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Polyphenols of *Myrica faya* inhibit key enzymes linked to type II diabetes and obesity and formation of advanced glycation end-products (*in vitro*): potential role in the prevention of diabetic complications

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Abstract

Myrica faya Aiton (fire tree, faya) is an underused species with a diverse flavonoid composition (anthocyanins, flavonols, ellagitannins) which can promote positive effects on human health. *M. faya* has been reported to possess high antioxidant activities, but its potential in the prevention of type II diabetes has not been evaluated so far. In the present study, eight *M. faya* samples from different areas of Madeira and Azores archipelagos (Portugal) were collected to determine their phytochemical profile and then tested for their *in vitro* anti-diabetic and antioxidant activities. The analysed extracts showed strong inhibitory activities towards α -glucosidase, aldose reductase and glycation of bovine serum albumin (BSA) and moderate effects towards α-amylase and lipase (by comparison with reference compounds). Cyanidin-3-*O*-glucoside and ellagitannins were the main bioactive agents involved in the anti-diabetic effects of *M. faya*. Such results may provide important scientific evidence for further utilization of *M. faya* as dietary or nutraceutical products for the prevention and/or control of hyperglycaemia-associated complications.

Keywords: *Myrica faya*; Phenolic compounds; Type-2 Diabetes; Digestive enzyme inhibition; Aldose reductase; Protein glycation; Antioxidant activity.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycaemia) due to the defects in insulin-secretory response or resistance to insulin action (X. Zhang, Huang, Zhao, et al., 2015). Hyperglycaemia can induce non-enzymatic glycosylation of macromolecules (proteins, lipids, nucleic acids) and subsequent accumulation of advanced glycation end-products (AGEs) (Chinchansure, Korwar, Kulkarni, & Joshi, 2015; Wei et al., 2012). These compounds cause cellular and tissue damage by impairing protein function and clearance and lead to the development of some diabetic complications (retinopathy, neuropathy, nephropathy) (Harris et al., 2014; Yeh, Hsia, Lee, & Wu, 2017).

An effective therapeutic approach for reducing postprandial hyperglycaemia in type II diabetes mellitus (T2DM) is to delay the absorption of carbohydrates by inhibiting digestive enzymes activity (Podsędek, Majewska, Redzynia, Sosnowska, & Koziołkiewicz, 2014; S. Y. Wang, Camp, & Ehlenfeldt, 2012). Currently, acarbose, miglitol and voglibose are commonly used drugs to control hyperglycaemia in diabetic patients. However, these synthetic inhibitors are reported to cause several side effects such as flatulence, abdominal pain and diarrhea (Yan et al., 2016). There is some evidence that polyphenols from berry fruits can effectively inhibit digestive enzymes responsible for the metabolism of sugar and lipids (Edirisinghe & Burton-Freeman, 2016; McDougall, Kulkarni, & Stewart, 2008). Therefore, plant-derived products may provide, through diet, natural and safer anti-diabetic compounds for the control of hyperglycaemia and other diabetic complications (Edirisinghe & Burton-Freeman, 2016; Podsędek et al., 2014). In addition to the inhibition of digestive enzymes, phenolic compounds can also inhibit the catabolic activity of aldose reductase and prevent the formation of AGEs (Chinchansure et al., 2015; Harris et al., 2014; Liu et

al., 2011; W. Wang, Yagiz, Buran, Nunes, & Gu, 2011). Hence, they can potentially reduce both the hyperglycaemia state and their associated complications.

Myrica faya Aiton (syn. *Morella faya* Ait.), commonly called "fire tree", belongs to the genus *Myrica* in the family Myricaceae (Press & Short, 1994). This species is native of Macaronesia region (Azores and Madeira Archipelagos and the Canary Islands) and was spread over the coast of Iberia. It was taken to other continents by emigrants from Madeira and Azores and became invasive in Hawaii, Australia and New Zealand. It is a common evergreen shrub that usually grows around 8 m tall. The fruits ("wax-myrtle") are small, red to purple when ripe (Press & Short, 1994). They can be directly consumed, however, due to their astringency are more commonly used to produce jams and liquors and food colorants (Spínola, Llorent-Martínez, Gouveia, & Castilho, 2014). Recently, our research group reported that berries and leaves of *M. faya* were rich source of bioactive compounds (in particular, cyanidin-3-*O*-glucoside and other flavonoids) that contribute to their high antioxidant activities (Spínola et al., 2014). However, no further work has been carried out for other health-promoting properties of this species.

Considering the reported benefits of a similar species, *Myrica rubra* (bayberry), in the control of T2DM (C.-D. Sun et al., 2012; Yan et al., 2016; X. Zhang, Huang, Zhao, et al., 2015; Y. Zhang, Chen, Wei, Chen, & Ye, 2017), this study was focused on three main aspects: (*i*) inhibition of key digestive enzymes (α -glucosidase, α-amylase and lipase) linked to T2DM and obesity; (*ii*) inhibition of aldose reductase activity and prevention of the formation of AGEs (tested with BSA and fructose/ribose models); and (*iii*) evaluation of antioxidant activities towards free radicals. This is the first report on the potential anti-diabetic effects of *M. faya* extracts and may offer a natural source of potential alternative agents for the management of diabetic complications.

2. Material and methods

2.1. Chemicals and reagents

All reagents and standards were of analytical reagent (AR) grade unless stated otherwise. Ellagic acid (≥ 96%), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) ($ABTS^{\bullet+}$), 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$), 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) and methanol (99.9%) were purchased from Fluka (Lisbon, Portugal). Ammonium sulfate (≥ 99%), caffeic acid (≥ 98%), DL-glyceraldehyde (≥ 98%), β-nicotinamide adenine dinucleotide reduced (NADH, ≥94%), *N*-(1-Naphthyl)ethylenediamine dihydrochloride (NEDA, ≥ 98%), β-mercaptoethanol (≥ 99%), phenazine methosulfate (PMS, ≥ 90%), potassium persulfate (99%), sodium carbonate (100%), sulfanilamide (≥ 99%), *α*-glucosidase from *Saccharomyces cerevisiae* (type I), intestinal acetone powder from rat source of *α*-glucosidase, *α*-amylase from porcine pancreas (type VI-B), lipase (type II; from porcine pancreas), *p*-nitrophenyl-α-D-glucopyranoside (*α*-*p*NPG), *p*-nitrophenyl butyrate (*p*NPB), bovine serum albumin (BSA, ≥ 98%), D-(-)-ribose (≥ 99%), aminoguanidine hydrochloride (AMG, ≥ 98%), acarbose, orlistat and formic acid (98%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Folin–Ciocalteu's phenol reagent (FCR), gallic acid (> 98%), potassium acetate (> 99.5%), potassium chloride (99.5 – 100.5%), and sodium chloride (> 99.0%) were acquired from Panreac (Barcelona, Spain). 5-*O*-caffeoylquininc acid (5-*O*-CQA, > 95%), cyanidin-3-glucoside (C3G) chloride (> 98%), hesperidin (95-99%) and 1-deoxynojirimycin (1-DNJ; 95-99%) were obtained from Biopurify phytochemicals LTD (Chengdu, China). Myricitrin (MCT, > 98%) was acquired from Carbosynth (Berkshire, UK); human aldose reductase (HAR) from Prozomix (Northumberland, UK) and β-nicotinamide adenine dinucleotide

reduced tetrasodium salt hydrate (NADPH, ≥ 97%) from Calbiochem (MA, USA). Nitroblue tetrazolium chloride (NBT, 90%) was obtained from Acros Organics (Geel, Belgium), o-phosphoric acid (85%) from BDH AnalaR. Apigenin (> 99%), (+)catechin hydrated (> 99%) and protocatechuic acid (≥ 99%) were purchased from Extrasynthese (Genay, France). Aluminium chloride (98%), hydrochloric acid (37%), and quercetin dihydrate (> 99%) were acquired from Riedel-de Haen (Hanover, Germany), whereas acetic acid glacial from Fischer Scientific (Bishop Meadow, UK). Ethylenediaminetetraacetic acid (EDTA, > 99%), D-(-)-ribose, fructose, potassium iodate (99.5%), soluble starch (p.a.), sodium azide (> 99%) and sodium nitroprusside (99%) were obtained from Merck (Darmstadt, Germany). LC–MS grade acetonitrile (CH_3CN, 99%) (LabScan; Dublin, Ireland) and ultrapure water (Milli-Q Waters purification system; 18 M Ω cm at 23 °C; Millipore; Milford, MA, USA) were also used in this study.

2.2. Sample preparation and extraction of phenolic compounds

M. faya samples were collected in two different archipelagos of Portugal (Madeira and Azores) between July and September 2014. Details of collection places and voucher numbers are given in Table 1.

TABLE 1

For analysis, plant material was separated into leaves and fruits (fully ripe), destemmed, washed, lyophilized (Alpha 1-2 LD plus freeze dryer, CHRIST), ground to powder using a mechanic grinder, and stored at -20 ºC in sealed plastic bags. Phenolic extraction was conducted as previously reported (Spínola et al., 2014). An extraction solution composed of MeOH:H_2O (acidulated with 7% acetic acid) (80:20, v/v) was used

for berries; pure methanol was used for leaves. Duplicate extractions were made for each sample and the obtained dry extracts (DE) were stored at 4 ºC.

The total soluble solids (TSS) were determined in fresh berries pulp using a digital Atago RX-1000 refractometer. The TSS content varied between 13.4 and 16.3 ºBrix, which is in agreement with a previous report on *M. faya* (14.87 ºBrix)(Spínola et al., 2014); but higher than in *M. rubra* (8.74 – 11.67 ºBrix) (X. Zhang, Huang, Zhang, et al., 2015).

