Tart cherry juice consumed daily for 4 weeks does not impair or exacerbate biomarkers of metabolic function in at-risk overweight and obese subjects: A randomized, crossover pilot study

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Abstract. Currently, there is a worldwide epidemic of obesity, diabetes and cardiovascular disease (CVD), largely due to increased dietary caloric intake. A number of scientists and experts assert that the increased consumption of caloric sugar-sweetened beverages (SSBs) has significantly contributed to the risk of developing chronic disease, particularly obesity, since the worldwide consumption of sucrose has tripled over the past 50 years. With these trends, perturbations in metabolic biomarkers have often been noted. Thus, the present study examined whether the consumption of 8 oz/day (240 ml/day) of 100% tart cherry juice (TCJ) would adversely affect metabolic parameters in at-risk individuals. The present study was a 10-week 2x2 crossover, randomized, placebo-controlled dietary intervention in overweight and obese participants (BMI ≥25.0 kg/m^2). Participants were randomly assigned to consume for 4 weeks either 100% TCJ (240 ml/day) or a generic fruit punch followed by a 2-week washout and subsequent consumption of the alternate beverage for an additional 4 weeks. Comprehensive metabolic panels (hepatic and renal function), anthropometric measures, and food intake and physical activity questionnaires were collected and analyzed at 0, 4, 6 and 10 weeks. No significant alterations (P>0.05) in hepatic or renal function were noted from the start to the end of the study when comparing the TCJ to the placebo group. Moreover, there were no significant changes (P>0.05) in fasting blood glucose concentrations between pre- and post-consumption time points for either the placebo or TCJ groups. Dietary intake and physical activity levels were similar among all groups. In addition, no changes in body composition (percent body fat, lean body mass, etc.) or BMI were noted after 4 weeks of beverage consumption. It was thus concluded that 100% TCJ does not exacerbate already existing risk factors in an at-risk population and does not adversely affect hepatic or renal function.

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Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; HFCS, high-fructose corn syrup; NAFLD, non-alcoholic fatty liver disease; SSBs, sugar-sweetened beverages; TC, total cholesterol; TCJ, tart cherry juice; T2DM, type 2 diabetes mellitus; TG, triglycerides

Key words: tart cherry juice, overweight/obese, metabolic syndrome, liver/kidney function

Introduction

Currently, there is a worldwide epidemic of obesity, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) largely thought to be due to increased dietary caloric intake (1-3). A number of scientists and experts assert that the increased consumption of sugar-sweetened beverages (SSBs) has significantly contributed to these trends, particularly obesity, since the worldwide consumption of sucrose has tripled over the past 50 years (4-6). In the USA, 77% of all calories purchased from 2005-2009 contained sweeteners of which corn syrup, cane sugar, high-fructose corn syrup (HCFS) and fruit juice concentrate were listed as the most commonly used (7). A high SSB consumption reportedly contributes to a 12% increased risk of hypertension, 26% increased risk for T2DM and a 19% increased risk of CVD, suggesting that further research is required regarding dietary sources of simple sugars [mono-(glucose and fructose) and disaccharide (sucrose)] contained in beverages, such as fruit juice (8-10).

A conundrum exists regarding the consumption of fruit juice. The argument in favor of 100% fruit juice as a healthy beverage derives from the fact that Americans of all ages do not meet their daily fruit requirement and 100% fruit juice offers most of the nutrients of whole fruit in a less expensive, more user-friendly form (8,11). In fact, reducing or eliminating 100% fruit juice, and consequently nutrients and fiber contained within, could lead to unintended consequences, such as a reduced daily fruit intake and an increased consumption

of less nutritious, calorie-dense beverages, such as soft drinks (12,13). Moreover, numerous fruit juices are produced from exotic 'superfruits', such as noni, maqui, acai, goji, pomegranate, etc., due to their complement of beneficial bioactive, e.g., antioxidant, compounds, which can lead to robust health benefits (14,15). However, there is limited published information available on the toxicity profiles of some dietary fruit juices due to their prevalence in the food supply, common use and the general lack of evidence that would support safety concerns. As a result, there seems to be a misconception that fruit juices and smoothies are also low-sugar alternatives to SSBs (4). Although fruit juices may generally be considered safe, chronic consumption, similar to dietary triglycerides (TG), could cause metabolic perturbations, contributing to the risk of developing chronic diseases, such as non-alcoholic fatty liver disease (NAFLD), e.g., liver toxicity and renal dysfunction (16-18).

