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RESEARCH ARTICLE

Consumption of Fruitflow® lowers blood pressure in pre-hypertensive males: a randomised, placebo controlled, double blind, cross-over study

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ABSTRACT

In order to investigate whether the angiotensin converting enzyme-inhibitory tomato extract Fruitflow® would lower blood pressure after consumption, we conducted a randomised, double-blinded, placebo-controlled human intervention study, involving 12 pre-hypertensive people in a crossover design. Consuming a single dose of 150 mg Fruitflow® resulted in a significant reduction in 24-hour average blood pressure as well as average wake-period and sleep-period SBP, compared to placebo. Other parameters related to blood pressure, such as 24-hour average mean arterial pressure, pulse pressure, heart rate, central aortic systolic pressure and radial augmentation index were also reduced. In addition, the platelet aggregation response to ADP, measured 24 hours after consuming Fruitflow®, fell significantly compared to baseline, and compared to placebo. This pilot study clearly shows the beneficial effects of Fruitflow® on two important cardiovascular risk factors, high blood pressure and platelet hyperactivity.

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Fruitflow®; tomato extract; angiotensin converting enzyme; blood pressure; platelet aggregation

Introduction

Hypertension is one of the most important risk factors for cardiovascular disease (CVD) (Law et al. 2009; Palomo et al. 2012; Winter et al. 2013; Edwards and Simpson 2014). Hypertension is diagnosed when an individual has a systolic BP (SBP) $\geq$ 140 mmHg and/or a diastolic BP (DBP) $\geq$ 90 mmHg (stage 1 hypertension) (hypertension in adults: diagnosis and management. Clinical Guideline CG127, NICE, 2011 (2016 update) https://www.nice.org.uk/guidance/cg127). However, it is often asymptomatic to the individual and can remain unrecognised. Even when hypertension is diagnosed, the underlying cause is unknown in 95% of cases, making treatment selection challenging. Untreated hypertension can lead to CVD, stroke, hypertensive retinopathy, gout, kidney dysfunction, disability and even death (Ezzati et al. 2005). Thus, novel approaches for preventing and treating hypertension are needed.

The renin–angiotensin system has an important role in blood pressure homeostasis (Davis and Freeman 1976; Griendling et al. 1989; Boustany et al. 2004; Castrop 2015). Several blood pressure-lowering therapies, such as sodium reduction and diuretics, activate the renin–angiotensin system and raise plasma renin activity (Hall 1991; Yoshimura and Kawai 2010). In hypertensive patients with elevated plasma renin–angiotensin activity, a five-fold increased incidence of myocardial infarction was demonstrated (Winter et al. 2013). Angiotensin converting enzyme (ACE) (EC 3.4.15.1, dipeptidyl carboxypeptidase) is a glycoprotein peptidyldipeptide hydrolase that cleaves histidyl leucine dipeptide from angiotensin I forming the potent vasoconstrictor angiotensin II. Studies have demonstrated that angiotensin converting enzyme inhibitors (ACEI) significantly reduce the morbidity and mortality in patients with myocardial infarction, and the incidence of ischaemic events in patients with CVD (Alderman et al. 1991; Pfeffer et al. 1992; Law et al. 2009).

In recent years, there has been considerable interest in the potential for using natural food components as functional foods to treat hypertension, especially for people with borderline to moderately high blood pressure (pre-hypertension, classified as SBP of 120–139 mmHg and/or DBP of 80–89 mmHg) in whom the prescription of anti-hypertensive drugs is not warranted (Li et al. 2005; Huang et al. 2013; Kim and Andrade 2016). The polyphenols present in fruits

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and vegetables have been associated with a multiplicity of effects which affect various facets of the cardiovascular system (antioxidant properties, anti-platelet effects, formation of endothelial nitric oxide leading to vasodilation and lowering of blood pressure) (Griendling et al. 1989; Kowala et al. 1994; Chobanian et al. 2003; Fisher et al. 2003). In addition, some have been linked to inhibition of zinc metalloproteinases such as ACE (Actis-Goretta et al. 2003; Huang, Davidge and Wu 2013); the reported mechanism involves binding to the ACE C-domain (Yates et al. 2014). Guerrero et al. (2012) report that flavonoids with a catechol structure in the B-ring, a double bond between C2 and C3 in the C-ring, and a ketone group at C4 in the C-ring (such as luteolin and quercetin) have the strongest binding capacity, and that this binding capacity and resultant functional inhibition of ACE does not appear to be affected by glycosylation.

