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Original Research

Chardonnay grape marc/grape seed extract blends improve postprandial triglycerides and/or HDL cholesterol concentrations in adults with mild dyslipidemia in a randomized double blinded crossover trial

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ABSTRACT

Dyslipidemia is a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD). Chardonnay marc, the residual by-product of winemaking, is an underutilized agricultural product that remains rich in extractable and non-extractable nutrients, including polyphenolics (e.g., flavan-3-ols) and fiber, which may beneficially influence plasma lipids. This study evaluated whether ingestion of Chardonnay grape seed extract/marc blends could improve plasma lipids in adults with dyslipidemia. We hypothesized that a Chardonnay marc–rich blend (HM) would reduce total cholesterol and LDL-cholesterol (LDL-c), while a Chardonnay seed extract–rich blend (HE) would reduce total cholesterol, LDL-c, and triglycerides, without affecting HDL-cholesterol (HDL-c) or endothelial function. Twenty-four adults with mild dyslipidemia completed a 16-week randomized, double-blind, crossover trial involving three 3-week intervention periods (consuming 1500 mg of HM, HE, or microcrystalline cellulose (MCC)), each followed by a 3-week washout. Systolic blood pressure was significantly lower following HE (118.8 ± 2.8 mmHg) compared to HM (125.6 ± 2.5 mmHg). HDL-c con-

Abbreviations: AI, augmentation index; ANOVA, analysis of variance; Apo, apolipoprotein; ASCVD, atherosclerosis cardiovascular disease; AUC, area under the curve; BMI, body mass index; ChSF, Chardonnay seed flour; CM, Chardonnay marc; CMP, comprehensive metabolic panel; CONSORT, consolidated standards of reporting trials; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high density lipoprotein-cholesterol; HE, high extract blend; HM, high marc blend; iAUC, incremental area under the curve; IDL, intermediate density lipoprotein; LDL-C, low density lipoprotein-cholesterol; MCC, microcrystalline cellulose; NMR, nuclear magnetic resonance; oxLDL, oxidized low density lipoprotein; RHI, reactive hyperemia index; SBP, systolic blood pressure; SD, standard deviation; SEM, standard error of the mean; TC, total cholesterol; TG, triglycerides; VLDL-C, very low density lipoprotein-cholesterol; WHNRC, Western Human Nutrition Research Center.

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centrations were higher after HM (56.6 ± 2.6 mg/dL) and MCC (55.7 ± 2.5 mg/dL) compared with HE (52.4 ± 2.5 mg/dL), and the number of large HDL particles was lower following HE (7.1 ± 0.7 μmol/L) compared with MCC (7.7 ± 0.7 μmol/L). Additionally, postprandial triglyceride area under the curve was lower after HM compared with HE. These findings suggest that the broader nutrient complexity of Chardonnay marc may offer pleiotropic benefits for modifiable ASCVD risk factors (ClinicalTrials.gov: NCT03203915).

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) specifically afflicts the cardiovascular system and may lead to decreased blood flow or even a cardiovascular event. It is characterized by the hardening and thickening of blood vessels from the accumulation of fat, cholesterol, and other substances in arterial walls. The endothelial layer of blood vessels has a critical role in vascular tone thus has a large impact on blood pressure through vasoconstriction and vasodilation. Thus, an imbalance of vasoconstriction and vasodilation is one feature of endothelial dysfunction. Endothelial dysfunction (i.e., abnormal vascular reactivity) is one of the earliest indications of ASCVD [1]. Risk factors include overweight or obesity, high concentrations of low-density lipoprotein cholesterol (LDL-C), high triglycerides (TG), elevated blood pressure, low concentrations of high-density lipoprotein cholesterol (HDL-C), insulin resistance and physical inactivity [2,3].

The "French Paradox" sparked interest in red wine phenolic compounds, particularly resveratrol, and their relationship to cardiovascular protection [4]. In a recent meta-analysis evaluating grape polyphenols, predominantly from red grapes, authors point to positive benefits of grape phenolics on CVD risk factors but specifically call out whole grapes as having more benefit than extracts [5]. While much attention is on red wine and red grapes, white wines and their respective grapes have had less attention. When wine grapes are processed, the juice is used for winemaking and the marc (also called pomace, primarily the remaining skins and seeds) is treated as agricultural waste. In red winemaking, the marc is macerated before it is discarded, and in white winemaking the marc is discarded immediately after the juice is pressed. White wine grape marc retains both its extractable and nonextractable nutrients. With red wine grape marc, much of its extractable nutrients are lost to the wine itself.

Roughly 20% to 30% of crushed grapes are marc and with Chardonnay being the single most produced variety of wine grapes in California, there is high potential for diverting agricultural waste and recapturing the nutrient rich material for valorization. A recent review highlights Chardonnay marc as an upcycled coproduct of winemaking with complex sensory properties and health benefits [6]. Beyond being a rich source of phenolics, such as (-)-epicatechin, WellVine Chardonnay marc (CM) is high in dietary fiber with a diverse oligosaccharide profile [6–8].

Previous work with Chardonnay seed flour (ChSF) supplementation in diet induced obese hamster and mice models resulted in lower very-low density lipoprotein cholesterol (VLDL-C), LDL-C, total cholesterol (TC), overall weight gain, and hepatic fat accumulation compared to the nongrape comparator fed animals [9,10]. These data suggest that ChSF has potential to improve ASCVD risk factors. To date, only one previous human trial has supplemented ChSF, which demonstrated improvements in peripheral endothelial function but not in other ASCVD risk factors [11]. Participants were specifically recruited with endothelial dysfunction and had otherwise clinically normal lipid concentrations. Maintaining endothelial function is important for regulating both vascular tone and hemostasis, thus an improvement in endothelial function in the absence of lipid lower effects is still beneficial in reducing CVD.

Whether whole Chardonnay marc or its components have similar effects on lipoproteins in humans as seen in animal trials is unclear. The aim of our study was to evaluate and compare the effectiveness in modifying ASCVD risk factors, specifically plasma cholesterol and triglyceride concentrations, following supplementation with a Chardonnay marc rich blend and a Chardonnay seed extract rich blend in adult men and women with moderately elevated lipoprotein profiles. This study was the first to test these blends. Primary outcomes for the study included: clinical lipid profile and triglyceride response; secondary outcomes for the study included: peripheral endothelial function, apolipoproteins, lipid profiling and oxidized LDL. We hypothesized that TC and LDL-C concentrations would be lower following the Chardonnay marc rich blend supplementation, whereas there would be no effect on HDL-C, triglycerides, or peripheral endothelial function. Secondly, we hypothesized that the Chardonnay seed extract rich blend would lead to lower concentrations of TC, LDL-C, and TG but have no effect on HDL-C or peripheral endothelial function.

2. Methods and materials

2.1. Study participants

Men and women between the ages of 35 to 65 years were included in this study to increase the generalizability of the results. Other eligibility criteria included body mass index (BMI) >25 but <40 kg/m^2 and at least one marker of dyslipidemia defined as, TC >190 mg/dL but <300 mg/dL, LDL-C > 130 mg/dL but <180 mg/dL, HDL-C < 40 mg/dL (men)/<50 mg/dL (women) and TG >150 mg/dL but <400 mg/dL. These specific ranges were selected as they are the upper end of normal plasma lipid

concentrations. The broad lipid inclusion factor was a decision to increase the likelihood of recruiting participants on a constrained budget.

Participants were excluded from the study if they self-reported metabolic diseases (e.g., type 2 diabetes mellitus), cardiovascular disease, gastrointestinal disorders, or other chronic conditions; history of cardiovascular events, presence of atrial fibrillation, pacemaker or other internal electrical device controlling the rhythm or pacing of the heart; pregnancy or lactation; use of lipid-lowering, glucose-lowering, antihypertensive or weight-loss medication; use of antibiotics in the past 3 months (stool was collected for secondary microbiome analyses however, not reported here); food sensitivities, allergies or aversions to foods or food components provided in the standard meals or capsules; use of herbal/plant-based supplements, omega-3 fatty acids and fish oils in the past 6 months or any individuals who fell into vulnerable categories.