Fruit juices have been shown to induce mild to moderate adverse effects on typical metabolic biomarkers in different experimental models. For example, in rodent studies, the provision of fruit juice for 48 h significantly and dose-dependently increased liver enzyme, urea and creatinine levels, suggesting both nephrotoxicity and hepatotoxicity (19,20). In another study, the ingestion of pomegranate was associated with the deaths of young cattle without prior clinical signs, although gross subclinical pathological changes indicated hepatotoxicity (21). In a study on noni fruit (*Morinda citrifolia*), female mice fed fruit extracts for 6 months displayed chronic toxicity with clear hepatocellular necrosis, morphological changes in liver, and death after 3 months (22). In humans, cases of hepatotoxicity have also been reported following the consumption of noni juice. In two human case studies reported by Stadlbauer *et al* in a single report, individuals developed sub-acute hepatic failure and acute hepatitis following the consumption of 1.5 l juice for 3 weeks and 2 l juice for 3 months, respectively (23). The bottle gourd (*Lagenaria siceraria*), also known as lauki, ghia or dudhi, prescribed as part of traditional medicine, has been shown to cause numerous signs and symptoms of gastrointestinal and hepatic injury (24). Collectively, there are instances where dietary and/or medicinal fruit juices have increased the risk of hepatotoxicity.

Beverages, such as SSBs may also influence the risk of developing kidney disease (18). In the Jackson Heart Study (n=3,003) a higher consumption of SSBs was shown to elevate the risk of chronic kidney disease (CKD) in a community-based cohort of African-Americans (25). In the Tehran Lipid and Glucose Study (n=1,690), the consumption of >4 servings of SSBs was associated with a higher prevalence and incidence of CKD (26). In the Atherosclerosis Risk in Communities Study (n=15,745) the consumption of 1 SSB/day increased the prevalence of hyperuricemia and CKD with an odds ratio of 2.59 for those consuming >1 SSB/day (17). As mentioned previously, the consumption of star fruit juice also induces kidney degeneration and necrosis compared to the controls, indicating nephrotoxicity (19). In at least one case report, an individual who consumed star fruit developed acute kidney failure requiring dialysis (27). Thus, there are data suggesting the potential for some dietary and/or medicinal fruit juices to cause nephrotoxicity.

Emerging evidence supports the robust complement and activities of bioactive molecules in functional foods, e.g., tart cherries and beverages, such as tart cherry juice (TCJ). The authors have conducted studies previously with TCJ investigating the effects of consumption on inflammatory markers and uric acid in humans, and currently report on the effects of TCJ on body composition or metabolic parameters in at-risk individuals. The present study enlisted overweight and obese individuals at a higher risk for cardiometabolic abnormalities (due to increased adiposity) compared to those with normal body weights (BMI <25.0 kg/m^2) to consume 100% TCJ or the placebo beverage for 4 weeks (8 oz/day; 240 ml/day) to determine whether there were any changes in the levels of biomarkers of renal and/or hepatic function.

Materials and methods

Study subjects. The present study was a 10-week 2x2 crossover, randomized, placebo-controlled dietary intervention in overweight and obese participants (BMI ≥25.0 kg/m^2) who were ≥18 years old. Respondents were excluded if they were pregnant, diabetic, displaying unresolved infections or diseases (inflammation, CVD, cancer, inflammatory bowel disease and liver disease), and were current smokers (including e-cigarettes). Histories of medication and dietary supplement use were collected, and participants taking anti-inflammatory or lipid-lowering medications were excluded. The respondents were screened initially by telephone using a preliminary medical questionnaire to rule out underlying medical conditions. All subjects provided written informed consent. The protocols in the present study were approved by the Institutional Review Board at Arizona State University. This trial is registered with ClinicalTrials.gov with identifier, NCT03638362.

