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Effect of tamarind (*Tamarindus indica* L.) on the cardiometabolic health of patients living with HIV and elevated triglyceride levels: a dose–response double-blind, randomized exploratory trial†

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Background: The increase in cardiometabolic diseases in sub-Saharan Africa calls for sustainable remedies. In particular, people living with HIV (PLWH) have an increased risk of metabolic syndrome. Tamarind (*Tamarindus indica* L.), a fruit native to Africa, is rich in polyphenols and may optimize cardiometabolic health. In an exploratory trial, we assessed the potential of tamarind fruit juice to improve lipid metabolism in PLWH. *Methods*: We conducted a 4-week, parallel double-blinded trial of 50 patients equally allocated to two doses of tamarind juice. The primary outcome was triglycerides (TG), and eligible participants were aged 30 to 60 years with TG ≥ 150 mg dL^{-1}. Patients consumed 600 mL of tamarind juice daily, containing either 10% or 30% tamarind fruit pulp corresponding to 1556 mg or 1631 mg of the analyzed polyphenols, respectively. Fasted blood samples were analyzed for lipid profile. Blood pressure (BP) and vascular function were measured. Patients were required to maintain their habitual diet and lifestyle. Dietary intake, background polyphenol intake, and physical activity were measured. All analyses were performed according to intention-to-treat. Study registration was done at clinicalTrial.gov, NCT06058845. *Results*: The 30% fruit pulp juice significantly reduced TG by −39.8 mg dL^{-1} (95% CI: −67.7, −11.9), P = 0.006, corresponding to a 17.3% reduction of the baseline TG levels, while no statistically significant effect was noted for the 10% fruit pulp juice. None of the doses had a significant effect on total cholesterol, LDL, and HDL. The 10% fruit pulp juice significantly reduced systolic blood pressure (SBP), mean arterial pressure, and SBP (aorta) by −7.4 mmHg (95% CI: −14.5, −0.26), P = 0.043, −5.1 mmHg, 95% CI [−9.3, −0.99], P = 0.016, and −11.7 mmHg, 95% CI [−20.9, −2.6], P = 0.013, respectively. Physical activity, dietary intake, and background polyphenol intake between the study groups did not significantly change across the study period. *Conclusion*: Although our trial was not adequately powered to draw definitive conclusions, we showed that *T. indica* L. fruit juice potentially ameliorates TG metabolism and blood pressure homeostasis. This study provides a basis for future full-scale trials.

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1 Introduction

The prevalence of non-communicable diseases, in particular metabolic and cardiovascular diseases (CVD), has risen at a worrying rate in sub-Saharan Africa (SSA) and exerts insurmountable challenges to the social and healthcare fabric.[1–4] The ongoing nutrition transition in SSA exacerbates cardiometabolic dysfunction; this transition is described as a change from traditional diets to fast and ultra-processed foods and diets devoid of fruits and vegetables coupled with low physical activity.[1,2,5] This nutrition transition means a double burden for people living with HIV (PLWH), whose metabolic health is negatively affected by the adverse therapeutic effects of antiretroviral therapy (ART). Human Immunodeficiency Virus (HIV)

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and its treatment regimen ART have been shown to aggravate cardiometabolic risks.[6] For example, the metabolic syndrome of PLWH in SSA showed an upward trajectory from 21% in 2019 [6] to 23.9% in 2023.[7] HIV triggers a cascade of changes in cellular respiration, amplifying nutrient uptake due to the increased metabolic activity to invoke an antiviral response.[8] Such metabolic disturbances result in lipid and glucose dysregulation, a pathway for metabolic syndrome. HIV mediates chronic activation of the innate immune system with excessive production of pro-inflammatory cytokines such as MCP-1, IL-6, and TNF-α that mediate the risk of atherosclerosis and insulin resistance.[8,9] Despite the numerous health benefits, ART regimens, especially the much-preferred dolutegravir (DTG), are widely linked to hyperglycemia, hyperlipidemia, and insulin resistance.[7,10] Prolonged exposure to this deranged cellular respiration eventually overwhelms the endogenous defense system, resulting in oxidative stress, a precursor of atherosclerosis and attendant vascular pathologies. For example, triglyceride (TG) dysregulation is an independent mediator of CVD.[11] Despite the increase in cardiometabolic risks among PLWH in SSA, the management of these risks is through drug therapy. However, these drug-based therapies are rather expensive and often inaccessible, not to mention the additional pill burden on the patients.[7,12] Therefore, there is a need for sustainable, cheaper, evidence-based interventions.

Fruits and vegetables, thanks to the abundance of bioactive phytochemicals, particularly polyphenols, have been proven to regulate oxidative stress and improve cardiometabolic homeostasis.[13–15] Dietary polyphenols can potentiate lipid metabolism and attenuate several cardiometabolic risks in a dose–response relationship.[16] Despite the low consumption of fruits and vegetables across SSA, our recent study showed that several of Africa's neglected indigenous fruits and vegetables have a wealth of polyphenols with purported potency to reduce cardiometabolic risks.[17]

Tamarind (*Tamarindus indica* L.), a fruit native to Africa, is part of the traditional complementary and alternative medicine for cardiometabolic risks in SSA, despite the lack of scientific evidence to justify its use. *T. indica* L. is a leguminous tree belonging to the family Fabaceae and the monotypic genus *Tamarindus*. The tree bears edible fruits rich in polyphenols, especially phenolic acid (syringic acid and gallic acid) and flavonoids. The principal flavonoids in the *T. indica* L. fruit are flavan-3-ols, consisting of the oligomeric/polymeric proanthocyanidins and their monomers – epicatechins and catechins.[18–20] Flavan-3-ols are receiving increased recognition in modulating an array of cardiometabolic markers.[16,21–25] Syringic acid, or 4-hydroxy-3,5-dimethoxybenzoic acid, is a gallic acid derivative.[26] It effectively scavenges reactive oxygen species (ROS) and inhibits inflammation and lipid peroxidation, a key step in atherosclerosis pathogenesis and the attendant cardiometabolic diseases.[27,28] Syringic acid is explored in pharmacological analogs for diabetes and CVD.[29] We assessed the potential of *T. indica* L. fruit juice to augment TG metabolism in PLWH. We hypothesized that there would be a dose–response relationship in TG control following the intake of different doses of *T. indica* L. fruit juice.