It appears a plausible hypothesis that supplementation of the diet with sources of such flavonoid derivatives could have measurable effects on blood pressure. One known dietary source is the tomato, and several studies examining the effects of tomatoes and tomato products on blood pressure have been carried out (Cheng et al. 2017). However, reported results are conflicting, probably due to the high variability of extracts and compositions administered (Cheng et al. 2017). Such outcomes are common in studies involving dietary bioactive compounds, and highlight the need to work with standardised supplements. Recently, we showed that a commercially available, standardised tomato extract (branded as Fruitflow®, FF) exhibited strong ACE inhibitory potential *in vitro* (Biswas et al. 2014). FF is a lycopene-free, water-soluble extract from ripe tomatoes which was originally developed as a dietary antiplatelet. It contains a range of compounds with antiplatelet activities, of which up to 15% are reported to be flavonoids (O'Kennedy et al. 2006; O'Kennedy et al. 2017). A significant proportion of these are quercetin derivatives, mainly glycosides (O'Kennedy et al. 2016). A single dose of FF contains a minimum of 2.4 mg quercetin derivatives.

In order to investigate whether the ACE-inhibitory FF extract would lower blood pressure after consumption, we conducted a randomised, double-blinded, placebo-controlled human intervention study, involving 12 pre-hypertensive subjects in a crossover design. The primary endpoint was change in mean SBP (mmHg) between baseline and each follow up point after consuming 150 mg FF, compared to placebo. Secondary outcomes included changes in mean DBP, plasma ACE activity and platelet aggregation response. Changes in the central aortic systolic pressure (CASP) and the radial augmentation index (rAIx) were also measured in a subset of subjects.

Materials and methods

Study supplements

FF is commercially produced by DSM Nutritional Products, Basel, Switzerland, in syrup and in powder formats. The powder format was used in this study, at the EFSA-approved daily dose of 150 mg, the composition of which has been described previously (O'Kennedy et al. 2016). Briefly, a 150 mg dose of FF delivers up to 9 mg nucleoside derivatives, up to 10 mg simple phenolic conjugates (e.g. chlorogenic acid, other caffeic/phenolic acid derivatives) and up to 7 mg flavonoid derivatives, of which at least 2.4 mg are quercetin derivatives. The commercially produced FF is standardised to ensure minimum quantities of these three compound groups are contained in each manufactured ingredient batch, ensuring that intake of the bioactive components is consistent from batch to batch. Microcrystalline cellulose was used as a placebo control (Essential Nutrition Ltd, Brough, UK). Both supplements were encapsulated using size 00 Vegecaps (LGA, La Seyne-sur-Mer, France). Capsules were coded in accordance with a randomisation protocol. All supplements were identical with respect to appearance and only differed in coding of the capsules. The treatment code of the intervention supplements was blinded for subjects, investigators and staff involved in the conduct of the study.

Subjects

As this was the first study to examine the effects of FF on BP in humans, no information was available from which to determine the appropriate sample size to detect a significant effect. Therefore, the study was powered on the basis of the expected reduction in platelet function after consuming FF (7–15% reduction from baseline aggregation in response to optimal concentration of ADP agonist). To detect such a change from baseline aggregation with 90% power and $\alpha = 0.05$, requires a sample size of 10. A total of 18 apparently healthy adult males, aged 25–65 years, were recruited into the study, with 12 subjects ultimately completing the intervention. Suitability for inclusion into the study was assessed by using diet and lifestyle questionnaires and by medical screening, during which blood pressure and platelet function were assessed. Subjects with pre-hypertension (SBP 120–139 mmHg, DBP 80–89 mmHg) were included.

Any subject habitually consuming dietary supplements (for example, fish oils, evening primrose oil) suspended these supplements for a minimum period of 1 month before participating in the study. Subjects were also instructed to abstain from consuming drugs or foods known to affect blood pressure or platelet function for a 10-day period prior to participation. Written informed consent was obtained from all subjects prior to participation, and all study procedures were in accordance with the Helsinki Declaration of 1975 (revised in 1983). The study was approved by the local ethical committee at Oslo University Hospital, Norway (Reference No.: 2015/396) and was registered at www.controlled-trials.com (SRCTN33471815 DOI 10.1186/ISRCTN33471815).

