# 18

# Metabolism and Bioavailability of Olive Oil Polyphenols

María Gómez-Romero[1], Rocío García-Villalba[2], Alegría Carrasco-Pancorbo[1] and Alberto Fernández-Gutiérrez[1]
[1]*University of Granada*
[2] *CEBAS CSIC of Murcia*
*Spain*

## 1. Introduction

The significance of virgin olive oil (VOO), hinged to its many virtues in both gastronomy and health, is nowadays undeniable. Their protective effects are attributed to its high content of monounsaturated fatty acids and to the presence of some minor components, which add up to 2% of the weight. Among its several minor constituents, polar phenolic compounds, usually characterized as polyphenols, have become the subject of intensive research because of their biological activities, their influence on the organoleptic properties of VOO and their contribution to its oxidative stability (Bendini et al., 2007).

The phenolic fraction of VOO consists of a heterogeneous mixture of compounds belonging to several families with varying chemical structures. A brief description of the main classes of phenolic compounds contained in VOO is given below:

- *Phenolic acids.* There are two main series of these acids, depending on the carbon skeleton: benzoic acids (C6-C1: 3-hydroxybenzoic, *p*-hydroxybenzoic, protocatechuic, gentisic, vanillic, syringic and gallic acids) and cinnamic acids (C6-C3: *o*-coumaric, *p*-coumaric, caffeic, ferulic and sinapic acids).
- *Phenolic alcohols.* The two most important in VOO are hydroxytyrosol (Hyty) and tyrosol (Ty), although two Hyty derivatives, its acetate and its glucoside, can be also found. Hyty and Ty only differ in a hydroxyl group in the *meta* position.
- *Secoiridoids.* They are present exclusively in plants of the Olearaceae family. The olives mainly contain the polar oleuropein (Ol) and ligstroside (Lig) glycosides. Ol is the ester of elenolic acid (EA) with Hyty, and Lig is the ester of EA with Ty. Ol and Lig aglycones (Ol Agl and Lig Agl, respectively) are formed by removal of the glucose moiety from glycosides by endogenous β-glucosidases during ripening, oil extraction and storage.
- *Lignans.* (+)-1-Pinoresinol, (+)-1-hydroxypinoresinol and (+)-1-acetoxypinoresinol are the most reported compounds in olive oil.
- *Flavonoids.* The main flavonoids present in VOO are apigenin and luteolin, which are originated from their corresponding glucosides present in the drupe.

The qualitative and quantitative composition of VOO hydrophilic phenols is strongly affected by the agronomic and technological conditions of production (Servili et al., 2004). Among agronomic parameters, the cultivar, the fruit ripening degree, the agronomic

techniques used and the pedoclimatic conditions are the aspects more extensively studied (Tovar et al., 2001; Uceda et al., 1999). Moreover, by modulating technology, it is possible to some extent to optimize the transfer of some polar minor constituents into the oil or reduce their level (Boskou, 2009). The influence of variety, extraction system, ripening degree and storage in the polyphenolic content of a VOO has been extensively discussed in the literature (Boskou, 2009; Uceda et al., 1999).

Wide ranges of total polar phenols concentration have been reported in olive oils (50-1000 mg/kg), although the most usual value is found between 100-350 mg/kg (Boskou et al., 2006). In general, the most abundant phenolic compounds in VOO are aglycones deriving from secoiridoids. Trying to establish levels of individual phenols, Servili & Montedoro (2002) calculated average values of 7 phenolic compounds from a considerable number of samples of industrial olive oils. They concluded that Hyty and Ty were found only in trace amounts (less than 10 mg/kg oil) and the most abundant phenols were decarboxylated Ol Agl (63-840 mg/kg), Ol Agl (85–310 mg/kg), and decarboxylated Lig Agl (15-33 mg/kg). Brenes et al. (2002) published values ranging from 3-67 mg/kg for 1-acetoxypinoresinol, and from 19-41 mg/kg for pinoresinol in 5 Spanish olive oils, data that can be completed with the researches carried out by Romero et al. (2002) and Tovar et al. (2001). Levels of luteolin have been found to be around 10 mg/kg in some Spanish olive oils (Brenes et al., 1999) or ranging between 0.2-7 mg/kg for Greek oils (Murkovic et al., 2004). Carrasco-Pancorbo et al. (2006) developed a method to quantify 14 individual phenols belonging to different families in 7 Spanish extra-virgin olive oils (EVOOs). They also quantified them, finding the following contents (mg/kg): simple phenols: 6.8-11.5; complex phenols: 70.5-799.5; lignans: 0.81-20.6; and flavonoids: 1.4-8.6.

