulin and HOMA-IR; no changes in TC, LDL-c, TAG, circulating cytokines	Duarte *et al.*, 2020[250]
Cashew apple	RCT, CO, 4 weeks	*n* = 20 (M, trained/untrained), NW, 2 (SD 3) years	3·5 ml/kg/d		Isoenergetic control drink without (poly)phenols	↑ fat oxidation during high-intensity exercise in trained and untrained subjects	Prasertsri *et al.*, 2013[251]
Cashew apple	RCT, DB, CO, 4 weeks	*n* = 20 (M, trained/untrained), NW, 20 (SD 3) years	3·5 ml/kg/d		Isoenergetic control drink without (poly)phenols	↑ exercise-induced leucocyte and resting neutrophil counts in trained men	Prasertsri *et al.*, 2019[252]

Juices were 100% juice unless otherwise stated. Abbreviations: BMI, body mass index; BP, blood pressure; CO, crossover; DB, double-blind; DBP, diastolic blood pressure; F, female; FG, fasting blood glucose; FMD, flow-mediated dilation; HDL-c, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, LDL-cholesterol; M, male; NW, normal weight (BMI: 18,5–24,9 kg/m^2); OB, obesity (BMI: >30 kg/m^2); OL, open label; OW, overweight (BMI: 25–30 kg/m^2); PWV, pulse wave velocity; RCT, randomised controlled trial; RT, randomised trial; SBP, systolic blood pressure; TAG, triglycerides; TC, total cholesterol; VCAM-1, vascular cell adhesion molecule; ↓, decreased level; ↑ increased level

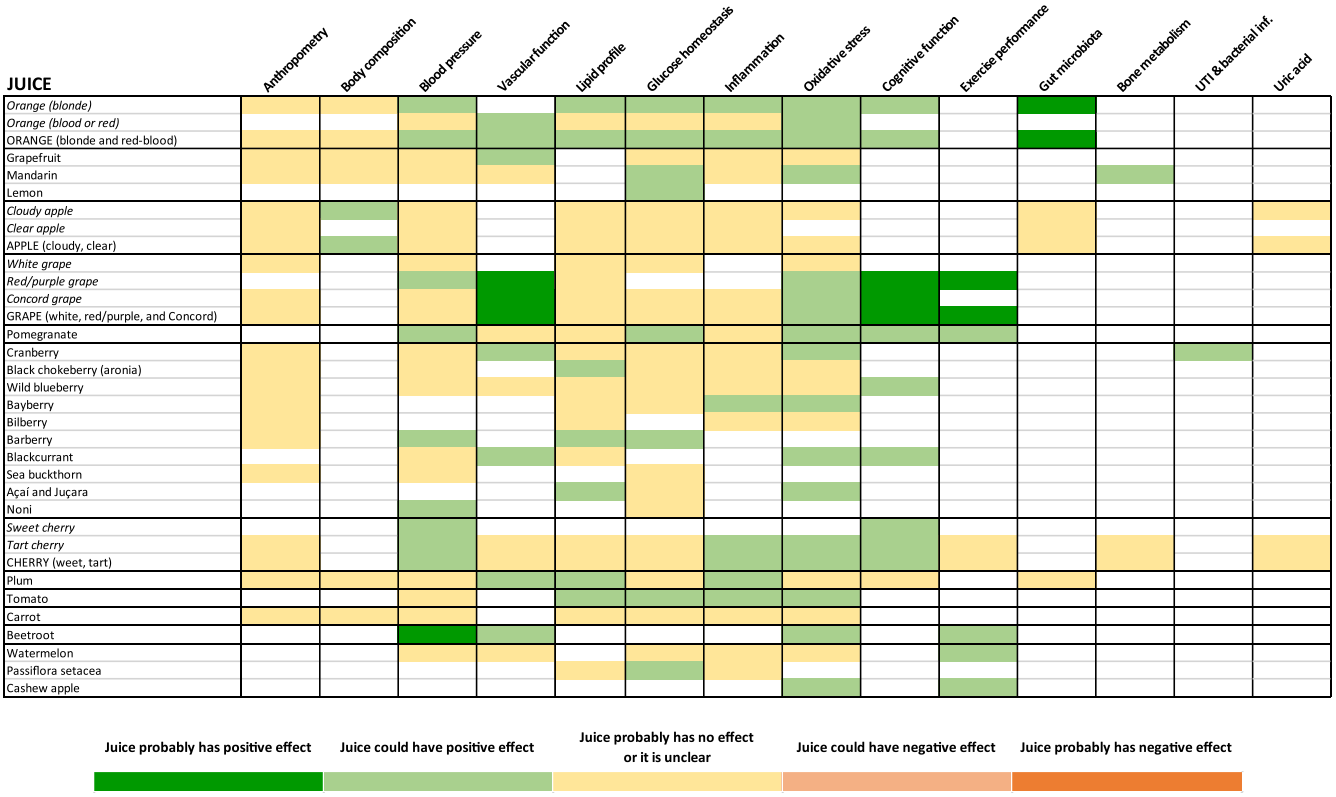

Fig. 2. Potential impact of specific 100% FVJ on human subject health for the main outcomes addressed in the literature. Categories have been attributed considering the evidence presented for each juice and adopting a conservative approach, indicated in 'summary of the evidence'

consistent effects have been seen in studies, perhaps due to heterogeneity in populations and exercise protocols.

