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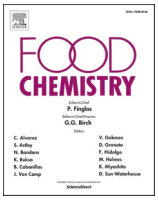

Effect of drying treatments on the global metabolome and health-related compounds in tomatoes

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ABSTRACT

Drying fruits and vegetables is a long-established preservation method, and for tomatoes, in most cases sun-drying is preferred. Semi-drying is relatively a new application aimed to preserve better the original tomato properties. We have assessed the effects of different drying methods on the phytochemical variation in tomato products using untargeted metabolomics and targeted analyses of key compounds. An LC-MS approach enabled the relative quantification of 890 mostly semi-polar secondary metabolites and GC–MS analysis in the relative quantification of 270 polar, mostly primary metabolites. Metabolite profiles of sun-dried and oven-dried samples were clearly distinct and temperature-dependent. Both treatments caused drastic changes in lycopene and vitamins with losses up to > 99% compared to freeze-dried controls. Semi-drying had less impact on these compounds. *In vitro* bioaccessibility analyses of total phenolic compounds and antioxidants in a gastrointestinal digestion protocol revealed the highest recovery rates in semi-dried fruits. Semi-drying is a better way of preserving tomato phytochemicals, based on both composition and bioaccessibility results.

1. Introduction

Tomatoes and their products are widely consumed worldwide and consumption has already been correlated with reduced rates of coronary heart disease and diverse types of cancer (Ilahy, Hdider, Lenucci, Tlili, & Dalessandro, 2011; Pernice, Parisi, Giordano, Pentangelo, Graziani, Gallo, et al., 2010). Fresh tomatoes are especially rich in vitamin C (on average 20 mg/100 g) which meets 40% of the recommended daily intake (Abushita, Daood, & Biacs, 2000; Siddiqui, Chakraborty, Ayala-Zavala, & Dhua, 2011). In addition, tomatoes contain a range of other micronutrients, including phenolic acids, flavonoids and carotenoids, all contributing to the relatively high antioxidant activity of the fruits (Siddiqui & Dhua, 2015). The level of bioactive compounds is of potential importance not only for food preservation and shelf life, but also for human health. Regarding tomato processing, it is well-known that different food processing methods, as well as different treatments (e.g. temperature and pressure) can all impact the final level of metabolites including antioxidants in the fruit. Such effects must be properly considered when optimizing industrial processing methods/steps and conditions in order to produce the best product possible (Capanoglu, Beekwilder, Boyacioglu, De Vos, & Hall, 2010). Furthermore, the composition of bioactives in tomato is also influenced by the genotype (cultivar), and hence this should also be taken into account when selecting the most suitable processing method for specific materials (Siddiqui, 2013).

Drying is the oldest method used for the preservation of foods (Lewicki, 2006). The benefits of controlled drying of fruits are multiple – such as extending storage time, improvement of final product quality and protection against microbial growth by lowering water activity. Furthermore, drying also has a logistical impact as it simplifies packaging requirements and reduces weight/volume for more economic transportation (Simal, Femeńıa, Llull, & Rossello´, 2000). Drying is the simple process of removing water and depends on several factors including the temperature, air flow rate and relative humidity, the initial

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moisture content and the physical nature of the material (Akpinar, Bicer, & Yildiz, 2003).

In particular, convective hot-air drying, with the application of temperatures between 50 and 70 °C, is extensively used in the food industry as a preservation technique. However, through this process, food products can be exposed to too high temperatures which can cause extensive shrinkage, cracking and hardness, decreased bulk density and lower rehydration ability. This hot-air drying can also be deleterious to the final flavour, color and nutritional value of the dried product (Maskan, 2000). On the other hand, the usually milder and thus slower, open-air sun-drying approach has already been used for millennia to dry grains, vegetables, fruits, and other agricultural materials. However, the practical disadvantages of open-air, sun-drying include difficulties in monitoring the drying process. Uncontrolled drying temperatures and time, weather uncertainties, high labor costs and the large surface area requirements limit its usage for large-scale application. Furthermore, under certain conditions, infestation by insects or pathogens and contamination by airborne sand, dust or other foreign materials can seriously impair the final quality of the dried products (Togrul & Pehlivan, 2004).

Sun-drying may take several days (7–10 days), depending on the drying season and temperature, so it is regarded as a slow process compared to other modern drying methods and as a result, sun-dried tomatoes are considered to have their own distinct quality (And & Barrett, 2006). Sun-drying makes it possible to retain and concentrate aroma and generally avoids the undesirable caramelization of natural sugars which can result in a burnt aftertaste and undesirable browning as is often found with the more intense drying methods (Ruiz, Zea, Moyano, & Medina, 2010; TDF, 1999). In tomato, sugars and organic acids contribute to the dry matter content, making their concentration levels critical in determining fruit palatability since they are the key compounds responsible for the sweet and sour/acid tastes of these fruits, respectively (Paolo, Bianchi, Morelli, Speranza, Campanelli, Kidmose, et al., 2019).

Tan, Ke, Chai, Miao, Luo, and Li (2020) subjected three distinct tomato cultivars to both freeze-drying and oven-drying at 70 °C for 12 h and demonstrated that freeze-drying produced better results in terms of appearance and polyphenol content, while oven-drying was found to be better in terms of preventing lycopene degradation. In another study, tomatoes were sun-dried, oven-dried at 60 °C for 36 h, vacuum oven-dried at 60 °C and 0.025 mbar vacuum pressure for 36 h, and freeze-dried, and subsequently compared for their content of total phenolics, ascorbic acid and antioxidant activity (Gümüşay, Borazan, Ercal, & Demirkol, 2015). Results indicated that all three quality parameters were significantly reduced by both oven-dried methods as compared to the original fresh fruit, while freeze drying did not affect their levels. Likewise, Kaur, Kaur, and Ahluwalia (2020) studied the effects of the drying temperatures (40, 50, and 60 °C, resulting in different water contents) on sliced tomato fruits (cv. Punjab Ratta) and investigated the subsequent storage for 180 days. Results indicated that the bioactive components were most effectively retained in samples dried at the highest temperature tested (60 °C) after drying and during storage. On the other hand, significant losses of bioactive chemical components were observed during storage in the samples dried at 40 °C, due to their relatively high water content (about 56%). In general, oven-drying treatments decrease the phenolic content of tomato products, however, contradictory results are also reported which likely are related to the applied drying temperatures and time, final moisture contents of the materials, fruit characteristics (dry matter content, sugar level, ripeness, etc.), shape and the thickness of the dried materials.

The study described here was designed to investigate the impact of two drying techniques on the phytochemical composition of two tomato varieties, including flavour-related compounds and health-related molecules such as phenolics, flavonoids, vitamins and lycopene, in a comprehensive manner using both targeted and untargeted metabolomics approaches. For this purpose, freshly-harvested tomatoes were dried either in an open field in the sun or in a hot-air oven at an increasing range of temperatures. Freeze-dried materials obtained from the same fresh tomatoes were used as controls, as freeze drying has been found to be the most effective way to preserve tomato phytochemical composition (Tan, Ke, Chai, Miao, Luo, & Li, 2020). We used two complementary untargeted metabolomics approaches to compare the metabolite composition of the contrasting dried samples: LC-MS was used for assessing semi-polar (mainly secondary) metabolites while GC–MS after derivatization was used to follow polar (mainly primary) metabolites. In addition, a number of dedicated targeted analyses were also performed: the levels of lycopenes and vitamins A (β-carotene), C and E (α-tocopherol) were assessed using HPLC, while spectrophotometric methods were used to estimate the total phenolic and flavonoid contents as well as the total antioxidant capacity, the latter determined by several methods. Finally, the bioaccessibility of the phenolic compound classes was investigated by performing an *in vitro* gastrointestinal digestion experiment in order to gain additional insights regarding the potential nutritional relevance of any observed changes.