2 Materials and methods

2.1 Study design

This was a single-center, 2-arm, 4-week randomized, double-blinded parallel exploratory trial with equal allocation ratios (1 : 1). Measurements were performed at three different timelines: (1) baseline, (2) midline (at 2 weeks), and (3) endline (at 4 weeks). The study was conducted between September and December 2023. We followed the Consolidated Standards of Reporting Trials (CONSORT) recommendations for randomized trials[30] and the CONSORT guidelines for randomized controlled trials in nutrition—the extension for pilot and feasibility studies.[31] All study procedures conformed to the Helsinki Declaration,[32] and the study protocol was registered at clinicaltrials.gov (NCT06058845). Research ethical approval was granted by Clarke International University and the Uganda National Council for Science and Technology (HS2923ES). All participants voluntarily gave informed written consent before recruitment.

2.2 Participants

Patients were recruited from the community-based model of HIV care in Wakiso district in Central Uganda. Eligible participants were PLWH aged ≥30 and ≤60 years with TG ≥ 150 mg dL^{-1}, managed on a DTG-based combination ART regimen (tenofovir, lamivudine, and dolutegravir). Patients were either stage I or II of the WHO clinical staging for HIV,[33] with 95% ART adherence in the last six months. Patients with tuberculosis co-infection, renal failure disease, liver cirrhosis, chronic pancreatitis or taking dietary supplements, or on treatment for dyslipidaemia, hypertension, or diabetes were excluded. Pregnancy, lactation, low blood pressure (<90/50 mmHg), and parallel participation in another clinical trial also made a patient ineligible. The study was announced during the drug refill days, and interested patients were provided with more information before participation. Demographic and medical information was obtained from all patients who consented.

2.3 Experimental protocol

2.3.1 Study interventions. The intervention products were two *T. indica* L., fruit juice products, containing 10% or 30% fruit pulp. Patients were assigned to consume 600 mL daily of either 10% or 30% juice products containing 1556 mg or 1631 mg of specific polyphenols, respectively, Fig. 1. In a separate product development and sensory evaluation study (see ESI methods†), a team of food and nutrition scientists at the Uganda Natural Chemotherapeutics Research Institute and Kyambogo University, Uganda, formulated four prototypes of *T. indica* L. fruit juice. The product prototypes were formulated based on fruit pulp proportions (10%, 20%, 30%, and 40%). The prototypes were subjected to a sensory evaluation (acceptability and preference tests) using untrained panelists (n = 69). After the sensory study, the 10% and 30% prototypes had the highest scores. These two juice prototypes were later produced by Asakawalo Enterprises Ltd, a local beverage-producing company, and given secret codes for concealment. Characterization of the phenolic content of the intervention pro-

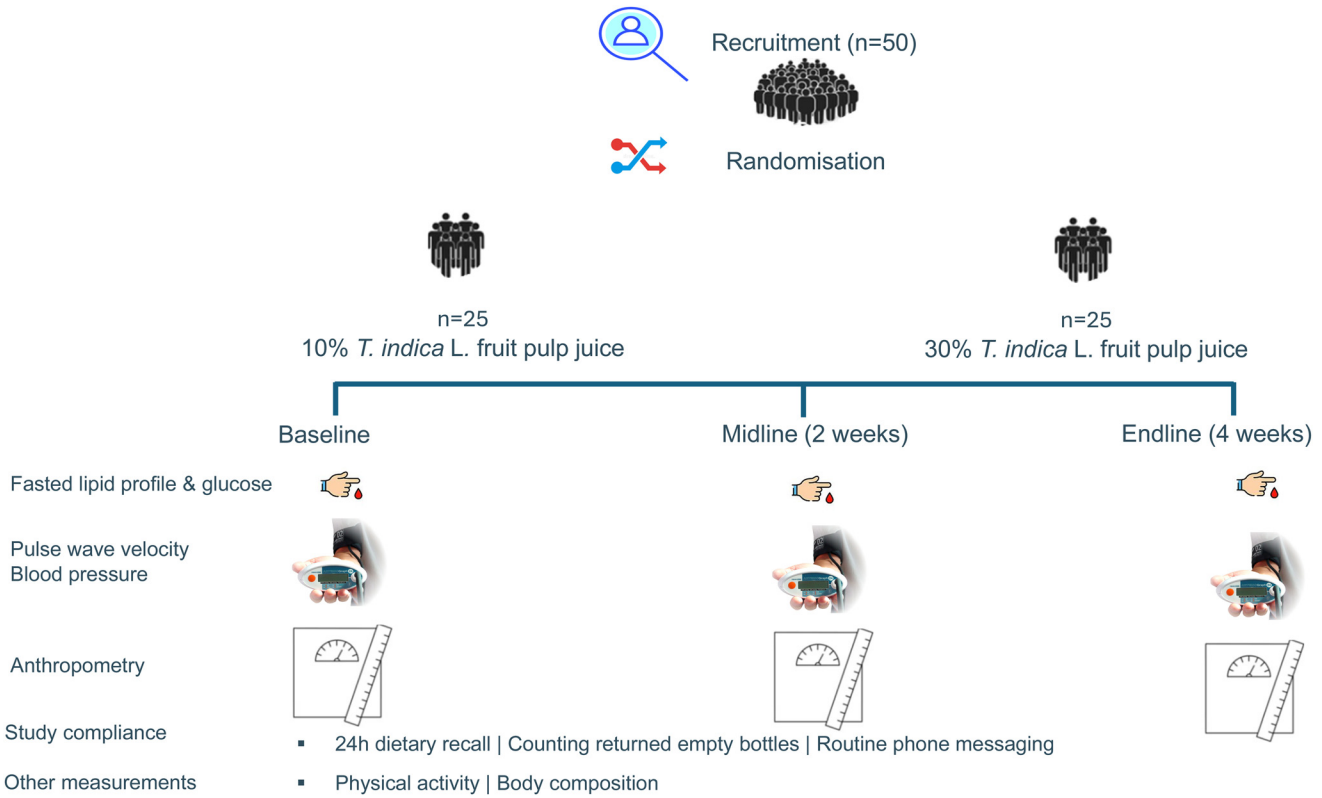

Fig. 1 Schematic overview of the study protocol evaluating the effect of a 4-week *T. indica* L. intake on cardiometabolic effects.and timelines.

ducts was performed by ultra-high performance liquid chromatography (UHPLC) in combination with triple quadrupole mass spectrometry (MS/MS) in the Pharmaceutical Analysis lab at KU Leuven, Leuven, Belgium.[34,35] Details of the phenolic characterization are provided in the ESI methods.† The phenolic profile of the intervention products is presented in Table 1.

2.3.2 Sample size determination. This was an exploratory trial, and no formal power calculation was performed. In our meta-analysis preceding this trial, we noted similar studies utilizing sample sizes ranging between 20 and 40.[16] This provided a reference for our pragmatic sample size of 40. To cater for the potential dropout rates, we inflated our sample size by 20%. A sample of 50 patients was deemed logistically feasible.