Participants were recruited between August 2017 and March 2019 from the Davis and greater Sacramento area through posting flyers, newspaper advertising, Craigslist advertisement, Western Human Nutrition Research Center (WHNRC) website and referrals. The first step in the screening process was an initial telephone assessment of medical history, self-reported height, weight, age, and interest in the study. Next, those who met the general criteria were scheduled for an in-person screening appointment to verify eligibility criteria such as BMI and drawing blood for dyslipidemia criteria.

Participants were asked to fast for 12 hours, leading up to their appointments. During the appointment, height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Ayrton Corporation, model S100) and weight was measured to the nearest 0.1 kg using an electronic scale (Tanita BWB-627A Class III electronic scale; Toledo Scale). Systolic and diastolic blood pressure, pulse and temperature were measured after participants rested undisturbed for 5-minute using a blood pressure monitor (GE CARESCAPE V100). Fasting blood was then drawn from an antecubital vein by a licensed phlebotomist using VacuTainers (Becton Dickinson, Rutherford, New Jersey) for a clinical comprehensive metabolic panel (CMP), lipid panel and complete blood count (CBC). Blood was sent to the UC Davis Medical Center clinical pathology laboratory for analysis. Participants also completed an additional detailed medical history questionnaire and the Stanford Brief Physical Activity questionnaire before concluding the visit. Participant screening characteristics are shown in Table 1.

The CONSORT (Consolidated Standards of Reporting Trials) diagram (Fig. 1) depicts the total number of people who responded to advertisements, who were screened for eligibility and who ultimately completed the study. A total of 31 participants (9 men, 22 women) enrolled into the study, data were collected from 27 participants (8 men, 19 women) and 24 participants (8 men, 16 women) completed the study in its entirety. Ethical approval for the involvement of human subjects in this study was granted by the Institutional Review Board of University of California, Davis, Clinical Committee A reference number 819462, dated December 19, 2015, and was approved annually through May 13, 2020 when participant enrollment was no longer active. The study "Metabolic Response to Chardonnay Grape Marc Powder" was registered on clinicaltrials.gov (NCT03203915). Study volunteers provided written informed consent to be screened and to participate in the full study if they qualified.

Table 1 – Age, BMI and clinical screening characteristics of participants with dyslipidemia[a].

	unit	Mean ± SEM
Age	years	53.9 ± 1.7
BMI	kg/m^2	28.1 ± 0.5
Systolic BP	mmHg	117.9 ± 2.2
Diastolic BP	mmHg	71.2 ± 1.5
Total cholesterol	mg/dL	230.5 ± 6.8
LDL-C	mg/dL	144.6 ± 4.8
HDL-C	mg/dL	54.9 ± 2.3
TC:HDL	mg/dL	4.4 ± 0.3
Non-HDL-C	mg/dL	175.6 ± 7.3
Triglycerides	mg/dL	132.1 ± 16.7

[a] Abbreviations: BMI, body mass index; BP, blood pressure; C, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; SEM, standard error of the mean; TC:HDL, total cholesterol to HDL ratio.

2.2. *Study design and timeline*

The study was a 16-week double-blinded, randomized control crossover design. Each intervention arm was 3-week followed by a 3-week washout period before beginning the next intervention arm (Fig. 2). All outcomes were predetermined. Primary outcomes of the study included: clinical lipid panel and postprandial triglyceride response; secondary outcomes included: peripheral endothelial function, NMR lipoprotein profiling, apolipoproteins, and oxidized LDL. Fecal microbiome secondary analyses were conducted but not reported here. If eligibility requirements were met, participants were oriented to study protocol and expectations. Participants were asked to maintain their usual dietary patterns, current physical activity habits and to maintain their current weight during the study. To track dietary patterns, participants used the Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool 2016 version when prompted by investigators. Participants were randomly prompted to track 7 days during active study periods. During active study periods, participants came to the WHNRC on a weekly basis to pick up capsules. On the third week of capsule pick up, participants also picked up a standardized dinner to consume the evening before testing. To limit subject burden and factoring in budgetary constraints, we were unable to conduct testing at the beginning of each intervention arm to collect baseline. Testing occurred at the end of the 3-week supplementation period. Participants were not required to come to the WHNRC during the washout period, but contact was maintained until the next active study period.

2.2.1. *Randomization and blinding*

A statistician randomized the sequence of the intervention by creating 6 blocks of the 6 permutations of the intervention sequence and randomly shuffled the order within each block. The generated list was given to the study coordinator to assign intervention sequence to participants once they completed

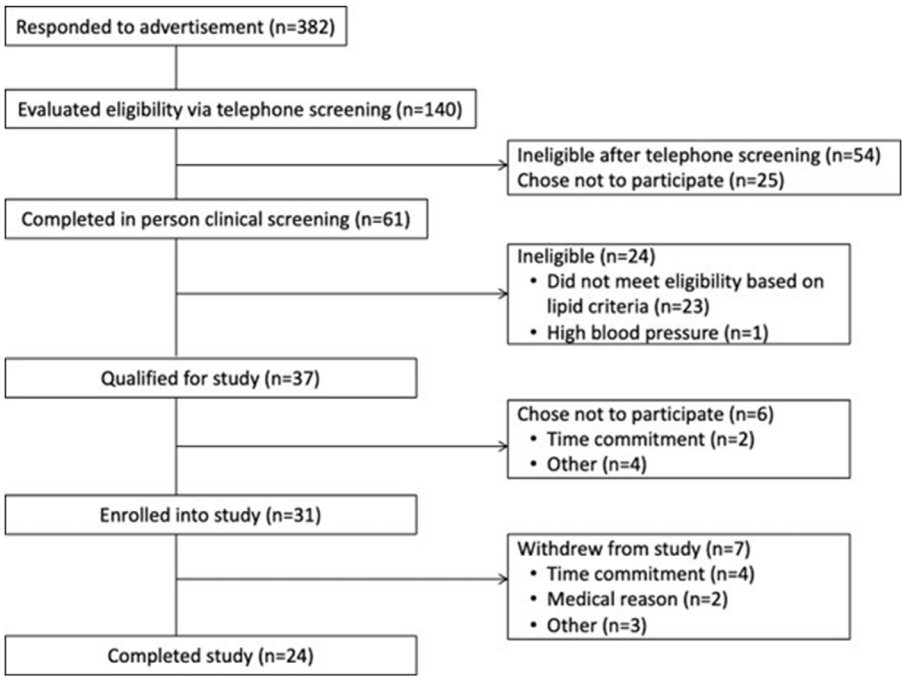

Fig. 1 – Consort diagram illustrates the recruitment, screening and enrollment of study participants.

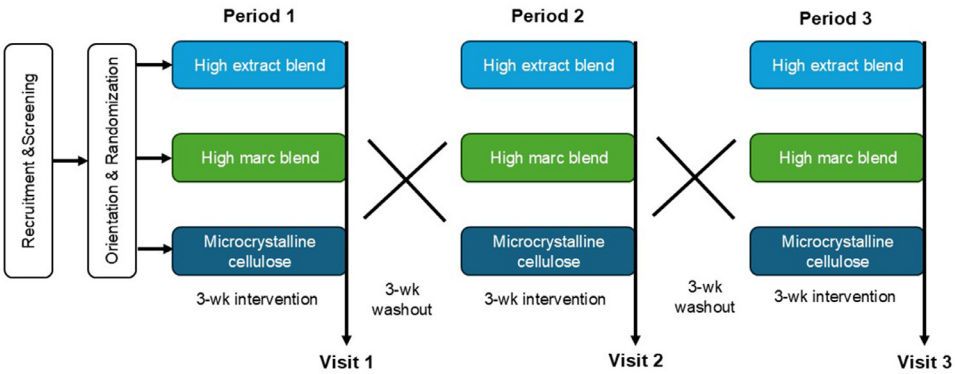

Fig. 2 – Study design that depicts randomization of interventions and study timeline.

the study orientation. Sonomaceuticals, LLC provided study capsules, which were coded by the manufacturer and then recoded with colored stickers by WHNRC's Metabolic Kitchen and Human Feeding Laboratory. Investigators were unblinded following the analyses of the outcome measures.