Intake of olive oil in the Mediterranean countries is estimated to be 30–50 g/day, based on the per capita olive oil consumption of 10–20 kg/year in Greece, Italy and Spain (Boskou, 2000; Food and Agricultural Organization, 2000). A daily consumption of 50 g olive oil with a concentration of 180 mg/kg of phenols would result in an estimated intake of about 9 mg of olive oil phenols per day (de la Torre, 2008; Vissers et al., 2004), of which at least 1 mg is derived from free Hyty and Ty, and 8 mg are related to their elenolic esters and also to Ol Agl and Lig Agl (de la Torre, 2008). Some other estimations have been made. For the Greek population (Dilis & Trichopolou, 2009), the daily per-capita intake is about 17 mg. Vissers et al. (2004) estimated that about 1 mg of the phenol intake per day (6 mmol) is derived from Hyty and Ty, about 8 mg (23 mmol) from the aglycones, and so the total phenol intake would be about 29 mmol.

## 2. Bioavailability of olive oil polyphenols

Accumulating evidence suggests that VOO may have health benefits; it can be considered as an example of a functional food containing a variety of components that may contribute to its overall therapeutic characteristics (Stark & Madar, 2002; Visioli & Bernardini, 2011). To explore and determine the mechanisms of action of olive oil polyphenols and their role in disease prevention, understanding the factors that constrain their release from the olive oil, their extent of absorption, and their fate in the organism is crucial. These issues can be described under the term *bioavailability,* borrowed from the field of pharmacology, redefined as "that fraction of an oral dose, either parent compound or active metabolite, from a particular preparation that reaches the systemic circulation" (Stahl et al., 2002). To simplify this definition, D'Archivio et al. (2010) explained that it simply means how much of the

ingested amount of polyphenols is able to exert its beneficial effects in the target tissues. It is important to realize that the most abundant phenolic compounds in our diet are not necessarily those that have the best bioavailability profile, either because they have a lower intrinsic activity or because they are poorly absorbed from the intestine, highly metabolized, or rapidly eliminated. In addition, the metabolites that are found in blood and target organs, resulting from digestive or hepatic activity, may differ from the native compounds in terms of biological activity (Manach et al., 2004).

Although the information concerning the bioavailability of most olive oil polyphenols is limited, intensive research has been carried out in the past decade. This fact is reflected in the number of reviews published since 2002 (Corona et al., 2009; Covas et al., 2009; de la Torre, 2008; Fitó et al., 2007; Tuck & Hayball, 2002; Visioli et al., 2002; Vissers et al., 2004). To address the bioavailability of olive oil phenolic compounds, we have reviewed *in vitro* and *in vivo (*both animal and human) studies on the absorption, transport, metabolism and excretion of olive oil phenolic compounds.

### 2.1 Absorption and disposition

Direct evidence on bioavailability of olive oil phenolic compounds has been obtained by measuring the concentration of the polyphenols and their metabolites in biological fluids, mostly plasma and urine, after ingestion of pure compounds or of olive oil, either pure or enriched with the phenolics under study. The majority of research regarding the bioavailability of olive oil polyphenols has been focused on three major phenolics: Hyty, Ty and Ol, as can be seen in **Tables 1** and **2**.

