Food Research International 105 (2018) 654–667

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Review

Hydroxytyrosol: Bioavailability, toxicity, and clinical applications

María Robles-Almazan[a,1], Mario Pulido-Moran[b,d,1], Jorge Moreno-Fernandez[c,d,1], Cesar Ramirez-Tortosa[a], Carmen Rodriguez-Garcia[b,d], Jose L. Quiles[c,d], MCarmen Ramirez-Tortosa[b,d,*]

[a] Department of Pathological Anatomy, Hospital Complex of Jaén, Avenida del Ejército Español, 10, Jaén 23007, Spain
[b] Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, University of Granada, University campus of Cartuja, Granada 18071, Spain
[c] Department of Physiology, Faculty of Pharmacy, University of Granada, University campus of Cartuja, Granada 18071, Spain
[d] Institute of Nutrition and Food Technology José Mataix, University of Granada, Biomedical Research Centre, Avenida del Conocimiento, Armilla, Granada 18016, Spain

ARTICLE INFO

Keywords:
Hydroxytyrosol
Olive oil
Chronic diseases
Inflammation
Reactive oxygen species (ROS)
Cancer

ABSTRACT

Many beneficial properties have been attributed to the Mediterranean diet. Over the years, researchers have attempted to learn which foods and which food components are responsible for good health. One of these components is hydroxytyrosol, an important phenolic compound present in olive oil.

Hydroxytyrosol is a molecule of high interest to the pharmaceutical industry due to its anti-inflammatory and antimicrobial qualities its role against cardiovascular diseases and metabolic syndrome and for its neuroprotection, antitumour, and chemo modulation effects. The interest in this molecule has led to wide research on its biological activities, its beneficial effects in humans and how to synthetize new molecules from hydroxytyrosol.

This review describes the vast range of information about hydroxytyrosol, focusing on its involvement in biological mechanisms and modulation effects on different pathologies. This review also serves to highlight the role of hydroxytyrosol as a nutraceutical and as a potential therapeutic agent.

1. Introduction

The Mediterranean diet (MD) has been widely studied due to its association with improved human health. This diet is based on a high intake of cereals, vegetables, fruits, olive oil (OO), nuts, and legumes, a low quantity of meat and meat products, and a moderate amount of fish and seafood and moderate drinking of alcohol. It is well established that the MD is very effective against: cardiovascular disease (Estruch et al., 2006; Goncalves et al., 2015), diabetes (Salas-Salvado et al., 2014), inflammation (Martinez-Gonzalez et al., 2015), cancer (Couto et al., 2011), and aging (Gonzalez-Alonso et al., 2015; Varela-Lopez et al., 2015).

Many of the benefits associated with the MD are the result of a high intake of antioxidants and anti-inflammatory elements present in several components of this diet, especially with a high adherence to the diet (Diamanti et al., 2014; Gonzalez-Alonso et al., 2015; Granados-Principal et al., 2012).

There is much evidence of the health-beneficial effects of the MD because of the consumption of olive oil. This product contains large amounts of monounsaturated fatty acids and also antioxidants like (poly)phenols, which are responsible for the organoleptic characteristics, the auto-oxidation stability and all properties of olive oil in relation to health (Buckland & Gonzalez, 2015; Gonzalez-Alonso et al., 2015; Lopez-Miranda et al., 2010).

This review focuses on one of the most important components of olive oil's (poly)phenol group: hydroxytyrosol (HT).

