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By Bogdan-Stefan Negreanu-Pirjol

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In Vitro Hypoglycemic Potential, Antioxidant and Prebiotic Activity after Simulated Digestion of Combined Blueberry Pomace and Chia Seed Extracts

Elena Mihai[1], Bogdan-Stefan Negreanu-Pirjol[2]*, Oana Craciunescu[1]*, Teodora Ciucan[1], Andreea Iosageanu[1], Ana-Maria Seciu-Grama[1], Ana-Maria Prelipcean[1], Elena Utoiu[1], Viorica Coroiu[1], Ana-Maria Ghenea[3] and Ticuta Negreanu-Pirjol[2,4]

[1] National Institute of Research and Development for Biological Sciences, Department of Cellular and Molecular Biology, Splaiul Independentei Bvd., no. 296, Bucharest, 060031, Romania; elena.mihai@incdsb.ro (E.M.); oana.craciunescu@incdsb.ro (O.C.); teodora.ciucan@incdsb.ro (T.C.); andreea.iosageanu@incdsb.ro (A.I.); ana.seciu@incdsb.ro (A.M.S.G.); anamaria.prelipcean@incdsb.ro (A.M.P.); elena.utoiu@incdsb.ro (E.U.); viorica.coroiu@incdsb.ro (V.C.)

[2] "Ovidius" University of Constanta, Faculty of Pharmacy, Capitan Aviator Al. Serbanescu Street, no. 6, Campus, Corp C, Constanta, 900470, Romania; bogdan.negreanu@univ-ovidius.ro (B.S.N.P.); ticuta.negreanu@univ-ovidius.ro (T.N.P.)

[3] Santo Raphael srl, 020335, Bucharest, Romania; anamaria.ghenea@steauadivina.ro (A.M.G.)

[4] Academy of Romanian Scientists, Ilfov Street, no. 3, Bucharest, 050044, Romania

* Correspondence: bogdan.negreanu@univ-ovidius.ro (B.S.N.P.); oana.craciunescu@incdsb.ro (O.C.)

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Abstract: The aim of this study was to investigate the hypoglycemic potential by *in vitro* α-amylase inhibition, the antioxidant and prebiotic activity of a mixture of blueberry pomace hydroalcoholic extract (BP) and chia seed aqueous extract (CS) in a weight ratio of 5:1 (BCM) for further use as ingredient of functional food. BP was preliminary characterized by total phenolic and flavonoid content and HPLC analysis, while total carbohydrate content was determined for CS. BCM mixture had the ability to inhibit α-amylase activity by 1.36 times higher compared to BP extract, at a concentration of 1 mg/mL. The mixture also showed better free DPPH radical scavenging activity, compared to that of individual extracts, with an IC_{50} value of 603.12 µg/mL. *In vitro* testing indicated that both serum and colon reaching products of simulated intestinal digestion of BCM presented cytoprotective activity against oxidative stress in Caco-2 cell culture and inhibited the reactive oxygen species production. In addition, the colon reaching product of BCM digestion had the capacity to significantly ($p<0.05$) stimulate the growth of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus*, revealing the prebiotic potential. All these results indicated that the combination of BP and CS extracts could be further recommended as main ingredient of novel functional food.

Keywords: berry polyphenols; chia polysaccharides; simulated digestion; hypoglycemic activity; reactive oxygen species; gut microbiota.

1. Introduction

The production of berry and grape juice yields a series of by-products, such as seeds, peel and residual pulp, collectively known as pomace [1-3]. Pomace contains up to 20-30% of the original fruit tissue and it is often used as animal feed, compost, biogas production or it is discarded as waste. However, pomace of different berries (strawberry, blueberry, raspberry, blackberry, cranberry) represents a natural source of phenolic acids, flavonoids, anthocyanins, proanthocyanidins, in different quantities which could be valorized as bioactive compounds for functional food with significant positive effects on human health, due to their antioxidant, anti-inflammatory, antimicrobial and antitumor

activity [4-7].

The fruits of *Vaccinium myrtillus L.* are known as one of the most trusted medicinal herb for treating diabetes [8] and to treat various cardiovascular disorders, including microvascular and macrovascular complications. The blueberry fruits do not present direct hypoglycemic action, but their constituents could help to improve the integrity of blood vessels reducing their damage, which is associated with diabetes. This action could be attributed to anthocyanins, which represent the major component of phenolics, but mainly due to the presence of a complex content of bioactive compounds, such as flavonols (quercetin, myricetin), mainly in glycosylated form [9], phenolic acids like abscisic acid, responsible for amelioration of the symptoms of type 2 diabetes after oral administration, targeting the peroxisome proliferator-activated receptor gamma (PPAR-γ) in a similar manner to that of thiazolidinediones class of anti-diabetic drugs [10].

Cinchonain I isomers of the flavonolignans, as another bioactive compound present in blueberries has been shown to increase plasma insulin levels in a similar way to glibenclamide after *in vitro* and *in vivo* oral administration [11]. Shi et al. (2017) have reported that anthocyanins significantly reduced glucose production by 24–74% in H4IIE hepatocytes [12]. However, even though blueberries do not exhibit a direct hypoglycemic action, the polyphenol-rich extract of blueberry fruits has an inhibitory activity towards the α-glucosidase enzyme and thus could be useful in controlling type 2 diabetes [13]. Also, phenolics compounds might be responsible for the high antioxidant potential reported for blueberry [14].