2.2.2. *Study capsules and test meals*

Participants consumed the study material in the form of capsules every day for 20 days at home and on the 21st day they consumed their last set of capsules on their test day. Three different study capsules were used. Two capsules had proprietary blends of Chardonnay grape seed extract and whole WellVine Chardonnay marc of varying ratios and one capsule of only microcrystalline cellulose (MCC), which served as the nongrape placebo control. The study capsules were designated: high Chardonnay grape seed extract blend (HE), high Chardonnay marc blend (HM) and MCC (Table 2). Randal Optimal Nutrients, LLC manufactured study capsules (Santa Rosa, CA) and Eurofins (Petaluma, CA) analyzed the nutrient composition (Table 3). Folin-Ciocalteu assay was used to quantify total phenolics and a high-performance liquid chromatography method developed by Sakakibara et al. was used to quantify total catechins [12,13]. Further compositional analysis was not completed on the encapsulated material, however Sinrod et al. [8] has reported the phenolic composition of the same WellVine Chardonnay marc and Chardonnay seed extract components of the interventions and estimated amounts in the study material are found in Table 3.

Participants consumed 3 capsules (or 1500 mg) of study material, daily. Dosage for this pilot trial was determined by the sponsor to minimize subject burden and practical application in the market. They were instructed to consume all 3 capsules with their first meal of the day. To monitor compliance, participants were asked to complete a daily capsule checklist to note how many capsules were consumed and what time they were consumed. They were asked to come to the WH-

Table 2 – Study capsule experimental material relative compositions[a].

Content	Chardonnay seed extract (HE)	Whole Chardonnay marc (HM)	Microcrystalline cellulose (MCC)
MCC	N/A	N/A	↑
HE	↑	↓	↓
HM	↓	↑	N/A

Abbreviations: HE, high grape seed extract blend; HM, high grape marc blend; MCC, microcrystalline cellulose; N/A, not applicable or not present; ↑, higher amounts; ↓, lower amounts.

[a] Interventions were a proprietary blend, where each blend was created independent of the others.

Table 3 – Nutrient composition of Chardonnay-derived interventions per 1500 mg dose[a].

	High extract blend	High marc blend
Energy (kcal)	0.2	5.6
Total carbohydrate (mg)	37.0	997.7
Total protein (mg)	5.4	144.5
Total fat (mg)	4.0	108.0
Total dietary fiber (mg)	26.7	720.9
Total polyphenol (mg GAE)	119.7	75.0
Total catechins (mg)	10.7	5.6
Gallic acid (mg)	0.12	0.34
Vanillic acid (mg)	0.08	0.03
(-)-Epigallocatechin (mg)[b]	1.03	0.45
(+)-Catechin (mg)[b]	5.70	1.53
(-)-Epigallocatechin gallate (mg)[b]	0.05	0.04
(-)-Gallocatechin (mg)[b]	0.07	2.01
(-)-Epicatechin (mg)[b]	6.44	1.91
(-)-Epicatechin gallate (mg)[b]	0.28	0.07
(-)-Gallocatechin gallate (mg)[b]	0.05	0.01
(-)-Catechin gallate (mg)[b]	0.43	0.05
Trans-polydatin (mg)[b]	0.02	0.00
Trans-resveratrol (mg)[b]	0.01	0.04

[a] Abbreviations: GAE, gallic acid equivalents.

[b] Estimated based on Sinrod et al. [8].

NRC on a weekly basis to pick up each week's worth of capsules and to return the previous weeks packaging along with any unconsumed capsules. Compliance was defined as 80% overall capsule consumption per study arm.

On the capsule pick up during the week leading up to testing, participants also received a standardized meal to consume the evening prior of the test day. The Harris- Benedict equation, using information collected from the in-person screening visit, was used to estimate caloric needs for study meals. The pretest dinner consisted of chicken and angel hair pasta with cream sauce, nutrient composition information available in Table 4. The caloric values of the meals distributed were either 500 kcal or 800 kcal, based on 30% of 1700 kcal and 30% of 2700 kcal, respectively. Participants were instructed to consume only this meal for dinner and to begin their 12-hour fast after consuming the meal. The test day breakfast meal consisted of a breakfast casserole with egg, rice, potatoes, turkey sausage, cheddar cheese and mango-orange juice. Participants also consumed the last set of capsules with breakfast. Test day meals were scaled to meet 30% of daily caloric needs based on the Harris-Benedict equation estimation.

2.3. Protocols

2.3.1. Metabolic testing

Participants arrived at the WHNRC in the morning, following a 12-hour fast for a 6-hour metabolic test day. Height was measured to the nearest tenth of a centimeter using a wall-mounted stadiometer, weight was measured using an electronic scale and these were used to calculate BMI. Participants rested silently before having their blood pressure measured. A licensed phlebotomist drew fasting blood through the antecubital vein into vacutainers. Blood was subsequently drawn at 1, 2 and 3 hours after consuming the high fat challenge meal (previously described). Published literature suggests a range between 3 and 6 hours for a postprandial TG peak, highlighting the wide variability in human response [14–19]. Ultimately 3 hours was chosen due to the history of previous studies conducted at WHNRC (unpublished data) demonstrating that TG peak occurred on average roughly around 3 hours.

Once blood was drawn, serum vacutainers were held at room temperature for 30 minutes to coagulate, meanwhile, plasma vacutainers were immediately chilled on ice. All vacutainers were centrifuged in a refrigerated centrifuge (Centra CL3R, International Equipment Co.) for 10 minutes at 100 x g at 4 °C, then aliquoted to cryotubes with a transfer pipet before storing at −80 °C until ready for analyses. All 3 test days followed the same protocol.

2.3.2. EndoPAT

Peripheral endothelial function was measured noninvasively using the EndoPAT 2000 (Itamar Medical, Israel). Participants were instructed to lay supine, limit movement, refrain from engaging in conversation with the investigator and to stay conscious throughout the measurement. Finger probes were placed onto the participants two index fingers and a blood pressure cuff on their upper nondominant arm. The dominant arm, without the blood pressure cuff, was used as the control arm. The EndoPAT measurement included 7 minutes of baseline, 5 minutes of occlusion and 5 minutes of postocclusion. During the baseline measurement, the EndoPAT measured normal, nonoccluded blood flow through the finger probes. During the occlusion period, the blood pressure cuff was inflated to 120 psi to occlude blood flow to the nondominant arm for 5 minutes. Lastly, after the occlusion period, the blood pressure cuff was immediately released and measured for an additional 5 minutes. The Reactive Hyperemic Index (RHI), a measure of endothelial dysfunction, was calculated as the post-to-pre occlusion signal ratio of the nondominant, occluded arm to the same post to-pre occlusion signal ratio of the control arm. Normal vascular tone is considered >1.67. The Augmentation index (AI), a measure of arterial stiffness, was calculated based on the pulse wave of the EndoPAT signal in the occluded arm. Because the AI is related to heart rate, AI is corrected to a standard heart rate of 75 beats per minute (AI@75). Lower AI values indicate less arterial stiffness and

Table 4 – Nutritional composition of all study foods[a].