Following enrollment, the subjects were randomly assigned to consume either 8 ounces of 100% TCJ (R.W. Knudsen) or a generic, artificially flavored red fruit punch for 4 weeks with 5 patients per group. Following a 2-week washout period, the subjects were switched to the alternate beverage for an additional 4 weeks (Fig. 1). Participants were instructed to refrain from consuming other darkly pigmented fruits and juices during the study period, and were provided a detailed list with specific items, i.e., cherries, to avoid. Compliance was monitored by the review of diet records, a verbal interview and the return of empty beverage containers.

Dietary, medical and physical activity questionnaires and records were maintained by subjects and collected and reviewed by study personnel. The diet record listed all foods and beverages consumed (including placebo and tart cherry beverages), means of preparation, time of consumption, and amount/portion size and was analyzed using Food Processor Nutrition and Fitness Software (ESHA, version 8.5). The medical questionnaire included information on the use, dosage and frequency for medication and the use of dietary supplements. Physical activity was assessed by self-reporting using a standardized questionnaire and overall physical activity and/or exercise determined using a standardized scoring rubric.

Anthropometry. Following a ≥12-h fast, participants reported to the laboratory for the measurement of body weight (via calibrated scale), height (via calibrated stadiometer) and body

Table I. Macronutrient and energy intake by the study participants.

Nutrient	Placebo	Treatment	P-value
Energy, kcal/day	1,816±417	1,782±452	0.685
Protein[a], g/day	66±15	61±0.6	0.228
Carbohydrate, g/day	257±70	255±69	0.382
Total fat[b], g/day	57±70	56±16	0.377

Values are the means ± SD, n=10. No significant differences were observed between the groups. [a]The Wilcoxon test was used to transform non-normal data. [b]Data were transformed to achieve normality.

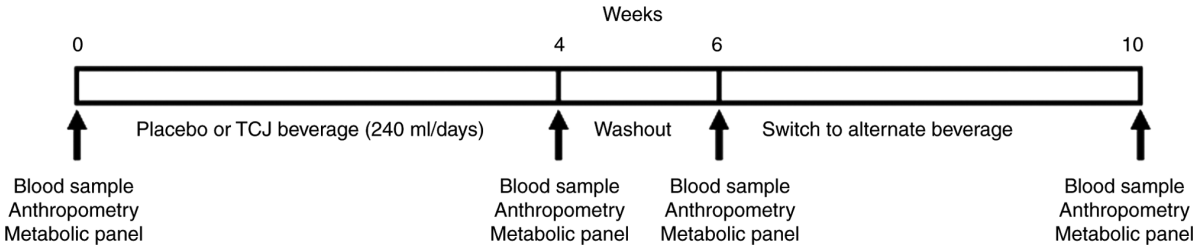

Figure 1. Experimental design of the present study. Following enrollment, the subjects were randomly assigned to consume either 8 ounces of 100% TCJ (R.W. Knudsen) or a generic, artificially flavored red fruit punch for 4 weeks. Following a 2-week washout period, the subjects were switched to the alternate beverage for an additional 4 weeks. TCJ, tart cherry juice.

composition [body fat percentage, fat mass, fat-free mass, total body water, basal metabolic rate (BMR)], as measured by bioelectrical impedance (TBF 300A Tanita Body Composition Analyzer). BMI and BMR were recalculated at each visit.