Previous studies showed that oral administration of phenolics in mice resulted in several beneficial actions, such as ameliorating the effects of high-fat diet through *in vitro* inhibition of α-amylase activity [15, 16], preventing insulin resistance by modulation of redox signaling pathways [17] and down-regulation of pro-inflammatory cytokines secretion [18]. After ingestion, phenolics have demonstrated prebiotic properties, stimulating the metabolism and adhesion of microbiota colonizing the gut [19, 20]. In a simulated media mimicking the intestinal environment, they stimulated the probiotics growth and inhibited pathogenic bacteria, interfering with the process of microbial adhesion [21, 22].

In Romania, blueberries production is continuously growing, being the second largest after strawberry, due to good climate easy implementation of food safety [23] potential for significant economic benefits [24] and a longer harvesting period than in other Central European countries. As a result, blueberry pomace was selected for the present study, in order to provide scientific data on its potential valorization due to bioactive compounds content and biological properties.

Other dietary compounds that proved a plethora of health advantages, including on patients with type 2 diabetes [25] are the polysaccharides, despite they were usually considered only as a source of energy. Thus, it was shown that grain-derived polysaccharides could inhibit the key digestive enzymes, α-glucosidase and α-amylase, involved in postprandial blood sugar levels [26]. Moreover, polysaccharides have exerted prebiotic activity by stimulating the development of beneficial microorganisms in the digestive system [27, 28].

Chia (*Salvia hispanica*) seeds were selected, in the present study, as a significant source of soluble fiber polysaccharides [29]. Previous experiments *in vitro* have demonstrated the antioxidant, anti-inflammatory and antidiabetic activity of chia seeds, while *in vivo* function of the digestive tract was improved after their consumption [29].

Numerous bioactive compounds, such as phenolic components and mainly, flavonoids such as myricetin, kaempferol, quercetin and chlorogenic acid, and polyunsaturated fatty acids (PUFAs) like linoleic and α-linolenic acids are present in chia seeds, being responsible for the antioxidant activity [30, 31]. Chlorogenic acid could lower blood sugar levels, applying its effects by hindering the α-glucosidase enzyme in charge of breaking glucose and carbohydrates during digestion [32, 33]. However, the chia seeds

contain high amount of dietary fiber responsible for the decrease of the risk of coronary heart disease and type 2 diabetes [34, 35].

Currently, the use of phenolics in nutraceuticals is limited due to their low bioavailability, poor solubility and instability [36, 37]. Present researches aim to develop mixtures of phenolics and other natural bioactive compounds, such as polysaccharides or proteins, in order to optimize their benefits for the human health [38, 39].

In this context, the present study aimed to investigate the α-amylase inhibition, antioxidant and prebiotic capacity of a mixture of blueberry pomace and chia seed extracts in experimental models *in vitro*, before and after simulated gastrointestinal digestion, to provide novel ingredients for functional food development.

2. Materials and Methods

2.1. Materials

Blueberry (*Vaccinium myrtillus* L.) pomace (dry powder of seeds, skin and residual pulp) was obtained by S.C. Santo Raphael srl, Bucharest, Romania, as a by-product of juice production from blueberries harvested from the Research Institute for Fruit Growing, Pitesti, Romania, in 2020. Chia (*Salvia hispanica* L.) seeds with Argentinian origin were purchased from Bio Fino, Piatra Neamt, Romania.

HPLC standards of gallic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ferulic acid, rutin, luteolin 7-glucoside, kaempferol 3-glucoside, myricetin, resveratrol and quercetin were purchased from Merck (Germany). High purity, thermostable α–amylase from Bacillus sp. (3000 U/mL) (E.C. 3.2.1.1) was purchased from Megazyme (Ireland). Folin-Ciocalteu reagent, 2,2-diphenyl-1-picrylhydrazyl (DPPH), HPLC-grade acetonitrile 99.9%, 3,5-dinitrosalicylic acid (DNS), acarbose, pepsin from porcine gastric mucosa (E.C. 3.4.23.1), trypsin from porcine pancreas (E.C. 3.4.21.4), bile salts and other chemical reagents of analytical purity were purchased from Sigma-Aldrich (Germany), unless otherwise specified. The Caco-2 human intestinal epithelial cell line from ECACC (Sigma-Aldrich) was used at passage 20. The Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), glutamax, non-essential amino acids and a mixture of penicillin-streptomycin-neomycin (PSN) were purchased from Sigma-Aldrich (Germany).

2.2. Preparation of bioactive extracts and their mixture

Blueberry pomace powder was incubated in ethanol:water 70:30 (v/v), in a ratio of 1:10 (w/v) under magnetic stirring, at room temperature, for 24 h. The extract was centrifuged at 9000 g, for 20 min and the residue was subjected to a second extraction, in the same conditions. The supernatants were reunited, evaporated in a rotary evaporator (Heidolph, Germany) to obtain a blueberry pomace extract (BP), which was stored in a desiccator, until further analyses.

