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RESEARCH ARTICLE

Hypoglycemic and Hypolipemic Effects of a New Lecithin Formulation of Bergamot Polyphenolic Fraction: A Double Blind, Randomized, Placebo-Controlled Study

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Abstract: ***Objective:*** Hyperlipemia represents an independent risk factor in the development of atherosclerosis in patients undergoing type 2 diabetes mellitus (DM). Moreover, the pharmacological treatment of dyslipemia in patients undergoing type 2 DM (*e.g.* by means of statins), is accompanied by relevant side effects and oral supplementation with natural antioxidants, such as Citrus polyphenols, has recently been suggested to improve cardioprotection in such patients. However, due to the poor gastrointestinal absorption of polyphenols, novel formulations have recently been developed for getting a better bioavailability of polyphenolic rich fractions of citrus species extract rich in polyphenols.

Methods: Here, we investigated the effect of standard bergamot polyphenolic fraction (BPF®) as well as of its phytosomal formulation (BPF Phyto), in patients with type 2 DM and hyperlipemia. A randomized, double blind, placebo-controlled study was carried out in 60 patients suffering from type 2 DM and mixed hyperlipemia.

Patients were divided into three groups: one receiving placebo, the second receiving standard BPF and the third BPF Phyto.

Results: In the groups receiving BPF and BPF Phyto, a significant reduction of fasting plasma glucose, serum LDL cholesterol and triglycerides accompanied by increased HDL cholesterol was observed. This effect was associated with significant reduction of small dense atherogenic LDL particles, as detected by means of proton NMR Spectroscopy, thus confirming the hypolipemic and hypoglycemic effect of bergamot extract both when using standard formulation as well as BPF Phyto. No differences were seen in the therapeutic response among groups receiving BPF and BPF Phyto, thus suggesting a substantial bioequivalence in their hypoglycemic and hypolipemic profile. However, when comparing the pharmacokinetic profile of naringin (the major component of BPF) and its metabolites, in patients treated with BPF Phyto, an at least 2,5 fold increase in its absorption was found, confirming in human studies the better profile of BPF Phyto compared to standard BPF.

Conclusion: These data suggest that better absorption and tissue distribution of BPF Phyto formulation represents an innovative approach in supplementation treatments of cardiometabolic disorders.

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1. INTRODUCTION

Growing body of evidence suggests that dietary polyphenols, particularly flavonoids, may have an important role in counteracting the pathophysiological mechanisms which lead to the development of hyperlipemia either combined or not with Type 2 Diabetes mellitus (DM) [1].

These beneficial effects are generally attributed to their anti- oxidant properties, as well as to more specific mechanisms such as the modulation of metabolic enzymes, nuclear receptors, gene expression and multiple signaling pathways [2-3]. Bergamot (Citrus Bergamia Risso et Poiteau) is an endemic plant of the Calabrian region in the Southern Italy with a unique profile of flavonoid and flavonoid glycosides detectable in its juice and albedo.

Bergamot differs from other Citrus fruits because of the composition and the particularly high content of its flavon-

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oids [4,5] able to counteract the detrimental effect of hyperlipidemia through a multi-action mechanism. In particular, naringin has already been reported to be active in animal models of atherosclerosis [6], while neoeriocitrin and rutin have been shown to inhibit LDL oxidation [7]. Moreover, two glycosilated flavonoids exclusive of bergamot-derivatives identified as melitidine and bruteridine (neohesperidosides of hesperetin and naringenin, respectively), were found possessing a structural similarity to the physiological substrate of HMG-CoA reductase, thereby exhibiting statin-like proprieties [8]. Recently, clinical studies have highlighted, the therapeutic potential of bergamot derivatives [9-11]. In particular, in patients with metabolic syndrome (MS), bergamot polyphenolic fraction (BPF) improves serum lipidic profile and normalizes blood glucose [12-15]. The hypolipemic effect might be due to its ability to reduce hepatic TG accumulation and to down-regulate the activity of the phosphatidate phosphohydrolase, the rate-limiting enzyme for triglycerides synthesis [16]. Moreover, *in vitro* studies show that naringenin and hesperetin were able to reduce the activity of acyl CoA:cholesterol acyltransferases (ACAT), thus decreasing the availability of lipids needed for the assembly of apoB-containing lipoproteins [17].