Biomedical analysis. Fasting blood samples were drawn by standard venipuncture protocols into lithium heparin vacutainer tubes (Thermo Fisher Scientific, Inc.). A comprehensive metabolic panel reagent disc, which included an assay for glucose, was used to concurrently measure biomarkers of liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, total bilirubin and alkaline phosphatase (ALP)] and nitrogen balance/kidney function [blood urea nitrogen (BUN), creatinine and albumin], using a Piccolo Blood Chemistry Analyzer (Abaxis Inc.). Briefly, 100 μl of whole blood was transferred from each vacutainer (prior to centrifugation) to a reaction disc (Piccolo Comprehensive Metabolic Panel, Abaxis, CA) with preloaded, partitioned, test-specific reagents including diluents, surfactants, and preservatives for each tested analyte (sodium, potassium, total protein, total carbon dioxide, total bilirubin, blood urea nitrogen, calcium, AST, ALP, albumin, ALT and glucose). For a description of the specific reactions for analytes, please refer to www.abaxis.com. Remaining blood was centrifuged at 1,100 x g at 4˚C for 20 min and plasma was archived in 0.5 ml aliquots at -80˚C.

Statistical analysis. All data obtained during the present study were analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0.2, 2009. Values are expressed as the means ± standard deviation (SD). The sample size for the present study was 10 (5 participants began with the placebo intervention and 5 participants began with the treatment intervention). Differences in participant electrolyte and metabolite concentrations were considered significant at $P<0.05$ and considered a trend at $P\geq0.1$ and $P>0.05$. All data were tested for normality and transformed when necessary using the Friedman Test or Wilcoxon Signed Ranked Test. The means of each paired group were analyzed using the Student's t-test.

Results

Dietary intake and physical activity. Dietary records were collected and analyzed at each visit and, upon analysis; no significant differences in the dietary intake patterns of macronutrients or total energy were observed between the groups (Table I). The data presented in Table I, when expressed as the percentage of total caloric intake, e.g., kcal from fat/total daily kcals (from carbohydrates, proteins and fats), further indicated that the participants were consuming an average of 68.0±1.1, 16.7±1.7 and 15.3±2.0% of kcal from carbohydrates, proteins and fats, respectively. The Food and Nutrition Board of the Institutes of Medicine (IOM) recommends consumption levels for carbohydrates (45-65% of energy), proteins (10-35% of energy) and fat (20-35% of energy), as indicated. The participants in the present study averaged marginally above the recommended range for carbohydrates and below the recommended levels for fat. No significant differences were noted in either physical activity or exercise levels and the participants as a group exhibited light to moderate overall activity.

Anthropometric measurements. Data for anthropometric indices for the participants were collected and analyzed; no significant differences were noted between any of the parameters between the groups (data not shown) The average body

Table II. Physical characteristics and fasting glucose levels of the study participants.

							Fasting glucose (mg/dl)			
							Placebo		TCJ	
Participant no.	Weight (kg)	Height (m)	BMI (kg/m^2)	Age (years)	Sex	Category	Pre	Post	Pre	Post
1	96.16	1.82	27.3	40	F	Overweight	92	94	97	100
2	83.55	1.69	28.3	33	M	Overweight	94	91	100	97
3	85.82	1.74	28. 6	25	F	Overweight	103	102	98	98
4	106.51	1.60	29.2	61	M	Overweight	116	116	108	107
5	94.08	1.64	29.3	54	F	Overweight	89	94	93	94
6	80.38	1.68	32	38	F	Obese	97	99	98	96
7	79.29	1.55	33	31	F	Obese	99	103	106	113
8	110.86	1.73	35.1	47	F	Obese	117	114	110	107
9	75.48	1.54	37.2	24	F	Obese	105	109	103	108
10	75.57	1.66	41.6	28	F	Obese	88	88	93	92
Mean	88.77	1.66	32.2	38.1	8:2	5:5	100	101	100.6	101.2
STD	12.62	0.09	4.6	12.5	F:M	ov/ob	10.3	9.6	6	7

TCJ, tart cherry juice.

Table III. Effects of beverage consumption on biochemical profile.

