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Effect of hydroxytyrosol and olive leaf extract on 1,2-dicarbonyl compounds, hydroxymethylfurfural and advanced glycation endproducts in a biscuit model

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ABSTRACT

The antiglycative activity of hydroxytyrosol (HT) and olive leaf extract (OLE) was investigated in wheat-flour biscuits. Quercetin (QE) and gallic acid (GA) were used as reference of antiglycative activity of phenolic compounds. HT, OLE, QE and GA were added in the range of 0.25–0.75% (w/w). Samples were compared against a control recipe baked at 180 °C/20 min. HT biscuit was able to inhibit efficiently the formation of hydroxymethylfurfural (HMF) and 3-deoxyglucosone (3-DG), as well as reduced the formation of overall free fluorescent AGEs and pentosidine. The inhibition of the 3-DG and HMF formation was directly and significantly correlated under controlled baking conditions. However, samples formulated with OLE exerted similar antiglycative capacity against pentosidine and Nε-carboxyethyl-lysine, although the amount of HT in the biscuit was 100-fold lower than the biscuit formulated with HT. Methylglyoxal, 3-DG, and glyoxal were the predominant 1,2-dicarbonyl compounds after baking but only 3-DG was significantly reduced by HT.

1. Introduction

The development of the Maillard Reaction (MR) plays a pivotal role as responsible of the organoleptic, textural, and nutritional properties during thermal processing of foods (O'Brian & Morrisey, 1989). Basically, MR is a complex cascade of consecutive and parallel reactions initiated by the condensation of an amino residue of protein and a carbonyl group of a sugar, leading the formation of a myriad of compounds named as Maillard reaction products (MRPs). However, 1,2-dicarbonyl compounds are not only intermediates but also potent promotors of the MR that through its interaction with lysine and arginine side chains of proteins lead to the formation of a set of structures named advanced glycation endproducts (AGEs) (Poulsen et al., 2013). 1,2-dicarbonyls may also form from other pathways, such as the autoxidation of glucose and peroxidation of lipids being also named as advanced

Abbreviations: MR, Maillard reaction; AGEs, advanced glycation endproducts; ALEs, advanced lipoxidation endproducts; HT, hydroxytyrosol; OLE, olive leaf extract; MGO, methylglyoxal; GO, glyoxal; 3-DG, 3-deoxyglucosone; HMF, hydroxymethylfurfural; CML, N^{ε}-carboxymethyl-lysine; CEL, N^{ε}-carboxyethyl-lysine; QE, quercetin; GA, gallic acid.

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lipoxidation endproducts (ALEs) (Vistoli et al., 2013). This is the case of N^{ε}-carboxymethyl-lysine (CML) and N^{ε}-carboxyethyl-lysine (CEL) that both are AGEs/ALEs. However, pentosidine is a crosslinking AGE formed from the oxidative reaction of lysine and arginine residues with pentoses, hexoses, ascorbate or 3-deoxyglucosone (3-DG) (Henle, Schwarzenbolz, & Klostermeyer, 1997). Since the chemical structure of dietary AGEs is shared by those produced in the organism, it is believed that the consumption of thermally treated food rich in AGEs could increase the total body AGEs load (Birlouez-Aragon et al., 2010; Poulsen et al., 2013). Studies have reported that a typical diet provides 25–75 mg of AGEs per day and approximately 10% of ingested AGEs are absorbed (Sebekova & Somoza, 2007; Yamagishi, Matsui, & Nakamura, 2008). Since a significant correlation has been found between ingested and circulating AGEs in humans, dietary AGEs are suggested to be implicated in the development of glycation and inflammation associated with the aging process, and complications associated to chronic pathologies such as diabetes, atherosclerosis, and neurodegenerative disease, among others (Van Nguyen, 2006). However, the biological consequences of the dietary AGEs are still under debate.

Nowadays the research on natural glycation inhibitors has taken a special interest. A number of phenolic compounds have been reported to exert an antiglycative action under simulated physiological conditions (Mesias et al., 2014; Peng, Ma, Chen, & Wang, 2011). However, there are few studies addressing the relationship between phenolic compounds and the inhibition of the formation of dietary AGEs in thermally processed foods (Srey et al., 2010; Zhang, Chen, & Wang, 2014). Bakery products, and particularly biscuits and bread, have been used as a reproducible food models. Biscuit composition (sugar, protein, shortening, leaving agents), baking conditions (temperature, time), in parallel with the pH, moisture, and water activity are the most important variables contributing to the extent of the MR (Charissou, Ait-Ameur, & Birlouez-Aragon, 2007; Gökmen, Açar, Serpen, & Morales, 2008). Generally, the antiglycative activity of the phenolic compounds it has been attributed to dicarbonyls-trapping capacity and antioxidant activity through the free radical scavenging and metal ion chelation (Peng et al., 2011; Srey et al., 2010).