Wild passionfruit juice. *Passiflora setacea* or sleep passionfruit is a wild passionfruit species particularly rich in *C*-glycoside flavones, such as orientin, homoorientin, vitexin and isovitexin[250]. Duarte *et al.* (2020)[250] observed that 3 h after 250 ml *P. setacea* juice consumption, HDL-C levels slightly increased significantly in twelve overweight males, while they did not change after placebo intake (Table 13). Furthermore, insulin levels and HOMA-IR decreased significantly 3 h after *P. setacea* juice, whereas no changes were observed after placebo. TC, LDL-C, TG, glucose and inflammatory cytokines were not affected by the treatment. The nutrigenomic study revealed genes differentially expressed after *P. setacea* juice consumption, some involved in processes such as inflammation, cytokine–cytokine receptor or cell adhesion[250].

Cashew apple juice. The cashew apple is a product of cashew nut (*Anacardium occidentale*) manufacturing. The effect of cashew apple juice was investigated on high-intensity exercise, and the potential beneficial effect was related to its content of vitamin C, anacardic acids (phenolic lipids) and branch chain amino acids (Table 13). Prasertsri *et al.* (2013)[251] suggested that 4-week consumption of 3·5 ml/kg/d of cashew apple juice (245 ml/d for a 70-kg subject) enhanced fat oxidation during high-intensity exercise in trained and untrained subjects; thus, it could be beneficial for endurance performance. In another study with the same design (4-week, 3·5 ml/kg/d), Prasertsri *et al.* (2019)[252] found that cashew apple juice enhanced exercise-induced leucocyte and resting neutrophil counts in trained men, highlighting that the possible mechanism for this effect was a reduction in oxidative stress.

Summary of the evidence

Epidemiological evidence, although heterogeneous, has demonstrated that moderate consumption of FVJ may have a positive or neutral association with human subject health. The results of this review on intervention studies for specific 100% FVJ also accounted for a beneficial or neutral impact of juice consumption on many health outcomes. Most of the studies in the literature have been focused on anthropometry and cardiometabolic markers (BP, vascular function, lipid profile, glucose metabolism, inflammatory markers and oxidative stress status), with some research also addressing cognitive and exercise performance, bone metabolism, gut microbiota composition and bacterial infections. A summary of the potential impact of each 100% FVJ on human subject health for the outcomes assessed is provided in Fig. 2. This review spotted that no significant harmful effects were observed for any juice, while moderate or major benefits were seen on particular outcomes for many juices. A total of 100% FVJ did not significantly impact anthropometric parameters or body composition. Major beneficial effects on BP were related to beetroot juice consumption, as well as orange, pomegranate, and cherry juices. FMD improved significantly after red and Concord grape juices, while juices made from

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cranberry, plum and beetroot may also positively influence endothelial function. Other cardiometabolic markers related to the lipid profile and glucose homeostasis showed improvements after consumption of some juices like orange or tomato juices. Inflammatory and oxidative stress markers also improved after orange, tart cherry and tomato juice consumption, but the literature on these outcomes is generally difficult to assess as many markers with different biological significance are usually considered and may yield contrasting results. Benefits at the cognitive level were found after red and Concord grape and sweet and tart cherry juices, while only red grape juice and beetroot showed clear improvements in exercise performance. Other less-explored outcomes indicated that orange juice could positively modulate gut microbiota composition, whereas cranberry juice might have a moderate influence on bacterial infections.