	Placebo		TCJ			
Biochemical parameter	Pre	Post	Pre	Post	Reference range	P-value placebo vs. TCJ
Sodium, mmol/l	146.6±5.4	145.2±3.8	147.4±5.9	142.8±5.0	128-145	0.221
Potassium, mmol/l	4.8±0.4	5.0±0.6	4.7±0.4	5.1±1.3	3.6-5.1	0.828
Chloride, mmol/l	108.4±3.4	107.3±3.3	107.6±4.4	105.6±3.1	98-108	0.310
Calcium, mg/dl	9.4±0.5	9.5±0.4	9.5±0.5	9.7±1.3	8-10	0.683
Blood urea nitrogen[b], mg/dl	12.7±2.9	12.2±2.5	13.6±3.1	13.0±3.1	7-22	0.428
Creatinine, mg/dl	0.9±0.2	0.9±0.1	0.9±0.2	0.9±0.3	0.2-1.6	0.794
Alkaline phosphatase[b], U/l	61.2±21.4	60.2±12.9	61.9±17.4	65.4±25.4	53-128	0.328
Alanine transferase[b], U/l	23.1±9.5	22.4±4.4	22.4±6.9	26.5±14.1	10-47	0.439
Aspartate transferase[b], U/l	27.1±4.3	26.2±2.2	27.9±4.8	29.9±7.3	11-38	0.176
Total bilirubin[a], mg/dl	0.6±0.1	0.6±0.2	0.6±0.1	0.5±0.1	0.2-1.6	0.121
Albumin[a], g/dl	3.9±0.3	3.91±0.3	4.0±0.3	4.0±0.6	3.3-5.5	0.574
Total protein[a], g/dl	7.4±0.5	7.4±0.4	7.5±0.6	7.8±1.4	6.4-8.1	0.395
tCO_2, mEq/l	26.1±1.8	26.2±1.9	27.9±3.5	26.2±3.5	23-29	0.823

Values are the means ± SD. No significant differences between groups were observed. [a]The Friedman test was used when transforming data that did not achieve normality. [b]Transformed to achieve normality. TCJ, tart cherry juice.

weight was 88.77±12.62 kg (195.7±27.8 pounds) and average BMI was 32.2±4.6 kg/m^2, indicating the group was overweight (n=5; BMI 25.0-29.9 kg/m^2) and obese (n=5; ≥30.0 kg/m^2) (Table II). There were 8 Caucasian females and 2 Caucasian males in the cohort.

Biomarkers of metabolic function. As part of the comprehensive metabolic panel, fasting glucose levels were measured at each laboratory visit. It was observed that 7 of the 10 participants exhibited fasting blood glucose levels ≥100 mg/dl, which is suggestive of impaired fasting glucose and pre-diabetes (Table II). In total, 4 of the 5 overweight individuals and 3 of the 5 obese individuals displayed glucose levels ≥100 mg/dl with no clear association with BMI. There were no significant differences between pre- and post-consumption glucose concentrations within groups or between beverage groups, supporting no adverse effect of TCJ on glycemia.

In addition, no significant differences were noted between electrolyte levels when comparing pre- vs. post- treatment or between the juice and placebo groups. Plasma sodium,

potassium, chloride and calcium levels were all within accepted, standardized reference ranges, indicating no perturbation in electrolyte balance (Table III). Following the consumption of TCJ for 4 weeks, the hepatic enzyme levels in plasma did not differ significantly between any of the groups. ALP, ALT and AST, hallmark indicators of liver health, were all within normal reference ranges, indicating no adverse effects, i.e., hepatotoxicity, of TCJ or the placebo beverage. Total bilirubin, albumin and total protein (albumin + globulins) levels were also within normal reference ranges, indicating normal liver function as well as renal function. Normal plasma BUN and creatinine concentrations confirmed the lack of adverse effects of TCJ consumption on renal function under the conditions of the present study.