Study design

This was an acute study comparing two interventions in a crossover design, with the interventions separated by a period of at least seven days. All study activities were undertaken at the Nutrition Dept. of the Faculty of Medicine, University of Oslo, Norway. Each intervention period was of 24-hour duration. Subjects presented at the Nutrition Department facility and baseline measurements, including fasted baseline blood samples, were taken. Breakfast was then supplied, and together with the intervention supplement (either FF or placebo supplement), consumed shortly (within 30 min) before the start of daytime ABP recordings. Supplements were consumed in the presence of study investigators. After breakfast, monitors were fitted and calibrated, and recording began. ABP and other outcome measures were monitored over a 24-hour period, during which time subjects carried out their normal activities while consuming a restricted diet (avoiding foods known to affect blood BP or platelet function, by consulting a comprehensive list supplied). At the end of the 24-hour monitoring period, subjects returned to the facility, a 24-hour fasted blood sample was taken, and data retrieved from the monitoring devices. Subjects were then given breakfast and were free to leave the facility, returning after a minimum of seven days to repeat the procedure for the second intervention as necessary.

Study samples and phlebotomy

Overnight fasted blood samples were collected from all participants at baseline ($t = 0$) and at the end of the 24-hour monitoring period ($t = 24$) for each intervention. For measurement of platelet aggregation, blood was mixed with 3·8% trisodium citrate (9:1 (v/v), blood/citrate). For preparation of serum, blood was taken into empty tubes without addition of anticoagulant and allowed to stand at room temperature until clotted.

Study measurements

24-Hour ambulatory blood pressure monitoring

For the primary outcome measure, 24-hour ambulatory blood pressure monitoring (ABPM, Spacelabs monitor type 90 217; Spacelabs Healthcare, Snoqualmie, WA) was used to record blood pressure readings at 30 minute intervals during the awake-period (from commencement until 10 PM) and at 60 minute intervals during the sleep-period (from 10 PM to 6 AM). The monitor also recorded mean arterial pressure (MAP), pulse pressure (PP) and heart rate (HR) at these time points. Each subject used the same ABPM monitor for both interventions. Wake-period BP and sleep-period BP were divided based on the subject's sleeping hours and hours awake, as indicated in their diaries, and were reviewed by the staff. Data were reviewed blinded, and when more than one measurement was recorded per hour the closest evaluable value to the hourly schedule was considered. The quality of ABPM recording was evaluated with reference to the latest guidelines from the Working Group on BP Monitoring from the European Society for Hypertension (O'Brien et al. 2013). Data from recordings where $\geq$70% expected measurements were valid, and which included at least 20 wake-period and at least seven sleep-period measurements were accepted.

In addition to the primary outcome ABPM monitor, a subset of subjects was requested to wear a medically-approved non-invasive device worn as a wrist watch, which recorded the pulse at the wrist and used mathematical processing of the signal to calculate derivable parameters related to the radial pulse wave (BPro® Radial Pulse Wave Acquisition Device, HealthSTATS, London, UK). The wrist-worn monitor was applied and calibrated according to the manufacturer's instructions. Six of the subjects wore the additional device, which in addition to ABP monitoring allowed recordal of additional exploratory parameters of interest, CASP and rAIx.

Platelet aggregation assay

Fasted, sodium citrate anti-coagulated blood collected at $t = 0$ and $t = 24$ h for each intervention was centrifuged at 200 g for 10 minutes to prepare platelet-rich plasma (PRP). Platelet aggregation in PRP was monitored using an aggregometer by Helena Laboratories

(AggRAM™, Helena Laboratories, Beaumont, TX) at a constant stirring speed of 1000 rpm and at 37 °C. Aggregation was initiated by addition of ADP agonist (Helena Laboratories, Beaumont, TX), and the maximum area under the aggregation curve (AUC) was recorded. Effects on platelet aggregation observed after interventions were expressed as the percentage change in AUC after consumption of extract or placebo, as compared with baseline values (Biswas et al. 2014).