2. Material and methods

2.1. Reagents and chemicals

LC-MS grade methanol, formic acid, *tert* butyl methyl ether, ethanol, acetonitrile, butylated hydroxytoluene (BHT), sudan (internal standard), TRIS buffer, NaCl, $CHCl_3$, ethyl acetate, KOH, Na_2SO_4, Na_2CO_3, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), K_2HPO_4, KH_2PO_4, Diethylene Triamine Pentaacetic Acid (DTPA) Folin & Ciocalteu's phenol reagent, 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ), glacial acetic acid, $FeCl_3{\cdot}6H_2O$, HCl, quercetin-3-rutinoside trihydrate, gallic acid, (±)-6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), NaOH, $AlCl_3{\cdot}6H_2O$, $NaNO_2$, $CH_3COONa{\cdot}3H_2O$, $CuCl_2{\cdot}2H_2O$, ammonium acetate, neocuproine, KCl, $NaHCO_3$, $MgCl_2{\cdot}6H_2O$, $(NH_4)_2CO_3$, $CaCl_2{\cdot}2H_2O$, pepsin, pancreatin, bile salts, ribitol, glutamic acid, dialysis bag (dialysis tubing cellulose membrane-flat width 33 mm), *n*-hexane, isoamyl alcohol, 5,7,22-ergostatrien-3β-ol, catalase, trimethylamine, *O*-methylhydroxylamine hydrochloride, pyridine, *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) were obtained from Merck/Sigma-Aldrich (Germany) and sodium salicylate from Fluka (Munich/Germany).

2.2. Tomato fruit samples

The sun-dried ripe fruits of two commercial tomato varieties, Redsky and Heinz 9780, were obtained from two companies in Turkey. These manufacturers also provided the original fresh fruits in three biological replicates, for comparison to their sun-dried equivalents.

For the sun-drying application, both companies used identical treatments. Briefly, freshly harvested fruits of both Heinz 9780 (company 1-İzmir, Turkey-38°38′08.1″N 27°03′11.3″E) and Redsky (company 2-Manisa, Turkey-38°53′52.2″N 27°44′46.8″E) varieties were sorted to remove damaged fruits, washed, and cut vertically into two parts. Before drying, following standard commercial practice, the tomatoes were salted to accelerate the drying process and to protect the samples from microbiological spoilage. Sun-drying treatments took 6–7 days in the months July and August 2017 at temperatures of about 30–40 °C under direct day-light until reaching a constant weight. The moisture content of sun-dried tomatoes generally ranges from 19.38 ± 0.36% to 21.63 ± 2.36% (Owureku-Asare, Oduro, Saalia, Tortoe, & Ambrose, 2018). After drying, the tomatoes were collected, cleaned with a brush, vacuum packed and transported to the Food Engineering Department of Istanbul Technical University (ITU), where they were directly frozen in liquid nitrogen and then ground to a fine powder for storage at −20 °C before further analysis.

The semi-drying process was performed using the Redsky variety

only (company 2). After similar sorting, washing and cutting treatments as described above, the fruit halves, without added salt, were dried in an oven for approximately 5–6 h at 60–65 °C until they reached a final moisture content of 75–85%. At the end of this semi-drying process, the tomatoes were quickly frozen, packed, and stored in the freezer at −20 °C before transportation to ITU for further analysis.

Oven drying was performed at the laboratories of ITU, in a standard oven (Memmert, Buechenbach, Germany) at 60, 80, 100, and 120 °C. Tomatoes of cv. Redsky were weighed at various time intervals during drying and this process was continued until no further weight-loss was observed.

After both industrial processing (sun-drying and semi-drying) and laboratory-scale oven drying, all samples were freeze-dried using an ALPHA 1–2 LDplus freeze dryer (Osterode am Harz, Germany) set at −60ºC and 0.086–0.096 mbar, in order to obtain the same moisture content in all samples before analysis. For reference, the original fresh fruits from both companies were also directly freeze-dried. Then, fine homogenous powders of all the freeze-dried tomato samples were obtained by means of a pre-cooled IKA A11 grinder (Staufen, Germany) with liquid nitrogen, and these dry powders were then used for all subsequent analyses.

2.3. LC-MS profiling of semi-polar compounds

Aqueous-methanol extracts, which include semi-polar phytochemicals such as flavonoids and alkaloids, were prepared according to Capanoglu, Beekwilder, Boyacioglu, Hall, and de Vos (2008) with slight modifications. Aliquots (30 mg) dry tomato powder was weighed and 1.2 mL 75% MeOH containing 0.1% formic acid was added to each sample. Samples were sonicated (Branson 3510, Hampton) for 15 min at 20 °C at maximum frequency, and then centrifuged at 16,000×*g* (Eppendorf Centrifuge 5810R and 5415R- Ontario, Canada) before transferring the clear supernatant into clean HPLC vials. All samples were obtained and dried as three biological replicates and extracted as described above. In addition, three quality control samples (QC, technical replicates) were prepared using equal amounts of a pool of all sample powders. These semi-polar extracts were used for spectrophotometric determinations as well as for generating semi-polar metabolite profiles using untargeted LC-MS (Bakir, Capanoglu, Hall, & de Vos, 2020). The chromatographic separation was with water and acetonitrile, both containing 0.1% formic acid, in a 45 min gradient from 5 to 35% acetonitrile, generated by an Acquity HPLC (Waters, Milford, MA, USA) at a flow rate of 0.19 mL/min. Five μL of sample extract was injected and a Luna C_{18} column, 2.0 × 150 mm with particle size of 3 μm (Phenomenex, Torrence, USA) and oven temperature of 40ºC was used to separate the compounds. Detection of eluting compounds was with firstly, a PDA detector (Waters) set at 210–600 nm and secondly, an LTQ-Orbitrap FTMS hybrid mass spectrometer (Thermo Scientific, Bremen, Germany). Negative electrospray ionization was applied for detecting a mass range of *m/z* 90–1350 at a mass resolution of 70,000 FWHM, with a capillary temperature of 295 °C, sheath gas flow of 40 mL/min, capillary voltage at −33 V and source voltage at 4.5 kV, conform earlier LC-MS based metabolomics studies on tomato fruits (Bakir, Capanoglu, Hall, & de Vos, 2020; Ntagkas, de Vos, Woltering, Nicole, Labrie, & Marcelis, 2020) and other plant materials (Garrido, Engel, Mumm, Conde, Cunha, & De Vos, 2021; Mokochinski, Mazzafera, Sawaya, Mumm, de Vos, & Hall, 2018; Pegiou, Zhu, Pegios, De Vos, Mumm, & Hall, 2021) using the same platform.

The annotation of selected metabolites was manually performed, based on correspondence of the observed accurate mass of the molecular ion with a mass deviation threshold of 5 ppm, chromatographic retention time, UV/VIS absorbance spectrum (from the PDA) and any available in-source fragmentation information, with previously annotated tomato compounds (Bakir, Capanoglu, Hall, & de Vos, 2020).