Discussion

Few studies have evaluated the associations between the dietary intake of fruit juices, and intermediate biomarkers of cardiometabolic risk, particularly in the context of hepatic and renal function in individuals at-risk for or exhibiting metabolic syndrome (11,28-30). SSBs are consumed globally and have been associated with adverse health outcomes, including weight gain, T2DM and CVD (31-34). Other studies have reported higher systolic blood pressure (hypertension) among those with higher SSB consumption, likely due to associated weight gain (35-37). A recent cohort study (n=13,440 adults ≥45 years) indicated that each additional 355 ml (12 oz) of SSB or fruit juice beverage consumed caused a significant 11 and 24% higher all-cause mortality risk, respectively (38). In the present 10-week 2x2 crossover, randomized, placebo-controlled dietary intervention in overweight and obese participants (BMI ≥25.0 kg/m^2), no significant alterations were noted in hepatic or renal function from the start to the end of the study when comparing the TCJ to the placebo group. Dietary intake and physical activity levels were similar among all groups. In addition, no changes were noted in body composition (percentage body fat, lean body mass, etc.) or BMI after 4 weeks of beverage consumption. It was concluded that 100% TCJ does not exacerbate already existing risk factors, viz., elevated fasting blood glucose, in an at-risk (for chronic disease) population or affect adversely hepatic or renal function.

Replacing fruit juice with whole fruits is associated with a lower risk of developing chronic diseases, i.e., T2DM; thus, whole fruit is the preferred dietary means of nutrient consumption from fruits (39). However, there are positive studies supporting the benefits of fruit juice consumption. In children, 100% fruit juice was associated, in part, with reaching daily values of vitamin C, folate and vitamin K intake (12). The consumption of deeply pigmented foods rich in polyphenolic anthocyanins (ACNs), with marked antioxidant and anti-inflammatory activity, has been shown to exert preventive effects against chronic diseases. In a placebo-controlled intervention (n=57), ACN-rich juice consumption for 9 weeks caused DNA protective and antioxidant effects, which were also observed unexpectedly in the placebo group (15). The authors of that study proposed that vitamin C was responsible for the placebo effect. Conversely, the effect of ingestion of different white grape juices (7 μl/g body weight) on biochemical serum profiles and oxidative stress in the liver of adult Wistar rats did not alter biochemical parameters (40). The ingestion of both grape juices elevated glutathione and total antioxidant capacity, with no effects on glucose or uric acid although consumption of 480 ml of antioxidant-rich Concord grape juice per day for 3 months increased insulin resistance and waist circumference in overweight individuals in a different clinical trial (41,42). Indeed, the authors also previously demonstrated that ACN-rich TCJ did not adversely affect blood glucose, but that serum urate (uric acid) was significantly reduced in a population at risk for metabolic syndrome and potentially gouty arthritis (43,44).

There has been increasing interest in ACN-rich tart cherries and their juice due to cumulative myriad health benefits and their purported protection against the development and elaboration of chronic diseases, as reviewed by Kelley *et al* (45). For example, investigators have demonstrated in numerous studies that tart cherry and/or TCJ clearly reduces potentially damaging oxidative stress, an event thought to be involved in the etiology of several pathologies (46-49). Moreover, given that oxidative stress is closely linked to inflammation, it is not unexpected that TCJ has been shown to significantly reduce undesired inflammation in numerous studies (45,47,50). There is also increasing information supporting an inhibitory role for TCJ in pro-inflammatory gouty arthritis and osteoarthritis, as well as the capacity to reduce exercise-induced pain, soreness and muscle damage often assumed, in large part, to be due to increased oxidative stress (47,51-53). Supportive evidence also suggests that tart cherries and TCJ can modulate risk factors for diabetes and CVD, which are also linked to oxidative stress (54-56). For example, TCJ reduces HbA1C levels, a marker of blood glucose control, in diabetic women with no changes in fasting glucose. Others have demonstrated reductions in both systolic and diastolic blood pressure presumably via, in part, the modulation of nitric oxide levels and vasorelaxation (57,58). Collectively, there is considerable evidence demonstrating the health benefits from tart cherry and TCJ consumption.