Serum ACE activity assay

Serum was prepared from fasted blood samples at $t = 0$ and $t = 24$ h for each intervention, and the effect of interventions on the serum ACE activity was measured using the ACE assay as described previously (Li et al. 2005). All measurements were performed in triplicates.

Statistical analysis

Data are presented as the mean ± SD. All variables were tested for normal distribution by use of the Kolmogorov–Smirnov test. Mauchly's test was used to confirm the sphericity of the data. A one-way repeated-measures ANOVA was used to compare platelet aggregation and ACE activity pre- and post-intervention ($t = 0$ and $t = 24$ h), followed by *post hoc* Bonferroni's *t*-tests (one tailed) for comparison of FF treatment with placebo. A value of $p < .05$ was considered statistically significant. BP measurements were recorded for 24 h and split between day/wake-time and night/sleep-time for analysis. Paired comparison was performed following the method of Borenstein et al., based on the pooled standard errors of each group (Borenstein et al. 2010).

Results

Subject characteristics

The characteristics of the subject group at baseline (pre-intervention) are shown in Table 1. No differences were detected between the two $t = 0$ baseline measurements, i.e. the intervention order had no effect on baseline parameters, so that pooled baseline data is presented. The average BMI was 27.04 ± 3.19 kg/m^2 and the average age was 44 ± 10 years ($n = 12$). These subjects were overweight. All were pre-hypertensive and exhibited a strong platelet aggregation response to ADP agonist. Thus, in terms of the parameters measured, the subject group was considered representative of apparently healthy, pre-hypertensive, overweight men.

Platelet responses to FF and placebo interventions were similar to previous reports

Figure 1 shows the platelet aggregation response to ADP in PRP at baseline ($t = 0$), and 24 hours after consuming 150 mg FF or placebo ($t = 24$ h). Baseline measurements were not significantly different between interventions (placebo – 82.7 ± 4.6%; FF – 78.5 ± 3.7%, $p = .067$). Consuming 150 mg FF significantly reduced the platelet aggregation response at $t = 24$ h from baseline levels, whereas consuming the placebo supplement did not (reduction from baseline aggregation of 16.5%, $p = .0003$ and 5%, $p > .05$, respectively). The difference between treatments was significant ($p < .05$). The magnitude of the effect on platelets is similar to previous reports.

Compared to placebo, FF reduced ABP measured by various indices, and had different effects on wake- and sleep-period measurements

Table 2 shows the effects of both treatments on 24-hour average, systolic and diastolic blood pressure, as measured by ABPM. The 24-hour average blood pressure (systolic/diastolic) was significantly lower (6%) after consuming 150 mg of FF than after consuming the placebo supplement, (118/76 vs. 126/81, $p < .05$).

Splitting the 24-hour period into distinct wake-period and sleep-period phases shows that this treatment effect was most significant during the

Table 1. Demographics of the study population, and baseline parameters relating to blood pressure and platelet function.

	Variable	*n*	Mean ± SD
Demographics of population at baseline	Age (years)	12	44 ± 10
	BMI (kg/m^2)	12	27.04 ± 3.19
Parameters relating to BP and platelet function at baseline ($t = 0$)	Platelet aggregation in response to ADP at $t = 0$ (%AUC)	24	80.8 ± 4.7
	Average BP at $t = 0$ (sphyngometer measurement) (mmHg)	24	128 ± 11/84 ± 8

Data are given as mean ± SD. All 12 subjects recruited were male. None were smokers. No differences were observed between $t = 0$ (baseline) data between interventions, thus data shown represent pooled data from both $t = 0$ timepoints.

