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ORIGINAL PAPER

Influence of Red Pepper Spice and Turmeric on Inflammation and Oxidative Stress Biomarkers in Overweight Females: A Metabolomics Approach

David C. Nieman · Lynn Cialdella-Kam · Amy M. Knab · R. Andrew Shanely

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Abstract Red pepper spice (RP) and turmeric (TM) are used as flavorings in foods and for medicinal purposes. Utilizing a randomized, doubled-blinded, placebo-controlled, crossover design (2-week washout), 4-week supplementation with RP (1 g/d) or TM (2.8 g/d) was tested for influences on inflammation and oxidative stress in 62 overweight/obese (body mass index≥27 kg/m^2) females (40–75 years) with systemic inflammation (C-reactive protein, CRP≥2 mg/l). Overnight, fasted blood samples were collected pre- and post-supplementation, and analyzed for oxidative stress (F_2-isoprostanes, oxidized low density lipoprotein), inflammation (CRP and seven inflammatory cytokines), and metabolic profiles using gas chromatography–mass spectrometry with multivariate partial least square discriminant analysis (PLS-DA). Pre- to post-supplementation measures of inflammation and oxidative stress for both RP and TM did not differ when compared to placebo (all interaction effects, $P>0.05$), and global metabolic difference scores calculated through PLS-DA were non-significant (both spices, $Q^2Y<0.40$). These data indicate that 4-week supplementation with RP or TM at culinary levels does not alter oxidative stress or inflammation in overweight/obese females with systemic inflammation, or cause a significant shift in the global metabolic profile.

D. C. Nieman · L. Cialdella-Kam · A. M. Knab · R. A. Shanely
Human Performance Lab, North Carolina Research Campus,
Appalachian State University,
Kannapolis, NC 28081, USA

D. C. Nieman (✉)
North Carolina Research Campus,
600 Laureate Way,
Kannapolis, NC 28081, USA
e-mail: niemandc@appstate.edu

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Abbreviations

AIx@75	Augmentation index normalized for a heart rate of 75 beats/min
ANOVA	Analysis of variance
BMI	Body mass index
CRP	C-reactive protein
CV	Coefficient of variance
GC-MS	Gas chromatography mass spectrometry
IL	Interleukin
IFNγ	Interferon gamma
LDL	Low-density lipoprotein
PCA	Principal component analysis
PLS-DA	Partial least square discriminant analysis
RP	Red pepper
TM	Turmeric
TNFα	Tumor necrosis factor alpha
TRPV1	Transient potential receptor vanilloid 1

Introduction

Spices and aromatic herbs are used as flavor enhancers, colorants, preservatives, and as potential medicinal agents in the prevention and treatment of disease [1, 2]. Cell culture and animal experiments support multiple nutraceutical roles for spices including antioxidant, anti-inflammatory, anti-pathogenic, hypolipidemic, anticancerigenic, thermogenic, vascular function, and antidiabetic influences [3]. The underlying mechanisms of spice-related activities are diverse and may involve the regulation of transcription factors, cytokines, protein kinases and other enzymes, adhesion molecules, redox status, and growth factors [4]. Two highly

investigated spices include red pepper spice (RP) and turmeric (TM), but human studies with randomized, double blinded, placebo controlled research designs are limited [5–9].

The hotness produced by RP is caused by high concentrations of capsaicinoids (0.5–1 %) composed mainly of capsaicin and dihydrocapsaicin [10, 11]. Capsaicin has been widely studied for its pain-reducing and anti-inflammatory effects, influence on weight management, and cardiovascular benefits [10]. The transient potential receptor vanilloid 1 (TRPV1), a non-selective cation channel chemically activated by capsaicin, may be involved in some aspects of inflammation control [10]. Intake of capsaicinoids ranges widely throughout the world, approaching 200 mg/person per day in some high-consuming countries, but only 1.5 mg/person per day in the U.S. and Europe [11]. The metabolism of capsaicinoids occurs primarily in the liver and metabolite formation is catalyzed by a variety of hepatic enzymes [12].