In addition, melitidine and brutieridine, in concert with naringin and other flavonone glycosides, might be responsible for the notable potency of BPF in reducing cholesterol levels, being 3-hydroxy-3-methylglutaryl derivatives of hesperetin and naringenin, respectively.

Finally, BPF has been shown to inhibit pancreatic cholesterol ester hydrolase (pCEH), thereby reducing the rate of dietary cholesterol absorption at the intestinal level [18]. As far as the vasoprotective effect of BPF is concerned, its antioxidant effect seems to play a major role. In particular, evidence shows that eNOS knockout mice exhibit a cluster of cardiovascular risk factors comparable to those of MS suggesting that a decreased eNOS activity might cause MS in humans, inducing an impaired NO-dependent vasodilation [11, 19, 20]. In particular, oxidative stress and inflammation observed in MS can explain endothelial dysfunction induced by eNOS-down-regulation. In this context, Citrus flavonoids, might attenuate an overproduction of oxygen reactive species in the vascular wall, by increasing the enzymatic activity of superoxide dismutase and catalase [21], thereby preventing endothelial dysfunction, as shown in patients treated with BPF. An additional beneficial effect of BPF might be related to its hypoglycemic activity: indeed, it has been demonstrated that naringenin, likewise to other polyphenols, could significantly increase AMP kinase (AMPK) activity and glucose uptake in skeletal muscle cells and liver [22-24]. Overall, these discoveries suggest that the supplementation of an ordinary diet with BPF is an alternative phytotherapeutic approach to better handling of prediabetic states in patients undergoing hypelipemia, because it induces a normalization of lipid profile, an amelioration of NO- dependent vasoreactivity and a reduction of blood glucose levels [8]. Besides these evidence, the rate of BPF absorption remains low and better formulation is required to increase BPF bioavailability in order to improve its efficacy and safety profile. Recently, a highly standardized BPF extract was formulated with the innovative food grade delivery system Phytosome® (BPF Phytosome®) [25]. In particular, this innovative strategy involves the use of lipid-compatible molecular complexes in which water-soluble phytoconstituents can be formulated into a lipid compatible molecules known as PHYTOSOME® [26, 27]. This new formulation of BPF has been proven to enhance the rate of polyphenol absorption in rats [25], and this suggests that BPF phytosomal (BPF Phyto) formulation may be relevant in reducing serum glucose and lipids in patients.

Here we investigated on the effect of BPF phyto in patients with hyperlipemia and type 2 DM by means of a double blind, randomized, placebo-controlled study. The effect of BPF Phyto was compared with standard BPF formulation.

2. MATERIALS AND METHODS

2.1. Preparation of BPF® and BPF Phytosome®

BPF® was prepared as previously described (9*). Citrus bergamia* Risso & Poiteau fruits were collected from plants located in a range of 90 Km from Bianco to Reggio Calabria, Italy. Bergamot juice was obtained from peeled-off fruits by squeezing. The juice was oil fraction- depleted by stripping, clarified by ultra-filtration and loaded on to a suitable polystyrene resin column able to absorb polyphenol compounds of molecular weight between 300 to 600 Da (Mitsubishi). Polyphenol fractions were eluted by a 1mM KOH solution. The basic eluate was incubated at a rocking platform to reduce the furocumarin content. The shaking time was adjusted proportionally to the amount of furocumarin contaminants. Next, the phytocomplex derived from the process performed to remove furocumarins was neutralized by filtration on cationic resin at acidic pH. Finally, it was vacuum dried and minced to the desired particle size to obtain BPF powder. BPF powder was analysed for flavonoid, furocumarin and other polyphenol content which was standardized at 40%. In addition, all toxicological analyses were performed, including heavy metal, pesticide, phthalate and sinephrine content which revealed the absence of known toxic compounds at significant levels (data not shown). Standard microbiological test showed the final BPF was free of mycotoxins and contaminating bacteria.

The main flavonoids identified in 38% BPF were neoeriocitrin (370 ppm), naringin (520 ppm), and neohesperidin (310 ppm).

Dietary phospholipids (sunflower lecithin) were formulated with 40% in weight standardized BPF extract (provided by HEAD Research group, Bianco, Italy) in order to enhance oral bioavailability of BPF main flavonoids. Tablets containing standard formulation with 650 mg of the BPF powder or 500 mg of BPF Phytosome (containing 200 mg of BPF Extract) were provided by Indena SpA (Milan, Italy). All procedures have been performed according to Food Supplement European Regulation. Tablets with no active ingredients were used as placebo.