2.4. GC–MS profiling of polar metabolites

Polar metabolites from tomato powders were extracted using a tertiary solvent extraction system which was composed of methanol, water, and chloroform as described by Carreno-Quintero, Acharjee, Maliepaard, Bachem, Mumm, Bouwmeester, et al. (2012) based on a modified protocol from Lisec, Schauer, Kopka, Willmitzer, and Fernie (2006). Briefly, 20 mg dry powder was weighed into a 2 mL safe-lock microcentrifuge tube. A total of 1.4 mL methanol to which glutamic acid (0.5 mg/mL) and ribitol (1 mg/mL) were added as internal standards, was pipetted into each sample with 0.2 mL water. The mixture was then vortexed and ultrasonicated for 15 min. After centrifugation at 16,000×*g* in an Eppendorf centrifuge for 10 min, 500 μL of the supernatant was transferred to a new microcentrifuge tube and 375 μL chloroform and 750 μL distilled water were added and vortexed to remove the non-polar moieties. Again, after centrifugation for 10 min, 50 μL of the polar methanol phase was transferred to a glass insert placed in a 2 mL glass vial. All prepared samples were then dried by vacuum centrifugation (Savant®, SPD121P, Thermo Scientific, Bremen, Germany) at room temperature overnight. Vials were then closed under an argon atmosphere with magnetic caps. Prior to analysis, dried samples were derivatized online using a TriPlusRSH autosampling/injection robot (Thermo Scientific) as described by Garrido, Engel, Mumm, Conde, Cunha, and De Vos (2021). First, 12.5 μL o-methylhydroxylamine hydrochloride (20 mg mL^{-1} pyridine) was added to the dried extracts and incubated for 30 min at 40 °C with agitation. Then, the samples were derivatized with 17.5 μL *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) for 60 min at 40 °C with agitation. An alkane mixture (C_{10}-C_{32}) was added to determine the retention indices of the metabolites. The derivatized samples were analyzed on a GC–MS system consisting of a Trace 1300 gas chromatograph (Thermo Scientific) with a PTV injector coupled to a TSQ8000 DUO-series mass spectrometer (Thermo Scientific). Each sample (1 μL) was introduced into the injector at 70 °C using a split flow of 19 mL min^{-1}. Chromatographic separation was performed using a VF-5 ms capillary column (Varian, Palo Alto, CA, USA; 30 m × 0.25 mm × 0.25 mm) including a 10 m guardian column with helium (5.0) as carrier gas at a constant column flow rate of 1 mL min^{-1}. The column effluent was ionized by electron impact at 70 eV. Mass spectra were acquired at full scan mode with a *m/z* range of 50 to 600 at an ion source temperature of 290 °C. A solvent delay of 420 s was set.

2.5. Untargeted LC–MS and GC–MS data processing

The MetAlign software package (https://www.metAlign.nl; Lommen (2009)) was used for LC–MS and GC–MS data pre-processing and peak alignment. The data obtained from MetAlign were then filtered for mass features being present in at least 3 samples and with a minimum intensity of 1000 or 50 ion counts for LC-MS and GC–MS, respectively. The resulting peak lists were imported into MSClust software (Tikunov, Laptenok, Hall, Bovy, & De Vos, 2012) to remove metabolite mass feature redundancy by clustering natural isotopes and fragments or adducts created in the mass spectrometer. For the LC-MS mass peak list, generated with low energy atmospheric pressure electrospray ionization, this script was set to create clusters (i.e. in-source mass spectra) of at least 2 highly correlating features; for the GC–MS mass peak list, which was generated with high energy electron impact (EI) fragmentation, a minimum of 5 correlating peaks per cluster (EI mass spectrum) was set. The resulting lists of relative intensities of each putative metabolite detected in each sample were used for multivariate analysis, after log-transformation and Pareto-scaling of the compound intensities (total ion counts at peak height).

For LC-MS compounds, the annotation of selected metabolites was manually performed, based on correspondence of the observed accurate mass of the molecular ion with a mass deviation threshold of 5 ppm, chromatographic retention time, UV/VIS absorbance spectrum (from the PDA), and presence of indicative fragments or adducts in the

obtained in-source mass spectra, as constructed by the MSClust tool, with previously annotated tomato compounds (Bakir, Capanoglu, Hall, & de Vos, 2020). In the case of GC–MS compounds, the obtained mass spectrum of each ion cluster was compared with that in available EI-spectral libraries, including the NIST2014 and the Golm spectral database (Hummel, Strehmel, Selbig, Walther, & Kopka, 2010), as well as an in-house library of derivatized standards. In addition, the experimentally obtained retention indices (RI) were compared with reported RIs for verification of the automated spectra annotations (Supp. Data Tables sheet "GC–MS-Metabolite intensities").

2.6. Analysis of sugars

Analysis of sugars was performed using the instructions given for Waters amide column with slight modifications. Briefly, 0.5 g dry tomato powder was weighed into a microcentrifuge tube and 1.5 mL acetone: water (50:50, v/v) was added and the mixture was shaken for 25 min on a shaker. Afterwards, the slurry was centrifuged for 5 min at 18,600×*g*. The sugar content of the supernatants was determined using a HPLC with a Refractive Index Detector (HPLC-RID) (Waters e2695 separation module with a Waters 2414 RI detector). An amide column (4.6 × 250 mm i.d., 3.5 μm, XBridge, Waters, USA) maintained at 40 °C was used for separation. An isocratic separation was used, with 75/25 acetonitrile/water including 0.2% triethylamine, at a 1 mL/min flow. Calibration curves of fructose and glucose (25–100 mg/mL) were used as external standards to quantify these compounds in the samples.

2.7. Analysis of lycopenes, and vitamins A, E and C

For both lycopenes and the vitamins A and E, lipophilic extracts were prepared according to (Bakir, Capanoglu, Hall, & de Vos, 2021). Briefly, 50 mg dry powder was weighed into 10 mL glass tubes, and 4.5 mL ice-cold MeOH/$CHCl_3$ (5:4), containing both 0.1% BHT as antioxidant and 3 μL/mL sudan as internal standard, was added. Tubes were vortexed for 10 s, left on ice for 10 min and sonicated for 10 min. Then 2.5 mL Tris/NaCl buffer (pH 7.5) was added and the tubes were again kept on ice for 10 min. Finally, samples were centrifuged for 10 min at 2,700×*g* and the lower chloroform phase was transferred to a new tube using a glass pipette. The remainder in each tube was then extracted twice with 1 mL $CHCl_3$ + 0.1% BHT. Per sample the three chloroform phases were pooled and dried in a heating block at 35 °C under a gentle stream of nitrogen gas. Dried lipophilic compounds were redissolved in 0.5 mL ethyl acetate with 0.1% BHT, tubes were vortexed for 10 *sec*, sonicated for 10 min and centrifuged once more. Supernatants were finally transferred to dark glass HPLC vials for analysis. Carotenoids and α-tocopherol were analyzed using HPLC (Waters Alliance e2695) with a photodiode array (PDA) detector (Waters 2996) coupled to a fluorescence detector (Waters 2475) using a 45 min gradient of methanol, *tert*-butyl ether and 80% methanol + 0.2% ammonium acetate on a YMC-Pack C30 column (250x4.6 mm, particle size 5 μm; YMC, USA) at 35 °C and a flow rate of 1 mL/min (Capanoglu, Beekwilder, Boyacioglu, Hall, and de Vos (2008). Lycopenes and β-carotene were analyzed using the PDA detector with scanning range 240–700 nm, and α-tocopherol by the fluorescence detector with excitation at 296 nm and emission at 340 nm. Calibration curves of authentic standards were used for quantification of the compounds in the tomato samples. The purity of *all trans*-lycopene was checked spectrophotometrically, based on its molar extinction coefficient ($E^{472\ nm} = 3450$) (de la Fuente, Oyarzun, Quezada, & del Valle, 2006).