2.3. Chromatographic analysis of methanolic extracts

The chromatographic separation was achieved using a Dionex ultimate 3000 series instrument (Thermo Scientific Inc.) equipped with a binary pump, an autosampler, a column compartment (kept at 30 ºC) and a diode array detector (DAD) hyphenated to a Bruker Esquire model 6000 ion trap mass spectrometer (Bremen, Germany). Separation was carried out on a Phenomenex Gemini C_{18} column (5 µm, 250 x 3.0 mm i.d.) using the same conditions as previously (Spínola et al., 2014).

2.4. Quantification of main polyphenols

For this quantitative analysis, one polyphenol was selected as the standard for each chemical family, and used to determinate relative concentrations by HPLC-DAD, as previously (Spínola et al., 2014). Caffeic and protocatechuic acids were used for hydroxycinnamic and hydroxybenzoic acids, respectively. Anthocyanins standard was C3G. Apigenin, (+)-catechin, ellagic acid, hesperidin and quercetin were the standards used for the flavones, flavanols, ellagitannins, flavanones and flavonols, respectively. Myricitrin (MCT) was used for the quantification of myricetin derivatives. Stock standard solutions (1000 mg L^{-1}) were prepared in methanol and six different concentrations (5 - 100 mg L^{-1}) were used for the calibration curves, plotting peak area versus concentration ($R^2 \geq 0.990$ in

all cases). Concentrations were expressed as mg g^{-1} of DE and total individual phenolic content (TIPC) was defined as the sum of the relative amounts of polyphenols in each extract.

2.5. Total phenolic and flavonoid contents

Total phenolic and flavonoid contents (TPC and TFC, respectively) were determined by colorimetric assays using the procedures detailed in a previous work (Spínola, Pinto, & Castilho, 2018). The amounts of total phenolics and total flavonoids were expressed as mg of gallic acid equivalents (GAE) g^{-1} DE and mg of rutin equivalent (RUE) g^{-1} DE, based on the respective calibration curves.

2.6. In vitro anti-diabetic and anti-obesity assays

α-Glucosidase (yeast and rat), α-amylase, lipase and BSA-glycation inhibition assays were performed using the procedures detailed in a previous work (Spínola et al., 2018).

The human aldose reductase (HAR) inhibitory assay was adapted from a previous publication (Muthenna, Suryanarayana, Gunda, Petrash, & Reddy, 2009). Twenty-five µL of extract solution (serial dilutions) were added to a 96 well-plate (UV-transparent), along with 25 µL of 10 mM DL-glyceraldehyde, 25 µL of HAR solution (1 mg mL^{-1}) and 50 µL of 0.5 mM NADPH. All solutions were prepared in 0.1 M phosphate buffer (pH 6.2) containing 0.2 mM ammonium sulfate and 5 mM β-mercaptoethanol. The decrease in the absorption of NADPH was measured at 340 nm (Victor3 1420 microtiter reader, Perkin-Elmer) over 0 and 20 min of incubation at 37 ºC. Quercetin was used as positive control. The obtained inhibitory activities were expressed as the IC_{50} value (mg mL^{-1} DE).

2.7. In vitro antioxidant activity

The *in vitro* antioxidant activity of *M. faya* extracts was determined by $ABTS^{\bullet+}$, DPPH, nitric oxide (NO) and superoxide (O_2^-) radicals assays, following the same procedures detailed in Spínola et al., (2018). The results were expressed as μmol of Trolox equivalent (TE) g^{-1} DE, based on the Trolox calibration curve.

2.8. Statistical Analysis.

Statistical analysis was performed using SPSS Statistics software v.20 (IBM SPSS Statistics for Windows, IBM Corp., USA). Data of all analysis, in triplicate, are expressed as mean ± standard deviation. A one-way analysis of variance (ANOVA) was performed to determine whether there are any statistically significant differences among parameters experimentally determined, followed by Tukey's HSD post-hoc test. Pearson correlation coefficients (*r*) were determined to corroborate relationships between selected parameters. A value of $p < 0.05$ was considered statistically significant.

3. Results and discussion

In this work, phytochemicals present in eight different *M. faya* samples were identified based on HPLC-ESI-MS^n information, data of authentic standards and published literature. More than 160 compounds were identified in *M. faya* samples (Tables S1-S2 and Figures S1-S2 - Supplementary Material). Anthocyanins and other flavonoids, phenolic acids, and ellagitannins were abundant; organic acids, terpenoids, lignans and oxylipins were also detected, similar to previously established profile (Spínola et al., 2014).

3.1. *Quantification of individual phenolic compounds*

Sixty-six polyphenols were quantified in *M. faya* samples *via* HPLC-DAD (Tables 2 and 3). Only the most abundant compounds were quantified, the low levels of minor components did not allow for an accurate quantification.

201 **TABLE 2 & 3**

202 In this analysis, significant variations ($p < 0.05$) in the phenolic composition of *M.*
203 *faya* from different locations were observed (Tables 2 and 3). These discrepancies are
204 probably due to climacteric and soil conditions. Samples collected in the northeast part of
205 Madeira Island (SX, RJ and PM) lived in different climacteric conditions than those in the
206 west/northwest (MX, FL, ASJ and BV). Additionally, samples from a different archipelago
207 (TC) have grown under completely different environmental conditions that are known to
208 impact qualitative and quantitative measurements (Manganaris, Goulas, Vicente, & Terry,
209 2014).
210 Analysis indicated that anthocyanins were the most abundant phenolics in berries (72.43 –
211 82.81%), followed by flavonols (6.85 – 15.46%), HBAs (3.36 – 5.27%), flavan-3-ols (1.02
212 – 6.04%), ellagitannins (1.88 – 3.54%), HCAs (1.16 – 2.96%) and flavones (0.29 – 0.71%).
213 C3G (**13**) was the absolute predominant phenolic in berries (67.20 – 76.07% of TIPC),
214 which agrees with previous works on *Myrica* spp. berries (Spínola et al., 2014; Yan et al.,
215 2016; X. Zhang, Huang, Zhang, et al., 2015).
216 *M. faya* berries showed higher TIPC than *Sambucus lanceolata* but lower than *Vaccinium*
217 spp. (27.22 and 84.13 - 90.68 mg g^{-1} DE, respectively) (Pinto et al., 2017; Spínola et al.,
218 2018), analysed under the same conditions.
219 *M. faya* leaves were composed mainly by flavonols (26.63 – 45.08%) >
220 ellagitannins (22.30 – 33.59%) ≈ flavan-3-ols (23.61 – 30.60%) > HBAs (4.38 – 8.30%).
221 Flavones and HCAs (< 1.15 %) were minor components (Table 3). In general, MCT (**112**)
222 was the main compound in leaves (13.19 – 24.36%), which is in agreement with previous
223 analysis of *Myrica* species (Spínola et al., 2014; Yang et al., 2011).

Digalloyl(epi)gallocatechin dimer (**75**) (6.00 – 15.73%), casuarin (**62**) (4.58 – 9.70%) gallo-(epi)catechin-*O*-gallate (**81**) (4.02 – 8.29%), and peduncalin I (**31**) (2.26 – 6.32%) were also relevant in leaves In this case, differences in phenolic contents were more notorious than in berries, especially for those collected in a different archipelago. Azorean sample (TC) showed the lowest content in flavonols, especially MCT (**112**), which is the major component in Madeira samples (Table 3). On the other hand, TC has higher HBAs, ellagic acid derivatives and flavanols contents. For example, compounds **46** and **75** more than double the average contents of Madeira samples (Table 3).

3.2. In vitro inhibition of digestive enzymes

Inhibition of carbohydrate-hydrolysing enzymes, such as α-amylase and α-glucosidase, by dietary polyphenols is a reasonable approach to prevent hyperglycaemia in diabetic patients, through reduction of sugar absorption in the intestinal lumen (Boath, Stewart, & McDougall, 2012; Podsędek et al., 2014; Yan et al., 2016).

TABLE 4

The tested extracts were potent yeast α-glucosidase inhibitors, IC_{50} values ranging from 0.18 – 0.83 mg mL^{-1} (Table 4). Leaves were more active than berries and 1-DNJ, a known glucosidase inhibitor agent extracted from mulberry (*Morus alba*) leaves ($p < 0.05$). Additionally, all extracts showed higher inhibitory activities than commercial drug acarbose ($p < 0.05$).

Yeast α-glucosidase is commonly used for anti-diabetic screenings of different berries extracts (Worsztynowicz, Napierała, Białas, Grajek, & Olkowicz, 2014; Yan et al., 2016). However, rat enzyme provides a better model to validate results since it closely mimics the human digestion system (Shai J., Magano R., Lebelo L., & Mogale M., 2011).

In the present work, we used mammal enzyme to mimic human behavior but also yeast counterpart for comparison purposes with other published data. The inhibitory activity of *M. faya* extracts against rat α-glucosidase was lower than against the yeast version of the enzyme (Table 4). According to literature, most yeast α-glucosidase inhibitors show a weaker or no activity on the mammalian enzymes, due to different aminoacids sequences of the catalytic regions of the enzymes (Shai J. et al., 2011). By contrast, acarbose and 1-DNJ displayed superior inhibitory activity on rat α-glucosidase (about 17 and 65 times higher, respectively); being the most effective inhibitors. Hence, the mammalian version the enzyme seems a preferable model to search for compounds with hypoglycaemic activity.

The analysed extracts presented a moderate α-amylase inhibitory capacity (Table 4). All samples exhibited much higher IC_{50} values than acarbose (0.02 mg mL^{-1}) ($p < 0.05$).

For the pancreatic lipase assay (Table 4), significant differences ($p < 0.05$) were found between *M. faya* samples. In this case, C3G standard presented the best inhibitory activities, even higher than orlistat (commercial drug).

The anti-diabetic effects derived of berry fruits might be partly derived through the effects carried out within the gastrointestinal tract, since polyphenols bind to proteins and cause conformational changes and subsequently the enzyme activity is affected (Edirisinghe & Burton-Freeman, 2016). High α-glucoside but lower α-amylase inhibitory potential is preferential in order to avoid certain side effects of acarbose, which are largely due to fermentation of undigested starch in the colon (Boath, Stewart, et al., 2012).