	Pre-test dinner (500 kcal)	Pre-test dinner (800 kcal)	Test day meal (700 kcal)
Total energy (kcal)	516	826	699
Total carbohydrate (g)	57.3	91.7	79.1
Total protein (g)	19.0	30.5	25.6
Total fat (g)	23.5	37.6	31.5
Total dietary fiber (g)	3.8	6.1	4.1
Total saturated fat (g)	13.6	21.7	15.9
% energy from carbohydrate	45.0	45.1	45.3
% energy from protein	14.9	14.9	14.5
% energy from fat	40.0	40.0	40.1
% energy from saturated fat	24%	24%	20%

[a] Two sizes of pre-test dinners were available and given to subjects based on body weights. The test day meal nutritional content was adjusted according to energy needs.

this measure is intended only for research purposes. Analyses were completed with the 24 participants who completed the trial and 3 participants who withdrew from the study.

2.3.3. *Lipoproteins*

To evaluate clinical lipid parameters related to ASCVD risk factors, fasting serum TC, LDL-C, HDL-C values were determined using an enzyme-linked colorimetric assay on a clinical chemistry analyzer (Cobas Integra 400+; Roche Diagnostics). All reagents were purchased from Roche Diagnostics and used based on the manufacturer's instructions. Analyses were completed with samples from 24 completed participants and available samples from 3 participants who withdrew.

2.3.4. *Triglycerides*

To evaluate ASCVD risk related to TG, serum TG was measured at fasting, 1, 2, and 3 hours postprandially. TG values were determined by an enzyme-linked colorimetric assay on the same analyzer as described. Reagents were purchased from Roche Diagnostics and assays were conducted based on the manufacturer's instructions.

Analyses were completed with samples from 24 participants who completed the trial and available samples from 3 participants who withdrew. Area under the curve (AUC) and incremental area under the curve (iAUC) were calculated for the postprandial response using the trapezoid rule. The iAUC calculation allowed values to be negative if they dropped below baseline. AUC was derived from the entire acute timeframe including fasting values and iAUC accounts for the acute response while not including the fasting area.

2.3.5. *NMR lipid profiling*

Lipoproteins are highly variable in size. Certain particles and particle sizes are thought to be more atherogenic than others, thus, to determine the distribution of lipoproteins and their respective sizes, plasma samples at fasting and 3 hours postprandial were sent to LabCorp for NMR LipoProfile analysis (LabCorp; Morrisville, NC). The lipid profiling included VLDL, chylomicron, intermediate density lipoprotein (IDL), HDL, LDL and TG particle concentration and sizing (small, medium, and large). This secondary analysis was completed with samples from 24 participants who completed the trial only.

2.3.6. *Apolipoproteins*

Apolipoproteins (Apo) are structural proteins of lipoproteins. Apo-AI is the primary structural protein of HDL-C, Apo-B is the primary constituent of atherogenic lipoproteins (i.e., VLDL-C, LDL-C, IDL-C), Apo-CIII has been associated with higher CVD risk and plays an important role in TG metabolism, and Apo-E is associated with reverse cholesterol transport [20–22]. Therefore, to evaluate atherosclerosis risk from a structural protein point of view, serum Apo-AI, -B, -CIII, and -E were measured at fasting, 2 and 3 hours postprandially. In addition, Apo-B:Apo-AI ratio was calculated to evaluate atherogenic risk [23]. Apo-AI, -B, -CIII and -E values were determined by an enzyme-linked colorimetric assay on the same analyzer as described, with reagents purchased from Kamiya Biomedical (Seattle, Washington) and analyses were conducted based on the manufacturer's instructions. This secondary analysis was completed with samples from 24 completed participants only. AUC and iAUC were calculated for the postprandial response.

2.3.7. *Oxidized LDL*

LDL-C may penetrate the endothelium and become susceptible to oxidation, which increases its atherogenicity [24]. To evaluate this aspect of atherosclerosis risk, plasma oxidized LDL (oxLDL) was measured at fasting, 1, 2, and 3 hours postprandially using an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) according to the manufacturer's instructions. This secondary analysis was completed with samples from 24 completed participants and 3 participants who withdrew. AUC and iAUC were calculated for the postprandial response.

2.4. *Statistical analyses*

Data from all volunteers who began the 16-week protocol with testing results were included in the primary intent-to-treat analyses, which included clinical lipoproteins and triglyceride response. Secondary analyses only included the full set of completing participants, unless otherwise stated—these analyses included Endopat, NMR lipid profiling, apolipoproteins, and oxLDL. All data were evaluated for normality using Shapiro-Wilk, were transformed if necessary and evalu-

ated for outliers. AUC and iAUC were calculated for all outcomes with postprandial measures using R (R statistical software). Linear mixed-model analysis of variance (ANOVA) was used to analyze variables on JMP Pro 16 (SAS Institute). For single variables, linear mixed model ANOVAs were constructed with the test day (within-subject measure) and interventions (between-subject measure) as main effects and test day by intervention interaction term represented the crossover effect. For time response variables, linear mixed model ANOVAs were constructed with the main effects: test day, sampling times (both as within-subject measures) and intervention (between-subject measure) as the main effects and included respective interaction terms. Tukey's test was used for multiple comparisons with statistically significant findings. Effect size, or the standard difference, was calculated for each intervention relative to each other for each outcome (Supplemental Table 1). All data are reported as mean ± standard error of the mean (SEM).

To determine the sample size needed for testing the effect of consuming the 2 Chardonnay marc blends along with a nongrape comparator on plasma TG concentration is a 6-sequence, 3-period, 3-treatment crossover design that is balanced with respect to first-order carryover effects. Each subject was randomized to 1 of 6 treatment sequences. Using *GLIMMPSE* (https://glimmpse.samplesizeshop.org/) [25] for power calculation and using a fasting concentration 177 mg/dL TG ± 40 mg/dL SD as an average high triglyceride concentration, testing 24 subjects using this design gives a power of 0.9 with an alpha of 0.05 to detect a 10% to 20% effect of grape marc blends on plasma TG.

3. Results

3.1. *Participant characteristics and compliance*

Participants were screened into the study with a mean BMI in the overweight category, total cholesterol in the borderline high range, LDL-C in the borderline high range, HDL-C in the normal range and triglycerides in the normal range (data found in Table 1). Participants were asked to maintain their weight and continue their current physical activity behaviors. The Stanford Brief Physical Activity questionnaire was used to assess the intensity of exercise of the participants. Of the 24 participants who completed, 1 data point was missing; 35% was categorized as light intensity activity, 35% as moderate intensity activity, 26% as high intensity activity and 6% as very high intensity activity. There were no significant changes in weight ($P = .37$) and BMI ($P = .32$), data are found in Table 5.

Participants were prompted to record 24 hours recalls on 7 random days per active study period. On average participants consumed about 1900 kcal/day across the 3 interventions. Carbohydrate intake was about 45% during the HE and HM interventions and 44% during the MCC intervention. Protein intake was about 17% of total caloric intake across the 3 interventions. Fat intake was about 38% during the HE and MCC interventions and 37% during the HM intervention.

Total participant compliance for HE was 99.1%, where 1 participant missed 1 day of intake, for HM was 99.7% where 3 participants each missed 1 day of intake and lastly for MCC was 100%. Participants reported forgetting to consume capsules as the reason for missing days of intake.

3.2. *Vascular and endothelial function*

There was a significant main effect of intervention on systolic blood pressure (SBP) ($P = .047$) but not on diastolic blood pressure (DBP) ($P = .34$, Table 5). Pairwise comparisons revealed a lower SBP following the HE supplementation compared to HM ($P = .038$). There was no difference between HM and MCC ($P = .56$) or between HE and MCC ($P = .29$). Lastly, no significant effect of intervention on RHI or AI@75 was seen following the supplementation period ($P = .96$ and $P = .29$, respectively, Table 5).