For the analysis of vitamin C, an extraction solution of 5% metaphosphoric acid with 1 mM DTPA (metal chelator) was prepared. To 30 mg powdered sample, 1.2 mL ice-cold extraction solution was added and the mixtures were sonicated for 15 min. Samples were centrifuged for 20 min at 20,000×*g*, and the supernatants were collected for analysis with HPLC-PDA using a YMC-Pack Pro C18 (150 × 4.6 mm, particle size 5 μm) column (YMC, USA) at 30 °C with a 17 min gradient of 100% to 75% 50 mM potassium phosphate buffer pH 4.4 (Capanoglu et al., 2008). An external L-ascorbic acid calibration curve was used for the quantification of vitamin C, by integrating the corresponding HPLC peak at 260 nm.

2.8. Ergosterol analysis

Ergosterol was extracted as described in (Ghiretti, Spotti, Strina, Sandei, Mori, & Attolini, 1995) and analysed according to Kadakal and Artik (2008). Briefly, 0.2 g dry sample was mixed with 5 mL H_2O, 5 mL EtOH, 7.5 mL MeOH and 1 g KOH, for simultaneous extraction of sterols and saponification of the lipid-derived, undesired molecules, and boiled for 45 min in a reflux (Elektro-Mag, Model MX 225, Ankara, Turkey) for extraction. After cooling, the extract was filtered using a separation funnel with the addition of water (25 mL) and *n*-hexane (5 mL) followed by shaking for 1 min. The *n*-hexane phase was then transferred to an Erlenmeyer flask. Residue in reflux was washed with 5 mL *n*-hexane and the separation step was repeated. Both *n*-hexane phases were combined, filtered over anhydrous Na_2SO_4 and dried under a gentle stream of nitrogen. The residue was then dissolved in 5 mL *n*-hexane and 20 μL of each extract was injected into an HPLC (SHIMADZU, LC-10 AD, Kyoto-JAPAN) with a C18 column (250 × 4.6 mm, Nucleosil Macherey-Nagel) maintained at 25 °C. An isocratic separation with *n*-hexane and isoamyl alcohol (95:5) at a 2 mL/min flow rate was employed and a PDA detector (SHIMADZU, SPD-M10A, Kyoto-JAPAN) was used for detection in the 190–700 nm wavelength region. A calibration curve of 5,7,22-ergostatrien-3β-ol solution was prepared as external standard at concentrations of 0.1, 0.5, 1, 2.5, 5, 10, 25 and 50 μg/mL. Chromatograms were evaluated using the Class-VP (version 5.03) package (Shimadzu Corporation, Tokyo-JAPAN) at a wavelength of 282 nm.

2.9. Spectrophotometric assays

The same aqueous-methanol extracts, prepared as described above for LC-MS profiling, were used in the spectrophotometric assays for total phenolic content (TPC), total flavonoid content (TFC) and total antioxidant capacity (TAC). TPC was determined according to (Singleton, Orthofer, & Lamuela-Raventos, 1999) and TFC conform (Dewanto, Wu, Adom, & Liu, 2002). Four different assays were applied to assess TAC of samples: the DPPH-radical scavenging activity assay (Kumaran & Karunakaran, 2006), the ABTS-radical scavenging activity assay (Miller & RiceEvans, 1997), the CUPRAC assay (Apak, Guclu, Ozyurek, & Karademir, 2004) and the FRAP assay (Benzie & Strain, 1996). TPC was reported in gallic acid equivalents, TFC in rutin equivalents, and TAC values in trolox equivalents, all per 100 g DW.

2.10. In vitro bioaccessibility assays

The *in vitro* bioaccessibility method was adapted from Minekus, Alminger, Alvito, Ballance, Bohn, Bourlieu, et al. (2014) with a few modifications. Saliva (pH 7.0), stomach (at pH 3.0) and intestinal (at pH 7.0) liquids were prepared. Pepsin, pancreatin, and bile salts were freshly prepared just before the analysis. Dried tomato samples (0.5 g powder) were used for each analysis. For the preparation of the intestinal liquid, 10.5 g $NaHCO_3$ was dissolved in 250 mL distilled water and 20 mL of this solution was transferred into a dialysis bag. All other steps were according to the protocol described by Minekus et al. (2014). At the end of the analysis, the stomach and the intestinal fractions (IN fraction: inside the dialysis bag) were collected, freeze dried and analyzed for their TPC, TFC, and TAC values.

2.11. Statistical analysis

All samples were analyzed in random sequences, with one QC sample placed at the start, one QC in the middle and one QC at the end of the LC-MS and GC–MS series, in order to avoid any grouping effect and to

enable checking for potential variation in instrument performance during analysis of each sample series. Statistical analysis was applied to samples by utilization of one-way analysis of variance (ANOVA) with Tukey's post-hoc test ($p < 0.05$) (SPSS v. 21; SPSS Inc., Chicago, IL). The differences between all samples and among samples were evaluated, and the results are reported as mean values ± standard deviation.

Principal components analysis (PCA) was applied after log transformation and Pareto scaling of the metabolite intensity data using SIMCA (V14 Sartorius Stedim Biotech; Umea; Sweden); hierarchical cluster analysis (HCA) of samples was applied using GeneMaths XT (Applied Maths; 1.6 software, Belgium), again after log transformation and scaling of intensity data.

3. Results and discussion

3.1. Untargeted metabolite profiling

LC-MS profiling of semi-polar (aqueous-methanol) tomato extracts revealed relative abundance values for 890 putative metabolites, i.e. clustered mass features based on their corresponding chromatographic retention and signal intensity patterns across all samples, and which were present in at least 3 samples (Supp. Data Tables, Sheet "LC-MS-Metabolite intensities"). The global differences and similarities between samples based on the relative intensities of these LC-MS metabolites were subsequently assessed in an unsupervised manner using PCA (Fig. 1). The PCA score plot shows that all biological replicates, produced separately from 3 tomato batches but using the same processing method, clustered closely together, indicating relatively high reproducibility within the initial fruit batch starting materials (freeze-dried controls) as well as their replicate drying treatments. On the other hand, a clear distinction was observed between each drying treatment, corresponding to both PC 1 and PC2 (together explaining 49% of the total variation); the freeze-dried samples, from both companies, and the semi-dried tomatoes (from company 2) were placed on the right side of the PCA plot, while oven-treated samples using a range of temperatures grouped together on the opposite side (PC1: 31.7% of the total metabolite variation), indicating oven-drying had the largest impact on the metabolite profile. The semi-drying process resulted in metabolite profiles relatively close to their freeze-dried controls, which indicates that this semi-drying process can be regarded as being the least invasive (at least for the tested variety 2, Redsky). HCA (Supp. Fig. 1) supported the results obtained by PCA: the samples were again clearly separated into two main groups: 'all oven-dried samples' and 'all others'. Both freeze-dried and semi-dried samples of cv. Redsky are grouped within the same sub-branch and are separated from the sub-branch of freeze-dried samples of cv Heinz 9780, indicating that the semi-drying process had less impact on the semi-polar metabolite profile than had the genetic (varietal) differences of these starting materials. In contrast, sun-dried samples of both varieties clustered together in a separate branch, suggesting the initial varietal differences are reduced by the sun-drying procedure. For both varieties, the sun-dried tomatoes were clearly separated from their oven-dried counterparts indicating that sun-drying results in different LC-MS profiles. The underlying mechanisms for these obvious differential effects of drying in sun (for about 6–7 days) versus oven, even after the mildest condition at 60 °C, are yet unclear but possibly may be related to different features of the drying processes and perhaps due to the fact that only the sun-dried tomatoes were salted before drying. This may have caused a series of biochemical reactions related to abiotic stress/dehydration physiological processes (Nasrollahi, Mirzaie-asl, Piri, Nazeri, & Mehrabi, 2014), especially concerning the rise in the levels of some secondary metabolites often involved in defense mechanisms (Shirasawa, Takabe, Takabe, & Kishitani, 2006).