Chia seeds were hydrated in distilled water, in a ratio of 1:5 (w/v) and occasionally stirred at room temperature, for 3 h. Then, polysaccharides extraction was performed in distilled water, in a ratio of 1:10 (w/v) in a Soxhlet equipment operated at 100 °C, for 1 h [40]. After filtration, the procedure was repeated using the remaining residue. In order to purify the extract, the reunited supernatants were mixed with chilled ethanol solution, in a ratio of 1:3 (v/v) and stored at 4 °C. After centrifugation at 9000 g, for 20 min, the purified extract of chia seeds (CS) was washed with distilled water, lyophilized and then, stored in a desiccator, until further analyses.

A mixture was prepared by combining BP and CS solutions in a weight ratio of 5:1 (BCM) and stirring on a magnetic plate, at 150 rpm, at room temperature, for 2 h.

2.3. Determination of total phenolic content (TPC), total flavonoids content (TFC) and total carbohydrate content

TPC of the extracts was determined using the Folin-Ciocalteu assay, as previously described [41] with minor modifications. Briefly, a sample volume of 150 µL was mixed

with 750 µL Folin-Ciocalteu reagent and incubated in the dark, for 5 min. Then, 2 mL of sodium carbonate solution (12%, w/w) were added and distilled water to reach 15 mL. The mixture was vortexed and incubated at room temperature, for 30 min. The optical density (OD) was read at 765 nm using a V-650 UV-VIS spectrophotometer (Jasco, Japan). The standard curve was built using different concentrations of gallic acid in the range of 0-500 µg/mL. The results were expressed as gallic acid equivalents (GAE) per 100 g dry weight (d.w.).

TFC was evaluated by aluminum chloride assay, as previously described [41]. Briefly, an extract aliquot (0.5 mL) was mixed with 1.5 mL methanol, 0.1 mL aluminum chloride solution (10%, w/w), 0.1 mL sodium acetate solution (1 M) and 2.8 mL distilled water. The mixture was incubated at room temperature, for 30 min and then the OD was read at 415 nm using a V-650 UV-VIS spectrophotometer (Jasco, Japan). The standard curve was built using quercetin solution in the range of concentrations 0-500 µg/mL. The results were expressed as quercetin equivalents (QE) per 100 g d.w.

Total carbohydrate content was determined according to AOAC standard [42] by subtracting the content of protein, lipid and ash.

2.4. HPLC analysis

HPLC analysis was conducted on an Agilent 1200 HPLC system provided with quaternary pump, degasser, thermostatted autosampler and diode-array detector. BP sample was filtered through regenerated cellulose membranes of 0.22 µm porosity and aliquots (10 µL) were injected on a Zorbax XDB-C18 reverse phase column, 5 µm, 4.6 i.d. x 150 mm (Agilent). The elution was performed using a mobile phase, consisting of solvent A (2 mM sodium acetate buffer, pH 3.05) and solvent B (acetonitrile), in the following linear gradient: 0-30 min, 2-20% B; 30-40 min, 20-30% B; 40-50 min, 30% B; and 50-60 min, 30-2% B, as previously described [43]. The peak identification was conducted by comparison of the retention time to that of phenolic acid and flavonoid standards. Different standard concentrations were used to build the calibration curves for the quantification of identified compounds by peak area integration using the Chemstation software. The results were expressed per 100 g d.w.

2.5. Determination of α-amylase activity inhibition

The α-amylase activity inhibition was performed according to the protocol of Apostolidis et al. [44] with minor modifications. A reaction mixture consisting of 50 µL phosphate buffer (100 mM, pH 6.8), 10 µL α-amylase (2 U/ml) and 20 µL sample was made in the wells of a 96-well microplate and incubated at 37 °C, for 20 min. Then, 20 µL of 1% starch solution was added and incubation continued at 37 °C, for 30 min. Then, 40 µL DNS solution was added and the mixture was boiled in a water bath, for 10 min. The OD of the mixture was read at 540 nm using a Spectrostar Nano microplate reader (BMG Labtech, Germany). A mixture containing distilled water in place of sample served as control. A solution of acarbose, known as α-amylase inhibitor, served as positive control. The α-amylase inhibition was calculated using the following equation:

$$\text{Inhibition of } \alpha\text{-amylase activity } (\%) = (OD_{control} - OD_{sample} / OD_{control}) \times 100 \quad (1)$$

The sample concentration (mg/mL) that inhibited 50% of the α-amylase activity (IC_{50}) was determined from the regression curve using Microsoft Excel 2018 software.