2.3.3 Randomization and blinding. A biostatistician not linked to the study developed a computer-generated sequence to randomly allocate participants to the two study arms. To ensure blinding, the products were packaged in identical amber bottles and assigned the code "GREEN" and "ORANGE" for 10% and 30% juice, respectively. The study arms were similarly coded "GREEN" or "ORANGE" to maintain double concealment.

2.3.4 Compliance and safety assessment. Participants were asked to maintain their habitual diet and lifestyle but restricted from consuming other *T. indica* L.-based foods/and beverages. Compliance with the study protocol was assessed by regular telephone inquiries every five days. Refilling was conducted weekly, during which participants returned empty study product bottles or unused study products which were counted to determine study compliance. In addition, consumption of the study products was also assessed through a 24-hour dietary recall of 2 non-consecutive days at midline and endline. A safety assessment was conducted by asking patients to contact a study staff member by phone if they experienced any adverse events related to the consumption of the study products. To assess tolerance to the study products, we requested patients to report any unusual events. The study nurse evaluated the reported adverse events.

2.3.5 Study outcomes and measurement protocols. The primary outcome was a 10 mg dL^{-1} reduction in TG. This

Table 1 Phenolic profile of the intervention products measured by UHPLC–MS/MS

	Polyphenol content in 600 ml of the juice prototypes	
Polyphenol (mg)	10% fruit pulp juice	30% fruit pulp juice
Procyanidin B2	730	68
(−)-Epicatechin	242	46
Taxifolin	32	64
Gallic acid	37	91
Syringic acid	515	1362
Total polyphenol*	1556	1631

The polyphenol content of the intervention products computed for the daily intake dose of 600 ml per participant. UHPLC–MS/MS, ultra-high-performance liquid chromatography–triple quadrupole mass spectrometry. *Total of the specific polyphenols analyzed in a targeted analysis.

effect size was informed by our recent meta-analysis.[16] Elevated TG levels are associated with a higher risk of CVD, and optimizing TG can provide insights into the overall cardiometabolic health.[11] From our meta-analysis, TG was more sensitive to polyphenol intake than the other lipid profile parameters.[16] Secondary outcomes included changes in fasting blood glucose (FBG), total cholesterol, LDL-c, HDL-c, body fat composition, BMI, waist circumference, pulse wave velocity (PWV), augmentation index (Aix), mean arterial pressure (MAP), and blood pressure.

Lipid profile (TG, total cholesterol, LDL-c, and HDL-c) and FBG were measured using the finger prick technique.[36,37] The tests were performed by a phlebotomist early in the morning, following an overnight fast before breakfast. Body fat composition was measured using Bodystat 1500 lite touch. The study nurse conducted office blood pressure measurements using a sphygmomanometer, Seca b12, in duplicate after a 3-minute rest with the patient seated.[38] Weight was measured using Seca 874 dr. Height was measured using a Seca height board. Waist circumference was measured using a non-stretchable standard tape measure. The waist measurement was taken at the level of the iliac crest, with the participant standing at the end of a gentle expiration.[39] Increased arterial stiffness was measured non-invasively using aortic pulse wave velocity (PWV).[40] Aortic PWV, MAP, SBPao, PP, PPao, and Aix were measured twice in the supine position on the right upper arm using an arteriograph (TensioMed, Budapest, Hungary).[41] The arteriograph is an operator-independent, non-invasive device that uses an oscillometric occlusive technique.[41,42] Physical activity was measured using the short form of the International Physical Activity Questionnaire (IPAQ).[43] Dietary intake assessment was a non-consecutive two-day, 24-hour dietary recall method. Participants estimated their food portion sizes using a photographic food atlas.[44] From the 24-hour dietary recalls, we calculated total energy, macro and micronutrients, fiber, and the background dietary polyphenol intake using the Phenol Explorer database.[45]

2.3.6 Statistical analysis. Data analysis was performed using SPSS software version 29. The intention-to-treat analysis approach was followed for all the analyses. Statistical analyses were performed on the primary outcomes before breaking the concealment. We assessed normality and sphericity using Kolmogorov–Smirnov and Mauchly's tests. At the baseline, categorical parameters were analyzed using Chi-square tests and two-sample *t*-tests for continuous variables and summarised as mean and standard deviation or proportions. Changes in TG and other secondary outcomes were assessed using multilevel linear models (repeated measures) with intervention types as the fixed effects and the time points of measurements (baseline, midline and endline) as the dependent variables. We used the analysis of covariance (ANCOVA) model to assess the adjusted treatment effect on changes in both the primary and secondary outcomes upon controlling for total energy intake, macronutrients, fiber, and physical activity. *Post-hoc* analysis was performed using the Bonferroni test. A *p*-value of <0.05 was used for statistical significance.

3 Results

3.1 Patient flow

Patient flow during the trial is illustrated in Fig. 2. Out of the 71 patients who met the inclusion criteria, 50, of whom 41 were female, were recruited into the study. Forty-six patients com-