2.2. Study Design

A double blind, randomized, placebo-controlled study was carried out in 60 patients suffering from mixed hyperli-

pemia (LDL cholesterol > 120 mg/dl and triglycerides > 175 mg/dl) and type 2 DM (serum glucose > 110 mg/dl) enrolled at the Clinical Trial Center of the International Research Center for Food Safety & Health (IRC-FSH) of University of Catanzaro "Magna Graecia".

After randomization, patients were taking placebo (Group 1), BPF 650 mg (Group 2) or BPF Phyto 500 mg (Group 3) twice a day before meals for 30 consecutive days.

2.3. Data Collection and Measurements

At baseline, all participants were asked to come in the morning after fasting for >10 h. Fasting blood samples were collected for measuring conventional risk factors of cardiometabolic diseases, including serum lipids, glucose, transaminases and inflammatory markers. Face-to- face interviews and physical examinations were performed by well-trained nurses or physicians. Demographic and lifestyle information was collected by a standardized questionnaire (see Table **1**).

Excessive drinkers with alcohol consumption of ≥20 g per day in males or ≥10 g per day in females were not included in this study.

2.4. Laboratory Measurements

Plasma samples were collected by venipuncture in EDTA-containing vials after a 12 h overnight fast on day 0 and after 30 days of treatment with placebo, BPF Phyto and standard BPF formulation, respectively, and stored at -20°C for the detection of hematological biomarkers. For the detection of Cmax (μMol/lt), Time to Cmax (min) and Area Under the Curve (min x μMol/lt) of naringin, naringenin and naringenin glucuronide, plasma samples were collected 0, 30, 60, 120, 240, 480 and 1440 min after taking placebo, standard BPF and BPF Pyto on day 0 and after 30 days of treatment.

Total cholesterol (in mg/dL), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and fasting plasma glucose, were evaluated at baseline and after 30 days of treatment with placebo, standard BPF and BPF Phyto. Under the same treatment schedule, lipoprotein particles were detected by means of proton NMR spectroscopy technique which simultaneously measures the particle concentrations of lipoprotein subclasses of different sizes. Each of the lipoprotein subclasses emits a distinctive NMR signal, the amplitude of which is directly proportional to the number of subclass particles emitting the signal. Importantly, variation in lipoprotein particle lipid composition does not alter the relationship between the NMR signal and the particle size. The NMR also provides calculated values for mean very-low-density lipoprotein (VLDL), LDL, Intermediate- Density Lipoprotein (IDL) and HDL particle sizes plus estimates of total and VLDL, TG and HDL cholesterol. NMR-based estimates of TG and HDL cholesterol were calculated using conversion factors that assume normal lipid content of the various subclasses.

2.5. Pharmacokinetic Studies

Reagents, drugs and supplements Naringin and naringenin (Purity (HPLC) ≥99%) were purchased from Extrasynthese (Genay, France). Naringenin glucuronide was kindly provided by Prof. Procopio, Catanzaro, Italy. HPLC-grade methanol, acetonitrile and acetic acid were purchased from Sigma-Aldrich (Saint Louis, USA).

All other chemicals and solvents used were of analytical grade. Bergamot Polyphenolic Fraction (BPF), patented by H&AD Srl (Trademark and patent No. 0001380456 by Herbal and Antioxidant Derivatives S.R.L.). The PHYTOSOME®, a patented technology developed by Indena S.p.A. (Milan, Italy), C18 Oasis®HLB cartridges purchased by Waters. BPF Phytosome (Indena S.p.A) consists of dietary phospholipids (sunflower lecithin) formulated with a standardized BPF extract (H&AD Srl).

2.6. Working Solutions and Calibration Standards

All chemicals were used as commercially available. The standardization of the method was developed using 99% pure standards of naringin and its metabolites naringenin and naringenin glucuronide mixed in a hydroalcoholic solution of MeOH/H2O 80:20 (v/v) to give the following concentrations: 1, 10, 50, 100, 500 ppm.