2.6. Determination of free radical scavenging capacity

The free radical scavenging capacity of samples was determined by free DPPH radical inhibition assay, as previously described [41]. Briefly, the capacity to inhibit free DPPH radicals was determined by mixing 1.35 mL of 0.25 mM DPPH methanolic solution with 150 µL sample of different concentrations (10-500 µg/mL) and 0.9 mL of 0.1 M Tris-HCl buffer, pH 7.4. Then, the mixtures were incubated in the dark, at room temper-

ature, for 30 min. The OD was read at 517 nm using a V-650 UV-VIS spectrophotometer (Jasco, Japan). A blank was obtained by sample replacing with the same volume of buffer. The results were calculated using the following equation:

$$\text{Free DPPH radical inhibition (\%)} = (OD_{blank} - OD_{sample}) / OD_{blank} \times 100 \quad (2)$$

Trolox, an analogue of vitamin E, with known antioxidant activity was used as positive control. The sample concentration (µg/mL) that inhibited 50% free DPPH radicals (IC_{50}) was determined from the nonlinear regression curve of DPPH inhibition vs. concentration plot using Microsoft Excel 2018 software.

2.7. *In vitro simulated gastrointestinal digestion*

In vitro simulated gastrointestinal digestion was performed in two successive steps, as previously described [45] with minor modifications. First, 2.5 mL sample was incubated in a simulated gastric juice, consisting of 20 mg/mL pepsin solution in 5 M HCl, pH 2, supplemented with 0.9% NaCl, in a shaking water bath fixed at 90 g and a temperature of 37 °C, for 2 h. At the end of the incubation, the post-gastric digestion product (PG) was cooled on ice and stored at -20 °C. In the second phase, an aliquot of PG sample was further digested in beaker with simulated intestinal medium, consisting of 25 mg/mL trypsin and 30 mg/mL bile salts dissolved in 0.1 M $NaHCO_3$ solution, pH 7.5. A dialysis bag (molecular weight cutoff of 12 kDa) was filled with a solution of 0.1 M $NaHCO_3$, pH 7.5 and placed into the beaker to gradually increase the pH, mimicking the gastrointestinal transition. The incubation was conducted in the dark, at 37 °C, for 2 h, with continuous stirring. At the end of the process, the solution from the dialysis bag contained the digestion products that can pass the intestine into the serum (PS), while the beaker solution contained the products that go into the colon (PC) following digestion. The samples were immediately frozen, until further analyses. For cell culture experiments, all samples (PG, PS, PC) were sterile filtered through 0.45 µm membranes.

2.8. *In vitro cytocompatibility testing by Neutral Red assay*

Human intestinal epithelial cells from Caco-2 cell line were seeded at a density of $1x10^5$ cells/mL, in the wells of a 96-well culture plate and cultivated in DMEM supplemented with 20% FBS, 1% glutamax, 1% non-essential amino acids and 1% PSN antibiotic mixture, in standard conditions of 5% CO_2 humidified atmosphere, at 37 °C, for 24 h. Then, cells were cultivated in fresh medium containing different concentrations of digested samples (100-1500 µg/mL), in standard conditions, for 24 h.

At the end of the incubation period, the cell viability was assessed by Neutral Red assay, as previously described [46]. Briefly, the cell culture media was replaced with 100 µL of 0.005% (w/w) Neutral Red solution and the plate was incubated in the dark, at 37 °C, for 3 h. Then, the cells were washed in phosphate buffered saline, fixed and the stain was extracted from the viable cells by gentle shaking, for 15 min. Untreated cells were used as control. Cells treated with 0.[illegible]M H_2O_2 served as positive control. The OD was read at a wavelength of 540 nm at a Spectrostar Nano microplate reader (BMG Labtech, Germany). The cell viability was calculated using the following equation:

$$\text{Cell viability (\%)} = (OD_{sample} / OD_{control}) \times 100 \quad (3)$$

2.9. *Determination of intracellular reactive oxygen species (ROS) production by flow cytometry*

The intracellular ROS production was determined in the same experimental model of adhered Caco-2 intestinal cells treated with 100 µg/mL digestion products, for 24 h, as described above. Then, the cells were oxidative stressed by treatment with 0.05 mM t-butyl hydroperoxide (t-BHP), for 30 min. The intracellular ROS production was determined by using the cell permeant fluorogenic dye 2',7'-dichlorofluorescein diacetate (DCFH-DA), as previously described [47]. Briefly, cells were incubated with 10 µM DCFH-DA, for 30 min and the reaction with free radicals led to the formation of DCF fluorescent product analyzed at a BD LSR II flow cytometer (Becton Dickinson, Franklin

Lakes, NJ, USA). Cells incubated in culture medium served as control. Cells treated with 12 µM ascorbic acid, known as antioxidant agent, served as positive control. The acquired histograms of fluorescence intensity served to calculate the percentage of ROS production using FACSDiva and FlowJo software.

2.10. Determination of the prebiotic effect

The prebiotic effect was evaluated in experimental models *in vitro* developed using microbial strains of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus*, as previously described [48] with minor modifications. Briefly, bacterial cultures were grown in MRS broth medium at 35 °C, for 24 h and the working culture was adjusted at a concentration of $1x10^8$ CFU/mL to 0.5 McFarland standard. The samples of non-digestible products (PC) (100 µg/mL) were incubated with microbial suspensions in the wells of a 96-well microplate, at 35 °C, for 24 h. The absorbance was read at 600 nm using a Sunrise microplate reader (Tecan). The values were proportional to the microbial growth. Untreated culture served as control.