Turmeric is a plant with creeping roots that are boiled, dried, and ground into a deep orange-yellow powder commonly used as a spice in curries and other South Asian and Middle Eastern cuisine [13]. TM contains over 300 different components including the active ingredient curcumin (3–5 %) [14]. *In vitro* and animal research shows that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation [3, 4, 13, 14]. Curcumin bioavailability is relatively low, however, is rapidly cleared and extensively conjugated in the gastrointestinal tract and liver [13, 15]. Serum curcumin concentrations peak 1–3 h after ingestion of large doses [15]. TM is exceptionally high in total antioxidant content, but the amounts used in the diet may be too small to have a meaningful influence on total antioxidant capacity [16].

Spices have been advanced as anti-inflammatory and antioxidant agents in the diet to help counteract the effects of systemic inflammation and the metabolic syndrome caused by obesity [17], but this hypothesis has not yet been tested in humans using acceptable study design procedures. The study hypothesis was that supplementation with RP or TM would reduce inflammation and oxidative stress, and improve vascular function in free-living, overweight females with underlying chronic inflammation (CRP≥2 mg/l). A crossover design under double-blinded, placebo controlled conditions was utilized with culinary levels of RP (1 g/d) and TM (2.8 g/d) that would be acceptable to U.S. adults. Metabolomics is the measurement of small molecules or metabolites present in biologic samples such as biofluids, tissues, and cellular extracts to elucidate the effect of a particular stimulus on metabolic pathways [18]. The use of metabolomics in nutritional sciences is gaining momentum, and global metabolomics profiling was utilized to help capture potential subtle perturbations in metabolites associated with RP and TM supplementation.

Materials and Methods

Subjects

Overweight and obese women (n=98) (body mass index (BMI) 27 kg/m^2 and higher) between the ages of 40 and 75 years were recruited via mass advertising and screened for elevated C-reactive protein (CRP) (≥2 mg/l). Sixty-four subjects were selected following screening, and all but three completed all aspects of the study. Subjects were apparently healthy with no overt chronic disease (specifically, coronary heart disease, stroke, cancer (other than skin), diabetes mellitus, rheumatoid arthritis), and not on dietary supplements or medications known to influence inflammation (in particular, non-steroidal anti-inflammatory drugs). Subjects agreed to maintain normal dietary and physical activity patterns during the 10-week study (*i.e.*, two 4-week supplementation periods with a 2-week washout period), and make no formal attempts to lose body weight. Written informed consent was obtained from each subject, and the experimental procedures were approved by the institutional review board for human studies at Appalachian State University.

Research Design

Subjects were randomized to RP or TM groups, and under double-blinded procedures ingested RP, TM, or placebo (PL) supplements daily for four weeks, with randomized crossover to the opposite condition (spice or PL) following a 2-week washout period. For each 4-week supplementation period, body composition, blood pressure, augmentation index, and blood samples were taken from all subjects pre- and post-supplementation after an overnight fast between 7:00–9:00 am, and always on the same day of the week. Diet records, and questionnaire responses to assess potential adverse effects and adherence to the supplementation regimen were administered pre-study, and after each 4-week supplementation period. The food records were analyzed using a computerized dietary assessment program (Food Processor, ESHA Research, Salem, Oregon). The symptom logs included questions on digestive health (constipation, heartburn, bloating, diarrhea, and nausea), hunger levels (morning, afternoon, and evening), energy levels (morning, afternoon, and evening), sickness (fever, cough, sore throat, stuffy nose, runny nose, and headache), pain (joint, muscle, and back), allergies, stress level, focus/concentration, and overall well-being. Subjects indicated responses using a 12-point Likert scale, with 1 relating to “none at all”, 6

"moderate", and 12 "very high". Subject compliance was monitored by regular email correspondence, and the return of supplement organizer trays after each supplementation period.