2.7. Sample Handling

The 4-ml aliquot of all blood samples was then divided into 2 aliquots (2 ml each) in order to collect plasma and serum. For plasma collection, EDTA (200 microliters) was added to one aliquot. For serum separation, the other aliquot was left in rest at room temperature (30 minutes). Then vials were centrifuged at 10,000 rmp for 10 min at 4 °C. From vials containing EDTA at most 200-600 microliters of plasma was decanted, aliquots were flash-frozen in liquid nitrogen and stored at -80° C for LC- UV analysis. From vials containing serum, about 1 ml was stored at 2-8 °C for later XL640 analysis. After the selection of the more accurate analytical method, naringin, naringenin and naringenin glucuronide were determined by UHPLC-UV post- Solid Phase Extraction (SPE).

2.8. Chromatographic Method and Pharmacokinetic Parameters

The chromatography separation was performed using a Dionex UHPLC UltiMate® 3000 Solvent Rack (Thermo Scientific) equipped with a reverse-phase C18 column Hypersil GOLD- (Dim.(mm) 250 x 4.6; Particle Sz. (μ) 5) operating at flow rate1.0 mL/min. The volume injected 20 μL. Pump model: LPG-3400SD 0-620 bar (9000 psi). Detection was performed by a Photometer MWD-3000 monitoring the absorbance signals between 210-350 nm and the data elaboration was carried out selecting the wavelength of maximum

absorption of the analytes: 280 nm. The mobile phase was A) trifluoracetic acid 0.1% (v/v) in aqueous solution and B) methanol; the gradient used was as follows: zero time condition was 5% A and it was increased to 95% A in 30 minutes.

Pharmacokinetic parameters were determined by means of a non-compartmental analysis using the WinNonlin Professional software version 3.3 (Phar-sight Corporation, USA). The linear trapezoidal method was used to calculate the area under the plasma concentration curve (AUC 0– 24) from time 0 until the detectable concentration at 24h. The maximum plasma concentration (Cmax) and the time needed to reach Cmax were determined by visual inspection of the experimental data.

2.9. Statistical Analysis

For continuous variables, differences between the BPF and baseline levels were assessed using Student's t test for independent samples. Data analyses were conducted using SPSS software (version 18.0). Moreover, the difference between baseline and post-treatment values was compared by t-test for dependent variables.

3. RESULTS

3.1. Effect of Placebo, BPF and BPF Phyto in Hyperlipemic and Hyperglycemic Patients

Demographics and glyco-lipemic serum profile in patients with type 2 DM at baseline as well as following 30 consecutive days of treatment with placebo, BPF and BPF Phyto are shown in Table **1**. Basal levels showed a mixed hyperlipemia (elevated total cholesterol plus hypertriglyceridemia) associated with moderate glucose elevation.

High LDL cholesterol was associated with reduced HDL cholesterol and elevated fasting serum glucose, suggesting the manifestation of MS. Patients treated with BPF (650 mg given orally twice a day before meals) or BPF Phyto (500 mg given orally twice a day before meals) for 30 consecutive days, a significant reduction of serum total cholesterol, LDL-C and triglycerides was found compared to placebo group (Fig. **1**). This effect was accompanied by significant reduction of serum glucose.

No differences were found between BPF or BPF Phyto groups of patients suggesting a substantial bioequivalence on their hypolipemic and hypoglycemic effect.

Table 1. Demographics and serum concentrations of total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides at baseline (T0) and after 30 day treatment (T0) with placebo, BPF (650 mg) and BPF Phyto (500 mg) twice a day, in 60 patients suffering from type2 DM with mixed hyperlipemia.

Demographics and Glyco-Lipemic Profile	Placebo N=20		BPF N=20		BPF Phyto N=20	
Age (yr)	52 ± 11		51±12		50±12	
Sex (M/F)	10/10		10/10		10/10	
BMI (kg/m^2)	29.4 ± 2.01		28.2 ± 1.53		29.5+1.98	
Cigarette smoking	0/10		0/10		0/10	
SBP (mmHg)	130 ± 5		132±6		134 ± 6	
DBP (mmHg)	78±5		80 ± 4		80 ± 5	
Co-morbidities	0/10		0/10		0/10	
Fasting plasma glucose (mg/mL)	T0	122±1.4	T0	120±1.6	T0	124±1.5
	T30	120±1.6	T30	98±1.3*	T30	96±1.4*
Total Cholesterol (mg/dL)	T0	267±12	T0	262±14	T0	261±16
	T30	260±10	T30	196±12*	T30	198±13*
LDL-C (mg/mL)	T0	174±4.4	T0	175±5.8	T0	174±5.7
	T30	166±5.2	T30	116±3.2*	T30	113±3.8*
HDL-C (mg/mL)	T0	43±3.4	T0	44±4.1	T0	44±4.4
	T30	44+3,6	T30	48+3,8*	T30	50+4.2*
Triglycerides (mg/mL)	T0	251±8	T0	252±9	T0	252±8
	T30	250+6	T30	170+7*	T30	173+6*

Data are expressed as mean ± SD for each value; a P value of <0.05 between values at baseline and after each treatment was taken as significant.