In this work, all tested samples successfully inhibit the assayed enzymes; in general, BV and TC were the most active samples. Similar to present work, other berry species (strawberries, black currants, raspberries, blueberries and rowanberries) showed the potential to modulate starch and fat digestion as they inhibit key digestive enzymes *in vitro*

(Boath, Grussu, Stewart, & McDougall, 2012; Podsędek et al., 2014). Berry extracts from *M. rubra* showed lower inhibitory activities towards yeast α-glucosidase (IC_{50} values ranged from 2.08 – 3.17 mg mL^{-1}) (Yan et al., 2016). On another study, *M. rubra* leaves extracts were also efficient pancreatic lipase inhibitors (IC_{50}: 0.25 – 0.73 mg mL^{-1}) (Y. Zhang et al., 2017).

TIPC was positively correlated with inhibition of targeted digestive enzymes ($r \geq -0.928$). Ellagitannins ($r \geq -0.894$), flavan-3-ols ($r \geq -0.879$) and flavonols ($r \geq -0.872$) were the main contributors for the obtained results. A strong correlation between yeast α-glucosidase inhibition by blueberries extracts and total phenolic amounts was also documented previously ($r \geq -0.880$) (S. Y. Wang et al., 2012).

It is known that α-glucosidase is susceptible to inhibition by a range of berries polyphenols (McDougall et al., 2008). Considering that C3G and MCT were dominant in berries and leaves extracts, respectively, the inhibitory activities of these pure substances were further evaluated in detail. C3G was an effective inhibitor of digestive enzymes (Table 4), being more potent than positive controls ($p < 0.05$) in yeast α-glucosidase and lipase assays. Previously, C3G was reported as an effective lipase inhibitor (Worsztynowicz et al., 2014). In the present work, a good correlation ($r \geq -0.843$) was observed among anthocyanins content and inhibition of digestive enzymes. α-Amylase seemed less sensitive to anthocyanins, which agrees with literature (Edirisinghe & Burton-Freeman, 2016; McDougall et al., 2008). In fact, if the α-amylase data are not considered, correlation is improved ($r \geq -0.947$). Anthocyanins, in particular C3G, are powerful α-glucosidase inhibitors (Akkarachiyasit, Charoenlertkul, Yibchok-Anun, & Adisakwattana, 2010; Boath, Grussu, et al., 2012; Yan et al., 2016). Moreover, a synergistic effect between acarbose and cyanidin glycosides from berries has been documented (Akkarachiyasit et al.,

2010; Boath, Grussu, et al., 2012). This combination might contribute to a reduction of the acarbose dosage needed for the control of hyperglycaemia and, consequently, to reduce undesired effects from its consumption (flatulence, diarrhea, liver toxicity). Notably, *Vaccinium* berries with higher anthocyanins contents displayed inferior inhibitory activities (Spínola et al., 2018) than *M. faya*. The lack of C3G on their composition could justify the obtained results. In this sense, C3G can be considered as one of the main active anti-hyperglycemic agents of *M. faya* berry extracts.

Our findings suggest that MCT is an active inhibitor of glucosidase, but the involvement of other compounds or matrix effects must occur (Yan et al., 2016). For example, fractions from *M. rubra* extracts showed higher inhibitory activities than isolated C3G and MCT, which indicated the involvement of synergistic effects of different polyphenols for the inhibitory effects (Yan et al., 2016).

Inhibition of α-amylase and lipase is more specific, being promoted mainly by tannins (hydrolysable and condensed) (Edirisinghe & Burton-Freeman, 2016; McDougall et al., 2008; Podsędek et al., 2014). Polymers of epigallocatechin-3-*O*-gallate were the main hypolipidaemic agents from *M. rubra* leaves (Y. Zhang et al., 2017). Hence, the higher amounts of tannins (flavan-3-ols and ellagitannins type) in *M. faya* leaves extracts could justify the obtained results (Table 4). The low tannin content of *Vaccinium* species studied by our work group (Spínola et al., 2018) and their weaker inhibitory activity corroborate with this hypothesis.

3.3. In vitro inhibition of human aldose reductase (HAR) and AGEs formation

Hyperglycaemia is responsible for the overactivity of the polyol pathway and non-enzymatic glycation of proteins, which are associated with retinopathy, neuropathy, and

nephropathy in diabetic patients (Grewal, Bhardwaj, Pandita, Lather, & Sekhon, 2016; Veeresham, Rama Rao, & Asres, 2014). In hyperglycaemia conditions, HAR reduces glucose to sorbitol, which is further oxidized to fructose by sorbitol dehydrogenase (Grewal et al., 2016; Suryanarayana, Kumar, Saraswat, Petrash, & Reddy, 2004). This overactivity of this metabolic pathway contributes to the formation of reactive oxygen species (ROS) and di-carbonyls that promote protein glycation (Grewal et al., 2016). Hence, reduction of HAR activity could be a potential therapeutic approach to prevent hyperglycaemia-induced complications (cataracts, neuropathy, and nephropathy) (Grewal et al., 2016; Suryanarayana et al., 2004; Veeresham et al., 2014).

In the present work, *M. faya* extracts inhibited the HAR activity (Table 4), although in lower extent than quercetin standard (positive control) ($p < 0.05$). C3G and MCT showed comparable activities to leaf extracts (Table 4). Except for berries of *Rubus grandifolius*, *M. faya's* were more effective than other berries studied by our research group under the same analytical conditions. *M. faya* leaves showed higher potencies than those of *Vaccinium cylindraceum*, *Elaeagnus umbellata* and *S. lanceolata* (Table S3 – Supplementary Material). TIPC was well correlated with the reported bioactivities ($r \geq -0.962$), ellagitannins and flavan-3-ols being the main contributors ($r \geq -0.921$). The inhibitory activity of Indian gooseberry (*Emblica officinallis*) against aldose reductase activity was also attributed to their ellagitannins content (Suryanarayana et al., 2004).

Protein glycation, also known as the Maillard reaction, is a non-enzymatic reaction that leads to the production of AGEs (Fig. 1). The first product of the glycation is the fast and highly reversible intermediate Schiff base (glucosamine), resulting from the reaction between a sugar in its open chain form and an amino acid from a protein. In the next step, Schiff base are converted to more stable Amadori products, which undergo a series of

reactions (dehydration, oxidation, rearrangement) resulting in a variety of carbonyl compounds. Adducts formed between dicarbonyl compounds and arginine and lysine residues of proteins, are called AGEs (Fig. 1) (Chinchansure et al., 2015; Yeh et al., 2017). AGEs formation promotes to the formation of reactive oxygen species (ROS) and inflammation *via* their binding to receptors for advanced glycation end products (RAGEs), that further increase oxidative damage and activation of pro-inflammatory agents (Wei et al., 2012). The enhanced intra- and extracellular accumulation of these adducts lead to cell dysfunction and is involved in the pathogenesis of retinopathy, neuropathy, and nephropathy (Chinchansure et al., 2015; Yeh et al., 2017). Inhibition of AGEs generation by phenolic compounds has been suggested as a reasonable potential therapeutic target for diabetic complications (Harris et al., 2014; Liu et al., 2011; W. Wang et al., 2011; Yeh et al., 2017).

FIGURE 1

M. faya showed potent inhibitory potential to glycation of BSA *in vitro* (IC_{50} < 3.35 mg mL^{-1} DE for both models) (Table 4). Leaves presented the highest anti-glycation activities ($p < 0.05$), but pure quercetin and C3G standards were the best inhibitors (Table 4). Quercetin has been documented as a powerful agent in the prevention of AGEs formation (Harris et al., 2014; Séro et al., 2013). Additionally, all tested extracts showed stronger inhibitions than aminoguanidine (AMG), an experimental anti-diabetic drug ($p < 0.05$). This might be due to the fact that AMG is not effective in the early stage of protein glycation since it acts as a carbonyl scavenger (Liu et al., 2011). The BSA-fructose model provided lower IC_{50} values (Table 4) than the ribose analogue ($p < 0.05$). This is explained by the higher reactivity of D-ribose in the glycation of proteins, among the reducing sugars

(D-glucose < D-fructose < D-ribose) (Wei et al., 2012). The percentage of open chain form of ribose is higher than in the other sugars due to the instability of the aldofuranose ring, favouring the reaction with the amino groups of proteins and subsequently a faster conversion of its Amadori products (Gugliucci, 2017; W. Wang et al., 2011). From a parallel work, berries of *Vaccinium* spp. (Spínola et al., 2018) and *Rubus grandifolius* (data to be published elsewhere) were more effective than *M. faya*. This is in agreement with the fact that phenolic-richer extracts usually exhibit stronger inhibitory effects (Liu et al., 2011; W. Wang et al., 2011).

The inhibition of AGEs formation was strongly correlated with TIPC ($r \geq -0.993$); ellagitannins, flavanols and flavonols contributed the most for the obtained activities ($r \geq -0.931$). In the present study, C3G showed significant inhibitory activities (Table 4), being comparable to that of quercetin in the fructose model. MCT was also a strong inhibitor of AGEs formation (Table 4), supporting its role in the obtained results.

3.3. In vitro antioxidant activities

The overactivity of the polyol pathway and increased AGEs formation, induced by hyperglycaemia, involves several oxidative processes that cause ROS formation (C.-D. Sun et al., 2012; Wei et al., 2012; Yeh et al., 2017; X. Zhang, Huang, Zhao, et al., 2015). These molecules are harmful in cellular metabolism and cause cell damage, contributing for the development and progression of diabetic complications (Fig. 1) (Grewal et al., 2016; Sancho & Pastore, 2012; S. Y. Wang et al., 2012). Therefore, an antioxidant-rich diet offers yet another perspective in the management/control of T2DM (C. Sun, Huang, Xu, Li, & Chen, 2013; Yan et al., 2016).