Red Pepper and Turmeric Supplements

Subjects ingested 2.8 g/d (for four weeks) TM, 1 g/d RP, or PL, with treatments randomized, counterbalanced, and double-blinded. The spices and PL (refined, white rice flour) were contained in identical looking blue gelatin capsules (two per day for RP or PL, five per day for TM or PL), and prepared by the McCormick Science Institute (Sparks, MD). The capsules were arranged by day of the week in supplement organizer trays with locking lids. Half of the capsules were consumed in the morning, and the other half in the evening, for each day of each 4-week periods of the study.

Body Composition

Height was measured using a stadiometer, and body mass and body composition were measured using a Tanita bioelectrical impedance (BIA) scale (Tanita Corporation of America, Inc., Arlington Heights, IL). Subjects were measured while standing erect, wearing light clothing, with bare feet on the analyzer foot pads.

Blood Pressure, Augmentation Index, Serum Diagnostic Chemistries

Blood pressure was measured by technicians following a 15-min seated rest. The SphygmoCor Central Blood Pressure and Pulse Wave Velocity Assessment System (AtCor Medical, Atasca, IL) was used to measure the augmentation index. The SphygmoCor system derives a calibrated blood pressure waveform at the ascending aorta from a peripheral pressure waveform, recorded non-invasively at the radial artery using a high-fidelity pressure transducer. Augmentation index, a measure of systemic arterial stiffness, was calculated as the ratio of amplitude of the pressure wave above its systolic shoulder to the total pulse pressure, and then normalized to a resting heart rate of 75 beats per minute (AIx@75). Blood samples were drawn from an antecubital vein with subjects in the seated position for at least 15 min after an overnight fast. A serum comprehensive diagnostic chemistry panel was performed by our clinical hematology laboratory.

Plasma Cytokine Measurements and C-Reactive Protein

Total plasma concentrations of seven inflammatory cytokines (interleukin-6 or IL-6, tumor necrosis factor alpha or TNFα, interferon gamma or IFNγ, IL-1β, IL-8, IL-10, IL-12p70) were determined using an electrochemiluminescence based solid-phase sandwich immunoassay (Meso Scale Discovery, Gaithersburg, MD). All samples and provided standards were analyzed in duplicate, and the intra-assay CV ranged from 1.7 to 7.5 %, and the inter-assay CV 2.4 to 9.6 %, for all cytokines measured. The minimum detectable concentration of IL-6 was 0.27 $pg \cdot ml^{-1}$, TNFα 0.50 $pg \cdot ml^{-1}$, IFNγ 0.53 $pg \cdot ml^{-1}$, IL-1β 0.36 $pg \cdot ml^{-1}$, IL-8 0.09 $pg \cdot ml^{-1}$, IL-10 0.21 $pg \cdot ml^{-1}$, and IL-12p70 1.4 $pg \cdot ml^{-1}$. Pre- and post-supplementation samples for the cytokines were analyzed on the same assay plate to decrease inter-kit assay variability. CRP was measured using an LX-20 clinical analyzer (Beckman Coulter Electronics, Brea, CA).

Oxidative Stress

Plasma F_2-isoprostanes were determined using gas chromatography mass spectrometry (GC-MS). Free F_2-isoprostanes were extracted with deuterated [$^2H_4$] prostaglandin $F_{2\alpha}$ added as an "internal" standard, and then added to a C18 Sep Pak column, followed by silica solid phase extractions. F_2-isoprostanes were converted to pentafluorobenzyl esters, subjected to thin layer chromatography, and converted to trimethylsilyl ether derivatives. Samples were analyzed by a negative ion chemical ionization GC-MS using an Agilent 6890 N gas chromatography interfaced to an Agilent 5975B inert MSD mass spectrometer (Agilent Technologies, Inc., Santa Clara, CA). Oxidized LDL was measured using standard protocols for a competitive ELISA kit (CV=9.7 %) (Mercodia Oxidized LDL Competitive Enzyme-Linked Immunosorbent Assay, Mercodia Inc., Sweden).