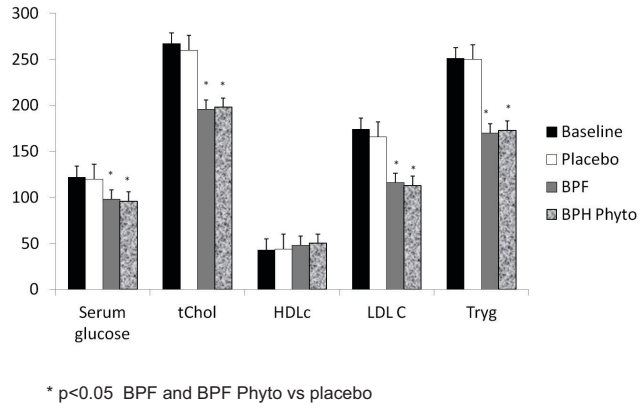

Fig. (1). The effect of placebo, BPF (650 mg), BPF Phyto (500 mg) twice daily in hyperglycemic and hyperlipemic patients.

Moreover, valuable rearrangement of lipoprotein particles was found in patients treated with BPF and BPF Phyto compared to placebo group (Fig. **2a-d**).

Indeed, patients following 30 days of BPF or BPF Phyto, showed relevant changes in mean particle diameters for VLDL, LDL, and HDL compared to the Placebo group. In particular, BPF and BPF Phyto were able to decrease the mean concentration of IDL particles, to increase large LDL and to decrease small LDL. Moreover, 30 day treatment with BPF as well with BPF Phyto an increase of total HDL particles, mainly due to the increase of large HDL, was observed. Also the re-arrangement of lipoprotein profile occurred with no significant differences between standard formulation of BPF and BPF Phyto group. Neither relevant side effects nor changes in red blood cells, white blood cell counts as well as transaminases were found throughout the study in all groups of patients receiving placebo, BPF and BPF Phyto, respectively (not shown).

3.2. Pharmacokinetics of Naringin and its Metabolites After Oral Intake of BPF, BPF Phyto and Placebo

Naringin in its native form and two flavanone metabolites were identified in plasma after the oral intake of BPF and BPF Phyto. In particular, naringin concentrations peaked at time 60- 80 min and declined significantly after 2-4h being not detectable at day 2 after the administration of BPF and BPF Phyto.

Citrus flavanones and their metabolites were not detecable in the plasma of patients at time 0, prior supplementation with BPF or BPF Phyto, or in the control subjects that had been given placebo. Fig. (**3**) represents the plasma concentration curves for naringin after supplementation with BPF or BPF Phyto.

Data were expressed as means and standard deviations. The following pharmacokinetic parameters (AUC 0-24h, C_{max} and Time to C_{max}) corresponding to naringin and its

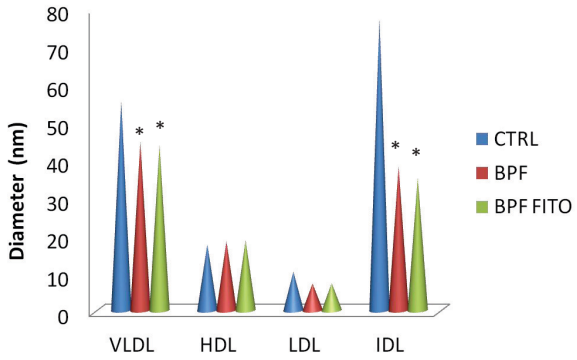

Fig. (2a). The effect of BPF (650 mg) or BPF Phyto (500 mg) twice daily in hyperglycemic and hyperlipemic patients on lipoprotein size.