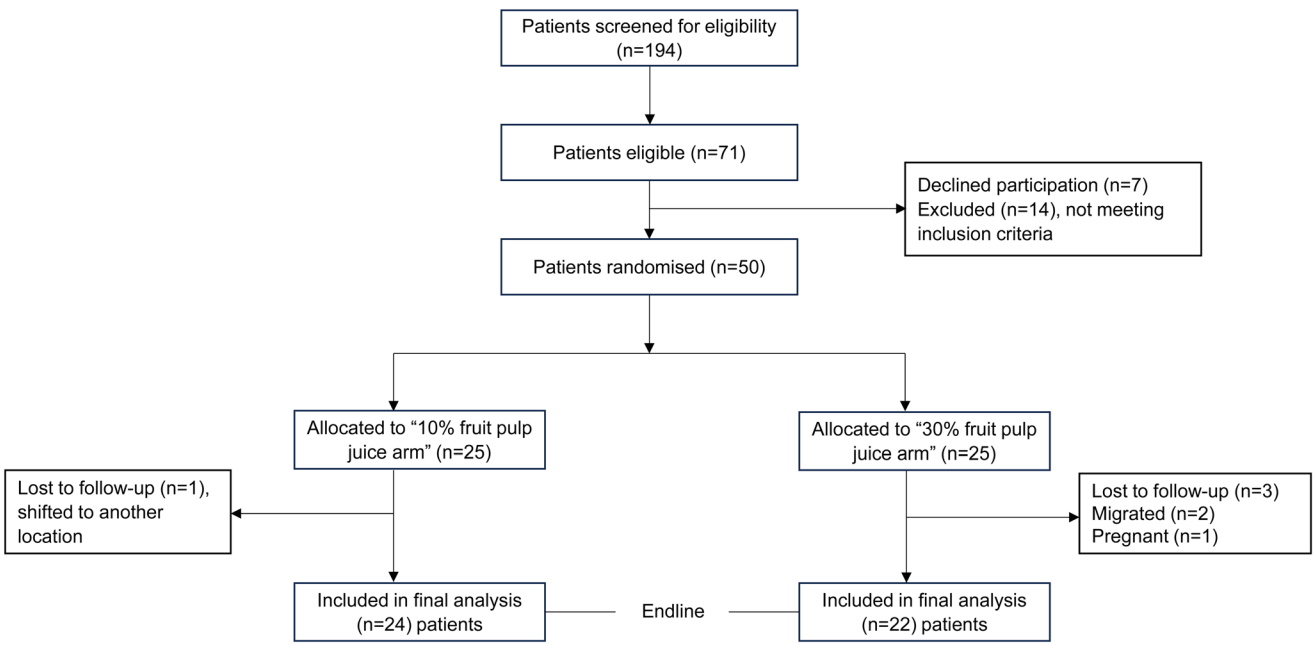

Fig. 2 CONSORT flowchart illustrating the patients' flow during the 4-week intake of *T. indica* L. fruit juice.

pleted the study and were included in the final analysis. The overall dropout rate was 8%. The sociodemographic characteristics of the study participants are presented in Table 2. Altogether, the mean age of the patients was 45.2 years. The majority (58%) of the patients had at least attained a secondary level of education. On average, patients had lived with HIV for 5.8 ± 3 years and had been on ART for 5.4 ± 2.8 years.

3.2 Study compliance

3.2.1 Study products. Out of the 2830 juice bottles supplied, 82 were returned and not consumed. Therefore, the calculated compliance rate of the study was 97%.

3.2.2 Dietary intake. At the baseline, the mean total energy intake was 2392 kcal, and only in the 30% fruit pulp juice arm did the total energy intake significantly change over time. Besides total fat, there was no significant difference in total energy intake, protein, carbohydrates, and fiber between the treatment groups during the study period. In terms of sodium intake, the baseline mean intake was 2794 mg and did not significantly change across the treatment groups, Table 3.

3.2.3 Dietary total polyphenol intake. The background polyphenol intake between the two study groups did not significantly vary across the study period, Table 2. However, within the 30% fruit pulp juice arm, there was a significant reduction (−280 mg, P = 0.010) in polyphenol intake at the endline. At the food group level, major sources of polyphenols were whole foods or derivatives of legumes (common beans and peanuts), roots and tubers (potatoes and sweet potatoes), and cereals (maize, rice, and wheat). Fruits were mainly bananas, melons, passion fruits, mangoes, and oranges, while vegetables included onions, eggplants, *Amaranthus*, tomatoes, and cabbage. Other high polyphenol sources included tea-based beverages, beer, and spices (curry powder). There was no report of additional intake of *T. indica* L on top of the study products.

3.2.4 Physical activity. The mean baseline physical activity level of patients in both study groups was 4696 ± 548 MET minutes. Physical activity levels did not significantly change between nor within groups over the entire study, Table 3.

Table 2 Sociodemographic characteristics of the participants at the baseline

Characteristics	10% fruit pulp juice arm (n = 25)	30% fruit pulp juice arm (n = 25)
Sex (F/M)	20/5	21/4
Age	45.6 ± 8.9	44.7 ± 9.8
Education (n, %)		
None	3 (12%)	2 (8%)
Completed primary level	10 (40%)	6 (24%)
Completed secondary level	6 (24%)	8 (32%)
Completed tertiary level	6 (24%)	9 (36%)
Employment (n, %)		
Employed	18 (72%)	19 (76%)
Not employed	7 (28%)	6 (24%)
Household size (n, %)		
<5 persons	10 (40%)	12 (48%)
≥5 persons	15 (60%)	13 (52%)
Time lived with HIV	6 ± 3.3	5.6 ± 2.6
Time lived on ART	5.5 ± 3.3	5.2 ± 2.3

Values are presented as mean (SD) or proportions (percentages). SD, standard deviation; ART, antiretroviral therapy; F, female; M, male. The average household size in Uganda is ∼5 persons.

3.3 Adverse events

We recorded complaints of mild gastrointestinal events, such as heartburn, loose stool, bloating, and nausea. The proportions of patients with such complaints are shown in ESI Table 1.† The complaints cleared in 5 days following the start of consumption of the study products and did not result in participant discontinuation.

3.4 Study outcomes

3.4.1 Primary outcome: reduction in TG. There was no significant difference in TG between groups (−17.7 mg dL^{-1}, 95%

Table 3 Dietary intake and physical activity levels of patients at different study timelines

Variables	10% fruit pulp juice arm			30% fruit pulp juice arm			P-value
	Baseline (n = 25)	Midline (n = 25)	Endline (n = 24)	Baseline (n = 25)	Midline (n = 23)	Endline (n = 22)	
Total energy (kcal)	2236 ± 1353	2532 ± 1305	2352 ± 1245	2548 ± 1258	2045 ± 1164	1697 ± 1231	0.099
Total CHO (%E)	63 ± 7	65 ± 9	64 ± 14	65 ± 13	60 ± 11	61 ± 12	0.434
Protein (%E)	12 ± 2	14 ± 2	13 ± 3	11 ± 2	10 ± 4	11 ± 7	0.432
Total fat (%E)	26 ± 4	23 ± 10	26 ± 11	28 ± 9	29 ± 13	29 ± 21	**<0.001**
PUFAs (%E)	7 ± 4	6 ± 3	6 ± 3	6 ± 2	8 ± 3	7 ± 3	0.162
MUFAs (%E)	9 ± 3	9 ± 3	8 ± 4	7 ± 2	8 ± 3	7 ± 3	**0.02**
Cholesterol (mg)	124 ± 86	86 ± 40	144 ± 112	162 ± 112	105 ± 45	131 ± 148	0.452
Fibre (g)	24 ± 17	23 ± 10	24 ± 10	32 ± 26	28 ± 21	29 ± 25	0.083
Sodium (mg)	2640 ± 1454	2758 ± 2126	2905 ± 1396	2948 ± 2733	2637 ± 1977	2939 ± 1473	0.235
Vitamin C (mg)	74 ± 41	99 ± 71	82 ± 35	91 ± 75	70 ± 43	64 ± 47	0.317
Polyphenols (mg)[a]	1112 ± 392	1039 ± 344	1020 ± 321	1208 ± 280	1014 ± 390	929 ± 370	0.446
PA [MET-min]	4612 ± 4007	4497 ± 3224	5020 ± 4615	4726 ± 3340	4050 ± 3124	4372 ± 3026	0.723

Two-way repeated measures analysis of variance followed by the Bonferroni *post hoc* test was used to compare the changes between the study groups over a 4-week study period; P < 0.05. Values are expressed as mean and standard deviation. PA, physical activity; CHO, carbohydrates; %E, percentage of total energy.[a] Background dietary polyphenol intake (not including the polyphenols in the test of *T. indica* L. juices).