Metabolomics Procedures

Samples were prepared for metabolomics profiling by spiking 300 μl of serum with 1.05 ml aliquot of two internal standards (0.2 mg/ml of p-chlorophenylalanine and heptadeconic acid in a 3:1 methanol/chloroform solution), derivitized with methoxyamine, and analyzed on an Agilent 7890A GC system coupled to an Agilent 5975C EI/CI Mass Selective Detector (Foster City, CA). The raw data files generated by GC-MS were converted to NetCDF format and processed using ChromaTOF software (v4.24, Leco Co., CA, USA). Metabolite annotation was performed by comparing unknown signal patterns from the study samples to those of reference standards from an internal library containing approximately 600 human metabolites (Sigma-Aldrich, St. Louis, MO) and the NIST and Leco/Fiehn metabolomics libraries. The average CV for heptadecanoic acid was less than 5 %. The mean CV of the internal standard across the entire sample analysis (158 injections) was 15.3 %.

Statistical Procedures

Data are reported as mean ± SE. Data for each supplementation group (RP and TM) were analyzed using a 2 (condition) x 2 (time) repeated measures ANOVA between subjects model, with pre- to post-supplementation changes calculated and compared using a Student's *t*-test. Diet record and symptom log data were analyzed in a similar fashion using a 2 × 2 repeated measures ANOVA. For the metabolomics data, all initial mathematical calculations including peak signal compensations, normalization to internal standards, and univariate analyses (nonparametric Mann–Whitney-Wilcoxon test) were performed using custom scripts in MATLAB R2010a (MathWorks, Inc., Natick, MA). Multivariate statistical analyses including principal component analysis (PCA) and partial least square - discriminant analysis (PLS-DA) were performed using SIMCA-P 12.0.1+ (Umetrics, Umeå, Sweden). PLS-DA was used to visualize the difference between global metabolic profiles for the three groups, with Q^2Y used for the predictive accuracy of the model (values of 0.4 or greater indicate a reliable model).

Results

Thirty-one (age 57.7±1.6 y) and 30 (age 55.7±1.4 y) female subjects completed all requirements for the RP and TM studies, respectively. Three subjects were unable to comply with the supplementation regimen and dropped out of the study. Figure 1 depicts a scatterplot relationship between BMI and pre-study CRP for all 61 subjects (r=0.25, P=0.048). BMI was 34.7±0.9 and 34.5±0.8 kg/m^2, and CRP 7.64±0.82 and 8.05±1.33 mg/l, for the RP and TM groups, respectively.

Supplementation with 1 g/d RP or 2.8 g/d TM over a 4-week period had no influence relative to PL on body weight, percent body fat, systolic blood pressure, augmentation index, serum glucose (Table 1), inflammation and oxidative stress biomarkers (Table 2), and all components of the diagnostic chemistry panel (data not shown). Data from the symptom logs indicated no difference pre- to post-supplementation relative to PL except for significant increases in heartburn and bloating symptoms in the RP group (data not shown). Three day food records revealed no pre- to post-4 week differences for energy, macronutrient, and micronutrient intake for RP and TM relative to PL (data not shown).

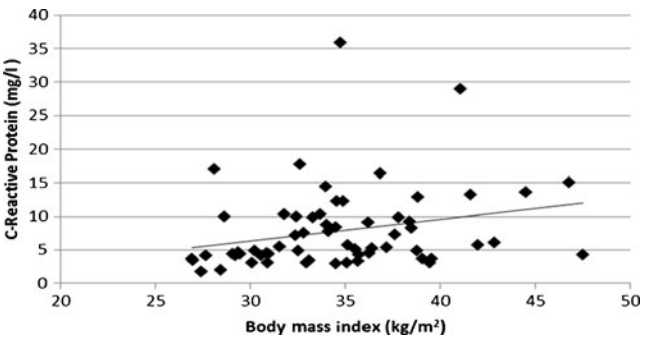

Fig. 1 Scatterplot relationship between BMI and pre-study CRP for all 61 subjects (r=0.25, P=0.048)