The results summarised in Fig. 2 should be considered carefully. They are just a simplification of the evidence to date, and several factors should be taken into account before promoting specific FVJ for some physiological targets. First, the population setting is key as different (patho)physiological conditions may lead to different effects depending on individual's health status. Individuals who are overweight or obese, with hyperlipidemia, T2D or other cardiometabolic issues cannot be addressed in the same way as healthy individuals. Medication or genetic polymorphisms may also limit the benefits of an intervention with a particular 100% fruit or vegetable juice. Age and sex are other aspects to keep in mind, as the response to the intervention may also change. Second, in line with the previous point, not all the dietary interventions with 100% FVJ may benefit the whole population as a high inter-individual response to these juices or their potential bioactive compounds have been reported. This does not obviously preclude juice consumption, but it should further encourage the juice community to deepen this pivotal point and strengthen the evidence behind the beneficial effects of FVJ on specific individuals. Although a 'one-size-fits-all' approach may be appealing from a commercial point of view, it does not necessarily reflect the current scientific evidence and may lead to controversial matters in the long term. Third, the size and number of daily/weekly servings determine the efficacy of any intervention with 100% FVJ, as evaluated from the available literature. Servings should also be considered within the diet of each individual, being aware of the fact that 'the more, the better' is something that usually never works in the nutrition of man. Indeed, several studies were conducted with serving sizes not consistent with dietary advice in most countries (for instance, with 400–800 ml/d); so, although these doses can be useful when assessing juice effects on human subject health, research conducted with lower doses (125–250 ml/d) may be a better help to rethink the role of 100% FVJ consumption on dietary guidelines. Last, most beneficial effects were linked to (poly) phenols or, in some cases, to other dietary components. Even though approaches focused on individual compounds or families of bioactives are scientifically supported, juices should be regarded as a whole, including not only other families of bioactives but also nutrient composition.

The evidence summarised in Fig. 2 is subject to some bias. The information on some juices and outcomes was relatively scarce, often limited to one or just a few articles. A cautious approach was followed, and major positive effects were only indicated when several works pointed out the same results and data were backed by meta-analyses. Moderate positive effects were shown even when only one or two works yielded a significant improvement in a particular outcome. Consequently, moderate benefits should be regarded as preliminary in some cases, although they may be helpful to drive further research efforts to confirm these promising results. On the other hand, beyond differences in population settings, there is a high heterogeneity among the existing studies on the health effects of 100% FVJ: doses, daily servings, periods of consumption, and juice compositions often varied among interventions. This diversity may limit the impact of the available research; so, when possible and compatible with the research hypothesis, further efforts should be directed to the use of more reproducible protocols. Good examples of similar research protocols were seen, for instance, for Concord grape, cranberry, tart cherry, QG plum and beetroot juice studies. On the other hand, juice composition is sometimes missing or is not correctly reported, the profile of macro-, micro-nutrients and bioactive compounds being quite incomplete. In addition, the use of non-selective spectrometric tools for the characterisation of juice bioactives, in particular in the case of phenolic compounds, does not allow for the identification of specific compounds in the juice but just the class. In this sense, juice composition is vital to evaluate the juice impact on health and better understand how to boost its potential beneficial effects through new agronomical/processing techniques. Last, not all the juices were 100% single-strength juices: some used concentrated juices that were reconstituted to the original juice or that were further diluted. Nevertheless, some juices are not commonly sold as 100% juice due to their organoleptic characteristics (for example, high acidity, bitterness, astringency, etc.), so the evidence presented is the closest to what a consumer may purchase and drink. On the other hand, some juices also included extracts rich in the bioactive compounds that are naturally presented in the juice: they were just considered to collect further evidence and serve for the design of new juice products with superior bioactive characteristics, as well as to make more sustainable juice productions by including by-products usually containing plenty of bioactive compounds, such as juice pomace.

Conclusions

100% FVJ appear to have a beneficial or neutral effect on the health of man in human subject intervention studies. Some juices have demonstrated the ability to exert potential preventive effects on some outcomes with others exerting effects on other health outcomes, which may be related to their differential composition in bioactive compounds. Further efforts should be devoted to this topic as robust, evidence-based conclusions are needed to demonstrate the beneficial impacts of 100% FVJ on human subject health and to support the development of dietary guidelines that inform population dietary choices. Lack of

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evidence may also jeopardise industry competitiveness through the use of unsupported statements.

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Authorship

P.M. conceptualised and designed the study; I.R. contributed to literature search and conducted data analysis and interpretation; P.M. visualised the data; I.R. and P.M. wrote the manuscript; C.M. and D.D.R critically reviewed the manuscript. All authors read and approved the final version.

Nomenclature

BMI-body mass index;
BP-blood pressure;
CRP-C-reactive protein;
CVD-cardiovascular disease;
FJ-fruit juice;
FMD-flow-mediated dilation;
FVJ-fruit and vegetable juice;
HDL-C-HDL-cholesterol;
HOMA-IR-homeostasis model assessment-insulin resistance;
hs-CRP-high-sensitivity CRP;
ICAM-1-intercellular adhesion molecule 1;
IL-n-interleukin-n;
LDL-C-LDL-cholesterol;
MDA-malondialdehyde;
ox-LD-Loxidised LDL;
PON-1-paraoxonase-1;
PWV-pulse wave velocity;
QG-Queen Garnet;
sICAM-soluble ICAM;
SSB-sugar-sweetened beverages;
sVCAM-soluble VCAM;
T2D-type 2 diabetes;
TC-total cholesterol;
TG-triglycerols;
TNF-α-tumour necrosis factor-alpha;
UTI-urinary tract infections;
VCAM-1-vascular cell adhesion molecule-1.

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