Some differentially accumulating phenolic compounds, as detected by the untargeted LC-MS approach, were selected and examined in detail and are indicated in Supp. Fig. 2. This selected set contained some compounds that are well-known and often studied in fresh tomatoes, as well as some compounds which were prominently observed after processing. While certain metabolites were either only or mostly observed in freeze-dried and semi-dried samples, such as naringenin chalcone, which is known to be present in freshly harvested tomatoes (Capanoglu, Beekwilder, Boyacioglu, Hall, & de Vos, 2008), others were significantly increased by the oven-drying treatment, such as naringenin and a caffeic acid hexoside. Several novel metabolites, i.e. not previously reported for tomato fruits, were also observed to appear after both sun-drying and

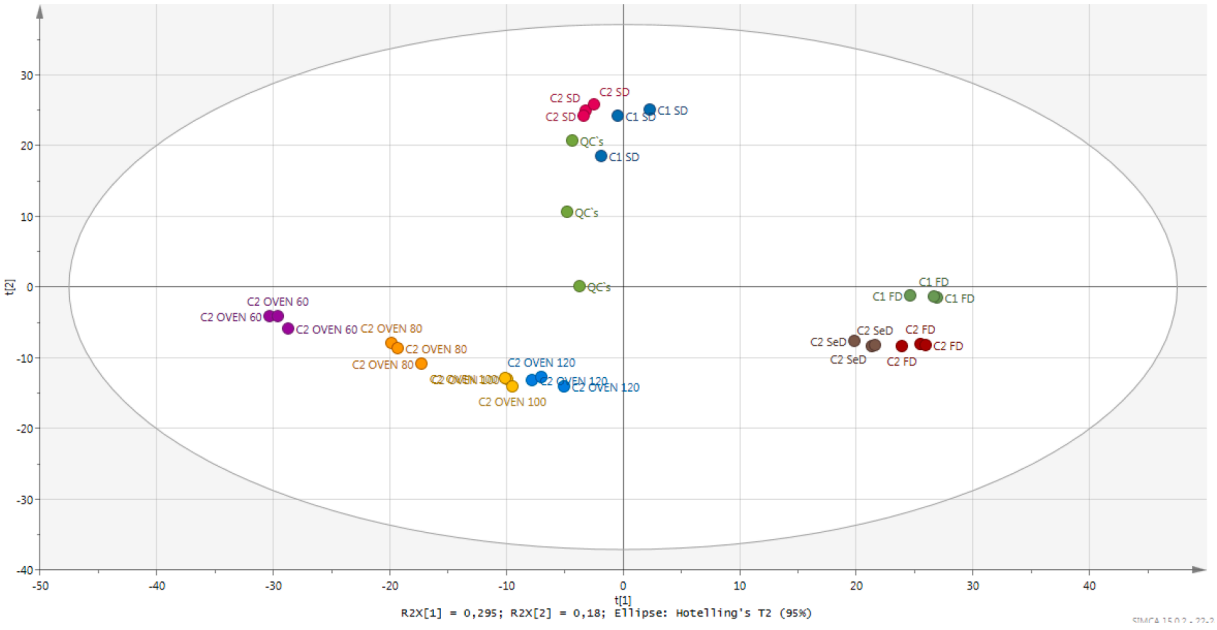

Fig. 1. PCA scores plot of dried tomato samples based on the profiles of semi-polar metabolites measured by LC-MS. C1 SD (Blue): Heinz 9780 variety sun-dried; C1 FD (Green): Heinz 9780 variety freeze-dried; C2 SD (Pink): Redsky variety sun-dried; C2 FD (Red): Redsky variety freeze-dried; C2 SeD (Brown): Redsky variety semi-dried; C2 OVEN 60 (Purple): Redsky variety oven-dried at 60 °C; C2 OVEN 80 (Orange): Redsky variety oven-dried at 80 °C; C2 OVEN 100 (Yellow): Redsky variety oven-dried at 100 °C; C2 OVEN 120 (Light blue): Redsky variety oven-dried at 120 °C, and QC's (green): QC samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

oven drying treatments: e.g., LC-MS compound 446, *m/z* $[M-H]^-$ = 210.0772, which is putatively identified as methoxy-tyrosine or salicyloylserinol. Glycoalkaloids such as α-tomatine were at higher levels in sun-dried samples compared to control (freeze-dried) and oven-dried tomatoes. On the other hand, β-tomatine was not observed in sun- and freeze-dried materials whilst, it was detected in samples dried above 100 °C. This is likely due to partial hydrolysis of the lycotetraose unit of α-tomatine induced at these high temperatures.

The PCA based on the polar (GC–MS) metabolite profiles of the tomato samples also showed a clear separation of the oven dried samples and the sun and semi-dried samples along PC1 which explained 25.9% of the total variation (Fig. 2). PC2 explained 12.3% of the variation and separated the freeze-dried, control samples from the other treatments. However, the distribution of samples due to the drying treatments was different between the primary (as measured by GC–MS, Fig. 2) and secondary metabolites (as measured by LC-MS, Fig. 1). While Fig. 1 shows a grouping of the semi-dried tomatoes with their freeze-dried controls, in Fig. 2 these semi-dried tomatoes are clearly separated from their freeze-dried controls and grouped with the sun-dried samples. In addition, in Fig. 2 all oven-dried tomato samples were separated along PC2, in contrast to along PC1 as in Fig. 1, with also apparently a less-pronounced effect of applied temperature on metabolite composition. Therefore, both sun-drying and semi-drying treatments affected the primary metabolites in a similar manner, while oven-drying had a lesser effect on these compounds and in an orthogonal manner. Some examples of differentially-accumulating primary compounds, detected by this GC–MS approach, are indicated in Supp. Fig. 3 where some metabolites were observed to be higher in sun-dried samples, while others were more abundant in oven dried tomatoes and again some others in the freeze dried ones.

3.2. Effects of drying on sugars

Sugars, dietary fiber, organic acids, phenolics, and minerals are the main constituents present in tomatoes (Kader, 2008). Accumulation of sugars, alongside organic acids, has been reported to impact significantly the intensity of tomato flavour (Causse, Saliba-Colombani, Lecomte, Duffe, Rousselle, & Buret, 2002). The glucose and fructose contents of the dried tomato samples as described here, were therefore also analysed in a targeted manner and their quantified sugar levels are presented in Fig. 3. Sun-drying resulted in a small but significant decrease (19%) in fructose, but not in glucose, in the cultivar tested, cv Redsky. Semi-drying of Redsky resulted in a reduction of both glucose and fructose (by 31% and 25%, respectively), as compared to the freeze-dried controls. Oven-drying at both 60 °C and 120 °C also resulted in a significant decrease in both fructose and glucose, while drying at the intermediate temperatures (80 °C and 100 °C) significantly increased the level of fructose but not of glucose. Evidently, each drying method had a specific impact on the final sugar levels in the dried products. In a recent paper (Jeyaprakash, Heffernan, Driscoll, and Frank (2020) it was reported that drying at 40 °C using a convectional air dryer did not induce a significant difference for both fructose and glucose levels.