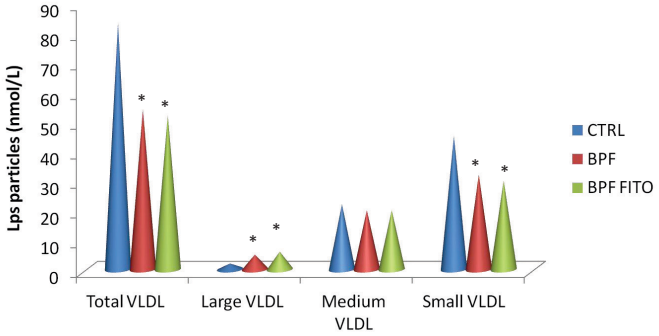

Fig. (2b). The effect of BPF (650 mg) or BPF Phyto (500 mg) twice daily in hyperglycemic and hyperlipemic patients on VLDL particles.

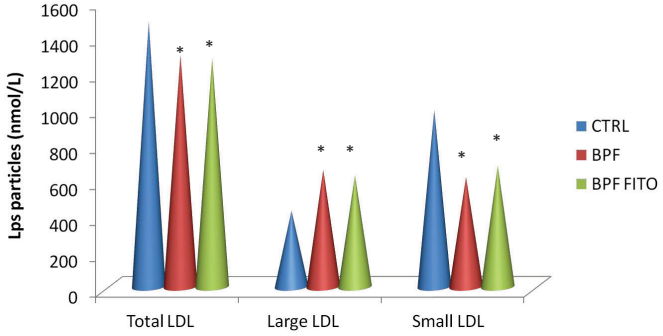

Fig. (2c). The effect of BPF (650 mg) or BPF Phyto (500 mg) twice daily in hyperglycemic and hyperlipemic patients on LDL particles.

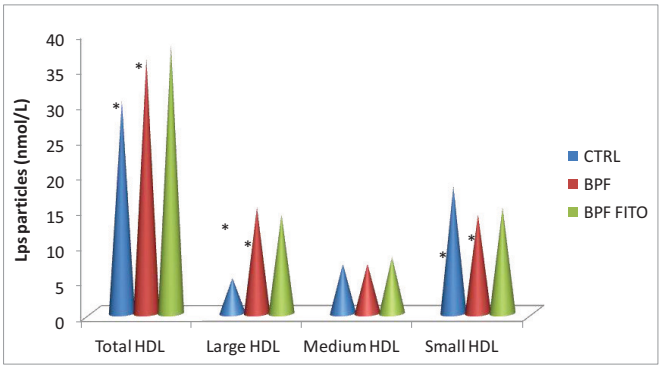

Fig. (2d). The effect of BPF (650 mg) or BPF Phyto (500 mg) twice daily in hyperglycemic and hyperlipemic patients on HDL particles.

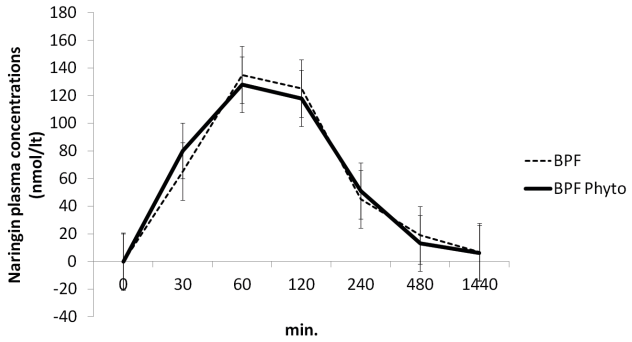

Fig. (3). Time v. plasma concentration curves for naringin in patients receiving BPF or BPF Phyto. Data were expressed as mean values and standard deviations.

metabolites in plasma of patients treated with BPF and BPF Phyto are summarised in Table **2**. Data, collected after single administration of BPF or BPF Phyto revealed that there were no significant statistical differences between the pharmacokinetic parameters corresponding to naringin, naringenin and naringenin glucuronide among patients of both groups, thus demonstrating that both formulations are equivalent in terms of plasma concentrations of major flavonone naringin and its metabolites.