2.11. Statistical analysis

The results were expressed as mean ± standard deviation (SD) from three independent experiments (n=3). The statistical analysis was performed on each control-sample or sample-sample pair of interest using two-tailed, paired Student's *t*-test (Microsoft Excel 2018 software). Statistical significant differences were considered at $p<0.05$.

3. Results and Discussion

3.1. Characterization of bioactive extracts

The results of preliminary analyses of BP and CS extracts are presented in Table 1.

Table 1. Total phenolic, flavonoids and carbohydrates content of blueberry pomace extract (BP) and chia seed extract (CS). The results are expressed as mean ± SD (n=3).

Sample	Total phenolic content (g GAE/100 g d.w.)	Total flavonoids content (g QE/100 g d.w.)	Total carbohydrates content (g/100 g d.w.)
BP	30.40 ± 1.28	1.89 ± 0.07	-
CS	3.93 ± 0.15	0.72 ± 0.03	70.78 ± 4.41

The results showed that BP had 30.40% TPC and 1.89% TFC. Similar TPC value (28.5 g GAE/100 g d.w.) was previously reported for the blueberry pomace extract prepared in HCl-methanol solution, at room temperature and the extraction H_2SO_4-methanol solution at 85 °C [49]. CS contained 70.78% carbohydrates content, as calculated by subtracting the content of protein, lipids and ash.

The results of HPLC analysis are presented in Table 2. The data indicated that gallic and chlorogenic acid were the main identified phenolic acids, while the flavonoids rutin, quercetin and luteolin 7-glucoside prevailed over the other identified compounds. Resveratrol was also quantified in BP extract, at a level of 103.43 mg/100 g d.w. A previous study identified similar composition of the acidified hydroalcoholic extracts of blueberry pomace [50].

Table 2. HPLC analysis of phenolic compounds in blueberry pomace extract. The results are expressed as mean ± SD (n=3).

Compound	Quantity (mg/100 g d.w.)
Gallic acid	5043.27 ± 181.03
Chlorogenic acid	1509.41 ± 61.37
Caffeic acid	200.60 ± 9.45

p-Coumaric acid	251.85 ± 8.75
Ferulic acid	118.14 ± 5.18
Rutin	609.78 ± 23.26
Luteolin 7-glucoside	262.11 ± 12.91
Kaempferol 3-glucoside	161.46 ± 6.76
Myricetin	175.18 ± 7.22
Resveratrol	103.43 ± 4.69
Quercetin	316.46 ± 11.84

3.2. Inhibition of α-amylase activity

Phenolic compounds, such as quercetin, rutin, catechin, procyanidins and tannic acid, could inhibit α-amylase activity through hydrophobic interaction [49]. In addition, diet with chia seeds could control the postprandial glycemia and manage the obesity risk in diabetes [52]. In the present study, the capacity of BCM mixture to inhibit α-amylase activity was comparatively assessed to both BP and CS individual extracts. The results are presented in Figure 1.

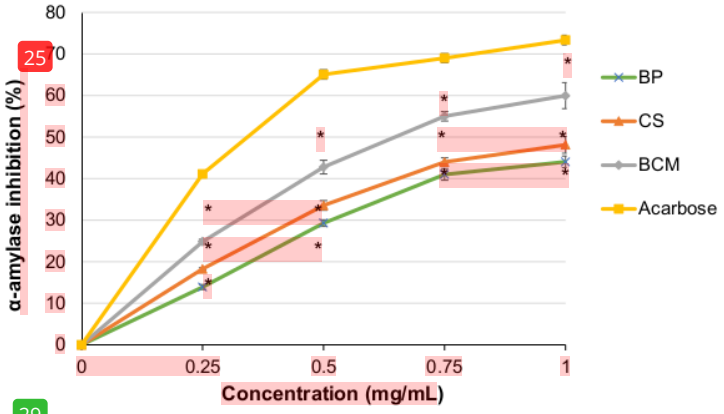


Figure 1. Inhibition of α-amylase activity in the presence of blueberry pomace extract (BP), chia seed extract (CS) and their mixture (BCM). Acarbose served as control. *$p<0.05$, compared to control.

The inhibition of α-amylase activity varied in a dose-dependent manner. The mixture presented the highest inhibition of α-amylase activity, close to that of acarbose, a known inhibitor of α-amylase activity. The mixture had higher value of inhibition than those of individual extracts, at each tested concentration. The calculated IC_{50} value of BCM was 0.69 mg/mL, while those of BP and CS were 1.28 and 1.07 mg/mL, respectively. Acarbose had an IC_{50} value of 0.31 mg/mL. These data indicated that the compounds from BCM could exert a synergistic action that led to inhibition of α-amylase activity.

Similar activity of different methanolic and aqueous extracts of fruit pomace derived from grapes, lemon, orange and pineapple was previously reported in the range of 8-28% α-amylase inhibition [1]. Phenolic compounds, like gallic and chlorogenic acid, acted as potent antidiabetic agents by inhibiting α-amylase and α-glucosidase activity *in vitro* and *in vivo* [53, 54]. It was observed that these antioxidant phenolic compounds were found in significant quantities in BP extract and BCM mixture prepared in the present study. In addition, previous *in silico* studies using docking program found novel phenolic inhibitors of α-amylase, such as corilagin, baicalein, quinoline, β-sitosterol, and identified the amino acids from the active situs of this enzyme involved in hydrophobic and/or hydrogen-bond interactions [55]. The mechanism of inhibition was described as a non-competitive polyphenol-enzyme interaction and, in the case of catechins, good correlation between the affinity towards the enzyme and the inhibitory potential was found [56].