After ingestion, olive oil polyphenols can be partially modified in the acidic environment of the stomach. The effect of such environment on aglycone secoiridoids has been examined *in vitro* by incubating the compounds at 37 ºC in simulated gastric pH conditions and during normal physiological time frames (Corona et al., 2006; Pinto et al., 2011). Although hydrolysis takes place releasing free phenolic alcohols, a significant amount remains intact and thus, enters the small intestine unmodified. Ol Agl and its dialdehydic form, however, are likely not absorbed as such in the small intestine; the major metabolites detected using the perfused rat intestine model were the glucuronide conjugates of the reduced form of both compounds (Pinto et al., 2011).

Manna et al. (2000) carried out studies on the transport kinetics of radiolabeled Hyty using differentiated Caco-2 cells. The only metabolite found in the culture medium was the methylated derivative (i.e. homovanillic alcohol - HVAlc). They also demonstrated that Hyty was transported across the membrane of the human enterocytes by a bidirectional passive diffusion mechanism. Caco-2/TC7 cell monolayers have been used to study the metabolism of other olive oil polyphenols, such as Ty, *p*-coumaric acid, pinoresinol, luteolin (Soler et al., 2010) and Hyty acetate (Mateos et al., 2011). Results showed that the methylated conjugates are the main metabolites and that the acetylation of Hyty significantly increases its transport across the small intestinal epithelial cell barrier, enhancing the delivery of Hyty to the enterocytes.

To study the potential hepatic metabolism of olive oil phenols, human hepatoma HepG2 cells were incubated for 2 and 18 h with Ty, Hyty and Hyty acetate (Mateos et al., 2005). Extensive uptake and metabolism of Hyty and Hyty acetate were observed, with scarce metabolism of Ty. Hyty acetate was converted into free Hyty and then metabolized;