CI [−70.1, 34.7], P = 0.499), which remained unchanged after adjusting for physical activity and dietary intake. In the 30% fruit pulp juice arm, the within-group effect was −39.8 mg dL^{-1}, 95% CI [−67.7, −11.9], P = 0.006, corresponding to a 17.3% reduction of the baseline TG levels, and −7.6 mg dL^{-1}, 95% CI [−34.3, 19.2], P = 0.568, resulting in a 5.7% reduction in the baseline TG for the 10% fruit pulp juice arm, Fig. 3. The interindividual variability in TG control ranged from −1.3% to −62% and −1.2% to −71.3% for the 10% fruit pulp juice and 30% fruit pulp juice arms, respectively.

3.4.2 Secondary outcomes. There was no statistically significant difference between the doses in the biochemical and anthropometric end points, Table 4, and parameters of cardiovascular function (Table 5 and ESI Table 2†). However, the 10% fruit pulp juice significantly reduced systolic blood pressure by −7.4 mmHg, 95% CI [−14.5, −0.26], P = 0.043, Fig. 4, MAP by −5.1 mmHg, 95% CI [−9.3, −0.99], P = 0.016, and SBPao by −11.7 mmHg, 95% CI [−20.9, −2.6], P = 0.013, ESI Table 3.†

4 Discussion

To the best of our knowledge, this is the first human study to investigate the effects of *T. indica* L. fruit beverage on the cardiometabolic health of PLWH. This study demonstrates the feasibility of conducting a full-scale trial to evaluate the potential benefits of *T. indica* L. on cardiometabolic health. Additionally, it provides valuable data for power calculations needed for larger trials. Although our trial was not adequately powered to draw definitive conclusions, we showed that *T. indica* L. fruit juice potentially ameliorates lipid metabolism and blood pressure homeostasis.

Although *T. indica* L. contains a range of phytochemicals, it has been shown that polyphenols are the most ubiquitous.[46] Hence, it is suggested that the cardiometabolic benefits of *T. indica* L. are potentially due to polyphenols.[18,46] Polyphenols potentiate lipid metabolism by reducing TG absorption and downregulating circulating apolipoprotein-B (ApoB) and remnant lipoproteins.[47] This indicates that polyphenols lower

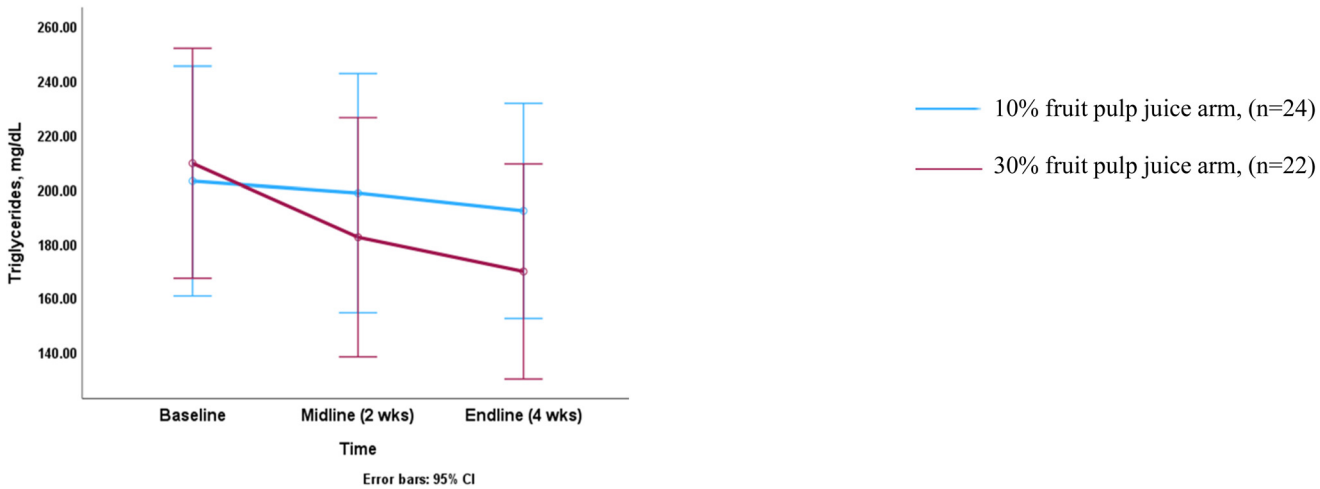

Fig. 3 Effect of a 4-week *T. indica* L. fruit juice intake on triglyceride metabolism.

Table 4 Effect of 4 weeks of *T. indica* L. fruit juice intake on biochemical and anthropometric parameters

	10% fruit pulp juice arm			30% fruit pulp juice arm				
Parameters	Baseline (n = 25)	Midline (n = 25)	Endline (n = 24)	Baseline (n = 25)	Midline (n = 23)	Endline (n = 22)	Intervention effect at endline (95% CI)	P-Value
TG (mg dL^{-1})	199.8 ± 19.6	223.3 ± 23.8	192.2 ± 18.4	209.8 ± 20.6	182.6 ± 24.8	170 ± 19.2	−17.7 (−70.1, 34.7)	0.499
Total cholesterol (mg dL^{-1})	168.3 ± 7.3	148.8 ± 8.2	158.2 ± 6.0	169.1 ± 7.6	162.7 ± 8.6	160.4 ± 6.3	−5.6 (−23.3, 11.99)	0.554
LDL-c (mg dL^{-1})	154.3 ± 30.7	95.3 ± 6.8	90.9 ± 7.4	97.8 ± 29	86.2 ± 6.4	89.3 ± 7.0	−22.4 (−53.3, 8.6)	0.151
HDL-c (mg dL^{-1})	40.5 ± 2.2	40.5 ± 1.9	41.5 ± 1.8	44.7 ± 2.3	44.5 ± 1.9	43.1 ± 1.8	3.2 (−2.01, 8.5)	0.221
FBG (mg dL^{-1})	106.3 ± 8.7	105.6 ± 7.7	101 ± 6.5	111.7 ± 9.1	112.9 ± 8	115.9 ± 6.8	−9.2 (−29.8, 11.4)	0.373
Fat mass (%)	35.9 ± 2.4	36.7 ± 2.3	38.8 ± 2.3	36.4 ± 2.5	35.8 ± 2.4	37.3 ± 2.4	−0.6 (−7.1, 5.8)	0.843
Body weight (kg)	82.8 ± 3.4	82.9 ± 3.3	82.8 ± 3.3	83.3 ± 3.4	83.7 ± 3.4	82.2 ± 3.3	−0.2 (−9.2, 9.2)	0.958
BMI (kg m^{-2})	32.3 ± 1	29.8 ± 2	31.3 ± 1.8	31.5 ± 1	29.3 ± 2.1	28.8 ± 1.9	−1.3 (−5.4, 2.9)	0.545
Waist circumference (cm)	105.9 ± 2.9	NA	104.3 ± 2.2	106.4 ± 3	NA	103.3 ± 2.3	−0.2 (−7.3, 6.8)	0.946