3.3. *Lipoproteins and lipid profiling*

Following the supplementation period, there was no significant main effect of intervention in fasting concentrations of TC, LCL-C, TC:HDL and non-HDL-C. Following the HM and MCC supplementation, there was a significant main effect of intervention with higher HDL-C concentrations in HM and MCC compared to HE ($P = .007$ and $P = .02$, respectively). There was no difference between HM and MCC ($P = .87$). Data are found in Table 5.

Among the VLDL and chylomicron particle species, the total number, large, medium, or small particles were not affected by intervention ($P = .11$, $P = .42$, $P = .12$ and $P = .97$, respectively). Among the LDL particles, there was no difference in the total number, large or small particles ($P = .51$, $P = .33$ and $P = .21$, respectively). Similarly, there were no significant differences in the total number of IDL particles ($P = .98$).

Among the HDL particles, there was no significant effect of intervention on total number, medium or small particles ($P = .52$, $P = .95$, $P = .83$, respectively). There was a significant effect of intervention on large HDL particles ($P = .03$; Fig. 3). Paired comparison tests reveal following the HE supplementation there are lower numbers of large HDL particles with 7.05 ± 0.7 μmol/L compared to MCC with 7.7 ± 0.7 μmol/L ($P = .03$) but no differences between HE and HM (HM with 7.6 ± 0.7 μmol/L of large HDL particles) ($P = .78$) or between MCC and HM ($P = .12$).

Finally, there was no effect of intervention on the mean particle sizes of VLDL, LDL or HDL ($P = .66$, $P = .95$ and $P = .10$, respectively). All data are found in Table 6, unless otherwise stated.

3.4. *Triglycerides*

Both fasting and postprandial triglyceride concentrations were evaluated. There were no significant differences between the fasting TG concentration following the supplementation period ($P = .16$). There was a trend towards significance in the main effect of intervention in the postprandial TG response ($P = .06$). There was a significant main effect of intervention ($P = .05$) in TG AUC, where HM had a significantly lower AUC than HE ($P = .041$) and no difference between MCC and HE ($P = .30$) or MCC and HM ($P = .57$). In TG iAUC, there was a trend towards a significant main effect of intervention ($P = .07$). Data are in Fig. 4.

Table 5 – Post-intervention weight, BMI and clinical characteristics in participants with dyslipidemia[1,2].

Parameter	MCC $N = 25$	HE $N = 25$	HM $N = 26$
Weight (kg)	78.1 ± 2.3	78.7 ± 2.3	77.3 ± 2.2
BMI (kg/m2)	28.2 ± 0.56	28.3 ± 0.58	28.1 ± 0.56
TC (mg/dL)	221.2 ± 9.1	221.8 ± 7.9	221.3 ± 6.5
LDL-C (mg/dL)	142.6 ± 6.3	142.8 ± 6.1	146.5 ± 6.2
HDL-C (mg/dL)	55.7 ± 2.5[a]	52.4 ± 2.5[b]	56.6 ± 2.6[a]
TC:HDL (mg/dL)	4.1 ± 0.3	4.5 ± 0.3	4.1 ± 0.2
Non-HDL-C (mg/dL)	165.5 ± 9.0	169.4 ± 8.2	164.7 ± 6.1
Triglyceride (mg/dL)	140.1 ± 17.5	156.0 ± 21.2	125.0 ± 12.0
Systolic BP (mmHg)	123.8 ± 3.7[a]	118.8 ± 2.8[b]	125.6 ± 2.5[a]
Diastolic BP (mmHg)	72.4 ± 1.7	69.9 ± 1.8	72.0 ± 1.8
RHI	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1
AI@75	6.3 ± 3.0	8.4 ± 3.4	12.5 ± 4.3
Apo-B:Apo-AI	0.72 ± 0.03	0.76 ± 0.03	0.70 ± 0.03

[1] Abbreviations: AI@75, augmentation index standardized to 75 beats per minute; Apo, apolipoprotein; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; LDL-C, low density lipoprotein cholesterol; MCC, microcrystalline cellulose; RHI, reactive hyperemic index; TC, total cholesterol; TC:HDL, total cholesterol to HDL-C ratio.

[2] Data are presented as mean ± SEM, intention to treat analysis used a total $n = 27$, n for each intervention was dependent on how many study arms were completed by the subject who dropped out. Parameter group means differ by ANOVA ($P < .05$) with a Tukey's post-hoc test if they do not share superscript annotations.

Table 6 – Post-intervention NMR-based lipoprotein particle concentrations and sizes[1,2].

	MCC	HE	HM
Total VLDL & chylomicrons (nmol/L)	661.0 ± 6.4	67.2 ± 6.5	57.4 ± 5.6
Large VLDL & chylomicrons (nmol/L)	6.2 ± 1.2	7.6 ± 1.5	5.9 ± 0.9
Medium VLDL (nmol/L)	19.0 ± 3.4	24.2 ± 3.8	16.7 ± 2.1
Small VLDL (nmol/L)	35.8 ± 5.0	35.40 ± 3.97	35.85 ± 4.3
Total LDL (nmol/L)	1283.2 ± 64.4	1326.7 ± 60.6	1300.9 ± 60.5
IDL (nmol/L)	236.7 ± 34.7	238.4 ± 28.9	222.58 ± 19.6
Large LDL (nmol/L)	419.5 ± 50.1	414.1 ± 51.3	460.3 ± 52.4
Small LDL (nmol/L)	627.2 ± 68.9	674.2 ± 738.9	617.8 ± 68.6
Large HDL (μmol/L)	7.7 ± 0.7[a]	7.1 ± 0.7[b]	7.6 ± 0.7[a,b]
Medium HDL (μmol/L)	10.7 ± 1.1	10.9 ± 1.3	11.1 ± 0.7
Small HDL (μmol/L)	15.4 ± 1.6	15.9 ± 1.3	15.9 ± 1.2
VLDL size (nm)	50.9 ± 1.7	51.5 ± 2.0	50.1 ± 1.7
LDL size (nm)	20.8 ± 0.2	20.9 ± 0.2	20.9 ± 0.2
HDL size (nm)	9.4 ± 0.1	9.3 ± 0.1	9.3 ± 0.1

[1] Abbreviations: HDL, high-density lipoprotein; HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; MCC, microcrystalline cellulose; VLDL, very low-density lipoprotein.

[2] Data are means ± SEM. Parameter group means differ by ANOVA ($P < .05$) with a Tukey's post-hoc test if they do not share superscript annotations.

3.5. *Apolipoproteins*

At fasting, there were no significant main effects of intervention on Apo-AI, Apo-B and Apo-CIII ($P = .15$, $P = .35$, $P = .2$, respectively; Table 7). However, there was a crossover effect on Apo-E ($P = .002$).

In the postprandial response, there were no significant effects of intervention in Apo-AI, Apo-B, Apo-CIII and Apo-E ($P = .10$, $P = .58$, $P = .73$, and $P = .19$, respectively). Similarly, no significant effects were seen in Apo-AI AUC, Apo-B AUC, Apo-CIII AUC ($P = .096$, $P = .37$, $P = .48$, respectively). Following the supplementation period, there were no significant effects in iAUC in Apo-AI, B, or E ($P = .95$, $P = .86$, $P = .25$, respectively); there was a trend towards significance in Apo-CIII iAUC ($P = .06$). Data are depicted in Figs. 5-8. There were no differences in Apo-B:Apo-AI ratio ($P = .11$, Table 5).

3.6. *Oxidized LDL*

There was no significant main effect of intervention on fasting oxLDL concentration ($P = .28$). In the postprandial oxLDL response, there was no significant effect ($P = .88$). There was no significant effect in oxLDL AUC ($P = .52$) or iAUC ($P = .52$). Data are depicted in Fig. 9.