Score plots from the PLS-DA models visualized the global metabolic differences between RP and PL conditions (Fig. 2a) and TM and PL conditions (Fig. 2b) using ratios (pre- to post-supplementation). The Q^2Y scores of the two PLS-DA models were below 0.4 (0.245 for RP, and 0.212 for TM), indicating that the global metabolic profile differences between 4-week supplementation periods with RP and TM compared to PL were non-significant.

Table 3 summarizes significant fold change comparisons between spice and PL conditions for individual metabolites. Fold changes were relatively small and disparate, with no consistent change pattern established for metabolite clusters or pathways. The small fold change (1.3) for the four metabolites related to RP supplementation had no apparent connection with each other. An equally dissimilar list of 10 metabolites for TM (fold change range of −1.6 to 1.4) included a decrease for an essential fatty acid (linolenic acid) and a decrease for a medium chain fatty acid (nonanoic acid), an increase in an essential amino acid (lysine), a decrease in a carboxylic ester (1,2-benzenedicarboxylic acid, diisooctyle ester), and changes in three amine-related metabolites (*n*-butylamine, trimethylamine, and 4-hydroxy-proline).

Discussion

Four weeks supplementation with 1 g/d RP (~10 mg capsaicin/d) or 2.8 g/d TM (~112 mg curcumin) had no influence on inflammation, oxidative stress biomarkers, or arterial stiffness relative to placebo in overweight/obese females with underlying systemic inflammation. This interpretation was strengthened utilizing a strong research design and the tool of metabolomics that showed no trial differences in global metabolic scores.

Spices possess many unique functional food properties that make them attractive for use as supplements or inclusion in healthful food products. TM and RP have high antioxidant content [16], and cell culture data support strong anti-inflammatory activity through a variety of pathways [1, 3]. Few randomized, placebo control studies in non-diseased humans, however, have been conducted with individual spices. Culinary-level doses of RP and TM were chosen, with supplements used for a relatively short time period by systemically inflamed but otherwise healthy females, and measured no apparent benefits on body weight, serum glucose, arterial stiffness, inflammation, and oxidative. Ahuja et al. [5, 6] reported no alterations in arterial stiffness, disease risk factors, and total antioxidant status in 36 subjects consuming 30 g/d of a chilli blend supplement

Table 1 Influence of RP (n=31) and TM (n=30) supplementation on body weight, systolic blood pressure, augmentation index, and serum glucose

Variable	Red pepper	Placebo	Turmeric	Placebo	Interaction *P*-values
Weight (kg)					
Pre-study	92.0±2.7	92.1±2.7	91.5±2.0	91.2±2.1	0.831
Post-4 weeks	92.3±2.7	92.5±2.7	91.6±2.0	91.8±2.0	0.255
Body fat (%)					
Pre-study	46.9±0.5	47.3±0.6	47.4±0.6	47.1±0.6	0.854
Post-4 weeks	46.2±0.7	46.5±0.6	46.9±1.3	46.7±0.6	0.890
Systolic BP (mmHg)					
Pre-study	133±3.5	133±3.5	123±2.4	124±2.2	0.616
Post-4 weeks	132±3.2	133±3.3	126±2.6	126±2.1	0.716
ALX75					
Pre-study	29.1±1.6	29.0±2.0	33.2±1.4	32.8±1.7	0.275
Post-4 weeks	27.5±2.0	30.9±1.7	33.6±1.3	31.2±1.1	0.281
Glucose (mmol/l)					
Pre-study	5.45±0.17	5.56±0.17	5.76±0.21	5.82±0.38	0.206
Post-4 weeks	5.54±0.18	5.54±0.18	5.91±0.39	5.82±0.32	0.615

(55 % cayenne chilli) using a 4-week, randomized, cross-over design. No differences in weight change between groups of overweight men and women consuming 6 mg/d capsinoids or placebo for 12 weeks was measured by Snitker et al. [7], but a small but significant capsinoid advantage in abdominal fat loss was reported. Fasting plasma glucose and lipids were unaltered in 11 healthy, young adult subjects supplemented with 2.8 g/d TM for four weeks [8].