3.3. Effects on lycopenes and vitamins A, C and E

The contents of health-related lycopenes and vitamins were determined by HPLC-PDA and are presented in Fig. 4. *All trans*-lycopene (Fig. 4a) was by far the most prominent lycopene form detected. Compared to the freeze-dried controls, the sun-drying treatment caused a 74% and 83% decrease of *t*-lycopene levels in C1 and C2 tomatoes, respectively. For C2, the relatively mild semi-drying conditions caused on average, a smaller decrease in *all t*-lycopene levels of 36% compared to the controls. Sun-drying also resulted in significant losses of vitamin E in both cultivars (Fig. 4b). Both lycopene and vitamin E were almost completely lost in the 60 °C oven-dried fruits, while remarkably their losses were less at higher temperatures and for vitamin E, even fell to zero at 100 and 120 °C. Vitamin A (β-carotene) contents (Fig. 4c) were not significantly affected by the sun-drying treatment for C1, however for C2 a clear decrease was observed after both sun-drying (-64%) and oven-drying at 60 °C (-79%) or 80 °C (-55%) but not at the two highest oven temperatures (100 and 120 °C). Semi-drying affected neither vitamin E (Fig. 4b) nor vitamin A (Fig. 4c) levels, as compared to the freeze-dried controls.

It is known that *all t*-lycopene degradation may occur in food products during their storage and processing (Nguyen & Schwartz, 1999) and isomerization and oxidation have been proposed to be the primary

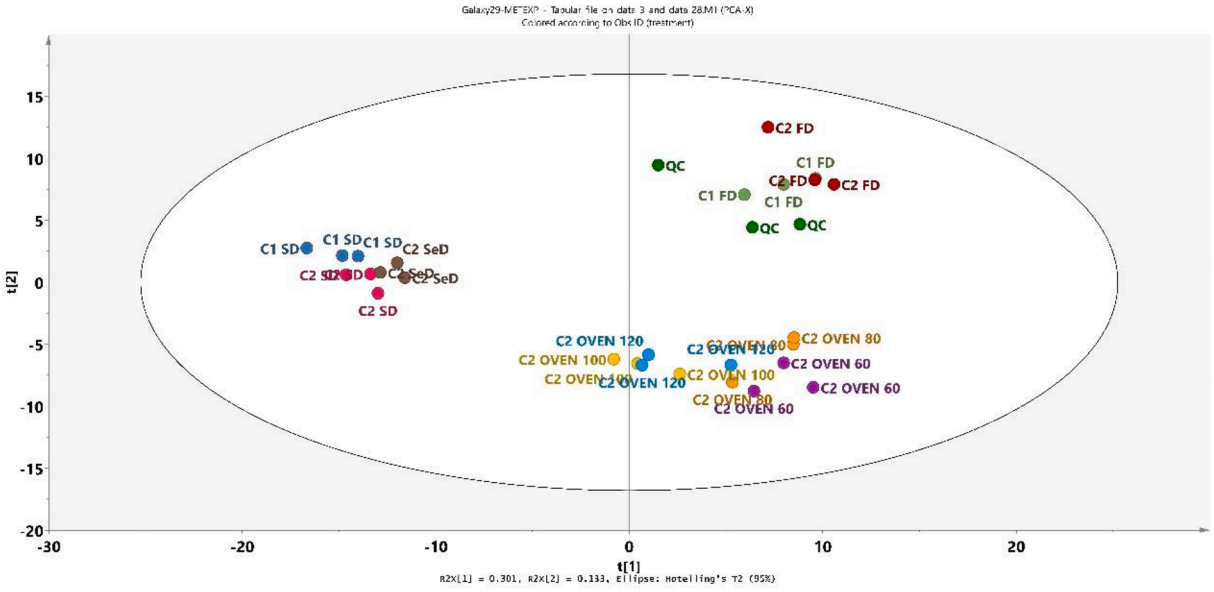

Fig. 2. PCA result plot of dried tomato samples based on the profiles of polar metabolites measured by GCMS. The distribution of samples was based on the drying treatment and variety. C1 SD (blue): Heinz 9780 variety sun-dried; C1 FD (light green): Heinz 9780 variety freeze-dried; C2 SD (pink): Redsky variety sun-dried; C2 FD (red): Redsky variety freeze-dried; C2 SeD (brown): Redsky variety semi-dried; C2 OVEN 60 (purple): Redsky variety oven-dried at 60 °C; C2 OVEN 80 (orange): Redsky variety oven-dried at 80 °C; C2 OVEN 100 (yellow): Redsky variety oven-dried at 100 °C; C2 OVEN 120 (light blue): Redsky variety ovendried at 120 °C. QC (green): QC samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

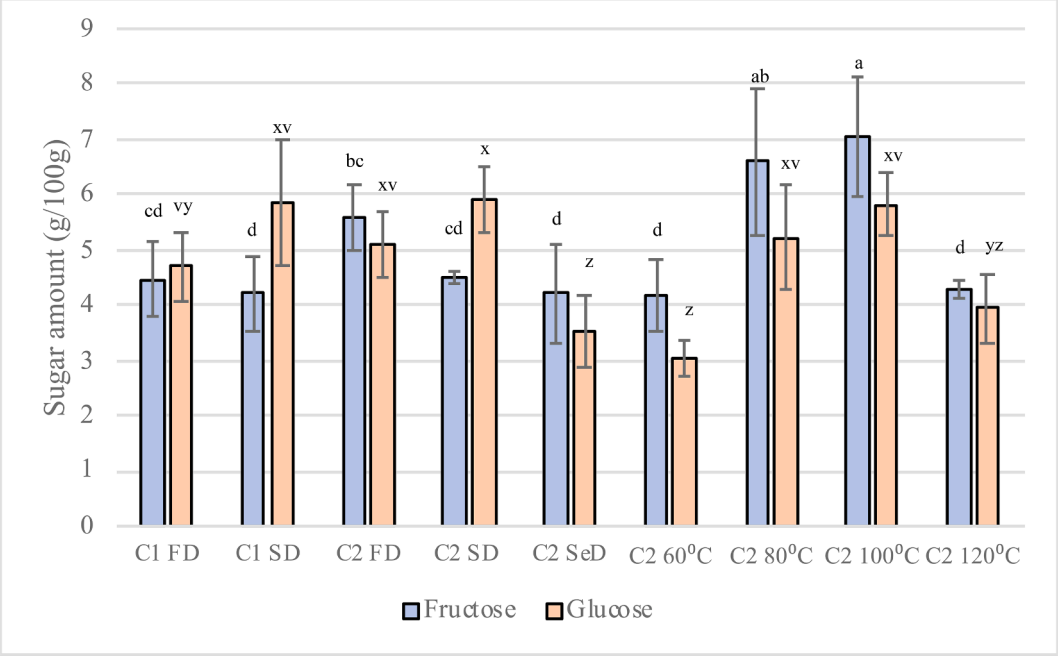

Fig. 3. Sugar content of samples measured by RI-HPLC. Results were expressed as mg fructose and glucose in 100 g dried sample. 3 biological samples were analyzed twice and the results were reported as the mean value ± standard deviation. Letters a to d and x to z over the bars indicate the statistical differences between samples regarding the fructose and glucose contents, respectively ($p < 0.05$). C1 FD: Heinz 9780 variety freeze dried; C1 SD: Heinz 9780 variety sun-dried; C2 FD: Redsky variety freeze dried; C2 SD: Redsky variety sun-dried; C2 SeD: Redsky variety semi-dried; C2 60 °C: Redsky variety oven dried at 60 °C; C2 80 °C: Redsky variety oven dried at 80 °C; C2 100 °C: Redsky variety oven dried at 100 °C; C2 120 °C: Redsky variety oven dried at 120 °C.