It was also found that phenolics represented a supportive treatment of type-2 diabetes and metabolic syndrome [57].

3.3. Free radical scavenging activity

The results of free DPPH radical scavenging activity of BCM and BP, CS individual extracts are presented in Figure 2.

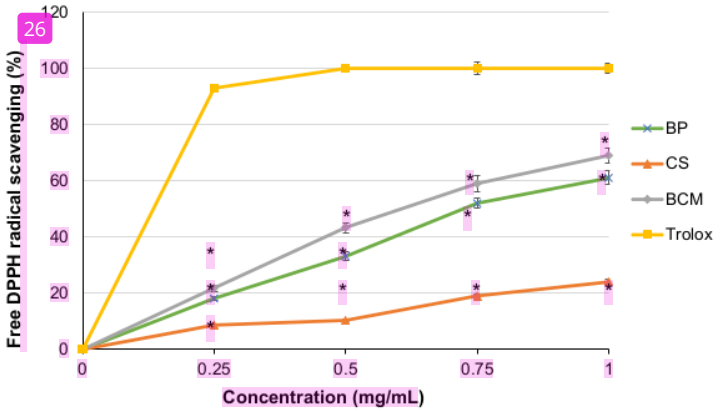


Figure 2. Free DPPH radical scavenging activity of blueberry pomace extract (BP), chia seed extract (CS) and their mixture (BCM). Trolox served as control. *$p<0.05$, compared to control.

These data showed that BCM mixture presented higher antioxidant activity than that of individual extracts. Accordingly, lower IC_{50} value (606.12 µg/mL) was calculated for BCM mixture, compared to that of BP (681.97 µg/mL). CS had a significantly higher IC_{50} value (2248.57 µg/mL), indicating low antioxidant activity and was not further tested in cell culture experiments. The IC_{50} value of Trolox, used as antioxidant control, was 127.02 µg/mL. The capacity of BCM mixture to scavenge free DPPH radicals could be due to the high phenolic content of BP, in accordance to a previous study reporting high correlation coefficient [49]. This activity was also influenced by the structural properties of phenolic constituents, such as the number and position of hydroxyl groups or other substituents [58]. In addition, it was shown that polysaccharides had a pronounced interaction with fruit polyphenols through covalent, hydrogen and hydrophobic bonds [59], which might increase the antioxidant capacity of such combinations [60].

3.4. In vitro cell cytocompatibility

A two-step gastrointestinal digestion was performed on BCM mixture and PG, PS and PC products were obtained. The results of *in vitro* cytocompatibility testing different concentrations of these products in Caco-2 intestinal cell line are presented in Figure 3.

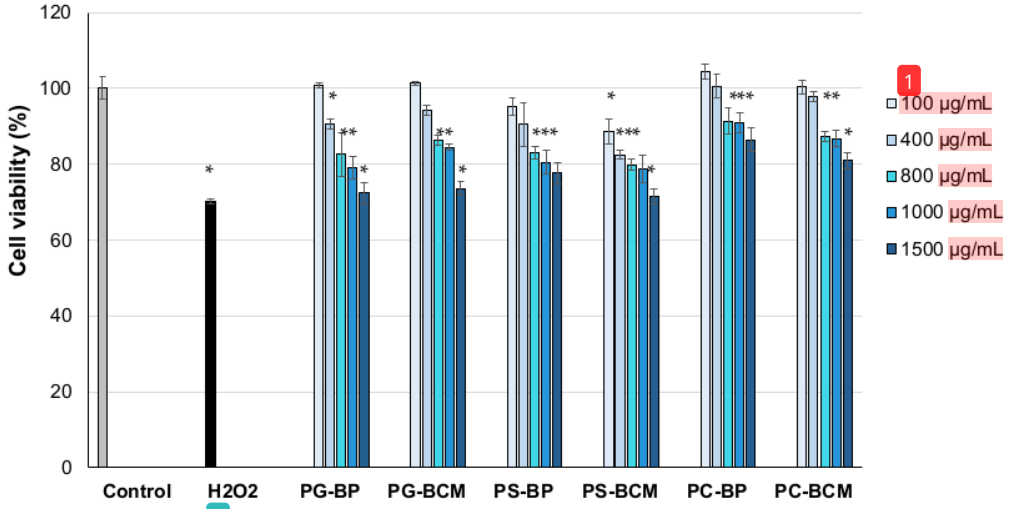
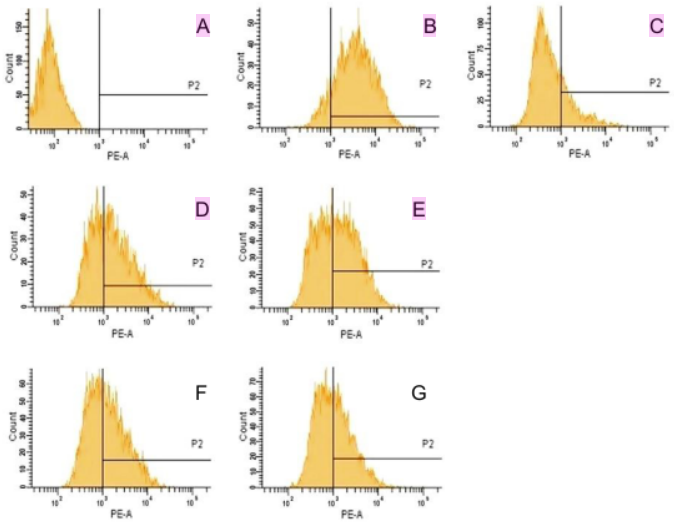