Abbreviations: MD, Mediterranean diet; HT, hydroxytyrosol; IUPAC, International Union of Pure and Applied Chemistry; ADME, absorption, distribution, metabolism and excretion processes; EVOO, extra virgin olive oil; HTA, HT acetate; Tyr, tyrosol; EFSA, European Food Safety Authority; VECs, vascular endothelial cells; ROS, reactive oxygen species; Mn-SOD, Mn-Superoxide dismutase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; CAT, catalase; cAMP, (cyclic adenosine monophosphate); cGMP, (cyclic guanosine monophosphate); PDE, phosphodiesterase; COX, cyclooxygenase; TxB2, thromboxane B2; TxA2, thromboxane A2; ICAM-1, Intercellular Adhesion Molecule 1; VCAM-1, vascular cell adhesion molecule 1; HAEC, aortic endothelial cells; TBARS, thiobarbituric acid reactive substances; LDH, lactate dehydrogenase; LDL, low density lipoproteins; NO, nitric oxide; TNF-α, tumour necrosis factor-alpha; PKC, protein kinase C; PGE2, prostaglandin E2; TGF-β1, transforming growth factor β1; Nrf-2, nuclear transcription factors NF-E2-related factor 2; HO-1, haem oxygenase-1; NQO-1, quinone oxidoreductase-1; BDNF, brain-derived neurotrophic factor; GAP43, growth associated protein 43; CDKs, cyclin-dependent kinases; FASN, fatty acid synthase; HER2, human epidermal growth factor receptor 2

* Corresponding author at: Department of Biochemistry and Molecular Biology II, Institute of Nutrition and Food Technology "José Mataix", Biomedical Research Centre, University of Granada, 18016 Armilla, Granada, Spain.
E-mail address: mramirez@ugr.es (M. Ramirez-Tortosa).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.foodres.2017.11.053
Received 4 July 2017; Received in revised form 12 November 2017; Accepted 19 November 2017
Available online 21 November 2017

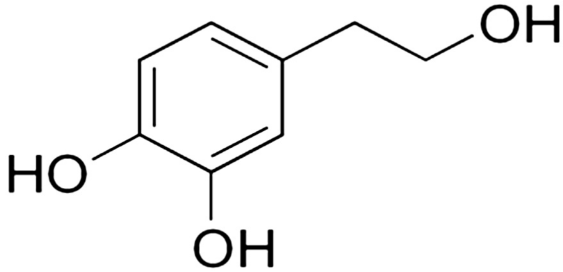

Fig. 1. Hydroxytyrosol structure.

2. Characteristics of HT

HT is an amphipathic phenol with a molecular weight of 154.16 g/mol and a phenylethyl-alcohol structure. It is also called 3,4-dihydroxyphenylethanol (DOPET) or 3,4-dihydroxyphenolethanol (3,4-DHPEA) or 4-(2-Hydroxyethyl)-1,2-benzenediol by the International Union of Pure and Applied Chemistry (IUPAC) system (Fig. 1). This compound is part of the soluble fraction from minority components of extra virgin olive oil and it is present at a very high concentration in the leaves of the olive tree (*Olea europaea L.*). HT is also one of the main compounds present in olive oil and it has been described as an antioxidant with many biological activities (Covas, de la Torre, & Fito, 2015; Perez-Bonilla, Salido, van Beek, & Altarejos, 2014). Due to the phenolic nature of HT, many studies have been carried out with different types of olive oils, enriched or not with this compound, to demonstrate its antioxidant, anti-inflammatory and antiatherogenic effects (Bernini, Merendino, Romani, & Velotti, 2013; Granados-Principal et al., 2014; Rodriguez-Morato et al., 2015). Additional studies have also focused on the antimicrobial (Medina, de Castro, Romero, & Brenes, 2006; Zoric et al., 2013) and dermatological properties (D'Angelo et al., 2005) of HT, thus showing the wide health-beneficial properties of this compound. Thanks to all these findings, HT has been postulated as a nutraceutical for preventing and treating different diseases.

The origin of HT is the hydrolysis of oleuropein which happens during the ripening of the olives, and during the storage and elaboration of table olives (Charoenprasert & Mitchell, 2012). When olives are processed to get their oil by crushing them, three different (poly)phenol-enriched layers are obtained: olive mill wastewater, pomace, and olive oil. Due to the amphipathic character of HT, it can be found on these three phases on a free form, as acetate form or as part of more complex compounds like oleacein, verbascoside, and oleuropein (Boskou, 2008).

On the other hand, the content of HT in olive oil depends on the kind of olive tree and olive, the location of the plantation, the oil quality, and the olive oil elaboration process (Romero et al., 2004).