4. DISCUSSION

Here, we have confirmed previous results showing that Bergamot-derived polyphenolic fraction, reduces cholesterol, triglycerides and glucose in patients with Type 2 DM [22-23]. This effect is accompanied by reduction of LDL-C and elevation of HDL-C, thus suggesting a beneficial effect in the lipemic profile of patients undergoing MS. The added value and novelty of data reported in this study using BPF in such a subgroup of patients with elevated cardiometabolic risk, is also displayed by prominent re-arrangement of lipoprotein particle profile found following 30 day BPF treatment. Indeed, BPF reduced LDL small-size, atherogenic particles and enhanced large-size anti-atherogenic HDL lipoprotein particles. This effect highlights that BPF leads to an attenuation of atherogenic risk in patients with Type 2 DM. Our data also show that using BPF in Phytosome leads to bioequivalent response in patients, an effect associated to better polyphenolic oral absorption. In fact, BPF Phyto, compared to standard BPF formulation, leads to near 2,5 fold increase in the rate of naringin serum concentration, an effect confirmed by measurement of its metabolite naringenin and naringenin glucuronide. This effect was accompanied by substantial comparable response of BPF Phyto on serum lipemic and glycemic responses of patients with type 2 DM, including the significant re-arrangement of lipoproteins which are addressed to a lesser atherogenic profile compared to placebo-treated group. As for BPF standard formulation, the effect of BPF Phyto occurred in the absence of significant side effects, thereby confirming the safety profile of both formulations. Our experiments confirm previous *in vitro* and pre clinical studies carried out in rats, showing that using BPF in Phytosome significantly enhances polyphenol absorption when given orally [25-27] and shed new light into studies concerning oral supplementation with citrus polyphenols.

In recent years, a greater understanding of flavonoid absorption and metabolism has been achieved. Flavonoid glycosides are thought to reach the small intestine intact, and it is believed that they may require deglycosidation for absorption across the intestine [28, 29].

The presence of naringin in the plasma of patients treated with standard BPF or BPF Phyto demonstrates that the deglycosidation of naringin is not always necessary for its absorption. Although in previous studies [30] naringin has been administered as a pure compound, whereas in the present study citrus flavanones were administered in the form of a bergamot extract (as it occurs in nature) either in standard and in phytosomal formulation. In both cases, naringin was detected into a range of effective concentrations, being BPF Phyto much more suitable for oral administration due to the better absorption displayed in patients. Furthermore, our data show that three different flavanone forms were found in plasma of both BPF and BPF phyto-treated patients, thus demonstrating naringin absorption after an oral intake of bergamot extract: naringin in its native form, naringenin and naringenin glucuronide. These results confirm the bioavailability of BPF flavanones and their metabolites in diabetic patients after the oral administration of BPF in standard formulation as well as in Phytosome settings. The aglycone naringenin showed the highest rate of absorption but the lowest extended exposure and lowest retention time in the body. Both naringin and naringenin glucuronide showed high extended exposure values, whereas naringenin glucu-

Table 2. Pharmacokinetic parameters of naringin and its metabolites (naringenin and naringenin glucuronide) in patients receiving BPF or BPF Phyto.

Flavonone	Cmax (μMol/L) BPF	Cmax (μMol/L) BPF Phyto	Time to Cmax (min) BPF	Time to Cmax (min) BPF Phyto	AUC_{0-24} (min x μmol/l) BPF	AUC_{0-24} (min x μmol/l) BPF Phyto
Naringin	0,135 ± 0,02	0,128 ± 0,03	60 ± 8	60 ± 12	25,18 ± 4	23,26 ± 5
Naringenin	0,026 ± 0,04	0,020 ± 0,03	90 ± 12	90 ± 16	2,70 ± 0,6	2,64 ± 0,5
Naringenin glucuronide	0,048 ± 0,06	0,038 ± 0,03	120± 14	120 ± 15	5,45 ± 0,8	4,88 ± 0,8

ronide presented the highest values for retention time, remaining in the body for approximately 8 h. All these effects are highlighted when phytosomal formulation of BPF is used.

CONCLUSION

In conclusion, our data show that BPF formulated with Phytosome displays a better absorption and pharmacokinetic profile compared to standard formulation. Furthermore, BPH Phyto showed a substantial bioequivalence compared to standard BPF in terms of efficacy (hypolipemic and hypoglycemic effect) in type 2 diabetes and an identical safety profile.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were approved by Regione Calabria-sez. Area centro-Medical Ethics Committee, city of Catanzaro, Italy. Reference No. 185, 21 September 2016.

HUMAN AND ANIMAL RIGHTS

No Animals were used for studies that are the basis of this research. All human proceed followed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

All participants provided written informed consent prior to participation.

CONFLICT OF INTEREST

AR, PA, MR, GP are employees of Indena S.p.A., Milan, Italy. EB is consultant for Indena S.p.A., Milan, Italy.

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