Two-way repeated measures analysis of variance, followed by the Bonferroni *post hoc* test was used to compare the changes between the study groups over a 4-week study period; $P < 0.05$. Data are presented as mean ± SEM. TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NA, not applicable.

Table 5 Effect of 4 weeks of *T. indica* L. fruit juice intake on markers of vascular function

Parameters	10% fruit pulp juice arm			30% fruit pulp juice arm				
	Baseline (n = 25)	Midline (n = 25)	Endline (n = 24)	Baseline (n = 25)	Midline (n = 23)	Endline (n = 22)	Intervention effect at endline (95% CI)	P-Value
SBP (mmHg)	133 ± 3.9	131.2 ± 3.4	125.6 ± 3.2	129.7 ± 4.2	127.6 ± 3.7	126.1 ± 3.4	−2.2 (−10.8, 6.5)	0.617
DBP (mmHg)	84.5 ± 2.5	80.5 ± 2.5	79.5 ± 2.3	83.1 ± 2.7	82.9 ± 2.6	83.3 ± 2.5	−1.6 (−6.6, 3.4)	0.520
PWVao (m s^{-1})	9 ± 0.20	9.4 ± 0.24	9.5 ± 0.27	9.6 ± 0.22	9.4 ± 0.21	8.9 ± 0.25	−0.1 (−1.08, 1.09)	0.993
SBPao (mmHg)	132 ± 4.7	119.4 ± 6.8	120 ± 5.2	130 ± 4.9	125.3 ± 7.1	126.2 ± 5.4	−3.5 (−17.6, 10.6)	0.619
Aixao (%)	37.3 ± 3.3	40.5 ± 3.8	33.9 ± 3.4	34.9 ± 3.4	33.4 ± 3.9	34.7 ± 3.8	−2.9 (−11.3, 5.5)	0.492
MAP (mmHg)	97.4 ± 3.2	96 ± 2.7	93.9 ± 2.9	96.5 ± 3.3	92.6 ± 2.8	91.9 ± 3	−2.1 (−10.1, 5.8)	0.588
HR (1 min^{-1})	74.5 ± 2.5	72.2 ± 2.6	72.6 ± 2.9	77.8 ± 2.6	74.8 ± 2.7	74.3 ± 3	−2.6 (−9.5, 4.4)	0.462
PP (mmHg)	52.5 ± 3.5	48.7 ± 4.2	46.7 ± 3.4	49 ± 3.6	48.3 ± 4.4	47.2 ± 3.6	−1.5 (−10.5, 7.5)	0.745
PPao (mmHg)	52.2 ± 2.4	54.1 ± 2.6	50.8 ± 2	52.4 ± 2.5	52.6 ± 2.7	50.2 ± 2.1	−0.6 (−6.5, 5.3)	0.835

Two-way repeated measures analysis of variance followed by the Bonferroni *post hoc* test was used to compare changes between the study groups over a 4-week study period; $P < 0.05$. Data are presented as mean ± SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; PWVao, pulse wave velocity of the aorta; SBPao, systolic blood pressure of the aorta; Aixao, augmentation index of the aorta; MAP, mean arterial pressure; HR, heart rate; PP, pulse pressure; PPao, pulse pressure of the aorta.

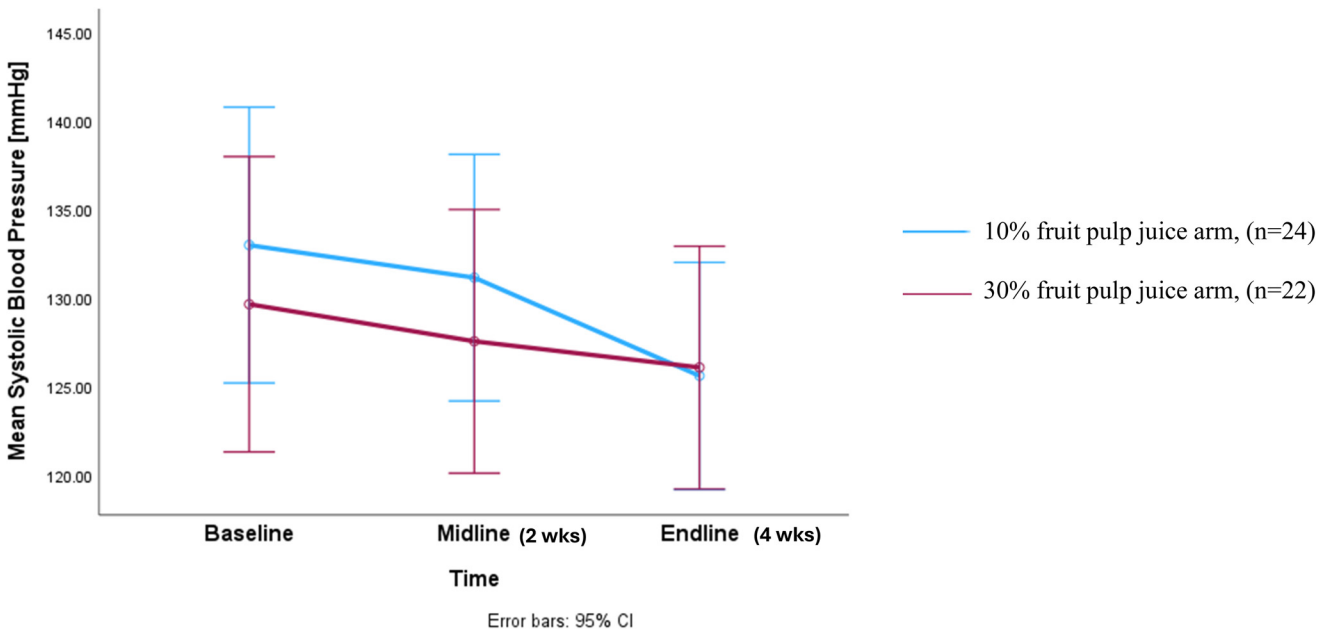

Fig. 4 Effect of a 4-week *T. indica* L. fruit juice intake on systolic blood pressure.