TABLE 5

In this work, *in vitro* antioxidant activities of *M. faya* extracts were determined towards synthetic ($ABTS^{\bullet+}$ and $DPPH^{\bullet}$) and biological radicals ($NO^{\bullet}$ and $O_2^{\bullet-}$). Leaves extract presented the highest activities ($p < 0.05$), which is corroborative with the measured TIPC (Table 3). In general, BV and TC samples were the most active extracts, while RJ the least (Table 5).

TIPC was strongly correlated with the obtained antioxidant activities ($r \geq 0.964$), ellagitannins, flavanols and flavonols being the main antioxidant compounds ($r \geq 0.938$). Similar results were found with *M. rubra* (X. Zhang, Huang, Zhang, et al., 2015; X. Zhang, Huang, Zhao, et al., 2015; Y. Zhang, Zhou, et al., 2016) and other berry species (Harris et al., 2014; Podsędek et al., 2014).

The high antioxidant activities of *M. rubra* have been documented in literature (C. Sun et al., 2013; Yan et al., 2016; X. Zhang, Huang, Zhang, et al., 2015). C3G and other flavonoid glycosides seem the key contributors (C.-D. Sun et al., 2012; Yan et al., 2016; X. Zhang, Huang, Zhao, et al., 2015) and we speculate the same behavior for *M. faya*. Leaves of *M. rubra* showed inferior values (2.58 - 3.43 mmol TE g^{-1} DE) towards $ABTS^{\bullet+}$ (Y. Zhang, Chen, et al., 2016; Y. Zhang, Zhou, et al., 2016). For DPPH assay, an opposing trend was observed for berries and leaves (2.92 – 3.97 and 3.00 – 4.93 mmol TE g^{-1} DE, respectively) (X. Zhang, Huang, Zhao, et al., 2015; Y. Zhang, Chen, et al., 2016; Y. Zhang, Zhou, et al., 2016). *S. lanceolata* berries, studied in a parallel work (Pinto et al., 2017), were less active towards free radicals than *M. faya*. *Vaccinium* berries showed the strongest activities (Spínola et al., 2018), while their leaves displayed inferior activities to *M. faya*. The stronger antioxidant activities of *Myrica* species seem linked to the high content of galloyl esters that enhance such properties and confer high radical scavenging properties (C. Sun et al., 2013; Y. Zhang, Zhou, et al., 2016).

4. Conclusions

In this study, the inhibitory potential of *M. faya* on key enzymes linked to T2DM and BSA glycation was evaluated for the first time. The tested extracts showed strong inhibition of glucosidase and AGEs formation and moderate activity towards α-amylase, lipase and aldose reductase (by comparison with reference compounds). This health-promoting properties can be partly attributed to the high antioxidant activities demonstrated by targeted samples against free-radicals. Among the identified compounds, C3G is positively linked to the aforementioned activities of berry extracts. In the case of leaves, we speculate that flavonoids, in particular ellagitannins, are the main anti-diabetic agents. Overall, variations in phenolic compositions in *M. faya* extracts reflect the diversity in potential bioactivities. BV and TC samples are distinguished by the more promising effects and are good candidates for further studies aiming the control/management of T2DM.

Conflict of interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication.

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559 **Figure Captions**

560 **Fig. 1** Non-enzymatic protein glycation pathway leading to the formation of advanced
561 glycation end-products (AGEs) and their role on the pathogenesis of diabetic
562 complications. ROS: reactive oxygen species; RAGEs: receptors for advanced glycation
563 end products.

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573 **Table 1** Information on collection area and date of *M. faya* samples studied in this work.

Sample	Collection Area		Collection Date	Voucher
MX	Machico (32º 44' 18.75''N, 16º 47' 37.92'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13165
FL	Faial (32º 46' 53.23''N, 16º 51' 47.34'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13239
ASJ	Arco de São Jorge (32º 49' 19.10''N, 16º 57' 2.21'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13237
BV	Boaventura (32º 44' 8.33''N, 16º 58' 33.28'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13235
SX	Seixal (32º 48' 10.45''N, 17º 6' 51.23'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13236
RJ	Ribeira da Janela (32º 50' 26.02''N, 17º 10' 4.19'' W)	Madeira Island, Madeira Archipelago	July 2014	MADJ13238
PM	Porto Moniz (32º 51' 17.15''N, 17º 10' 33.27'' W)	Madeira Island, Madeira Archipelago	August 2014	MADJ13280
TC	Terceira (38º 43' 0'N, 27º 4' 0'' W)	Terceira Island, Azores Archipelago	September 2014	MADJ14337

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576 **Table 2** Contents (mg g^{-1} DE) of main polyphenols present in *M. faya* berries extracts. Data
577 represent the mean ± standard deviation (*n* = 3). For compound identification please check Tables
578 S1 – S2 (Supplementary Material).

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Nº	Assigned identification	MX	FL	ASJ	BV	SX	RJ	PM	TC
Anthocyanins									
5	Delphinidin-*O*-hexoside	0.26 ± 0.01^{c}	0.10 ± 0.02^{a}	0.24 ± 0.01^{b}	0.31 ± 0.01^{d}	0.31 ± 0.01^{d}	0.24 ± 0.01^{b}	0.35 ± 0.01^{e}	0.31 ± 0.01^{d}
11	Delphinidin-*O*-hexoside	2.02 ± 0.02^{d}	1.87 ± 0.05^{c}	2.10 ± 0.01^{e}	2.34 ± 0.01^{f}	1.37 ± 0.04^{a}	1.67 ± 0.01^{b}	1.40 ± 0.06^{a}	1.60 ± 0.07^{d}
16	Cyanidin-3-*O*-glucoside	24.47 ± 0.05^{b}	26.54 ± 0.46^{b}	33.19 ± 0.25^{f}	32.01 ± 0.18^{e}	28.53 ± 0.10^{d}	23.73 ± 0.30^{a}	27.33 ± 0.61^{b}	27.20 ± 0.05^{cd}
48	Cyanidin-*O*-pentoside			0.17 ± 0.01					
50	Cyanidin-*O*-hexoside	0.28 ± 0.01^{c}		0.23 ± 0.01^{b}	0.15 ± 0.01^{a}			0.34 ± 0.01^{d}	
69	Cyanidin-*O*-(acetyl)hexoside	0.21 ± 0.01^{a}		0.20 ± 0.01^{a}	0.30 ± 0.01^{b}			0.33 ± 0.01^{c}	0.21 ± 0.08^{a}
Total		**27.24 ± 0.10^{b}**	**28.51 ± 0.54^{b}**	**36.13 ± 0.27^{f}**	**35.11 ± 0.21^{e}**	**30.21 ± 0.07^{c}**	**25.64 ± 0.32^{a}**	**29.75 ± 0.69^{b}**	**29.32 ± 0.13^{d}**
Hydroxycinnamic acids									
10	Caffeoylisocitrate		0.41 ± 0.01^{d}		0.12 ± 0.01^{a}		0.20 ± 0.01^{b}	0.33 ± 0.01^{c}	
56	Coumaric acid-*O*-hexoside	0.01 ± 0.01^{a}	0.02 ± 0.01^{b}				0.01 ± 0.01^{a}		
63	5-*O*-CQA				0.29 ± 0.01^{b}	0.21 ± 0.01^{a}			

7	Dihydro-Co-*O*-								0.08 ±
6	hexoside								0.01
1	B-*p*-tri-CoDOA	0.39 ±	0.69 ±	0.51 ±	0.54 ±	0.38 ±	0.48 ±	0.53 ±	0.79 ±
6		0.01[a]	0.02[d]	0.01[b]	0.01[c]	0.02[a]	0.01[b]	0.01[c]	0.01[e]
4									
Total		**0.40 ± 0.01[a]**	**1.12 ± 0.03[f]**	**0.51 ± 0.01[b]**	**0.95 ± 0.0[2]**	**0.59 ± 0.02[c]**	**0.69 ± 0.01[d]**	**0.86 ± 0.02[e]**	**0.87 ± 0.01[e]**
Hydroxybenzoic acids									
4	Galloyl-*O*-hexoside	0.25 ±	0.21 ±	0.19 ±	0.16 ±	0.21 ±	0.22 ±	0.18 ±	0.14 ±
		0.01[d]	0.01[c]	0.0[1]	0.01[a]	0.01[c]	0.01[c]	0.01[ab]	0.01[a]
1	Galloyl-*O*-hexoside	1.11 ±	1.03 ±	1.31 ±	1.45 ±	1.53 ±	1.30 ±	1.00 ±	1.08 ±
2		0.03[b]	0.01[a]	0.02[c]	0.03[d]	0.04[e]	0.01[c]	0.01[a]	0.01[f]
1	Galloylquinic acid			0.20 ±					
5				0.01					
2	Digalloyl-*O*-hexoside	0.39 ±	0.27 ±	0.20 ±	0.20 ±	0.27 ±	0.21 ±	0.10 ±	0.69 ±
7		0.01[d]	0.08[bc]	0.01[b]	0.01[b]	0.01[c]	0.01[b]	0.01[a]	0.01[e]
8	Trigalloyl glucose		0.24 ±		0.06 ±				
8			0.01[b]		0.01[a]				
1	Methyl gallate								0.05 ±
6	derivative								0.01
1									
Total		**1.75 ± 0.05[b]**	**1.75 ± 0.03[e]**	**1.90 ± 0.03[e]**	**1.87 ± 0.04[d]**	**2.01 ± 0.05[ef]**	**1.73 ± 0.02[c]**	**1.28 ± 0.01[a]**	**1.96 ± 0.07[g]**
Flavonols									
8	Dihydro-K-*O*-								0.29 ±
3	hexoside								0.01
9	M-*O*-hexoside	0.22 ±	0.16 ±	0.26 ±	0.25 ±	0.29 ±	0.24 ±	0.12 ±	0.25 ±