| Tested Phenol | Model system[a] | Methods | Metabolites Detected | Study Outcome | Ref. |
|---|---|---|---|---|---|
| [$^{14}$C] Hyty | Caco-2 cell monolayers | Transport kinetics: incubation with increasing concentrations (50-500 µM) at 37 and 4 $^{o}$C for 2 min. Transepithelial transport: incubation with 100 µM Hyty, glucose and mannitol | HVAlc | Hyty transport occurs via a passive diffusion mechanism, bidirectionally and in a dose-dependent manner. Hyty is quantitatively absorbed in the intestine | Manna et al., 2000 |
| Ol glycoside | Isolated rat intestine | In situ intestinal perfusion technique: infusion of aqueous solution (1 mM, 50 µl/min) at 37 $^{o}$C during 40 min in both iso-osmotic and hypotonic luminal conditions | | Ol in aqueous solution can be absorbed, albeit poorly, from isolated perfused rat intestine. The $P_{app}$ of Ol in hypotonic conditions is significantly higher | Edge-combe et al., 2000 |
| Hyty, Ty, Hyty-Ac | Hepatoma HepG2 cells | Cell uptake and metabolism of phenols: incubation with 100 µM at 37 $^{o}$C for 2 and 18 h | Hyty mono-gluc and methyl-gluc, HVA, Ty gluc, Hyty-Ac mono-gluc | Extensive uptake and hepatic metabolism of Hyty and Hyty-Ac with scarce metabolism of Ty; main derivatives formed: glucuronidated and methylated conjugates | Mateos et al., 2005 |
| Hyty, Ty, Ol | Caco-2 cell monolayers and rat segments of jejunum and ileum | | Hyty and Ty gluc, HVAlc, Hyty glutathionylated | Hyty and Ty were transferred across the cell monolayers and rat segments of intestine and were subjected to classic phase I/II biotransformation. No absorption of Ol | Corona et al., 2006 |
| Hyty, Ty, *p*-coumaric acid, pinoresinol, luteolin | Caco-2/TC7 cell monolayers | Phenols metabolism: incubation with 40, 50 and 100 µM at 37 $^{o}$C for 1, 6 and 24 h. Transport experiments in the AP, cellular and BL compartments: AP loading of phenol at 100 µM | *Hyty:* methyl, sulfate, methyl-sulfate. *Ty:* methyl, sulfate. *p-Coumaric acid:* disulfate, methyl. *Pinoresinol:* gluc, sulfate. *Luteolin:* gluc, methyl, methyl-gluc, | Limited intestinal metabolism. Major metabolites: methylated conjugates. Time-dependent efflux of various free and conjugated forms, showing preferential AP to BL transport after 24 h of incubation | Soler et al., 2010 |
| Hyty, Hyty-Ac | Caco-2/TC7 cell monolayers | Metabolism experiments and transport experiments in the AP and BL compartments: incubation with 50 µM at 37 $^{o}$C for 1, 2 and 4 h | *Hyty:* HVAlc. *Hyty-Ac:* Hyty, HVAlc, mono-gluc. | Hyty-Ac is better absorbed than free Hyty and serves to enhance delivery of Hyty to the enterocytes for subsequent metabolism and BL efflux) | Mateos et al., 2011 |
| Ol Agl, dialdehydic form of Ol Agl | Human Caco-2 cell monolayers and isolated lumen of rat intestine (jejunum and ileum) | Transport experiments using Caco-2 cells: incubation with 50, 100 and 200 µM at 37 $^{o}$C for 2 h; AP loading. Transport experiments using rat intestine: perfusion of methanol solution (100 µM) at 37 $^{o}$C during 80 min | Hyty, HVAlc, Hyty and HVAlc gluc, gluc conjugates of the reduced forms of tested compounds | Caco-2 cells expressed limited metabolic activity. Major metabolites using the perfused rat intestine model: gluc of the reduce forms. Secoiridoids in the parental form were little absorbed in the small intestine | Pinto et al., 2011 |

[a] Caco-2 cells: model system of the human intestinal epithelium; HepG2 cells: model system of the human liver; TC7 cells: spontaneously differentiating clone derived from the original Caco-2 cell population.
*Abbreviations:* AP: apical; BL: basolateral; gluc: glucuronide; Hyty: hydroxytyrosol; Hyty-Ac: hydroxytyrosol acetate; HVA: homovanillic acid; HVAlc homovanillic alcohol; Ol: oleuropein; Ol Agl: oleuropein aglycone; $P_{app}$: apparent permeability coefficient; Ty: tyrosol.

Table 1. *In vitro* studies carried out with olive oil polyphenols.

of the data from humans presented in the literature on the bioavailability refer only to the release of the polyphenols from the food matrix and their consequent absorption (D'Archivio et al., 2010; Vissers et al., 2004).

To address the bioavailability of olive oil phenols, we should exclude studies without a control diet and studies in which the amount of ingested phenols is not reported or could not be estimated (Miró-Casas et al., 2001a; Visioli et al., 2000a; Vissers et al., 2004). In other words, it is essential to characterize in depth the polyphenolic extract of the olive oil before starting bioavailability studies to assure their usefulness; since this fraction is quite complex and heterogeneous, it represents another requirement which difficults the whole process.

Advances in the understanding of olive oil polyphenols metabolism have been made possible by improvements in the analytical methodologies used, particularly high-resolution chromatographic systems with mass spectrometry as detector (Bai et al., 1998; Del Boccio et al., 2003; García-Villalba et al., 2010; Khymenets et al., 2011; Miró-Casas et al., 2003b). Performing metabolomic studies is challenging and requires measurements of a very high quality using powerful platforms. Even if the analyst uses proper tools, the fully structural assignment of the metabolites under study is sometimes very difficult due to the lack of the metabolite standards; fact which makes difficult the correct quantification too (D'Archivio et al., 2010; García-Villalba et al., 2010). The amount of information about the sample under study achieved in metabolomic studies is considerable, that is why for meaningful interpretation the appropriate statistical tools must be employed to manipulate the large raw data sets in order to provide understandable and workable information (Manach et al., 2009).