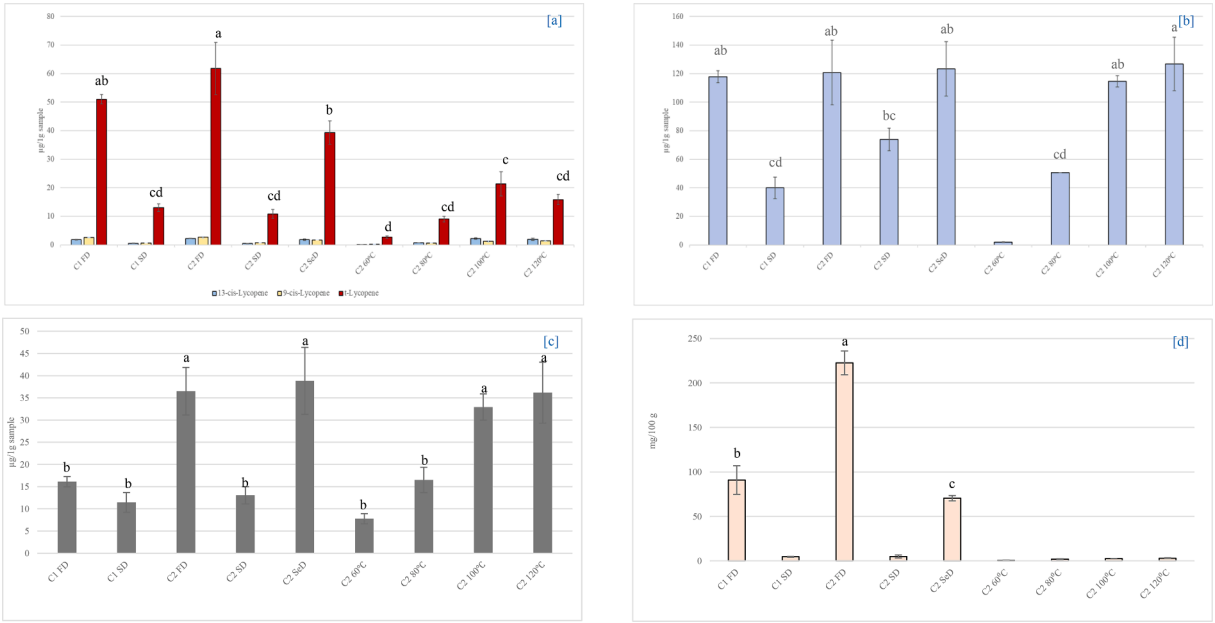

Fig. 4. Levels of lycopenes [a], vitamin E [b], vitamin A (β-carotene) [c] and vitamin C [d] in dried tomato samples measured by HPLC-PDA. Results were expressed as μg per 1 g dried sample [a, b and c], or mg per 100 g dried sample [d]. Different letters above the bars indicate statistical differences between samples ($p < 0.05$). C1 FD: Heinz 9780 variety freeze-dried; C1 SD: Heinz 9780 variety sun-dried; C2 FD: Redsky variety freeze-dried; C2 SD: Redsky variety sun-dried; C2 SeD: Redsky variety semi-dried; C2 60 °C: Redsky variety oven-dried at 60 °C; C2 80 °C: Redsky variety oven-dried at 80 °C; C2 100 °C: Redsky variety oven-dried at 100 °C; C2 120 °C: Redsky variety oven-dried at 120 °C.

causes of this degradation. For instance, a *cis*-lycopene form is produced from *all t*-lycopene by isomerization, and this cis form is reported to be more prone to oxidation (Boskovic, 1979). In previous studies, the stability of lycopene in dry tomato powders, after drying using several techniques, was investigated upon subsequent storage (Anguelova & Warthesen, 2000; Baloch, Khan, & Baloch, 1997; Lovric, Sablek, & Boskovic, 1970). It was observed that the loss of lycopene depended on both the drying method applied and the storage conditions.

With regard to vitamin C levels (Fig. 4d), both sun-drying and all oven-drying temperatures resulted in considerable degradation (≥99% as compared to their freeze-dried controls), while the semi-drying treatment resulted in a less dramatic loss (≈70%) of this vitamin.

3.4. Ergosterol

Ergosterol is the main fungal sterol and has been identified as a common metabolite in many fungal species (Kadakal, Nas, & Ekinci, 2005; Seitz, Mohr, Burroughs, & Sauer, 1977). While ergosterol can also occur in trace amounts in some bacteria, its presence in food products is almost exclusively associated with the presence of molds. Ergosterol content in tomato products can be significant (Ghiretti, Spotti, Strina, Sandei, Mori, & Attolini, 1995) and is regarded as a negative quality parameter (Graselli, Leoni, Sandei, & Mori, 1993). The maximum acceptable level of total ergosterol in a tomato product has been set to 15 mg per kg DW (Bertoni, Ghiretti, Sandei, Strina, & Leoni, 1994; Bocchi, Ghiretti, Sandei, Spotti, & Leoni, 1995; Ghiretti, Spotti, Strina, Sandei, Mori, & Attolini, 1995; Sio, Laratta, Giovane, Quagliuolo, Castaldo, & Servillo, 2000). The ergosterol levels of our analyzed dried tomato samples were never higher than 9 mg/kg, thus below the critical threshold (Supp. Fig. 4). In addition, it was observed that ergosterol levels were significantly decreased, compared to the freeze-dried controls, by each drying treatment but more specifically, by oven-drying: the highest oven temperatures gave the lowest ergosterol contents. Kadakal and Artik (2008) also demonstrated that ergosterol degradation increased with increasing heating times and increasing temperatures. Likely, ergosterol was already present in the fresh ripe fruits (and thus in the freeze-dried samples) and broken down upon subsequent drying in a temperature-dependent manner. Consequently, while high temperatures appear to have mainly negative consequences for the endogenous chemical composition of the tomato, especially for the health-relevant compound groups, for pathogen-related, undesirable contaminants these can actually be beneficial.

3.5. Effects of in vitro gastrointestinal digestion

In order to evaluate the contents of total phenolics (TPC), total flavonoids (TFC) and total antioxidant capacity (TAC, determined by 4 different assays) of the dried tomato fruits and the potential impact of digestion, these global food quality parameters were assessed before and after *in vitro* gastrointestinal digestion of each product (Fig. 5). Oven drying at 80 °C generally resulted in the highest TPC contents and antioxidant activities (ABTS-assay) of the tomato samples before their digestion. For some assays, levels after drying variety C2 were even higher than in the freeze-dried control. However, drying above 80 °C usually caused significant decreases in both TPC, TFC, and TAC levels. Based on the freeze-dried control samples, the samples obtained from company 2 tended to have higher TPC, TFC, and TAC values than those from company 1. These differences might be associated with the differences between the varieties or the original growing conditions of tomatoes and further research would be needed to clarify this. The sun-drying treatment did not decrease the TAC levels of either tomato varieties; on the contrary, it even resulted in a statistically significant positive effect in the CUPRAC-based assay. Results with dried figs also indicated no effect or just slight increases in TAC levels (based on ABTS and CUPRAC assays) during sun-drying, but nevertheless lycopene, vitamin C and vitamin E levels were drastically decreased (Kamiloglu & Capanoglu, 2015).