The lack of support in human studies for alterations in disease risk factors, inflammation, and oxidative stress when consuming RP or TM may be related to several factors including dosing paradigms, and absorption, distribution, metabolism, and excretion. The daily intake of capsaicinoids in

Table 2 Influence of RP (n=31) and TM (n=30) supplementation on inflammation and oxidative stress measures

Variable	Red pepper	Placebo	Turmeric	Placebo	Interaction *P*-values
Serum CRP (mg/l)					
Pre-study	7.64±0.82	9.48±1.71	8.05±1.33	7.44±0.98	0.091
Post-4 weeks	8.13±1.00	7.37±0.94	6.85±1.00	6.33±0.88	0.948
Plasma IL-6 (pg/ml)					
Pre-study	2.96±0.85	3.43±0.96	3.19±0.66	2.73±0.48	0.064
Post-4 weeks	4.14±1.06	2.80±0.96	2.21±0.34	2.75±0.53	0.136
Plasma IL-8 (pg/ml)					
Pre-study	4.81±0.40	5.14±0.52	4.93±0.51	4.85±0.49	0.177
Post-4 weeks	5.08±0.63	4.44±0.41	5.11±0.49	4.43±0.51	0.220
Plasma IL-10 (pg/ml)					
Pre-study	3.92±0.64	3.78±0.50	4.24±0.63	4.25±0.83	0.812
Post-4 weeks	3.60±0.46	3.71±0.54	3.48±0.54	3.59±0.87	0.881
Plasma TNF-α (pg/ml)					
Pre-study	6.08±0.78	5.79±0.52	6.97±0.63	6.33±0.61	0.811
Post-4 weeks	5.82±0.52	5.28±0.49	6.41±0.63	6.04±0.50	0.630
Plasma F_2-isoprostanes (pg/ml)					
Pre-study	95.1±4.0	99.8±4.3	88.8±2.6	91.2±3.3	0.744
Post-4 weeks	96.8±4.6	100±4.3	90.5±2.7	92.3±3.5	0.883
Plasma oxidized LDL (U/L)					
Pre-study	50.5±4.7	47.8±3.7	48.8±2.9	52.2±3.2	0.599
Post-4 weeks	50.9±4.3	46.6±4.3	44.3±3.0	44.6±3.2	0.373