A very interesting review written by D'Archivio et al. (2010) gives a critical overview about the difficulties and the controversies surrounding the studies aimed at determining the bioavailability of polyphenols. Summarizing, there are some essential steps to be followed to establish conclusive evidences for the effectiveness of polyphenols in disease prevention and in human health improvement: 1) determination of the distribution of these compounds in our diet, estimating their content in each food; 2) identification of which of the existing polyphenols are likely to provide the greatest effects in the context of preventive nutrition, and 3) assesment of the bioavailability of polyphenols and their metabolites, to evaluate their biological activity in target issues.

Even though the bioavailability studies are properly designed, we have to be aware of how many different endogenous and exogenous variables are involved and the difficulties that have to be faced. The main factors recognized as affecting olive oil polyphenols bioavailability can be grouped in the following categories: factors related to the polyphenol characteristics, food/food processing related factors, external factors and factors related to the host, as it can be observed in **Figure 1.** An in-depth discussion of every factor influencing the bioavailability of olive oil polyphenols has been made by Manach et al. (2004) and Cicerale et al. (2009).

## 4. Conclusions

To explore and understand the mechanism of action of olive oil polyphenols and their role in disease prevention and human health improvement, extensive studies of absorption, metabolism, excretion, toxicity, and efficacy are needed. Although *in vitro* studies can be

very useful and provide valuable information, they have to be completed with extensive *in vivo* research. The first requirement for a beneficiary dietary compound is that it enters into the blood circulation; therefore to demonstrate *in vivo* effects of olive oil phenolics it is necessary to assess first their *bioavailability*.

Analysis of plasma and urine provide valuable information on the identity and pharmacokinetics of circulating metabolites after ingestion. Since the metabolites sequestered in body tissues are not usually taken into account, results from urine samples could be an underestimation. There have been several studies which have determined the metabolites of the various olive oil polyphenols (mainly Hyty, Ty, and Ol) in human plasma and urine after oral intake, although the information is still scarce. The conjugation mechanisms that occur in the small intestine and later in the liver are highly efficient. The resulting metabolites are mainly glucuronate and sulfate conjugates with or without methylation across the catechol group (many are multiply conjugated).

Bioavailability studies are gaining increasing interest as food industries are continually involved in developing new products, defined as ''functional'' by virtue of the presence of specific antioxidants or phytochemicals. The difference between functional foods and medicines calls for moderation when the "medicinal" properties of individual food items, be it olive oil, are indicated. The correct message should be to select foods whose components have proven, albeit limited in magnitude, biological activities and build a balanced diet round them, to reduce several chronic diseases.

## 5. Acknowledgements

The authors are very grateful to Junta de Andalucía (Project P09-FQM-5469), to the International Campus of Excellence (CEI Granada 2009), to the Ministry of Education of Spain and to the Regional Government of Economy, Innovation and Science of Andalusia.

## 6. References

Bai, C.; Yan, X.; Takenaka, M.; Sekiya, K. & Nagata, T. (1998). Determination of Synthetic Hydroxytyrosol in Rat Plasma by GC-MS. *Journal of Agricultural and Food Chemistry*, Vol. 46, No. 10, (September 1998), pp. 3998-4001, ISSN 0021-8561

Bazoti, F.N.; Gikas, E.; Puel, C.; Coxam, V. & Tsarbopoulos, A. (2005). Development of a Sensitive and Specific Solid Phase Extraction-Gas Chromatography–Tandem Mass Spectrometry Method for the Determination of Elenolic Acid, Hydroxytyrosol, and Tyrosol in Rat Urine. *Journal of Agriculture and Food Chemistry,* Vol. 53, No. 16, (August 2005), pp. 6213–6221, ISSN 0021-8561