the secretion of VLDL by the liver.[48] The efficient assembly and secretion of chylomicrons depend on the availability of lipids, the presence of ApoB, and the function of microsomal triglyceride transfer protein (MTP). These components play a central role in the complex process of chylomicron formation and transport.[49] Another mechanism is the control of oxidative stress and attendant atherosclerosis resulting from deranged chylomicron metabolism.[50] The hypolipidemic effects of polyphenols are mainly attributed to syringic acid, gallic acid, proanthocyanidins, and epicatechins which are abundant in *T. indica* L.[18–20,28,48] Before fat absorption, dietary triglycerides are hydrolysed by pancreatic lipases. Proanthocyanidins have an inhibitory effect on pancreatic lipases, thereby downregulating the absorption of triglycerides.[48] Syringic acid and gallic acid have been shown to improve lipid metabolism by inhibiting the lipid metabolism marker enzymes lipoprotein lipase and 3-hydroxy-3-methylglutaryl CoA reductase.[28,51]

In our study, the intake of 1556 mg d^{-1} dose of specific polyphenols on top of the background polyphenol intake reduced LDL-c by −63.4 mg dL^{-1} (−1.6 mmol L^{-1}). Although this effect did not reach statistically significant levels, it is within clinically relevant thresholds. The American Heart Association/American College of Cardiology and the European Society of Cardiology, respectively, have recommended thresholds of 1.8 mmol L^{-1} and 1.4 mmol L^{-1} reductions in LDL-c to mitigate atherosclerotic CVD pathologies.[52] Furthermore, a meta-analysis of 327,037 participants revealed that for every 1 mmol L^{-1} decrease in LDL-c, the risk of cardio-

vascular events was reduced by 19%.[53] n3-PUFA diets and statin therapies are regarded as the gold standards in managing hyperlipidemia,[54] but both may not be easily feasible for vulnerable groups. *T. indica* L. holds promise as a more sustainable adjuvant food-based therapy for dyslipidemia in the SSA context.

There is a notable lack of human trials evaluating the cardiometabolic benefits of *T. indica* L. However, animal models have highlighted the effect of epicatechins on lipidemic control. For example, hypercholesterolemic hamsters fed on crude *T. indica* L. extract for ten weeks showed a reduction in total cholesterol, non-HDL-c, and TG by 50%, 73%, and 60%, respectively. This was coupled with an increased HDL-c level of 61%.[55] Additionally, *T. indica* L. has been associated with weight loss in animal models.[56,57] Both weight loss and reduction in fat mass have been shown to mediate TG homeostasis. In our study, neither body weight nor fat mass changed significantly; hence, changes in body weight or body fat mass did not mediate the TG-reducing effects of polyphenols in our study. Conversely, Asgary *et al.* reported that a daily intake of 10 g (total polyphenol content—45.7 mg g^{-1} of dry extract) of *T. indica* L. pulp for six weeks did not significantly reduce TG. However, the baseline TG levels in the study by Asgary *et al.* were within normal levels.[58]

The hypotensive effects observed in our study are linked to the wealth of flavan-3-ols in *T. indica* L. fruits. Flavan-3-ols block angiotensin-converting enzyme (ACE) activity, thereby reducing blood pressure. Hence, polyphenols have been called green ACE blockers.[59] A daily intake of 400–600 mg of flavan-3-ols is recommended for cardiometabolic protection.[23] At the same time, the European Food Safety Authority (EFSA) approved a claim that a 200 mg d^{-1} intake of cocoa flavan-3-ols is essential for vascular homeostasis.[24] Elsewhere, in the Cocoa Supplement and Multivitamin Outcome Study (COSMOS), flavan-3-ol intake averted 27% of CVD mortality and significantly reduced CVD events.[25] Flavan-3-ol increases the endothelial production and bioavailability of nitric oxide (NO), a signalling molecule for endothelial function.[24] Previously, Asgary *et al.*[58] reported that a daily intake of 10 g (total polyphenol content—45.7 mg g^{-1} of dry extract) of *T. indica* L. fruit pulp for six weeks resulted in a −4.7 mmHg reduction in SBP. The treatment effect of −7.3 mmHg reduction in systolic blood pressure (SBP) in our study is comparable to the hypotensive effects achieved by lifestyle modifications, including the Dietary Approaches to Stop Hypertension (DASH) intervention.[60] It has been shown that every decrease in SBP by −5 mmHg lowers the risk of stroke by 13%.[61] The 10% fruit pulp juice had a higher flavan-3-ol content (procyanidin and epicatechin) than the 30% juice. This is potentially why the SBP was significantly reduced in the former study arm but not in the latter. In addition, the difference in the mean baseline SBP for the 10% fruit pulp juice arm (133 ± 3.9 mmHg) was higher than that for the 30% pulp juice fruit arm (129 ± 4.2 mmHg), which could have contributed to the observed treatment outcomes. The former was within the range considered to be elevated blood pressure (≥130 mmHg). From a clinical perspective, it is easier to observe an effect when the baseline blood pressure is out of range. Additionally, the intake of dietary polyphenols in the background may have had an impact. While the background dietary polyphenol intake did not significantly change by the end of the study in the 10% fruit pulp juice group, it decreased significantly by 280 mg in the 30% fruit pulp juice group.