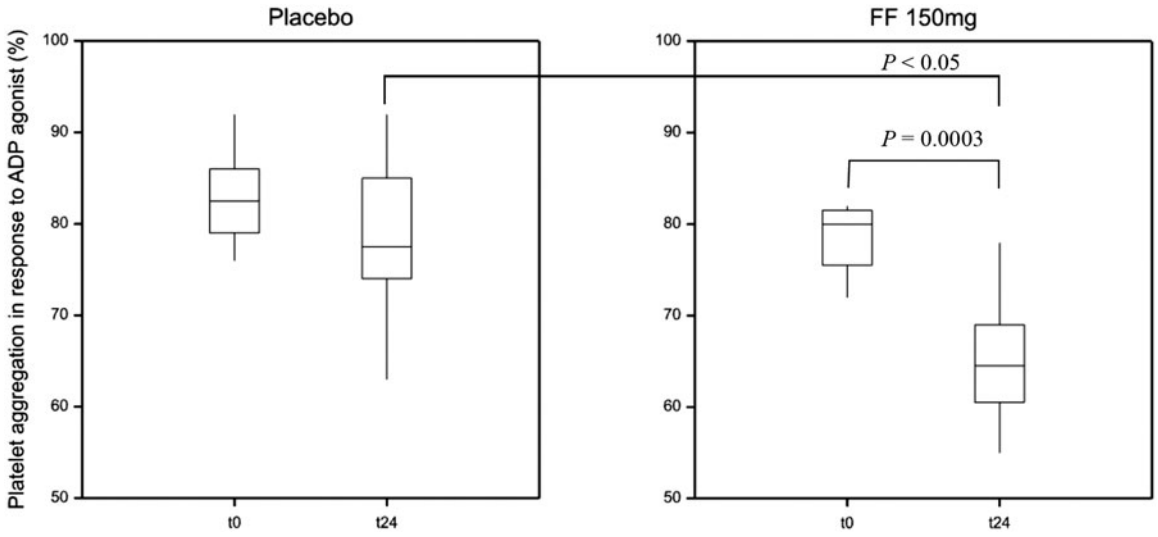

Figure 1. Effect of consuming 150 mg Fruitflow® on the platelet aggregation response to ADP in PRP. At timepoints t0 (prior to treatment ingestion) and t24 (24 hours after treatment ingestion), blood samples were taken and platelet aggregation initiated by addition of ADP agonist. The maximum area under the aggregation curve was recorded as % aggregation. The spread (minimum, maximum, interquartile range) and median of data recorded in the subject group for each treatment and time point are shown. There was no difference between treatments for the two t0 timepoints, nor was there a difference between t0 and t24 timepoints for the placebo treatment. For the FF treatment, a significant difference between t0 and t24 was observed. The difference between the placebo and FF treatments was also significant at the t24 timepoint.

Table 2. Effects of consuming 150 mg FF or placebo on 24-hour average, systolic and diastolic blood pressure.

	Placebo		150 mg FF	
	Systolic (mmHg)	Diastolic (mmHg)	Systolic (mmHg)	Diastolic (mmHg)
24 hour average	126 ± 15	81 ± 12	118 ± 13*	76 ± 10
Wake period	130 ± 12	84 ± 10	121 ± 12**	78 ± 9**
Sleep period	112 ± 14	70 ± 11	106 ± 16**	67 ± 10**

Data are presented as mean ± SD. Blood pressure measurements were recorded over a 24-hour timecourse using ABPM and split between day/wake-period and night/sleep-period for analysis. Differences between treatments were tested for significance using the method as described by Borenstein et al. (2010).
*$p < .05$.
**$p < .002$.

Table 3. Effects of consuming 150 mg FF or placebo on MAP, PP and HR over a 24-hour time course.

	Placebo	150 mg FF
Mean arterial pressure (MAP, mmHg)	95 ± 13	90 ± 10*
Pulse pressure (PP, mmHg)	45 ± 9	43 ± 10*
Heart rate (HR, BPM)	71 ± 10	67 ± 9*
% SBP measurements over 135 mmHg (wake-period) or 120 mmHg (sleep-period)	34	15*
% DBP measurements over 85 mmHg (wake-period) or 70 mmHg (sleep period)	41	30*
CASP	117 ± 13	102 ± 1*
rAIx	99 ± 6	92 ± 2*

Data are presented as mean ± SD, and represent 24-hour average values. For MAP, PP, HR and % SBP/DBP over limits measurements, recordal was carried out using the Spacelabs ABP monitor, $n = 12$. CASP and rAIx measurements were performed in a subgroup of the study population, using a non-invasive wrist worn monitor measuring the radial pulse wave, $n = 6$. Significant differences between treatments are indicated.
*$p < .05$.

wake-period, when both SBP and DBP were significantly lower after FF treatment than after placebo treatment (SBP and DBP dropped by approximately 7% compared to placebo values, $p < .002$). During the sleep-period, the treatment effect was still seen for SBP (FF treatment SBP 5% lower than placebo values, $p < .05$), but not for DBP.