Bazoti, F.N.; Gicas, E. & Tsarbopoulos, A. (2010). Simultaneous Quantification of Oleuropein and its Metabolites in Rat Plasma by Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry. *Biomedical Chromatography*, Vol. 24, (May 2010), pp. 506-515, ISSN 0269-3879

Bendini, A.; Cerretani, L.; Carrasco-Pancorbo, A.; Gómez-Caravaca, A.M.; Segura-Carretero, A.; Fernández-Gutiérrez A. et al. (2007). Phenolic Molecules in Virgin Olive Oils: A Survey of Their Sensory Properties, Health Effects, Antioxidant Activity and Analytical Methods. An Overview of the Last Decade. *Molecules*, Vol. 12, (August 2007), pp. 1679-1719, ISSN 1420-3049

Bonanome, A.; Pagnan, A.; Caruso, D; Toia, A.; Xamin, A.; Fedeli, E. et al. (2000). Evidence of Postprandial Absorption of Olive Oil Phenols in Humans. *Nutrition, Metabolism & Cardiovascular Diseases*, Vol. 10, No. 3, (June 2000), pp. 111-120, ISSN 0939-4753

Boskou, D. (2000) Olive oil, In: *Mediterranean Diets (World Review of Nutrition and Dietetics, Vol. 87),* A.P. Simopoulos, F. Visioli, (Eds.), pp. 56-77, Karger Press, ISBN 978-3-8055-7066-4, Basel, Switzerland

Boskou, D.; Tsimidou, M. & Blekas, D. (2006). Polar phenolic compounds, In: *Olive Oil, Chemistry and Technology*, D. Boskou, (Ed.), pp. 73-92, AOCS Press, ISBN 978-1-893997-88-2, Champaign, IL, USA

Boskou, D. (2009). Phenolic compounds in olives and olive oil, In: *Olive Oil. Minor Constituents and Health,* D. Boskou, (Ed.), pp. 11-44, CRC press, ISBN 978-1-4200-5993-9, NY, USA

Brenes, M.; García, A.; García, P.; Rios, J.J. & Garrido, A. (1999). Phenolic Compounds in Spanish Olive Oils. *Journal of Agricultural and Food Chemistry*, Vol. 47, No. 9, (September 1999), pp. 3535-3540, ISSN 0021-8561

Brenes, M.; García, A.; Rios, J.J.; García, P. & Garrido, A. (2002). Use of 1-acetoxypinoresinol to authenticate Picual olive oils. *International Journal of Food Science & Technology*, Vol. 37, (November 2002), pp. 615-625, ISSN 0950-5423

Carrasco-Pancorbo, A.; Gómez-Caravaca, A.M.; Cerretani, L.; Bendini, A.; Segura-Carretero, A. & Fernández-Gutiérrez, A. (2006). Rapid Quantification of the Phenolic Fraction of Spanish Virgin Olive Oils by Capillary Electrophoresis with UV Detection. *Journal of Agricultural and Food Chemistry,* Vol. 54, No. 21, (October 2006), pp. 7984-7991, ISSN 0021-8561

Caruso, D.; Visioli, F.; Patelli, R.; Galli, C. & Galli, G. (2001). Urinary Excretion of Olive Oil Phenols and their Metabolites in Humans, *Metabolism: Clinical and Experimental*, Vol. 50, No. 12, (December 2001), pp. 1426–1428, ISSN 0026-0495

Cicerale, S.; Conlan, X.A.; Sinclair, A.J. & Keast, R.S.J. (2009). Chemistry and Health of Olive Oil Phenolics. *Critical Reviews in Food Science and Nutrition,* Vol. 49, No. 3, (March 2009), pp. 218-236, ISSN 1040-8398