The European Food Safety Authority (EFSA Panel on Dietetic Products, Allergies, & protection of LDL particles from oxidative damage, 2011) concluded a positive health opinion on the contribution of olive oil polyphenols against the oxidative stress. The olive leaf is a by-product with high content in phenolic compounds such as oleuroside, verbascoside, luteolin, rutin, hydroxytyrosol (HT), tyrosol or ferulic acid (Lee et al., 2009; Quirantes-Piné et al., 2013) being the oleuropein the majority secoiridoid. The HT can be present in free form but mostly in its glycosylated form and esterified with elenolic acid forming the oleuropein. Then, the olive leaf has recently received particular attention as ingredient bioactive in pharmaceuticals, cosmetics and nutraceuticals. Navarro and Morales (2015) described the antiglycative activity of HT is mainly mediated by the trapping of 1,2-dicarbonyl compounds in simulated physiological conditions which is relevant at a physiological scale. However, information on the effectiveness of the antiglycative capacity of HT in a food model against specific AGEs is still not conclusive.

Recently, Mateos et al. (2016) pointed out that HT is a promising functional ingredient in biscuits since it is highly bioavailable and lowers postprandial oxidized-LDL levels. Since HT maintains their bioactivity after baking, it could be plausible that its antiglycative capacity will remain as well. Then, the aim of the present study was to investigate the efficacy of HT and an olive leaf extract (OLE) with high content in HT to mitigate the fluorescent AGEs formation and specifically of AGEs as CML, CEL and pentosidine in different biscuit formulations. In parallel, dicarbonyl trapping capacity and inhibition of the formation of HMF were investigated to get more insight into the mechanism of action.

2. Material and methods

2.1. Chemical and materials

The ingredients of model biscuits were purchased from local supermarkets. Olive leaves (*Olea Europaea* Picual variety, Córdoba, Spain), MGO (40% aqueous solution), GO (40% aqueous solution), 5-methylquinoxaline (5-MQ), o-phenylenediamine (OPD), sodium borohydride, perfluoropentanoic acid (purity > 97%), heptafluorobutyric acid (HFBA), perfluoropentanoic acid (purity > 97%), Hydroxymethylfurfural (HMF), quinine sulphate, quercetin (QE) and gallic acid (GA) standards were provided by Sigma (St Louis, MO, USA). 3-deoxyglucosone (3-DG) was provided by Prof. Pischetsrieder (University of Erlangen-Nuremberg, Germany) and HT (purity > 99%) was acquired from Seprox Biotech (Madrid, Spain). Ethanol, hexane, ethyl acetate, hydrochloric acid were obtained from Panreac (Madrid, Spain). Potassium hexacyanoferrate, zinc acetate, formic acid, glacial acetic acid and high-performance liquid chromatography (HPLC)-grade methanol and acetonitrile were from Merck (Darmstadt, Germany). N^{ε}-carboxymethyl-l-lysine (CML, $\geqslant$97%), N^{ε}-carboxyethyl-l-lysine (CEL, $\geqslant$97%), CML-d2, CEL-d4, and pentosidine were obtained from PolyPeptide Laboratories (Strasbourg, France). The Milli-Q water was obtained by an Elix3 water purification system coupled to a Milli-Q Advance 10 module (Millipore, Molsheim, France). All other chemicals were of analytical grade and supplied by Panreac Quimica (Barcelona, Spain).

2.2. Equipment

Synergy™ HT-multimode microplate reader with an automatic reagent dispense and temperature control from Biotek Instruments (Winooski, VT, USA). HPLC Shimadzu (Kyoto, Japan) equipped with a quaternary pump (LC-20AD), an autosampler (SIL-20AHT), an oven (CTO-10ASVP), a diode-array detector (SPD-M20A) and a fluorescence detector (RF-20AXS). LC-MS/MS was performed with a 1200 HPLC system (Agilent Technologies, Palo Alto, CA, USA) coupled to a triple quadrupole (G6410B, Agilent Technologies) via electrospray ionization operating in positive mode.

2.3. Preparation of the Olive Leaf Extract (OLE)

An OLE containing a high proportion of HT was obtained according to Lee et al. (2009) with some modifications. Fresh olive leaves were washed, dried (40 °C/2 days) and ground. The powder (10 g) was mixed with 100 mL of ethanol:water:HCl (80:19.75:0.25; pH 2.5), and kept under shaking in darkness (37 °C/7 days). Then, pH was readjusted to 2.5 with 2 N HCl and the mixture kept in the dark for another 3 h before filtering. The supernatant was dried in a vacuum evaporator (Strike 300, Steroglass, Perugia, Italy) and then was extracted with hexane (25 mL, 3 times) and ethyl acetate (50 mL, 5 times). The ethyl acetate fraction (250 mL) was again dried under vacuum and dissolved in a methanol/water solution (60:40% v/v) to obtain a final OLE concentration of 1 mg/mL (stock solution) with a HT content of 0.15 mg/mL extract.

2.4. Preparation of biscuits

Model biscuits were prepared as described by Gökmen, Açar et al. (2008) with some modifications. Recipes were formulated with 95 g of wheat flour, 35 g of sucrose, 25 g of deionized water, 24 g of sunflower oil, 1.2 g of sodium bicarbonate, 1 g of salt