1		0.01^{c}	0.01^{b}	0.01^{de}	0.01^{d}	0.01^{f}	0.01^{cd}	0.01^{a}	0.01^{d}
9 2	M-*O*-(galloyl)hexoside	0.14 ± 0.01^{cd}	0.21 ± 0.01^{e}	0.14 ± 0.01^{cd}	0.09 ± 0.01^{a}	0.10 ± 0.01^{b}	0.12 ± 0.01^{bc}	0.09 ± 0.01^{a}	0.12 ± 0.01^{bc}
9 3	Ellagic acid-*O*-pentoside	0.16 ± 0.01^{c}		0.06 ± 0.01^{a}				0.11 ± 0.01^{b}	0.22 ± 0.01^{d}
1 0 8	M-*O*-pentoside		0.49 ± 0.01^{c}					0.11 ± 0.01^{a}	0.18 ±0.01^{b}
1 1 2	Myricitrin	1.36 ± 0.02^{c}	1.09 ± 0.02^{a}	1.13 ± 0.03^{a}	1.20 ± 0.02^{b}	1.53 ± 0.02^{d}	1.37 ± 0.03^{c}	1.38 ± 0.05^{c}	1.23 ± 0.02^{b}
1 2 1	Q-*O*-hexoside	0.07 ± 0.01^{a}		0.18 ± 0.01^{c}	0.12 ± 0.01^{b}	0.45 ± 0.01^{e}	0.17 ± 0.01^{c}	0.07 ± 0.01^{a}	0.28 ± 0.01^{d}
1 2 2	Q-*O*-(galloyl)hexoside	0.27 ± 0.01^{d}		0.10 ± 0.01^{a}	0.10 ± 0.01^{a}	0.17 ± 0.02^{b}	0.15 ± 0.01^{b}	0.19 ± 0.01^{c}	0.18 ± 0.01^{c}
1 2 7	Q-*O*-(galloyl)hexoside	0.20 ± 0.01^{b}		0.22 ± 0.01^{bc}	0.15 ± 0.01^{a}				0.21 ± 0.01^{b}
1 3 1	K-*O*-hexoside	0.15 ± 0.01^{a}	0.26 ± 0.01^{c}	0.25 ± 0.02^{c}	0.32 ± 0.01^{d}	0.27 ± 0.01^{c}	0.19 ± 0.01^{b}	0.14 ± 0.01^{a}	0.14 ± 0.01^{a}
1 3 6	K-*O*-hexoside	0.60 ± 0.01^{c}			0.20 ± 0.01^{a}	0.19 ± 0.01^{a}		0.27 ± 0.01^{b}	
1 3 7	Q-*O*-deoxyhexoside				0.24 ± 0.01^{a}			0.25 ± 0.01^{ab}	0.27 ± 0.01^{b}

139	K-*O*-(galloyl)hexoside	0.35 ± 0.01[b]	0.47 ± 0.03[c]	0.43 ± 0.01[c]	0.27 ± 0.01[a]	0.82 ± 0.01[d]		0.84 ± 0.01[d]
140	Dimethyl-M-*O*-pentoside						0.25 ± 0.01	
145	M-*O*-(galloyl)deoxyhexoside	0.42 ± 0.01[e]	0.38 ± 0.01[c]	0.35 ± 0.01[cd]	0.30 ± 0.02[b]	0.38 ± 0.01[d]		0.19 ± 0.01[a]
151	Q-*O*-(galloyl)deoxyhexoside	0.40 ± 0.01[c]		0.21 ± 0.01[a]	0.27 ± 0.01[b]		0.60 ± 0.01[e]	0.46 ± 0.01[d]
153	Q-*O*-(galloyl)deoxyhexoside		0.38 ± 0.02[b]	0.28 ± 0.01[a]		1.13 ± 0.01[d]	0.40 ± 0.01[b]	1.09 ± 0.01[c]
160	Quercetin							0.31 ± 0.01
Total		**4.34 ± 0.08[e]**	**3.44 ± 0.15[b]**	**3.61 ± 0.08[c]**	**2.93 ± 0.05[a]**	**3.57 ± 0.07[bc]**	**4.57 ± 0.13[e]**	**3.98 ± 0.08[d]**	**6.26 ± 0.20[f]**
Flavanols								
43	Gallo(epi)catechin	0.20 ± 0.01[ab]	0.76 ± 0.03[e]	0.12 ± 0.01[a]	0.11 ± 0.01[a]		0.12 ± 0.07[a]	0.23 ± 0.01[c]	0.34 ± 0.01[d]
45	Gallocatechin dimer			0.16 ± 0.01[a]	0.26 ± 0.01[b]				
71	Digalloyl(epi)gallocatechin dimer		0.50 ± 0.01[c]	0.38 ± 0.01[b]	0.32 ± 0.01[a]		0.37 ± 0.01[b]	0.58 ± 0.01[d]	
77	(+)Catechin	0.16 ±					0.25 ±		

9		0.01[a]				0.01[b]		
8	Gallo(epi)catechin-	0.04 ±	0.12 ±		0.05 ±	0.06 ±	0.05 ±	
1	*O*-gallate	0.01[a]	0.01[c]		0.01[ab]	0.01[b]	0.01[ab]	
8	Digallocatechin		0.45 ±			0.14 ±		0.28 ±
7	derivative		0.01[c]			0.01[a]		0.01[b]
9	Gallo(epi)catechin-*O*-gallate		0.46 ±			0.25 ±		
9			0.01[b]			0.01[a]		
Total		**0.40 ± 0.01[a]**	**2.29 ± 0.07[e]**	**0.66 ± 0.02[b]**	**0.74 ± 0.02[c]**	**0.39 ± 0.01[a]**	**0.80 ± 0.09[cd]**	**0.86 ± 0.02[d]**	**0.62 ± 0.01[b]**
Flavones								
8	Tricin-*O*-hexoside	0.25 ±					0.11 ±	0.21 ±
6	derivative	0.01[c]					0.01[a]	0.01[b]
Total		**0.25 ± 0.01[c]**					**0.11 ± 0.01[a]**	**0.21 ± 0.01[b]**
Ellagitannins								
3	Pedunculagin I	0.11 ±		0.39 ±	0.46 ±	0.24 ±	0.24 ±	0.18 ±	
1		0.01[a]		0.01[d]	0.01[e]	0.01[c]	0.01[c]	0.01[b]	
3	Pedunculagin I	0.13 ±	0. 19 ±		0.17 ±	0.37 ±	0.42 ±	0.23 ±	0.47 ±
9		0.01[a]	0.01		0.01[b]	0.01[d]	0.02[e]	0.01[c]	0.01[f]
5	Casuarinin	0.26 ±			0.14 ±	0.20 ±	0.21 ±	0.23 ±	
3		0.01[d]			0.01[a]	0.01[b]	0.01[b]	0.01[bc]	
6	Casuarinin	0.18 ±	0.44 ±		0.16 ±			0.06 ±	0.23 ±
5		0.01[bc]	0.01[e]		0.01[b]			0.01[a]	0.01[d]
6	Ellagitannin			0.26 ±	0.21 ±		0.16 ±		0.22 ±
7				0.01[d]	0.01[b]		0.01[a]		0.01[bc]
8	HHDP-*O*-hexoside	0.05 ±	0.14 ±			0.25 ±	0.06 ±		
0		0.01[a]	0.01[c]			0.01[d]	0.01[ab]		

8	Ellagitannin	0.10 ±						0.12 ±	
9		0.01[a]						0.01[ab]	
9	Ellagic acid-*O*-			0.17 ±		0.29 ±		0.22 ±	0.32 ±
3	pentoside			0.01[a]		0.01[c]		0.02[b]	0.02[cd]
Total		**0.83 ± 0.02[b]**	**0.77 ± 0.01[a]**	**0.82 ± 0.01[b]**	**1.14 ± 0.02[d]**	**1.35 ± 0.03[f]**	**1.09 ± 0.04[c]**	**1.04 ± 0.03[c]**	**1.24 ± 0.02[e]**
TIPC[1]		**35.20 ± 0.66[a]**	**37.88 ± 0.77[b]**	**42.74 ± 0.90[d]**	**43.63 ± 0.78[d]**	**38.12 ± 0.92[bc]**	**34.52 ± 0.57[a]**	**37.88 ± 0.85[b]**	**40.48 ± 0.25[c]**
TPC[2]		44.86 ± 1.04[a]	43.04 ± 1.50[a]	59.09 ± 2.81[d]	62.94 ± 1.93[e]	50.21 ± 2.69[c]	47.20 ± 1.89[b]	51.18 ± 0.84[c]	53.86 ± 1.92[c]
TFC[3]		8.02 ± 0.39[cd]	7.73 ± 0.18[c]	8.51 ± 0.29[d]	9.24 ± 0.43[e]	7.47 ± 0.23[b]	7.66 ± 0.18b[c]	6.68 ± 0.24[a]	10.74 ± 0.52[f]

[1]Total individual phenolic content; [2]determined by the Folin-Ciocalteau method (mg GAE g^{-1} DE); [3]determined by the aluminium chloride method (mg RUE g^{-1} DE). MX: Machico; FL: Faial; ASJ: Arco de São Jorge; BV: Boaventura; SX: Seixal; PM: Porto Moniz; TC: Terceira; B: benzoyl; HHDP: Hexahydroxydiphenoyl; CoDOA: coumaroyl-2,7-anhydro-3- deoxy-2-octulopyranosonic acid; K: Kaempferol; M: Myricetin; Q: Quercetin. Bold values represent the sum of each type of components. Means in the same line not sharing the same letter are significantly different at $p < 0.05$ probability level.

588 **Table 3** Contents (mg g^{-1} DE) of main polyphenols present in *M. faya* leaves extracts. Data
589 represent the mean ± standard deviation (n = 3). For compound identification please check Tables
590 S1 – S2 (Supplementary Material).