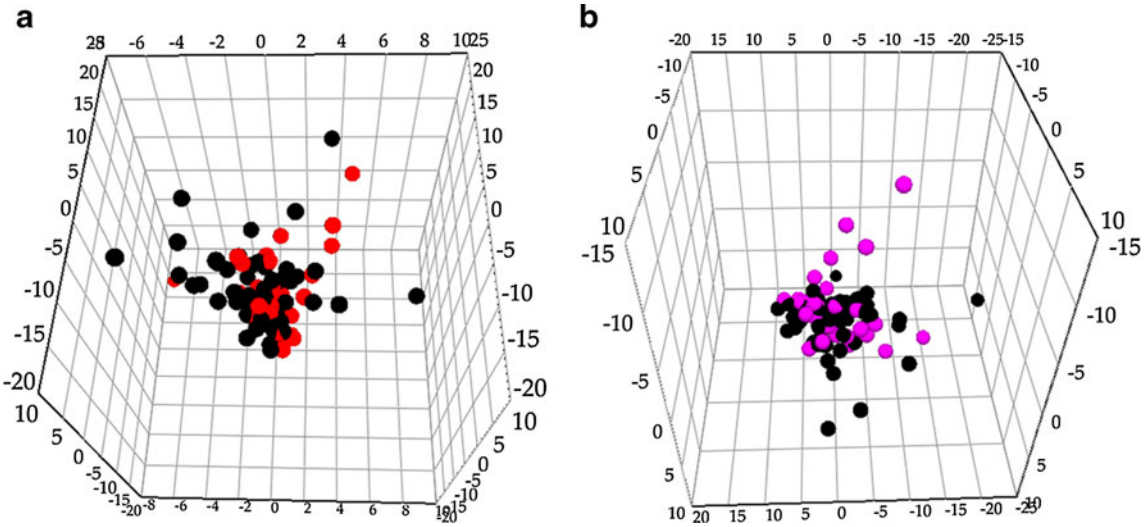

Fig. 2 Score plots for (**a**) red pepper and (**b**) turmeric from the PLS-DA models

selected Asian countries and Mexico is estimated to be 25–200 mg/d, well above the dose used in this study [17]. The metabolism of capsaicinoids occurs rapidly through liver enzymes, and may limit bioactive effects [12]. Curcumin from TM has low bioavailability in humans, and is extensively conjugated in the intestine and liver, limiting *in vivo* bioactive effects when compared to the impressive *in vitro* influences of the parent molecule [13, 15]. For these reasons, attempts are being made to complex large doses of curcumin with other molecules to increase bioavailability and potential health benefits [13, 19–21].

Table 3 Fold changes in metabolites over four weeks, spice compared to placebo conditions

Metabolites, red pepper vs. placebo	Fold changes	*P*
D-Ribofuranose	1.3	0.0203
Phosphate	1.3	0.0342
Phosphoric acid, 2-aminoethanol	1.3	0.0453
1,2-Benzenedicarboxylic acid, diisooctyl ester	1.3	0.0493
Metabolites, turmeric vs. placebo		
1,2-Benzenedicarboxylic acid, diisooctyl ester	−1.6	0.0011
Linolenic acid	−1.5	0.0023
Myo-Inositol, phosphate	−1.5	0.0032
Nonanoic acid	1.4	0.0076
Lysine	1.4	0.0085
n-Butylamine	1.4	0.0102
Trimethylamine	−1.4	0.0113
4-hydroxy-proline	1.4	0.0152
d-Galactose	1.3	0.0180
3-Hydroxyisobutyric acid	−1.3	0.0335

This is the first metabolomics-based investigation of the influence of TM and RP supplementation on human health-related outcomes, and the hypothesis was that this methodology would capture shifts in metabolites related to subtle perturbations in inflammation and oxidative stress from ingesting culinary levels of RP spice and TM. Data from the GC-MS platform did not support this supposition, and only small changes were measured in several disparate metabolites. Cell culture and animal studies on plant extracts from fruits, vegetables, teas, spices, and herbs suggest that these can act as potent anti-inflammatory, antioxidant, or anticancer agents, and recent advances in metabolomics improve the potential for discovering underlying mechanisms and overall efficacy [22, 23]. The culinary levels of RP spice and TM used in this study, the 4-week duration of the study, and the use of overnight-fasted blood samples may have limited the potential for significant metabolite shifts to occur and be measured. Adding a liquid chromatography mass spectrometry (LC-MS) platform to the metabolomics analysis in this study may have increased the potential for measuring spice-related metabolites [24].

In summary, 1 g/d RP or 2.8 g/d TM supplements ingested for one month by systemically inflamed overweight and obese women failed to alter inflammation, oxidative stress, or arterial stiffness as measured through both traditional and metabolomics biomarkers. These negative findings should be considered within the context of the culinary doses used for four weeks, the biomarkers chosen for this study, and subject numbers. Future research should emphasize higher doses, spice mixtures and blends of selected phytochemicals, and longer supplementation periods to determine if humans receive health benefits from spice ingestion [25–28].

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