HT is also present in the leaves of olive trees on a free form and also taking part in the structure of a complex of different elements. Some authors have determined that HT in VOO, and by-products of oil mechanical extraction process can be found mainly as aglycon derivatives of oleuropein and demethyoleuropein (3,4-DHPEA-EDA, 3,4-DHPEA-EA), doing very difficult to find HT as free form (Fabiani et al., 2006; Servili et al., 2004). Will be during the storage of the OO when the level of HT increase as a consequence of the hydrolysis of the secoiridoids. Other authors found that HT only was found in EVOO with a polyphenol content greater than 200 ppm (Montedoro, Servili, Baldioli, & Miniati, 1992). The extraction process of both HT and other (poly)phenols is commonly carried out in presence of methanol, ethanol or both, to induce the enzymatic activity of galactosidase to generate HT from oleuropein (Briante et al., 2002; Briante, La Cara, Febbraio, Patumi, & Nucci, 2002; Fernández-Mar, Mateos, García-Parrilla, Puertas, & Cantos-Villar, 2012).

In the last ten years, it has been found that HT is also present in red and white wines, with higher concentration in the first one. However, these concentrations are always lower than they usually are in extra virgin olive oil or extracts from leaves. The average concentration of HT found in the scientific literature for different type of wines and olive-leaf extracts (commonly employed as tisanes)(Di Tommaso, Calabrese, & Rotilio, 1998; Fernández-Mar et al., 2012; Minuti, Pellegrino, & Tesei, 2006; Quirantes-Pine et al., 2013; Ramirez-Tortosa, Pulido-Moran, Granados, Gaforio, & Quiles, 2014) are reported in Table 1. In spite of HT has been directly linked with OO, most of the authors have detected it in a very low concentration in VOO, reaching an average of 1.8 mg of HT per kg of 210 different VOO evaluated samples, obtained in industrial plants (Servili et al., 2004). Similar results to Servili et al. (2004) were obtained by Ocakoglu, Tokatli, Ozen, and Korel (2009). Other authors showed that the concentration of free HT on a Picual variety of OO could only reach values around 200 μol per kg of OO after seven months of storage (García, Brenes, Romero, García, & Garrido, 2002).In addition, Godoy-Caballero, Acedo-Valenzuela, and Galeano-Diaz (2012) showed a range of concentration of HT from 9 up to 21 μg of HT per gram of OO, depending on the variety of them.

Table 1
Average concentration of HT in different foods.

Food	HT average content
White wine	2 mg/l
Aged red wine	20 mg/l
Red wine	3 mg/l
Olive tree leaves	12 mg/g

In contrast, other authors showed a high that the concentration of HT can oscillate from 0.5 to 60 mg of HT per kg of OO (Alarcón Flores, Romero-González, Garrido Frenich, & Martínez Vidal, 2012). Similar results were obtained by García-Villalba et al. (2010), where HT achieved up to 20 mg per kg of OO. This large discrepancy may be due in part to differences in extraction procedures and chromatographic methods employed for the analysis of the phenolic compound from VOO (Servili et al., 2004). To date, this issue and the development of methodologies to quantify phenols in EVOO have been extensively discussed (García-Villalba et al., 2010).

Nowadays, many researchers are looking for new forms of HT to improve the ADME (absorption, distribution, metabolism and excretion) processes, its stability and its health-biological features. These studies are focused on changing the solubility of HT in order to increase its bioavailability and its plasma half-life (Mateos et al., 2011). Almost all experiments have been carried out in *in vitro* models. Some of these new isolated compounds, their biological activities and their synthesis methods have been reviewed by Bernini et al. (Bernini et al., 2015):

HT Esters: the most important compound of this group is HT acetate which is found in extra virgin olive oil. HT acetate has demonstrated a higher antioxidant capacity than HT. In addition, nitro-ester derivatives have shown beneficial effects in Parkinson's disease associated to their antioxidant properties (Trujillo et al., 2014).

HT Alkyl Ethers: a new class of lipophilic HT derived with high cytotoxic activities in A549 lung cancer cells and MRC5 non-malignant lung fibroblasts (Calderon-Montano et al., 2013).

HT analogues: with similar structure to HT but different substituents on the aromatic ring and/or a different length of the alcoholic chain.

HT thioderivatives: containing thioacetate, thiol, and disulphide groups.

HT derived isochromans: also presents in extra virgin olive oil methanolic extracts.