591

No	Assigned identification	MX	FL	ASJ	BV	SX	RJ	PM	TC
Hydroxycinnamic acids									
56	Co-*O*-hexoside								0.21 ± 0.01
14	B-*p*-tri-CoDOA	0.07± 0.01^{cd}	0.03 ± 0.01^{a}	0.05 ± 0.01^{bc}	0.04 ± 0.01^{ab}		0.08 ± 0.01^{de}	0.04 ± 0.01^{ab}	0.03 ± 0.01^{a}
Total		**0.07± 0.01^{cd}**	**0.03 ± 0.01^{a}**	**0.05 ± 0.01^{bc}**	**0.04 ± 0.01^{ab}**		**0.08 ± 0.01^{de}**	**0.04 ± 0.01^{ab}**	**0.24 ± 0.01^{f}**
Hydroxybenzoic acids									
12	Galloyl-*O*-hexoside	3.13 ± 0.06^{e}	3.25 ± 0.10^{ef}	3.58 ± 0.04^{gh}	2.12 ± 0.03^{ab}	2.76 ± 0.01^{c}	1.99 ± 0.08^{a}	2.97 ± 0.05^{d}	3.45 ± 0.29^{g}
15	Galloylquinic acid	2.08 ± 0.09^{d}	2.65 ± 0.06^{f}	2.39 ± 0.05^{e}	1.42 ± 0.01^{a}	1.61 ± 0.01^{b}	2.02 ± 0.04^{d}	1.76 ± 0.07^{c}	3.19 ± 0.02^{g}
18	Gallic acid	1.67 ± 0.03^{d}		0.79 ± 0.02^{b}	0.83 ± 0.01^{bc}	0.94 ± 0.18^{c}	0.56 ± 0.02^{a}		
88	Trigalloyl-*O*-hexoside	0.22 ± 0.01^{c}	0.23 ± 0.01^{c}	0.25 ± 0.01^{cd}	0.16 ± 0.01^{b}	0.18 ± 0.01^{b}	0.12 ± 0.01^{a}	0.10 ± 0.01^{a}	0.49 ± 0.03^{e}
106	Tetragalloyl-*O*-hexoside			0.47 ± 0.02^{b}				0.12 ± 0.01^{a}	1.13 ± 0.03^{c}
Total		**7.10 ± 0.29^{e}**	**6.13 ± 0.35^{d}**	**6.69 ± 0.25^{d}**	**4.49 ± 0.09^{a}**	**5.38 ± 0.04^{bc}**	**5.07 ± 0.36^{b}**	**5.51 ± 0.23^{c}**	**8.36 ± 0.50^{f}**
Flavonols									
91	M-*O*-hexoside	3.11 ± 0.09^{d}	2.43 ± 0.18^{c}	3.58 ± 0.16^{e}	5.39 ± 0.17^{f}	3.10 ± 0.01^{d}	1.75 ± 0.06^{b}	1.17 ± 0.01^{a}	1.22 ± 0.04^{a}
92	M-*O*-(galloyl)hexoside	3.70 ± 0.04^{d}	2.84 ± 0.06^{b}	7.23 ± 0.32^{g}	9.77 ± 0.15^{h}	6.09 ± 0.08^{f}	3.38 ± 0.03^{c}	2.32 ± 0.08^{a}	4.19 ± 0.03^{e}
104	Quercetin-*O*-rutinoside	0.64 ± 0.02^{d}	0.57 ± 0.01^{c}		0.23 ± 0.01^{a}	0.34 ± 0.01^{b}	0.78 ± 0.02^{e}	0.65 ± 0.01^{d}	

10	M-*O*-pentoside							0.57 ± 0.01[b]	0.14 ± 0.01[a]
11	Myricitrin	15.91 ± 0.03[b]	21.57 ± 0.53[f]	19.59 ± 0.09[e]	18.47 ± 0.38[d]	23.55 ± 0.11[g]	17.59 ± 0.09[c]	21.66 ± 0.28[f]	13.27 ± 0.31[a]
12	Q-*O*-hexoside	0.20 ± 0.01[b]	0.28 ± 0.01[c]	0.12 ± 0.01[a]	0.33 ± 0.01[d]	0.19 ± 0.01[b]	0.27 ± 0.01[c]	0.35 ± 0.01[d]	0.70 ± 0.01[e]
13	Q-*O*-(galloyl)hexoside	2.00 ± 0.06[cd]	1.97 ± 0.07[c]	2.88 ± 0.05[f]	2.66 ±0.03[e]	3.75 ± 0.01[g]	1.83 ± 0.07[c]	1.52 ± 0.03[b]	0.57 ± 0.02[a]
14	K-*O*-hexoside	0.68 ± 0.03[c]	0.62 ± 0.01[b]	0.86 ± 0.02[f]	0.77 ± 0.03[e]	0.71 ± 0.02[cd]	0.77 ± 0.01[e]	0.60 ± 0.02[b]	0.44 ± 0.01[a]
15	Q-*O*-deoxyhexoside	0.60 ± 0.03[ab]	0.79 ± 0.03[c]	1.15 ± 0.01[e]	1.42 ± 0.03[f]	0.56 ± 0.01[a]	0.91 ± 0.03[d]	0.88 ± 0.03[d]	0.57 ± 0.02[a]
16	K-*O*-(galloyl)hexoside	0.37 ± 0.02[a]	0.51 ± 0.01[c]	0.83 ± 0.01[e]	0.43 ± 0.01[b]	0.55 ± 0.01[c]	0.33 ± 0.01[a]	0.55 ± 0.01[c]	0.63 ± 0.01[d]
17	Dimethyl-M-*O*-pentoside	0.32 ± 0.01[c]			0.19 ± 0.01[a]			0.25 ± 0.01[b]	
18	M-*O*-(galloyl)hexoside	0.20 ± 0.01[a]		0.24 ± 0.01[b]	0.18 ± 0.01[a]		0.42 ± 0.02[d]	0.34 ± 0.01[c]	
19	K-*O*-deoxyhexoside	0.76 ± 0.01[b]	0.58 ± 0.01[a]	0.90 ± 0.03[c]	1.24 ± 0.04[e]	0.60 ± 0.01[a]	0.76 ± 0.03[b]	1.11 ± 0.04[d]	1.17 ± 0.02[d]
20	M-*O*-(galloyl)deoxyhexoside	3.00 ± 0.08[d]	2.89 ± 0.13[c]	2.32 ± 0.07[b]	1.17 ± 0.02[a]	3.73 ± 0.04[f]	2.92 ± 0.03[cd]	2.26 ± 0.06[b]	3.24 ± 0.11[e]
21	Q-*O*-(galloyl)deoxyhexoside	1.16 ± 0.03[a]	1.27 ± 0.46[ab]	1.84 ± 0.02[d]	3.61 ± 0.12[e]		1.06 ± 0.10[a]	1.40 ± 0.02[c]	
22	Q-*O*-			0.23 ±	0.17 ±				0.36 ±

5	(acetyl)deoxyhexoside			0.01[b]	0.01[a]				0.01[c]
2									
1	Q-*O*-	0.13 ±	0.16 ±	0.22 ±		0.33 ±	0.25 ±	0.14 ±	0.13 ±
5	(galloyl)deoxyhexoside	0.01[a]	0.01[ab]	0.01[c]		0.01[d]	0.01[c]	0.01[a]	0.01[a]
3									
1	Quercetin								0.16 ±
6									0.01
0									
Total		**32.78 ± 0.5[b]**	**36.48 ± 1.53[c]**	**41.99 ± 0.86[d]**	**46.04 ± 1.13[e]**	**43.50 ± 0.36[d]**	**33.02 ± 0.52[b]**	**35.77 ± 0.64[c]**	**26.79 ± 0.63[a]**
Flavanols									
3	Gallocatechin	0.26 ±	0.26 ±	0.42 ±		0.36 ±	0.20 ±	0.61 ±	0.31 ±
2		0.01[b]	0.03[b]	0.02[e]		0.02[d]	0.01[a]	0.01[f]	0.02[c]
4	Gallocatechin	2.38 ±	3.30 ±		1.28 ±				
3		0.01[b]	0.06[c]		0.05[a]				
4	Gallo(epi)catechin-	2.52 ±	3.63 ±	6.44 ±	5.84 ±	5.68 ±	4.69 ±	4.92 ±	10.24 ±
6	Gallo(epi)catechin-*O*-gallate	0.01[a]	0.03[b]	0.04[e]	0.03[d]	0.10[d]	0.03[c]	0.12[c]	0.28[f]
7	Digalloyl(epi)gallocatechi	2.68 ±	2.28 ±	0.55 ±			3.33 ±	7.54 ±	
1	n dimer	0.39[e]	0.28[d]	0.02[a]			0.09[b]	0.26[c]	
7	Digalloyl(epi)gallocatechi	6.93 ±	5.51 ±	6.00 ±	10.63 ±	7.60 ±	8.29 ±	6.16 ±	15.82 ±
5	n dimer	0.19[d]	0.17[a]	0.13[c]	0.40[g]	0.07[e]	0.08[f]	0.18[b]	0.22[h]
8	Gallo(epi)catechin-*O*-	7.25 ±	6.74 ±	6.54 ±	7.20 ±	6.06 ±	6.36 ±	3.89 ±	4.41 ±
1	gallate	0.07[f]	0.19[de]	0.12[d]	0.06[f]	0.01[c]	0.22[d]	0.10[a]	0.12[b]
8	Digallo(epi)catechin	2.03 ±	2.96 ±	2.04 ±	0.70 ±	2.77 ±	1.48 ±	2.99 ±	
7	derivative	0.05[c]	0.12[e]	0.09[c]	0.02[a]	0.02[d]	0.11[b]	0.11[e]	
9	Gallo(epi)catechin-*O*-	2.16 ±	1.82 ±		3.43 ±	1.71 ±	2.00 ±	1.93 ±	
9	gallate	0.02[c]	0.01[a]		0.07[d]	0.07[a]	0.06[b]	0.03[b]	
Total		**26.21 ± 0.67[c]**	**26.50 ± 0.70[c]**	**21.99 ± 0.61[a]**	**28.08 ± 0.59[d]**	**24.18 ± 0.52[b]**	**26.35 ± 0.39[c]**	**28.04 ± 0.96[d]**	**30.78 ± 0.50[e]**
Flavones									
8	Tricin-*O*-hexoside		1.06 ±		0.87 ±				0.64 ±
6	derivative		0.01[c]		0.01[b]				0.01[a]
9	Tricin-*O*-hexoside	0.41 ±				0.43 ±			
4	derivative	0.01[a]				0.01[a]			
Total		**0.41 ± 0.01[a]**	**1.06 ± 0.01[d]**		**0.87 ± 0.01[c]**	**0.43 ± 0.01[a]**			**0.64 ± 0.01[b]**