As well as recording the BP values at 30/60 minute intervals, the ABP monitors tagged each SBP reading above 135 mmHg for the wake-period, and above 120 mmHg sleep during the sleep period. For DBP, the equivalent limits were 85 mmHg during the wake-period and 70 mmHg during the sleep-period. Table 3 shows the % of measurements for SBP and DBP

which were higher than these limits during the recordal time.

After consuming the FF supplement, individually measured high SBP events reduced by 57%, and high DBP events by 27%, compared to placebo ($p < .05$).

Compared to placebo, FF positively affected other physiological parameters related to 24-hour BP and vascular health

Table 3 shows the effects of the two treatments on the secondary outcome measures. Consuming 150 mg FF resulted in significant decreases in MAP, PP and HR over the 24-hour timecourse, all of which were approximately 5% lower than the equivalent measurements obtained after consuming placebo ($p < .05$). In the smaller subject group which measured CASP and rAIx ($n = 6$), differences between treatments also reached statistical significance. CASP measurements were 13% lower after consuming FF than after placebo ($p = .048$), and rAIx measurements were 8% lower ($p = .046$).

Effects of FF on ACE activity were not statistically significant ex vivo *in this small subject group*

ACE activity in the serum obtained from subjects before and 24 hours after consuming the treatments was measured. Although there was reduction of the serum ACE activity 24 hours after consuming 150 mg FF (1.16 ± 0.10 units) compared with placebo (1.18 ± 0.14 units), the difference between treatments was not significant ($p = .06$).

This was an acute study, and compliance with the intervention regimes was not an issue as both were consumed in the presence of the investigators. The supplements were well tolerated, and no adverse events related to treatments were reported.

Discussion

Two recently published reviews which examined the strength of the relationship between tomato intake and CVD benefits clearly set out the limitations of the data currently available, stating that although more than 50 studies are available on this topic, the majority are underpowered and results are mixed (Cheng et al. 2017; Thies et al. 2017). The reviews concluded that currently available data are strongest in support of a possible relationship between tomato intake and emerging markers of CVD, such as lipid peroxidation, DNA damage, platelet activation and inflammatory markers, all of which were correlated with tomato intake (but not with lycopene intake). We hypothesised that the polyphenol components of the tomato, which are concentrated in the standardised tomato extract FF, might interact with ACE and redox-based components of these emerging markers, and potentially underlie effects on more complex physiological systems such as blood pressure regulation.

The present study aimed to test whether FF, taken as a single acute dose, could lower 24-hour average and SBP in pre-hypertensive subjects. We can report that consuming a single dose of 150 mg FF resulted in a significant reduction in 24-hour average BP, as well as average wake-period and sleep-period SBP, compared to placebo. 24-hour average BP fell from the pre-hypertensive range to the normotensive range (SBP < 120 mmHg, DBP < 80 mmHg). Other parameters related to BP, such as 24-hour average MAP, PP, HR, CASP and rAIx, were also reduced. In addition, the platelet aggregation response to ADP, measured 24 hours after consuming FF, fell significantly compared to baseline, and compared to placebo.

BP parameters measured after FF consumption were lowered by 5–8%, compared to measurements after placebo consumption. Such effects represent clinically significant changes. The biggest differences in BP parameters between treatments were observed during the wake-period. This may reflect the dosage administration pattern, which was a single administration given at the start of the monitoring period. The polyphenol components of the FF supplement would be converted to metabolites within a few hours after consumption, so that the profile of circulating bioactives would be expected to alter considerably over the course of 24 hours. In addition, the main regulators of blood pressure such as the renin–angiotensin–aldosterone system (RAS), and the concentrations of cortisol and catecholamines, follow circadian rhythms. Therefore, the timings of administration of a substance acting on these pathways may be important. Further work is clearly required on the dosage pattern needed to obtain an optimal and persistent effect on BP parameters.