There have been several reports that the dietary consumption of some fruit juices exerts adverse effects. For example, in female albino rats fed star fruit juice (dose range of 250-5,000 mg/kg), acute studies suggested the juice was safe up to the highest level. However, after 48 h, liver enzyme (AST, ALT and ALP), urea and creatinine levels were significantly higher in a dose-dependent manner compared to the control (19). Moreover, the authors of that study concluded that the juice of *Averrhoa carambola* was both nephrotoxic and hepatotoxic in rats after 28 days (4 weeks), a time interval used in the current study. In a different study, rats (n=5) orally treated with juice for 14 days after initial storage of the juice for either 0, 1, or 3 h, liver enzyme (ALT, ALP and AST), urea and serum creatinine levels were once again significantly elevated (19). Damage also occurred at the hepatocellular level with significantly increased serum ALT following the consumption of juice stored for 3 h (20). The ingestion of pomegranates has been associated with the deaths of young cattle without prior clinical signs, although marked weakness and discoloration of mucous membranes were noted in one animal. Gross pathological changes

included widespread subcutaneous and serosal hemorrhages with acute periacinar to midzonal hepatocellular necrosis characteristic of toxicity (21). In a study on noni fruit (*Morinda citrifolia*), commonly used as a functional beverage with medicinal properties, mice were fed water extracts of fruit (two doses each). After 6 months, the study demonstrated that the fruit extract caused chronic toxicity at the highest dose (2 mg/ml water) with clear hepatocellular necrosis, reduced liver length, increased liver enzymes, i.e., AST and reduced albumin and ultimately 40% mortality within 3 months (22). In humans, 2 cases of hepatotoxicity following noni juice consumption were reported by Stadlbauer *et al* (23). A 29-year-old male with previous toxic hepatitis developed sub-acute hepatic failure (determined via transjugular or percutaneous liver biopsy) following the consumption of 1.5 l noni juice over 3 weeks, mandating urgent liver transplantation. A 62-year-old woman without pre-existing liver disease or dysfunction, developed acute hepatitis following the consumption of 2 l of noni juice over a period of 3 months (23). The bottle gourd (*Lagenaria siceraria*) also known as lauki, ghia or dudhi is prescribed as part of traditional medicine for T2DM, hypertension, liver diseases, weight loss and other associated problems. However, there have been reports of adverse effects after juice consumption with complaints of abdominal pain, diarrhea, and vomiting (with blood). Endoscopic results displayed profuse gastric bleeding with profound, frequent ulceration of the distal esophagus, stomach and duodenum. Liver enzymes levels were also elevated indicating hepatic toxicity (24). While there are a plethora of beneficial bioactive agents in fruits and consequently fruit juices, there may also be potentially deleterious molecules and/or precursors (59,60). In rodent studies, the provision of juice obtained from *Morinda citrifolia* (noni) fruit caused significant hepatotoxicity, likely due to the anthraquinones in the seeds and skin, which exhibits quinone reductase inducer activity involved in detoxification of quinones. Studies report that anthraquinone activity is 40-fold more effective than l-sulforaphane, a bioactive organosulfur isothiocyanate in cruciferous vegetables (22,23).

The fructose hypothesis alleges the fructose component common to all major caloric sweeteners and naturally occurring sweetened fruit juice plays a unique and causative role in the increasing rates of CVD, hypertension, T2DM, cancer and NAFLD. One report, however, concludes that fructose intake at normal population levels and patterns does not cause biochemical outcomes substantially different from other dietary sugars (61). Ounce for ounce, some 100% fruit juices may have more sugar than SSBs, but on average, most have a similar energy density and sugar content (62). For example, 250 ml of apple juice typically contains 110 kcal and 26 g of sugar; 250 ml of cola typically contains 105 kcal and 26.5 of sugar. TCJ (240 ml) contains 159 kcal and 33 g of sugar per cup (~16-17 g fructose). An additional consideration is that 100% fruit juices, although nutrient-rich, contain little or no fiber which confers a higher glycemic index to juice.