Ellagic acid									
deriatives/Ellagitannins									
8	HHDP-*O*-hexoside		0.27 ± 0.01[a]	0.46 ± 0.02[c]	0.23 ± 0.01[a]				0.33 ± 0.01[b]
1	Pedunculagin I derivative								0.31 ±
9									0.01
2	Pedunculagin I					3.61 ±		2.24 ±	
2						0.13[b]		0.22[a]	
3	Pedunculagin I	3.62 ±	4.09 ±	3.36 ±	3.07 ±	2.24 ±	3.00 ±	4.34 ±	6.44 ±
1		0.01[d]	0.18[e]	0.07[c]	0.10[b]	0.01[a]	0.01[b]	0.16[e]	0.27[f]
3	Casuarinin								1.07 ±
7									0.04
3	HHDP-*O*-hexoside			0.30 ±	0.47 ±			0.49 ±	
8				0.01[a]	0.01[b]			0.01[b]	
3	Pedunculagin I	3.23 ±	2.73 ±	4.45 ±	3.78 ±	3.45 ±	4.12 ±	3.96 ±	5.94 ±
9		0.13[b]	0.16[a]	0.01[e]	0.18[c]	0.11[b]	0.18[e]	0.09[cd]	0.28[f]
4	Ellagic acid derivative	2.89 ±	3.74 ±	2.63 ±	2.61 ±	3.91 ±	2.58 ±	4.52 ±	2.50 ±
9		0.01[c]	0.13[d]	0.02[ab]	0.14[e]	0.11[d]	0.05[a]	0.11[e]	0.01[a]
5	Casuarinin	1.44 ±	1.14 ±	2.00 ±	2.93 ±	2.19 ±	0.94 ±	2.80 ±	1.34 ±
3		0.02[d]	0.05[b]	0.01[e]	0.01[g]	0.08[f]	0.04[a]	0.06[g]	0.04[c]
6	Casuarinin	6.35 ±	6.56 ±	5.04 ±	5.74 ±	4.94 ±	3.82 ±	5.54 ±	9.76 ±
2		0.05[d]	0.09[e]	0.23[b]	0.20[c]	0.04[b]	0.25[a]	0.33[bc]	0.27[f]
6	Casuarinin	0.99 ±	1.37 ±			0.50 ±	1.64 ±		0.72 ±
5		0.01[c]	0.04[d]			0.01[a]	0.06[e]		0.01[b]
7	Pedunculagin II								0.31 ±
3									0.01
8	HHDP-*O*-hexoside	0.95 ±	0.66 ±	0.84 ±	1.16 ±	1.18 ±	0.83 ±	0.90 ±	2.59 ±
0		0.02[c]	0.03[a]	0.03[b]	0.03[d]	0.06[d]	0.03[b]	0.01[c]	0.05[e]
8	Ellagitannin	1.44 ±	1.11 ±	2.46 ±	2.84 ±	1.19 ±	2.03 ±	1.31 ±	1.17 ±
9		0.01[d]	0.05[a]	0.01[f]	0.12[g]	0.05[b]	0.02[e]	0.04[c]	0.06[g]
9	Ellagic acid-*O*-pentoside			0.89 ±				1.15 ±	1.31 ±
3				0.01[a]				0.01[b]	0.07[c]
Total		**20.91 ± 0.27[b]**	**21.67 ± 0.86[bc]**	**22.43 ± 0.28[c]**	**22.83 ± 1.05[c]**	**23.21 ± 0.59[c]**	**18.96 ± 0.64[a]**	**27.25 ± 0.79[d]**	**33.79 ± 1.12[e]**
TIPC[1]		**87.48 ± 1.26[b]**	**91.87 ± 1.46[c]**	**93.15 ± 2.16[c]**	**102.35 ± 2.00[e]**	**96.70 ± 1.25[d]**	**83.45 ± 1.91[a]**	**96.61 ± 2.08[d]**	**100.60 ± 1.49[e]**
TPC[2]		212.43	226.49	248.76	251.5 ±	232.64	219.29	239.25	257.76

	± 3.68[a]	± 6.99[bc]	± 5.18[e]	5.71[ef]	± 3.33[c]	± 3.97[ab]	± 4.62[d]	± 3.09[e]
TFC[3]	57.91 ± 1.01[b]	61.57 ± 2.04[c]	63.89 ± 1.82[cd]	67.38 ± 1.50[d]	65.35 ± 1.39[d]	54.89 ± 1.52[a]	55.31 ± 2.57[ab]	71.41 ± 1.70[e]

[1]Total individual phenolic content; [2]determined by the Folin-Ciocalteau method (mg GAE g^{-1} DE); [3]determined by the aluminium chloride method (mg RUE g^{-1} DE). MX: Machico; FL: Faial; ASJ: Arco de São Jorge; BV: Boaventura; SX: Seixal; PM: Porto Moniz; TC: Terceira; B: benzoyl; HHDP: Hexahydroxydiphenoyl; DOA: deoxy-2-octulopyranosonic acid. Bold values represent the sum of each type of components. Means in the same line not sharing the same letter are significantly different at $p < 0.05$ probability level.

601 **Table 4** *In vitro* inhibitory activities (IC_{50} : mg mL^{-1}) of *M. faya* extracts towards digestive
602 enzymes, human aldose reductase and bovine serum albumin (BSA) glycation. Data represent the
603 mean ± standard deviation (n = 3).

	α-Glucosidase		**α-Amylase**	**Lipase**	**Aldose reductase**	**BSA-glycation**	
	Yeast	Rat				Ribose	Fructose
Berries							
MX	0.76 ± 0.01^{g}	4.51 ± 0.13^{j}	1.38 ± 0.02^{i}	5.75 ± 0.19^{k}	0.91 ± 0.04^{k}	3.23 ± 0.06^{l}	1.85 ± 0.02^{h}
FL	0.75 ± 0.01^{g}	4.22 ± 0.11^{j}	1.25 ± 0.03^{g}	5.30 ± 0.20^{ij}	0.84 ± 0.03^{j}	2.99 ± 0.09^{j}	1.72 ± 0.04^{g}
ASJ	0.69 ± 0.02^{f}	4.35 ± 0.15^{j}	1.19 ± 0.02^{f}	4.83 ± 0.13^{h}	0.80 ± 0.02^{i}	2.72 ± 0.03^{i}	1.59 ± 0.02^{e}
BV	0.72 ± 0.01^{f}	3.78 ± 0.11^{i}	1.08 ± 0.03^{g}	4.98 ± 0.10^{ij}	0.72 ± 0.03^{h}	2.67 ± 0.11^{j}	1.66 ± 0.05^{f}
SX	0.78 ± 0.02^{g}	4.40 ± 0.11^{j}	1.22 ± 0.03^{hi}	5.78 ± 0.10^{k}	0.98 ± 0.02^{l}	3.07 ± 0.08^{jk}	1.80 ± 0.04^{g}
RJ	0.83 ± 0.03^{h}	4.63 ± 0.10^{k}	1.68 ± 0.02^{j}	6.15 ± 0.2^{l}	1.05 ± 0.02^{m}	3.35 ± 0.09^{l}	1.79 ± 0.03^{g}
PM	0.71 ± 0.03^{g}	3.85 ± 0.12^{i}	1.53 ± 0.04^{h}	5.46 ± 0.2^{j}	0.88 ± 0.03^{k}	2.94 ± 0.07^{j}	1.74 ± 0.03^{f}
TC	0.73 ± 0.02^{g}	3.91 ± 0.14^{i}	0.99 ± 0.02^{f}	5.26 ± 0.12^{h}	0.74 ± 0.03^{h}	2.86 ± 0.04^{i}	1.69 ± 0.02^{e}
Leaves							
MX	0.31 ± 0.01^{d}	1.41 ± 0.05^{g}	0.66 ± 0.01^{d}	2.04 ± 0.07^{e}	0.50 ± 0.02^{g}	1.53 ± 0.02^{g}	0.77 ± 0.02^{c}
FL	0.27 ± 0.01^{c}	1.29 ±	0.65 ± 0.01^{d}	2.24 ± 0.05^{f}	0.45 ±	1.42 ± 0.04^{f}	0.83 ±