Figure 3. The cell viability of Caco-2 cells treated with post-gastric (PG) and post-intestinal (PS, PC) digestion products of blueberry pomace extract (BP) and BCM mixture, for 24 h, assessed by Neutral Red assay. The results were expressed as mean ± SD (n=3). *p<0.05, compared to the untreated cells (control).

The values of cell viability varied in a dose-dependent manner. The PG-BCM had good cytocompatibility in the range of concentrations 100-1000 µg/mL, the cell viability values being close to that of control cells (100%) at the concentration of 100 µg/mL, and higher than 80% at concentrations between 400-1000 µg/mL. At 1500 µg/mL, the cell viability was 73.6%, indicating moderate cytocompatibility. PS digestion product of BCM was also cytocompatible up to 1000 µg/mL (cell viability >80%) and a value of 71.6% was recorded at 1500 µg/mL. PC digestion product of BCM was cytocompatible and had values of cell viability higher than 80%, at all tested concentrations. The digestion products of BP had similar degree of cytocompatibility to that of BCM mixture. Based on these data, the cytocompatible concentration of 100 µg/mL digestion products was selected for further experiments in Caco-2 cells.

3.5. Effect on intracellular ROS production

An experimental model *in vitro* was used to assess the effect of PS and PC digestion products of BCM mixture on the modulation of intracellular ROS production in oxidative stressed Caco-2 intestinal cell culture. The histograms acquired by flow cytometry and the calculated percentages of ROS production are presented in Figure 4.



Histogram	Sample	ROS production (%)
B	Oxidative stressed group	100.00 ± 4.03
C	PS-BP	46.70 ± 2.24*,#
D	PS-BCM	41.43 ± 1.56*,#
E	PC-BP	36.41 ± 2.13*,#
F	PC-BCM	34.86 ± 1.06*
G	Ascorbic acid (control)	30.16 ± 2.12*

Figure 4. Quantification of ROS production in oxidative stressed Caco-2 cells (B) treated with 100 µg/mL of gastrointestinal digestion products PS-BP (D), PS-BCM (E), PC-BP (F) and PC-BCM (G), performed by flow cytometry. Untreated cells (A) and cells treated with 12 µM ascorbic acid (C) served as control. The results are expressed as mean ± SD (n=3). *p<0.05, compared to the oxidative stressed group; #p<0.05, compared to ascorbic acid-treated group.

The results indicated that all tested samples had the capacity to significantly (p<0.05) decrease the ROS level, compared to the oxidative stressed cells. It is worth to emphasize that, in the case of cells treated with PC digestion product of BCM, the ROS level was diminished at a similar value to that of cells treated with ascorbic acid, a known antioxidant agent. An antioxidant capacity was also observed in case of cells treated with PS-BCM, but the levels of ROS production were slightly higher, compared to that of PC-BCM digestion product. These results confirmed that the compounds from BCM mixture could maintain their antioxidant activity after gastrointestinal digestion. The digestion products of BP presented antioxidant capacity, but at a lower extent than those of BCM.

The results were in accordance to a previous study on polyphenolic extracts of blueberry pomace showing their capacity to inhibit ROS generation in H_2O_2-treated keratinocytes [61]. Moreover, pre-treatment of cells with blueberry phenolic extract could protect them from H_2O_2-induced oxidative stress through the p-38 mitogen-activated protein kinase metabolic pathway [62]. In a similar study on blackberry phenolic extracts, it was reported their anti-ROS activity in cultured cells, after simulated gastrointestinal digestion, a process known to affect their stability and bioavailability *in vivo* [63]. Previous research reported the beneficial effect of grape polyphenols administration in mice for lowering the intestinal ROS level [64].

3.6. Prebiotic effect

The results of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* growth in the presence of digestion products reaching the colon are shown in Figure 5.