The amounts of simple sugars and the relative ratios may also be a consideration. In a study comparing the fructose concentration of commonly consumed beverages, 15 beverages had a fructose-glucose ratio exceeding 55% with a mean fructose content of 59% (63). In a study commissioned by the International Society of Beverage Technologists, 80 random beverages known to be sweetened with HFCS-55 were tested. The mean fructose content of these beverages was 55.6% (61). A number of beverages, however, have a fructose content >55% and there may be significant biological differences in response to differing ratios, i.e., 50:50, 60:40, likely due to well-established differences between glucose and fructose metabolism (62,64,65). In short, the excessive supply of fructose to the liver enhances hepatic *de novo* lipogenesis and increases lipid levels associated with hepatic insulin resistance. A 12-week intervention where 13% of diet energy as fructose was served in the habitual diet of 71 men with abdominal obesity, an increased body weight, liver fat content (steatosis) and post-prandial TG levels were observed. Replacing energy requirement with 10% juice also significantly increased low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB) and post-prandial TG levels compared to baseline levels (63). In a 6-month dietary intervention study, subjects consuming one liter of SSB/day exhibited increased TG, cholesterol and liver fat (60). In a previous study conducted in our laboratory, individuals consuming 8 ounces TCJ per day for 4 weeks exhibited a significant increase in erythrocyte sedimentation rate (ESR), an indicator of chronic inflammation, but not the TCJ suggesting the SSB was altering this biochemical parameter (43).

There are several limitations to the current study that may affect the interpretation of the results yet be relevant for the design of future studies. First, the present study was a small pilot study with 10 participants. As a result, the results may not be applicable to larger populations and may not be relevant all races, sexes and/or nationalities. Moreover, the small sample number, although generally considered acceptable for a pilot study, may have been limiting for elaborating potentially significant effects if present. Subsequent studies should aim for larger cohort sizes with more refined inclusion criteria as pilot studies reveal which are most likely amenable to intervention. Another consideration is the length of each arm and the washout period. Chronic consumption of TCJ beyond 4 weeks may lead to different results and although we noted no significant differences due to a carryover effect, e.g., 2-week washout period, this may be too short of an interval for other products. The experimental design, however, was based on other published designs. In the present study, a sweetened, artificially colored fruit punch was used, which arguably may not be as effective as desired for a placebo regarding optimal matching of astringency and the presence of sediment although the colors of the beverages were matched as closely as possible and the caloric and carbohydrate values were similar. Other studies have used fruit-flavored drink mixes, e.g., Kool-Aid, sports beverages, water, synthetic orange-flavored beverages, etc. supporting the placebo selection in the present study (16,47,53). Furthermore, in a previous meta-analysis, Wang *et al* reported selections for placebo beverages in 12 studies, which included modified sports beverages, synthetic orange-flavored drinks, water, and a generic control drink matched for sugar composition (66).

Important discrepancies between studies, such as the type of fruit juice, dose, duration, study design and measured outcomes contribute to inconsistencies in results between studies and complicates interpretation. As a result, it becomes difficult to provide evidence-based public recommendations regarding the consumption of fruit juices and potential effects on metabolic parameters (63). Given that no association purportedly exists between 100% fruit juice and most risk factors for CVD, including changes in glucose homeostasis, lipid concentrations and blood pressure, the current evidence does not suggest that 100% fruit juice consumption markedly affects the risk of CVD (34,59,67). Evidence exists that 100% fruit juice is associated with major chronic diseases, but the existing body of evidence is too limited to robustly support any expert opinion recommending changing the current guidelines on 100% fruit juice consumption (8). Presently, the World Health Organization (WHO) recommends reducing the intake of free sugars to <10% and ideally <5% of the total daily energy intake (63). More randomized, placebo-controlled clinical trials are required to confirm the health effects of consuming 100% fruit juice and cohort analyses should report both energy-adjusted and energy-unadjusted associations (8,68).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

KRM initiated and designed the study and secured the funding from the Cherry Marketing Institute. KRM interpreted the data and prepared the manuscript. JB and LB recruited, screened and provided informed consent to respondents under the supervision of KRM, as well as collected, processed and analyzed, in part, data, samples and questionnaires. All authors critically reviewed the manuscript and all authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Arizona State University Institutional Review Board. Prior to entering the study, all respondents and participants were provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare no competing financial and/or personal interests.

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