		0.08[f]			0.02[f]		0.01[d]
ASJ	0.21 ± 0.01[b]	1.13 ± 0.05[e]	0.57 ± 0.02[e]	1.93 ± 0.10[e]	0.40 ± 0.03[d]	1.38 ± 0.02[f]	0.67 ± 0.01[c]
BV	0.20 ± 0.01[a]	1.16 ± 0.06[e]	0.61 ± 0.02[b]	1.60 ± 0.02[d]	0.37 ± 0.01[c]	1.15 ± 0.05[d]	0.68 ± 0.02[b]
SX	0.27 ± 0.01[ab]	1.26 ± 0.03[f]	0.63 ± 0.02[c]	1.68 ± 0.05[d]	0.40 ± 0.03[d]	1.33 ± 0.04[e]	0.73 ± 0.01[c]
RJ	0.33 ± 0.01[e]	1.53 ± 0.04[h]	0.67 ± 0.03[e]	2.34 ± 0.04[g]	0.52 ± 0.02[g]	1.58 ± 0.03[h]	0.87 ± 0.02[d]
PM	0.25 ± 0.01[b]	1.35 ± 0.07[fg]	0.76 ± 0.01[c]	1.89 ± 0.06[e]	0.43 ± 0.01[ef]	1.30 ± 0.04[e]	0.76 ± 0.0[c]
TC	0.18 ± 0.01[a]	1.09 ± 0.06[e]	0.58 ± 0.01[b]	1.49 ± 0.02[c]	0.36 ± 0.01[b]	1.21 ± 0.02[c]	0.65 ± 0.02[b]
Reference compounds							
Acarbose	2.06 ± 0.04[i]	0.12 ± 0.01[b]	0.02 ± 0.001[a]	-	-	-	-
1-DNJ	0.65 ± 0.02[g]	0.01 ± 0.01[a]	-	-	-	-	-
Orlistat	-	-	-	0.47 ± 0.02[b]	-	-	-
AMG	-	-	-	-	-	9.56 ± 0.36[m]	2.29 ± 0.13[i]
Quercetin	-	-	-	-	0.10 ± 0.01[a]	0.11 ± 0.01[a]	0.24 ± 0.02[a]
C3G	0.38 ± 0.02[e]	0.23 ± 0.01[c]	0.97 ± 0.03[j]	0.30 ± 0.01[a]	0.38 ± 0.01[bc]	0.24 ± 0.01[b]	0.18 ± 0.01[a]

Myricitrin	0.63 ± 0.04^{fg}	0.39 ± 0.02^{d}	2.02 ± 0.10^{k}	0.51 ± 0.03^{b}	0.49 ± 0.02^{g}	0.27 ± 0.02^{b}	0.22 ± 0.01^{a}

MX: Machico; FL: Faial; ASJ: Arco de S. Jorge; BV: Boaventura; SX: Seixal; RJ: Ribeira da Janela; PM: Porto Moniz; TC: Terceira. 1-DNJ: 1-Deoxynojirimycin; CBE: Conduritol B epoxide; AMG: Aminoguanidine; C3G: Cyanidin-3-*O*-glucoside; N.I.: no inhibition. Means in the same column not sharing the same letter are significantly different at $p < 0.05$ probability level.

610 **Table 5** Antioxidant activities of *M. faya* extracts measured by four different *in vitro* assays (results
611 are expressed as mmol TE g^{-1} DE). Data represent the mean ± standard deviation (n = 3).

		ABTS	DPPH	NO	O_2^-
Berries					
	MX	1.20 ± 0.04^{b}	0.35 ± 0.01^{a}	0.21 ± 0.02^{ab}	0.19 ± 0.01^{bc}
	FL	1.30 ± 0.04^{c}	0.43 ± 0.01^{c}	0.24 ± 0.02^{d}	0.20 ± 0.01^{c}
	ASJ	1.43 ± 0.05^{e}	0.47 ± 0.01^{d}	0.31 ± 0.01^{f}	0.21 ± 0.01^{d}
	BV	1.50 ± 0.04^{g}	0.54 ± 0.02^{f}	0.25 ± 0.01^{d}	0.23 ± 0.02^{e}
	SX	1.32 ± 0.04^{cd}	0.43 ± 0.01^{c}	0.23 ± 0.01^{c}	0.19 ± 0.01^{bc}
	RJ	1.14 ± 0.04^{a}	0.35 ± 0.01^{a}	0.19 ± 0.01^{a}	0.17 ± 0.01^{a}
	PM	1.36 ± 0.04^{d}	0.41 ± 0.01^{bc}	0.22 ± 0.02^{bc}	0.18 ± 0.01^{a}
	TC	1.45 ± 0.05^{fg}	0.50 ± 0.02^{e}	0.28 ± 0.01^{e}	0.21 ± 0.01^{d}
Leaves					
	MX	7.89 ± 0.37^{i}	1.72 ± 0.03^{i}	0.82 ± 0.02^{hi}	0.43 ± 0.01^{f}
	FL	7.95 ± 0.19^{j}	1.75 ± 0.04^{ijk}	0.84 ± 0.02^{ij}	0.45 ± 0.02^{g}
	ASJ	8.33 ± 0.17^{l}	1.78 ± 0.04^{k}	0.89 ± 0.02^{k}	0.49 ± 0.02^{i}
	BV	8.65 ± 0.22^{m}	1.94 ± 0.04^{m}	0.94 ± 0.01^{l}	0.54 ± 0.02^{k}
	SX	8.15 ± 0.24^{k}	1.76 ± 0.01^{j}	0.84 ± 0.03^{ij}	0.47 ± 0.01^{h}
	RJ	7.59 ± 0.32h	1.84 ± 0.03^{l}	0.79 ± 0.02^{g}	0.42 ± 0.02^{f}
	PM	7.95 ± 0.14^{j}	1.58 ± 0.04^{g}	0.85 ± 0.02^{j}	0.45 ± 0.02^{g}
	TC	8.82 ± 0.18^{n}	1.66 ± 0.02^{h}	0.88 ± 0.02^{k}	0.51 ± 0.01^{j}

612 MX: Machico; FL: Faial; ASJ: Arco de S. Jorge; BV: Boaventura; SX: Seixal; RJ: Ribeira da Janela; PM:
613 Porto Moniz; TC: Terceira. Means in the same column not sharing the same letter are significantly different at
614 $p < 0.05$ probability level.

615

616 **Highlights:**

617 • Phenolic composition of *Myrica faya* samples from Macaronesia is reported.

618 • Anthocyanins and flavonols were the main components of berries and leaves.

619 • Extracts were active against key enzymes linked to type-2 diabetes and obesity.

620 • High inhibitory activities were observed for protein glycation.

621 • *M. faya* is a dietary/nutraceutical source of hypoglycaemic compounds.

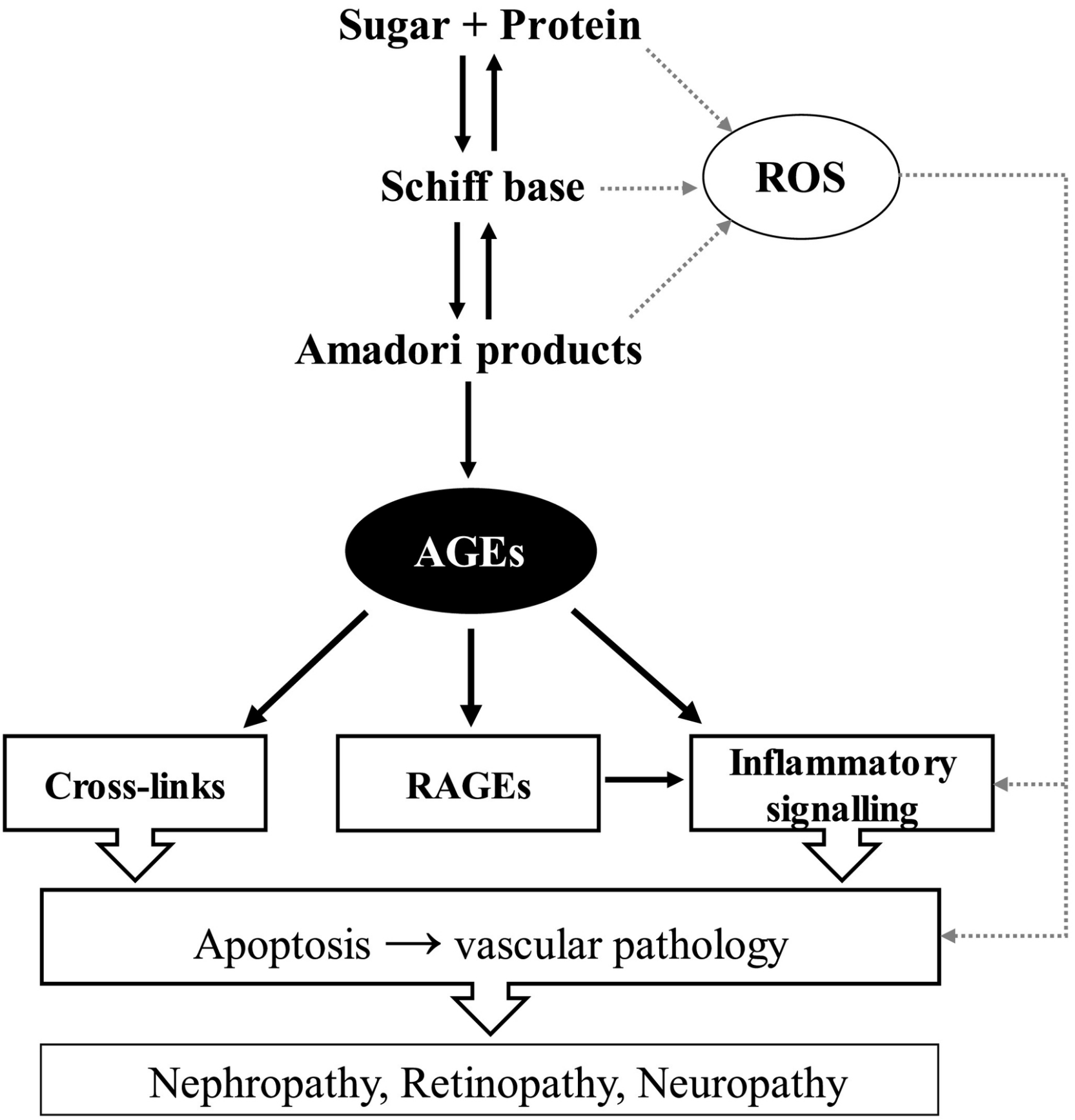
Sugar + Protein
Schiff base
Amadori products
ROS
AGEs
Cross-links
RAGEs
Inflammatory signalling
Apoptosis → vascular pathology
Nephropathy, Retinopathy, Neuropathy

Figure 1