4. Discussion

Supplementing Chardonnay seed flour was found to lower fasting TC, LDL-C and VLDL-C in high fat diet-induced obese hamsters [9]. Following the supplementation of 4.8 g/d of Chardonnay seed flour by participants with impaired peripheral endothelial function but normal lipid concentration, they

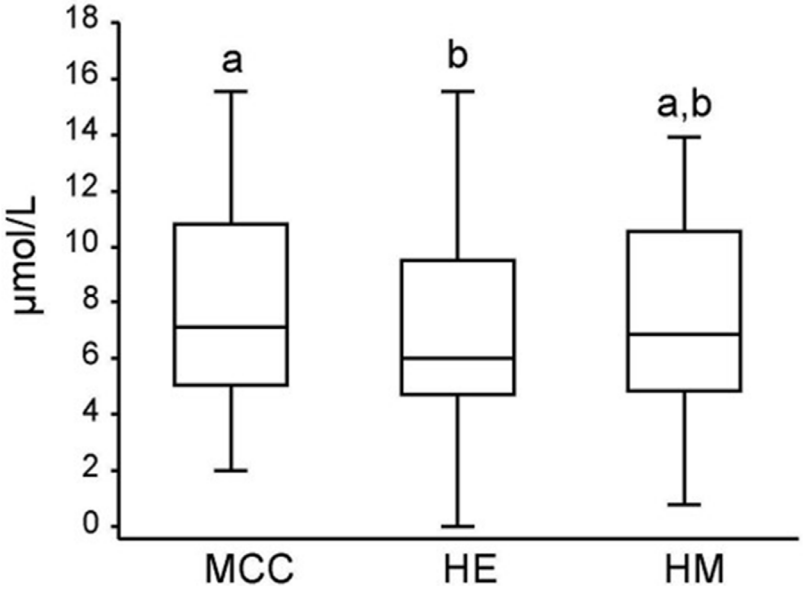

Fig. 3 – Large HDL particle data are shown as box and whisker plots by intervention. Different letters indicate significant differences in paired comparisons. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

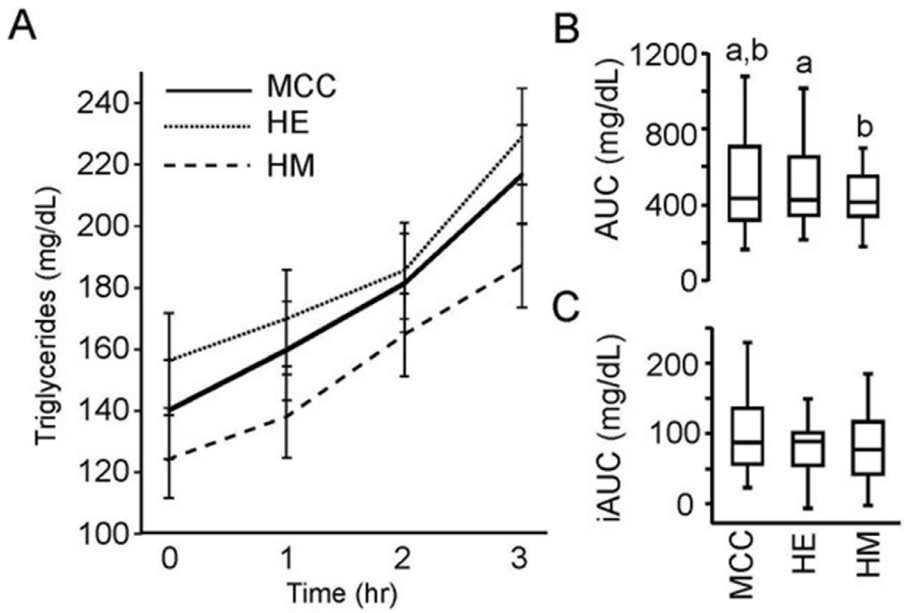

Fig. 4 – Panel A: Postprandial triglyceride response following high fat meal challenge. Data are shown as mean ± SEM. There is a trend towards significance in the main effect of intervention ($P = .06$). Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are depicted. There is a significant main effect of intervention with AUC between HE and HM interventions. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

had improvements to peripheral endothelial function but had no impact on lipoprotein concentrations [11]. Our study was the first to use encapsulated whole Chardonnay marc in humans, where we enlisted an overweight dyslipidemic cohort to evaluate a variety of ASCVD-associated end points for a response to this intervention. Our results differed from those found in the obese hamsters. We hypothesized that both Chardonnay blends would beneficially impact TC and LDL-C and that only the high extract blend would positively impact TG, but we saw no impact on TC, LDL-C from either blend and only the high marc blend had an impact on postprandial TG. Notably, the Chardonnay seed flour supplementation dosage was substantially higher in the hamster model compared to our study where whole CM was used with Chardon-

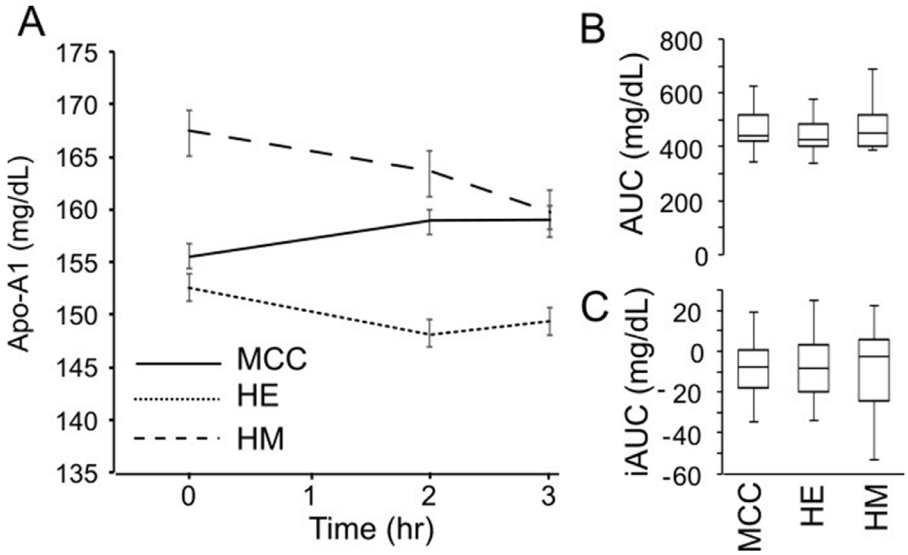

Fig. 5 – Panel A: Postprandial Apo-AI response following a high fat meal challenge. Data are means ± SEM. Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are shown. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

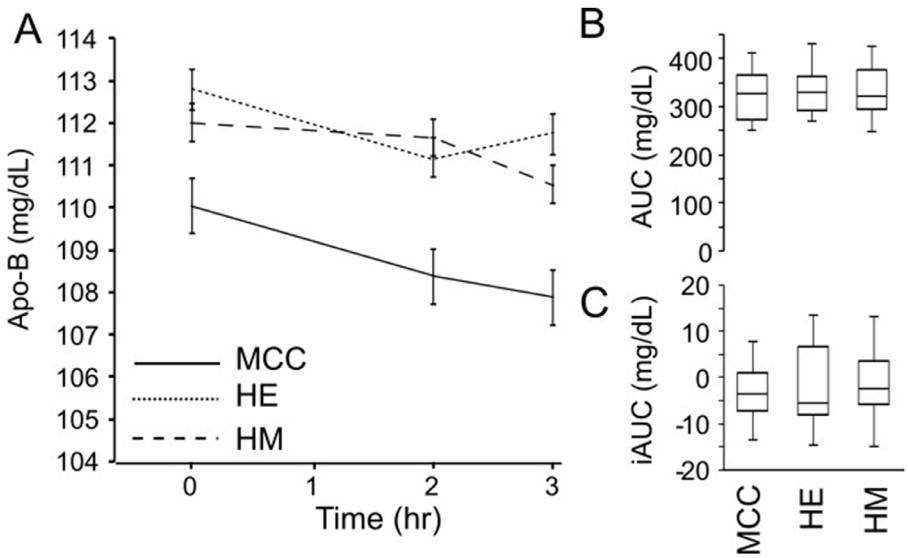

Fig. 6 – Panel A: Postprandial Apo-B response following a high fat meal challenge. Data are means ± SEM. Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are shown. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

nay seed extract blended to modestly increase the phenolic content.