Not only was average BP reduced over the 24-hour period, but the amount of time subjects in which BP fell into the Stage 1 hypertensive range was reduced, after FF consumption. After consuming FF, the overall number of recorded SBP measurements tagged as hypertensive was 57% lower than after placebo, and the overall number of DBP measurements tagged was 27% lower. Thus even in pre-hypertensive subjects, a significant number of intermittent hypertensive episodes may occur, and FF may be of benefit in reducing these.

Assessment of test substance efficacy in BP reduction by using peripheral BP measurements is known to both under- and over-estimate efficacy of some drugs (e.g. amlodipine and atenolol, respectively). CASP, which measures the pressure at the root of the aorta, is increasingly used in assessing drug efficacy, to avoid such issues. We included 24-hour average CASP as an exploratory measurement in this study, using a new non-invasive device which measured the radial pulse wave at 15 minute intervals throughout the 24-hour period. The results were promising, showing a reduction in 24-hour average CASP after FF administration compared to placebo administration. Although data were collected in only six subjects, this gives some reassurance as to the reliability of the ABPM measurements, as well as being an interesting finding in itself.

No clear indication was obtained from the study data to support a single mechanism of action for the effects of FF on BP *ex vivo*. Since FF is known to inhibit serum ACE activity, the study measured this parameter before and after supplementation. However, although ACE activity was lower after FF administration than after placebo administration, the difference was not significant. It is again possible that the timings of blood samples were not optimal; equally probably, the study may simply have been too small to investigate effects on this complex system. We observed large inter-individual variability in serum ACE activity, requiring a greater sample size to address variability issues and allow conclusions as to whether ACE inhibition is at the root of FF effects on BP.

It is also possible that FF affects endothelial NO, possibly through its polyphenol content, which could help to regulate oxidative stress and improve NO bioavailability. NO is known for its important relaxant properties and influence on blood pressure (Deanfield et al. 2005). One indication from the study data which supports such an effect of FF comes from the small set of rAIx measurements obtained by monitoring the radial pulse wave in a subset of the study subjects. The rAIx is a marker of the aortic wave reflection, and can be considered a measure of vascular stiffness. Lowering the augmentation index and peripheral vascular resistance is considered desirable for lowering central BP. Our data show that 24-hour average rAIx values were significantly lower after FF consumption than after placebo consumption. Due to the small number of subjects for which measurements were collected, and the relatively new method by which they were gathered, it will be necessary to investigate this pilot finding further before firm conclusions can be drawn. FF may lower blood pressure via several possible mechanisms as it contains a range of compounds with bioactivities. However, we believe that the quercetin content of FF (at least 2.4 mg quercetin derivatives per dose) could plausibly cause such effects. Quercetin has been shown to lower blood pressure in animal models and human studies via antioxidant effects, inhibition of ACE activity, and improved vascular function (Hackl et al. 2002; Larson et al. 2012; Serban et al. 2016). Results also suggested an inhibitory effect of quercetin on the ACE (as also observed with FF) similar to that of captopril (Hackl et al. 2002; Biswas et al. 2014). However, the majority of these mechanisms have been identified using animal models treated with quercetin, and relatively few have been corroborated in human studies.

The present study had several limitations. The acute design, while suitable for a pilot study, limits conclusions as to how effective the FF supplement might be in real-world use. The total number of study participants used was relatively small, and all were male. Further, the complete absorption and metabolic kinetics of FF constituents are not fully understood, compounding difficulties in establishing clear mechanisms of action. Future investigations are warranted to address questions specific to efficacy, bioavailability and complete metabolite profiles.

However, the pilot study clearly shows the beneficial effects of FF on two important cardiovascular risk factors, high blood pressure and platelet hyperactivity. The study results support the further investigation of FF as a functional ingredient to help normalise blood pressure in an at-risk population. From a public health standpoint, it has been reported that every 1 mmHg reduction in SBP could prevent approximately 10,000 CVD deaths each year in the USA. Thus, FF supplementation could be a promising dietary approach to achieve and maintain healthy blood pressure.

Disclosure statement

Both Niamh O'Kennedy and Asim K. Duttaroy are the members of the Scientific Advisory Board of Provexis plc, the study sponsor. Main Uddin, Dipankar Biswas and Abhik Ghosh have no conflicts of any potential interest.

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