Gümüşay et al. (2015) also investigated the effect of diverse drying treatments on the tomato phenolic content and antioxidant activity and showed that freeze-drying results in maintaining better antioxidant properties (19% increase was observed by freeze-drying compared to fresh samples, while a 39% decrement was observed after sun-drying). This result was explained by an improved extraction efficiency having less detrimental effects on the antioxidant compounds. For semi-dried tomatoes, (Toor & Savage, 2006) showed a decrease of 35% in the total antioxidant activity compared to that of fresh samples, based on the ABTS assay. However, in our study no statistically significant differences were observed between semi-dried and freeze-dried samples. Kaur, Kaur, and Ahluwalia (2020) worked with convection air drying at 40, 50 and 60 °C and they concluded that drying at 60 °C was the most effective temperature to retain the highest levels of bioactive constituents (phenolics, flavonoids and antioxidant activity) in tomatoes.

In some studies, a high correlation between TAC and ascorbic acid content has been observed irrespective of the antioxidant assay method used in diverse fruits such as orange (Gardner, White, McPhail, & Duthie, 2000) and guava (Thaipong, Boonprakob, Crosby, Cisneros-Zevallos, & Byrne, 2006). In our study, we observed that the best

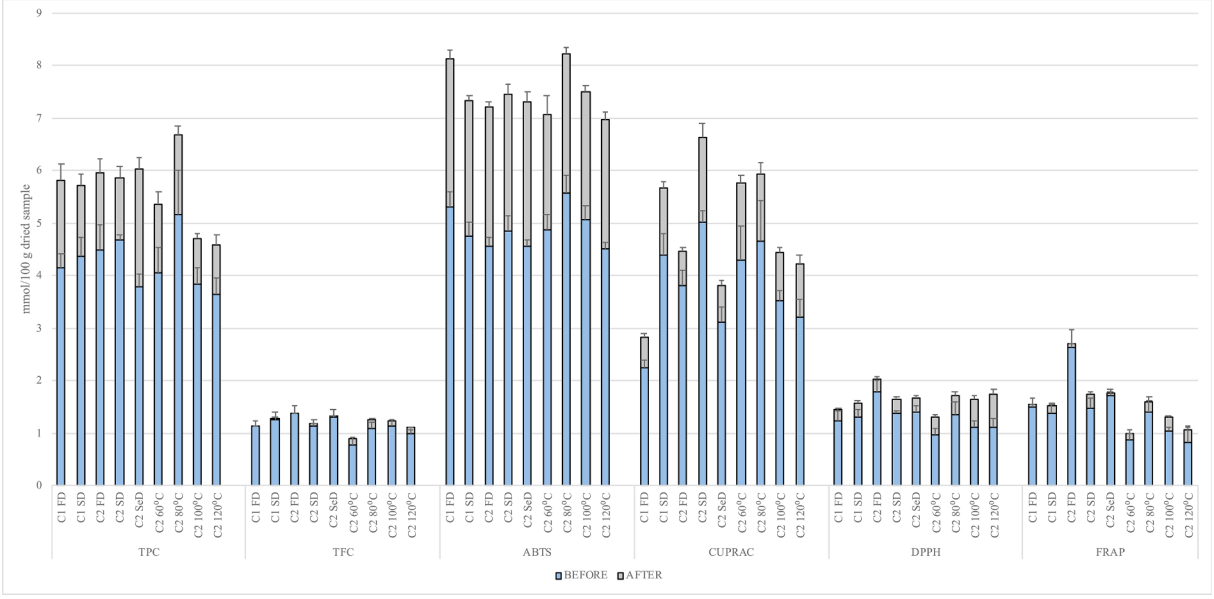

Fig. 5. Levels of TPC, TFC and TAC (4 assays: ABTS to FRAP) in dried tomatoes before (blue bars) and after (grey bars) their *in vitro* gastrointestinal digestion. Results were expressed as mmol gallic acid, mmol rutin or mmol trolox in 100 g dried sample for TPC, TFC and TAC analysis, respectively. Values represent mean values (n = 3 biological replicates). C1 FD: Heinz 9780 variety freeze-dried; C1 SD: Heinz 9780 variety sun-dried; C2 FD: Redsky variety freeze-dried; C2 SD: Redsky variety sun-dried; C2 SeD: Redsky variety semi-dried; C2 60 °C: Redsky variety oven-dried at 60 °C; C2 80 °C: Redsky variety oven-dried at 80 °C; C2 100 °C: Redsky variety oven-dried at 100 °C; C2 120 °C: Redsky variety oven-dried at 120 °C. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

linear correlation between vitamin C and TAC results across all samples was for the FRAP assay (r = 0.89), followed by the DPPH assay (r = 0.79), while a low value (r = -0.28) was obtained for the ABTS assay.

An *in vitro* bioaccessibility assay was applied directly to all of the dried samples and the spectrophotometric assay values obtained after the simulation of the gastrointestinal digestion system were compared to the initial levels of each measured attribute in the starting material, in order to be able to calculate recovery percentages (Supp. Fig. 5). In general, based on their TPC values, the freeze-dried samples had relatively higher recovery rates compared to the sun- and oven-dried samples, while the semi-drying treatment revealed the highest recovery value of 59%. On the other hand, the TAC data revealed completely different recovery percentages, depending on the method applied. For all drying treatments, the highest TAC recovery percentages were mostly obtained with the ABTS method, whereas the FRAP assay (which had a high correlation with vitamin C levels before digestion) resulted in the lowest recovery values. According to a previous study, paste processing and drying of fresh tomatoes caused significant increases in TAC values after *in vitro* gastrointestinal digestion compared to values for the fresh fruit (Kamiloglu, Demirci, Selen, Toydemir, Boyacioglu, & Capanoglu, 2014). On the other hand, Tomas, Beekwilder, Hall, Sagdic, Boyacioglu, and Capanoglu (2017) also suggested that industrial processing of tomatoes improves the *in vitro* bioaccessibility of antioxidants. However, it should be considered that the processing methods and parameters applied, as well as the genotype and the growing conditions of the fruits may each impact the content and thus bioaccessibility and bioavailability of specific bioactives.

4. Conclusion

Dried fruits and vegetables are often ready to be consumed, but they can also be consumed after rehydrating by boiling or cooking. Semi-dried products are gaining increased interest in recent years since consumers prefer a softer texture and an eating quality which is more similar to the fresh product. Monitoring the changes in phytochemicals during drying or other treatments is essential to be able to learn the fate of bioactive compounds during food processing. In this study, sun-dried, semi-dried and oven-dried (at 60, 80, 100 and 120 °C) tomatoes were analyzed to investigate the impact of drying treatments on the overall metabolome and health-related components in the tomato products. Based on our comprehensive metabolomics analyses, it is clear that a range of compounds, including antioxidants, are differently affected by the various practical drying procedures tested. The total antioxidant capacity values observed are the result of different compositions of specific antioxidant compounds in these dried tomato products. The precise roles of these differential antioxidant profiles in relation to potential human health or food product stability is however still unclear, and warrants further investigation.

CRediT authorship contribution statement

Sena Bakir: Conceptualization, Investigation, Formal analysis, Writing – original draft. **Robert D. Hall:** Conceptualization, Resources, Methodology, Supervision, Writing – review & editing. **Ric C.H. de Vos:** Conceptualization, Resources, Methodology, Supervision, Writing – review & editing. **Roland Mumm:** Conceptualization, Resources, Methodology, Supervision, Writing – review & editing. **Çetin Kadakal:** Investigation, Formal analysis. **Esra Capanoglu:** Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodchem.2022.134123.

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