High density lipoprotein cholesterol (HDL-C) is involved with reverse cholesterol transport (RCT), in other words, it transports cholesterol from peripheral tissues to the liver to be removed from the body by the gallbladder, positioning it as an important factor in reducing ASCVD risk [26]. Following the high extract supplementation, there was a significant decrease in HDL-C plasma concentrations compared to both the microcrystalline cellulose and high marc blend interventions. In the Chardonnay seed flour hamster study, there was a trend towards lowered HDL-C following the Chardonnay seed flour supplementation, thus the results from the present study support that observation. NMR lipid profiling showed a decreased number in large HDL particles following high extract supplementation compared to microcrystalline cellulose. Large HDL particles are thought to be the primary HDL species responsible for reverse cholesterol transport, but this concept is still debated as some groups have found positive associations with reduced ASCVD while others have found no association [27–30]. Apo-AI is associated with all HDL particles, and it has been argued that Apo-AI has more relevance in ASCVD mortality [27,31]. The current study did not observe changes in Apo-AI across interventions.

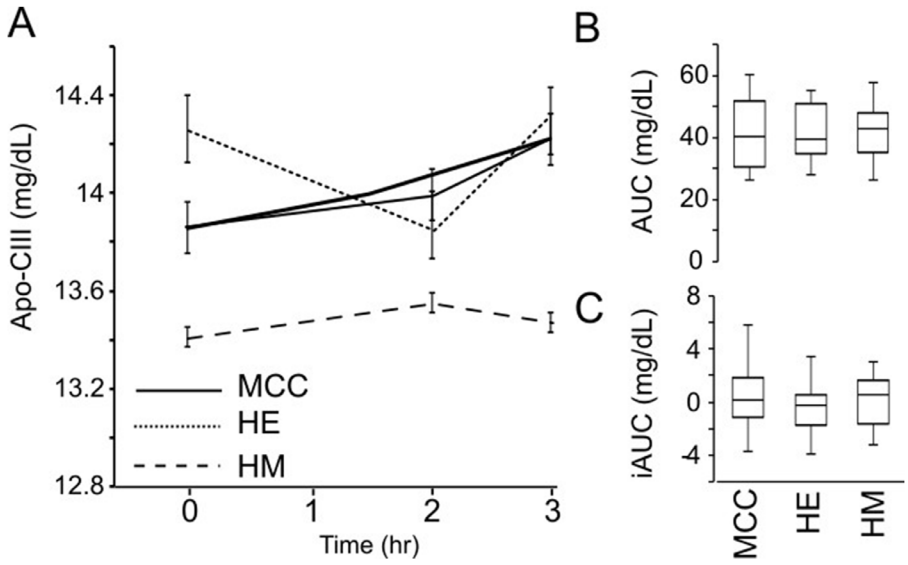

Fig. 7 – Panel A: Postprandial Apo-CIII response following a high fat meal challenge. Data are means ± SEM. Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are shown. There is a trend towards significance in the incremental area under the curve (*P* = .06). HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

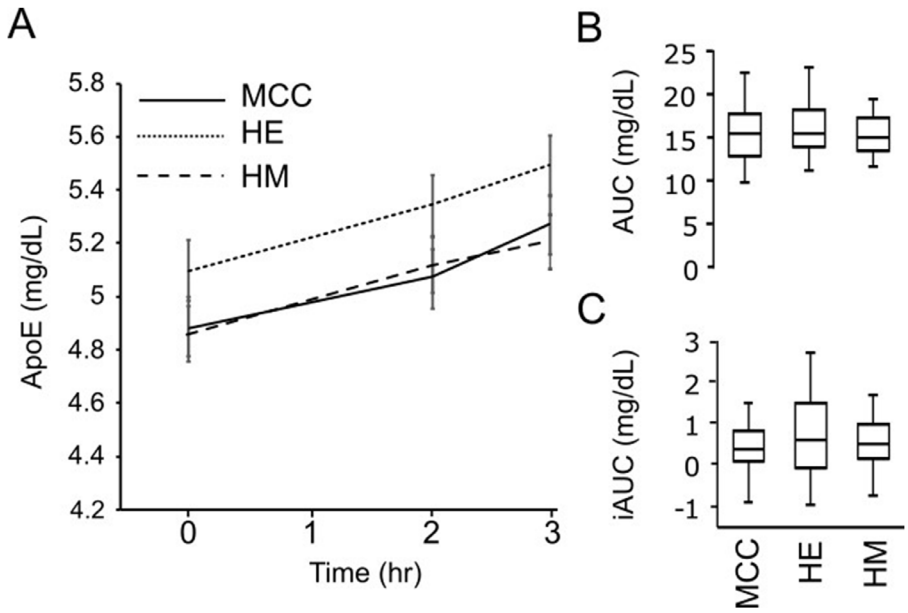

Fig. 8 – Panel A: Postprandial Apo-E response following a high fat meal challenge. Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are shown. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

Fasting triglycerides have long been part of the atherosclerosis conversation, while nonfasting triglyceride is emerging as a practical and relevant measure of CVD risk [32]. Epidemiological studies have pointed to the relationship between high nonfasting TG and CVD compared to fasting TG [15,16,33,34]. While only a statistical trend, there was a pattern of a lower postprandial TG response following the high marc blend intervention. More importantly, a summary measure of postprandial triglycerides, the TG AUC following the high marc blend supplementation was significantly lower compared to high extract blend intervention. Studies that utilized grape seed extract or pure (-)- epicatechin, demonstrated a reduced TG response [35–37]. However, the high extract blend intervention resulted in the highest TG response, which does not align with previous results that suggested higher flavan-3-ol content decreased TG response. The high marc blend intervention resulting in a trend towards lower TG response, and a lower TG AUC may suggest that high flavan-3-ol content alone is not the

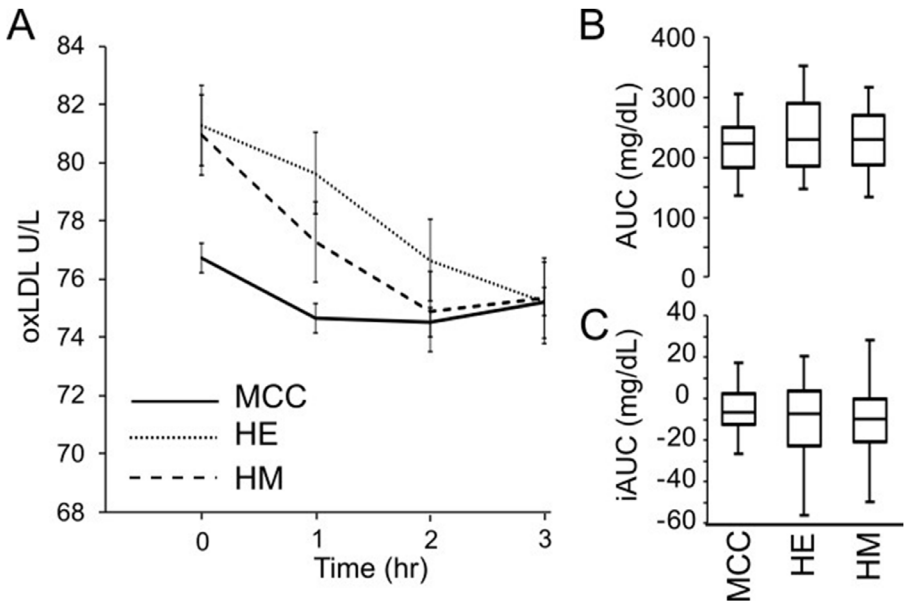

Fig. 9 – Panel A: Oxidized low density lipoprotein cholesterol (LDL-C) response following a high fat meal challenge over 3 h. Data are means ± SEM. Panel B: Area under the curve (AUC) and incremental area under the curve (iAUC) are shown. HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.