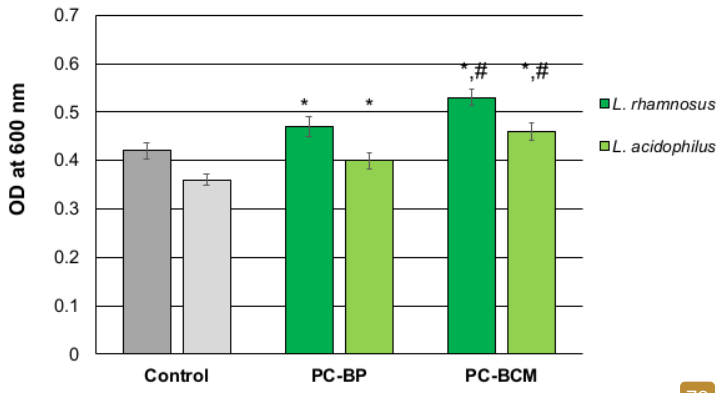


Figure 5. Growth of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* cultivated in the presence of 100 µg/mL of digestion products reaching the colon (PC) of blueberry pomace extract (BP) and BCM mixture, after 24 h of treatment. The results are expressed as mean ± SD (n=3). *p<0.05, compared to untreated control; #p<0.05, compared to PC-BP.

These data indicated that cell growth of both *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* bacterial strains was superior in the presence of PC-BCM digestion product, compared to that of untreated control. Thus, the sample has induced a stimulating effect on the growth of each tested strain of *Lactobacillus*, after 24 hours of treatment. Also, significantly (p<0.05) higher values were recorded in the cells treated with PC-BCM, compared to those treated with PC-BP. These results demonstrated that BCM mixture had better capacity to up-regulate the growth of lactic acid bacteria strains. In addition, they suggested a synergistic action of bioactive compounds from BCM mixture to stimulate probiotics and gut health.

Several *in vitro* and *in vivo* studies indicated the bioactivity of berry polyphenols on balancing between beneficial *Bacteroidetes* and *Firmicutes* through decrease of short-chain fatty acids production [65]. Blueberry anthocyanin extracts presented prebiotic activity [66], while consumption of a phenolic extract have modulated the gut microbiota of mice, increasing the relative abundance of *Bifidobacteria* and revealing anti-obesity effects [67]. Phenolic extracts of elderberry skin were also reported to stimulate the growth of the probiotic strain of *Lactobacillus rhamnosus*, being recommended for obtaining functional, pro-health food [48]. The combination of phenolics and probiotic strains induced significant beneficial effects on gut motility and microbiota in an *in vivo* model on *Drosophila* and in a simulated model of human gastrointestinal tract, compared to that of each component, providing novel solutions for chronic metabolic diseases [68]. Moreover, chia seeds have high nutritional and therapeutic potential, in particular for gut microbiota due to their chemical composition rich in soluble fiber polysaccharides. Still, there is scarce scientific literature on the prebiotic effect of chia seed polysaccharides. A recent study has reported that chia mucilage protected the probiotics encapsulated in a food film and stimulated their survival increase [69]. Similar studies have reported that oligosaccharidic fractions extracted from grape seeds exerted prebiotic activity towards *Lactobacillus acidophilus*, improving *in vitro* bacterial growth [19].

4. Conclusions

This study has demonstrated the ability of a new mixture of blueberry pomace and chia seed extracts to inhibit α-amylase activity, suggesting hypoglycemic potential, and

to scavenge free DPPH radicals. *In vitro* experimental models have shown that bioactive compounds from BCM maintained their antioxidant capacity after simulated intestinal digestion, indicating potential advantages for their bioavailability and digestive tract health. Stimulation of lactic acid bacteria growth in the presence of colon reaching digestion products of BCM showed the prebiotic potential. All these bioactivities were exerted by the mixture of pomace and chia seed extracts at a higher extent than the individual extracts, suggesting a synergistic action of combined compounds. In conclusion, this new valuable vegetal mixture is recommended for further testing as ingredient of novel functional food with hypoglycemic, antioxidant and prebiotic properties.

Author Contributions: E.M., O.C. and B.S.N.P. have designed the study and had major contributions in writing the manuscript; E.M., T.C., E.U. and A.M.G. performed extraction and biochemical experiments; E.M., T.C., E.U., A.M.G. and T.N.P. analyzed and interpreted the data; A.I. and V.C., performed cell culture experiments, data processing and interpretation; A.M.S.G. conducted flow cytometry experiments, analyzed and interpreted the data; A.M.P. conducted microbial experiments, analyzed and interpreted the data; writing and editing the manuscript, O.C., B.S.N.P., A.I., V.C. and T.N.P.; supervision, O.C., B.S.N.P. and T.N.P. All authors wrote, read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

BP: blueberry pomace extract; CS: chia seed extract; BCM: mixture of BP and CS extracts in a ratio of 5:1 (w/w); DPPH: 2,2-diphenyl-1-picrylhydrazyl; DNS: 3,5-dinitrosalicylic acid; DMEM: Dulbecco's Modified Eagle Medium; FBS: fetal bovine serum; PSN: penicillin-streptomycin-neomycin mixture; d.w.: dry weight; TPC: total phenolic content; TFC: total flavonoids content; OD: optical density; GAE: gallic acid equivalents; QE: quercetin equivalents; PG: gastric digestion product; PS: intestinal digestion product that pass into the serum; IC: intestinal digestion product that go into the colon; t-BHP: tert-butyl hydroperoxide; ROS: reactive oxygen species; DCFH-DA: 2',7'-dichlorofluorescein diacetate; SD: standard deviation.

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