The biological effects of polyphenols rely on their bioavailability, which involves their absorption, distribution, metabolism, and excretion.[14] This bioavailability largely depends on the phenolic chemical structure, digestive stability, food matrix, and the role of gut microbiota.[62–69] Hence, the content of polyphenols in a diet may not necessarily correlate with high bioavailability. It is important to note that bioavailability significantly accounts for the interindividual variability in cardiometabolic response observed following the consumption of polyphenols.[62,70] The effect of the food matrix (bioaccessibility) underpins the differences in cardiometabolic responses between purified extracts in the form of supplements and whole polyphenol-rich foods.[16,66] Furthermore, polyphenols in fresh fruits and their derivatives are affected by the polyphenol oxidase (PPO) enzyme that oxidizes polyphenols to *o*-quinones.[71] The effect of PPO on the bioavailability of flavan-3-ols in freshly prepared fruit smoothies with different PPO concentrations was recently examined in a crossover trial. The plasma flavan-3-ol metabolites were the lowest in smoothies with the highest PPO, and the substantial decline in the plasma flavan-3-ol metabolite recovery is a result of the postprandial PPO degrading activity of flavan-3-ols.[69] In freshly made fruit juices, PPO is highly correlated with polyphenol content—the latter increases with the pulp content, thereby increasing the enzyme substrates.[72,73]

In terms of chemical structure, oligomeric proanthocyanidins which are abundant in *T. indica* L fruits are among the polyphenols with the lowest bioavailability.[14,63] Hence, there is still a need for an extensive study of the bioavailability profile of *T. indica* L. polyphenols. The interaction between polyphenols and the gut microbial community is a bidirectional axis: (1) polyphenols act as prebiotics increasing the proliferation of gut microbial species and (2) the gut microbiota can metabolize polyphenols, producing an array of bioactive phenolic metabolites that modulate lipid and glucose metabolism.[63] However, the health of the gut microbiota is affected by chronic inflammatory diseases like HIV since the GIT is an active site for viral replication.[74,75] Furthermore, ART regimens especially protease inhibitors (PIs) are likely to cause more adverse effects on gut microbial ecology than non-PI regimens such as DTG.[76,77] Such alterations in gut microbial composition and diversity could upset polyphenol metabolism. In our trial, all patients were being managed on DTG; therefore, it can be argued that the effect of ART-mediated dysbiosis was potentially well controlled and did not antagonize the clinical polyphenol response.

The relevance of our study results can be viewed as follows. The management of cardiometabolic risks in SSA is primarily addressed with polypharmacy, which is often expensive and

inaccessible, and increases the pill burden among PLWH. Classical lifestyle interventions have shown that intentional weight loss confers beneficial cardiometabolic control.[78,79] However, in SSA, a large body size is construed as a sign of prosperity and freedom from HIV.[80] Similarly, among PLWH, weight loss is associated with stigma.[81] Such stigma casts doubt on the success of interventions premised on maintaining a healthy body weight. Based on one of our previous studies, we found that sociocultural perceptions consider fruits as snacks for children and vegetables as food for the poor. These findings hinder optimal fruit and vegetable consumption among Ugandans.[82,83] Evidence shows that dietary approaches that aim to add a healthy portion to one's habitual diet rather than completely change their menu are far more culturally acceptable.[84] One way to ameliorate gut health during HIV is by increasing prebiotic intake.[74] Polyphenols could provide a potent avenue to restore eubiosis in PLWH, given the high prevalence of dysbiosis in this patient group. The current intervention could promote the consumption of indigenous fruits, drawing on their cardiometabolic benefits.

4.1 Study limitations

The main limitation of this study is the absence of a placebo group. Furthermore, using polyphenol-rich juice instead of purified extracts suggests that the potential influence of other phytochemicals or nutrients on the study outcomes should not be discounted. Study compliance was assessed through self-reporting and counting of returned test product bottles, which often suffer from reporting bias. To objectively evaluate polyphenol intake, biochemical methods that identify and quantify structurally related epicatechin metabolites (SREMs) in urine have been proposed.[14,85] Although previous studies have produced conflicting results regarding follow-up duration, a 4-week follow-up period in the current study may have been short.[16] A follow-up period of 8 weeks and beyond has been shown to confer larger treatment effects.[16] We used a Point of Care (POC) lipid analyzer to assess the lipid profile. Compared to the classical laboratory-based references, POC analyzers have been shown to overestimate TG while underestimating HDL-c.[36] This was an exploratory study with inadequate statistical power. The importance of exploratory trials in public health interventions has been a topic of discussion. However, the Medical Research Council emphasizes the significance of such trials before conducting effectiveness studies. Exploratory trials provide valuable information for full-scale evaluation studies' optimization, refinement, and acceptability.[86]

5 Conclusion

The study showed that consumption of 30% pulp composition of *T. indica* L. fruit juice holds promise to improve TG metabolism. Although we cannot draw definitive conclusions as this is only an exploratory trial with no statistical power, it could be suggested that consuming fruit juice from *T. indica* L. with standardized polyphenol content ameliorates lipid homeostasis. We are convinced that this exploratory trial provides a basis for full-scale trials to further evaluate these health benefits.

5.1 Implications for future interventions

Based on our trial findings, we propose a full-scale 1 : 1 randomized non-inferiority parallel trial to compare the effects of 30% tamarind fruit pulp juice against the standard of care (statin) on triglycerides. Utilizing an effect size of −39.8 mg dL^{-1} (as observed in the trial) and a standard deviation (SD) of 78.6 mg dL^{-1} from our previous cross-sectional study,[12] a type I error rate of 0.05, a dropout rate of 20%, and a power of 80%, we will need 116 patients for this study, employing an allocation ratio of 1 : 1.

Regarding the intervention products, we observed an interesting phenomenon: although the pulp content of the two juices differed markedly (10% and 30%), their specific polyphenol content was quite similar (1537 mg and 1631 mg, respectively). More notably, the juice with 10% pulp exhibited higher levels of procyanidin B2 and (−)-epicatechin than the 30% pulp prototype, suggesting that even a low fruit pulp content can result in higher polyphenol concentrations. The two juice prototypes were manufactured in batches and this batch-wise production could imply that the batches of tamarind fruits may have differed. The tamarind fruits were primarily sourced from various regions; thus, the varying agroecological zones could influence the phenolic composition of the tamarind fruits. This discrepancy highlights important considerations in nutrition research. Formulating intervention food products to reflect "real-life settings" can seriously influence the efficacy/effectiveness of interventions, hence the need to standardize such foods. Standardization could involve developing a comprehensive framework that details the food's composition, bioactive compounds, preparation methods, and other factors that may influence nutritional quality. By implementing such a framework, researchers would be better positioned to replicate studies and safeguard the integrity of dietary recommendations. In the context of dietary polyphenols, the development of food-based dietary guidelines is constrained by inadequate characterization of foods. However, standardizing food interventions might overlook sensory preferences and cultural influences, which are important for study compliance in nutrition research.

Author contributions

TK, PY, MB, PO, BVDS, and CM designed the study. TK, KN, WN, and FK contacted and recruited study participants. TK, CM, KN, FK, and WN conducted the study. TV and DC performed the phenolic characterization of the intervention products. TK, PY, and CM performed the data analysis. TK wrote the first draft of the manuscript. All authors reviewed the final draft and approved the publication of this work.

Data availability

The datasets of this study will be made available upon request from the corresponding author.

Conflicts of interest

The authors have no competing interests to declare which are relevant to the content of this article.

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