Table 7 – Post-intervention fasting apolipoprotein concentrations[a,b].

	MCC	HE	HM
Apo-AI (mg/dL)	154.9 ± 5.0	151.8 ± 4.8	165.7 ± 9.5
Apo-B (mg/dL)	109.1 ± 3.6	112.1 ± 3.2	111.2 ± 3.2
Apo-CIII (mg/dL)	14.1 ± 0.8	14.7 ± 0.9	13.7 ± 0.6
Apo-E (mg/dL)	5.8 ± 0.9	6.0 ± 0.9	5.2 ± 0.4

[a] Abbreviations: Apo, apolipoprotein; HE, high Chardonnay extract blend; HM, high Chardonnay marc blend; MCC, microcrystalline cellulose.
[b] Data are mean ± SEM.

complete story behind the lower postprandial TG response. The present study did not include postprandial substrate oxidation measurements—in the Chardonnay seed flour studies, gene expression analyses showed an upregulation in genes related to β-oxidation [9,10]. It is conceivable that upregulation of these genes could be translated to increased fat combustion following a high fat meal and therefore a lower TG response.

While this study was not designed to evaluate mechanisms of action, Apo-CIII was measured to give an indication of whether this could be one aspect of how Chardonnay marc could be affecting TG concentrations as Apo-CIII inhibits TG hydrolysis and may contribute to the development of ASCVD [38]. The results did not show statistical differences in Apo-CIII response across the interventions, but the pattern of the response was similar to the postprandial TG response, where the high marc supplementation resulted in lower responses. In addition, Apo-CIII iAUC had a trend towards significance similar to the postprandial TG response. This result could be an indication of how Chardonnay marc may be affecting TG concentrations and should be further explored. In future studies, it may be interesting to also measure Apo-CII as it acts as a cofactor for lipoprotein lipase in TG hydrolysis [39].

Endothelial dysfunction is an early indication of ASCVD. The current study did not demonstrate an improvement in EndoPAT with either Chardonnay formulation, compared to the response to Chardonnay seed flour supplementation reported by Corban et al. [11]. Participants of the present study were relatively healthy and did not have endothelial dysfunction (defined as RHI <1.67), therefore this result aligned with our hypothesis that no improvements in endoPAT would be seen. This demonstrates that in a population with normal endothelial function, there is no change thus we would need to reexamine this outcome in a population with endothelial dysfunction to understand what impact Chardonnay marc may have.

Blood pressure is another early indication of ASCVD [40]. SBP was significantly lower following high extract blend compared to high marc blend. Flavan-3-ols have been cited to improve blood pressure through increasing nitric oxide to increase vasodilation [41,42]. The high extract blend delivered more total phenolics than the high marc blend, so it is possible that the lower SBP may be attributed to the higher phenolics (particularly (-)-epicatechin), but additional studies will need to validate this finding.

Oxidized LDL (oxLDL) plays a critical role in the pathophysiology of atherosclerotic progression [43,44]. The current literature on Chardonnay marc or seeds in ASCVD risk factors has not evaluated effects on oxLDL directly. However, animals supplemented with Chardonnay Seed Flour downregulate genes related to oxidative stress and reduce inflammatory markers, which have roles in the oxidation of LDL particles [9,10,44]. *In vitro* studies and animal models treated with (-)-epicatechin and grape powder, respectively, reduced LDL oxi-

dation and cellular uptake of oxLDL [45,46]. Previous studies supplementing humans with red grape marc extract or red grape seed extract have resulted in decreased oxLDL concentrations from baseline, which suggests that phenolics from Chardonnay marc could potentially have similar results due to similar phenolic profiles [47,48]. However, the present study saw no differences in oxLDL following the supplementation periods. These results do not support the red grape data but are similar to the nonsignificant oxLDL result following a pure (-)-epicatechin supplementation in humans [49].

The high marc blend predominantly had significant differences in the parameters discussed compared to the high extract blend. Compared to 1 serving of fresh black seedless grapes there is 156 mg GAE, green seedless grapes there is 110 mg GAE and high bush blueberries there is 328 mg GAE [50], HE had similar amounts with 119 mg GAE while HM had 75 mg GAE. This leads us to believe that phenolics cannot be the entire reason for changes in TG and HDL-c, given the phenolics were roughly half the amount of the high extract blend. WellVine Chardonnay marc is pressed Chardonnay grapes; thus the nutritional complexity of the whole grape matrix is maintained which may be contributing to the results.

4.1. *Limitations*

Both men and women were recruited on broad inclusion criteria where they only needed to meet one of the lipid qualifications. While this was a conscious decision for logistical recruitment reasons, it nonetheless introduced variability and heterogeneity into the sample population. Participants therefore entered the study with differing baseline CVD risk. On average, many of the lipid criteria at enrollment were on the low end of normal and could have increased variability, making it more difficult to detect appreciable differences. Our study population started out with a slightly lower fasting triglyceride concentration than the target population that was used for the power calculation therefore our study had a lower power than projected. We sought to evaluate a more general population by including both men and women, however we did not take menstrual cycle or menopause status into account when recruiting women, which could have affected the results as well. Cardiovascular risk for women increases with menopause as this life stage is associated with changes in body fat distribution, changes in estrogen and increased blood pressure [51]. Thus, our study outcomes could have also been impacted by life stage. While we had testing in 6-week increments, we are still uncertain whether we were consistently testing in the same phase of the menstrual cycle in premenopausal women. We could have estimated postmenopausal status to evaluate if it had an impact but opted not to attempt statistical comparisons between pre/postmenopausal status as we would be underpowered and would risk a type 2 error. To reduce participant burden, we did not have baseline testing at the beginning of each intervention arm and as a result, we were not able to determine changes in outcomes from beginning to end of each intervention.

The testing was a total of 4 hours when only 3 hours of postprandial data were collected, thus it is unclear whether the TG peak was captured, and we do not have information regarding TG clearance. Future studies should consider narrowing the studied population further to continue exploring the effectiveness of Chardonnay marc in improving postprandial TG. A longer postprandial period should be considered to evaluate the rise and fall of circulating triglycerides. In addition, the 3-hour postprandial timeframe likely captured the effects from the more bioavailable monomeric flavan-3-ols (e.g., (-)-epicatechin and (+)-catechin), but likely was not a long enough timeframe to capture the potential impact of the colonic fermentation products (e.g., valerolactones) [52] which may also have impacts on the outcomes, thus should be considered in future applications.

5. Conclusion

In conclusion, this trial demonstrated the pleotropic potential of the high marc supplementation to affect several ASCVD risk factors. Changes in SBP, HDL-C and nonfasting TG were observed in the present trial. All these outcomes have a role in ASCVD risk, however more research is needed to build upon these early results.

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Author declarations

FL and TA are employees of Sonomaceuticals, LLC; NLK and JWN have no conflicts to declare.

CRediT authorship contribution statement

Fanny Lee: Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Torey Arvik:** Writing – review & editing, Funding acquisition, Conceptualization. **John W. Newman:** Writing – review & editing, Visualization, Resources, Methodology, Investigation, Formal analysis. **Nancy L. Keim:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2026.02.009.

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