Coni, E.; Di Benedetto, R.; Di Pasquale, M.; Masella, R.; Modesti, D.; Mattei, R. et al. (2000). Protective Effect of Oleuropein, an Olive Oil Biophenol, on Low Density Lipoprotein Oxidizability in Rabbits. *Lipids*, Vol. 35, No. 1, (January 2000), pp. 45-54, ISSN 0024-4201

Corona, G.; Tzounis, X.; Dessì, M.A.; Deiana, M.; Debnam, E.S.; Visioli, F. et al. (2006). The Fate of Olive Oil Polyphenols in the Gastrointestinal Tract: Implications of Gastric and Colonic Microflora-Dependent Biotransformation. *Free Radical Research*, Vol. 40, No. 6, (June 2006), pp. 647-658, ISSN 1071-5762

Corona, G; Spencer, J.P.E. & Dessì, M.A. (2009). Extra Virgin Olive Oil Phenolics: Absorption, Metabolism, and Biological Activities in the GI Tract. *Toxicology and Industrial Health,* Vol. 25, (May-June 2009), pp. 285-293, ISSN 0748-2337

Covas, M.I.; Fitó, M.; Lamuela-Raventós, R.M.; Sebastiá, N.; de la Torre-Boronat, C. & Marrugat, J. (2000). Virgin Olive Oil Phenolic Compounds: Binding to Human Low Density Lipoprotein (LDL) and Effect on LDL Oxidation. *International Journal of Clinical Pharmacology Research.* Vol. 20, No. 3-4, (n.d.), pp. 49-54, ISSN 0251-1649

Covas, M.I.; de la Torre, K.; Farre-Albaladejo, M.; Kaikkonen, J.; Fito, M.; Lopez-Sabater, C. et al. (2006). Postprandial LDL Phenolic Content and LDL Oxidation are modulated

by Olive Oil Phenolic Compounds in Humans. *Free Radical Biology & Medicine*, Vol. 40, No. 4 (February 2006), pp. 608-616, ISSN 0891-5849.

Covas, M.I.; Khymenets, O.; Fitó, M. & de la Torre, R. (2009). Bioavailability and Antioxidant Effect of Olive Oil Phenolic Compounds in Humans, In: *Olive Oil. Minor Constituents and Health,* D. Boskou, (Ed.), pp. 109-128, CRC press, ISBN 978-1-4200-5993-9, NY, USA.

D'Angelo, S.; Manna, C.; Migliardi, V.; Mazzoni, O.; Morrica, P.; Capasso, G. et al. (2001). Pharmacokinetics and Metabolism of Hydroxytyrosol, a Natural Antioxidant from Olive Oil. *Drug Metabolism and Disposition,* Vol. 29, No. 11, (November 2001), pp. 1492-1498, ISSN 0090-9556

D'archivio, M.; Filesi, C.; Vari, R.; Scazzocchio, B. & Masella, R. (2010). Bioavailability of the Polyphenols: Status and Controversies. *International Journal of Molecular Sciences*, Vol. 11, No. 4, (March 2010), pp 1321-1342, ISSN 1422-0067

Day, A.J.; Mellon, F.A.; Barron, D.; Sarrazin, G.; Morgan, M.R. & Williamson, G. (2001). Human Metabolism of Flavonoids: Identification of Plasma Metabolites of Quercetin. *Free Radical Research*, Vol. 35, No. 6, (December 2001), pp. 941-952, ISSN 1071-5762

Dilis, V. & Trichopolou, A. (2009). Mediterranean diet and olive oil consumption-Estimations of daily intake of antioxidants from Virgin Olive Oil and olives, In: *Olive Oil. Minor Constituents and Health,* D. Boskou, (Ed.), pp. 201-210, CRC press, ISBN 978-1-4200-5993-9, NY, USA.

De la Torre-Carbot, K.; Jauregui, O.; Castellote, A.I.; Lamuela-Raventos, R.M.; Covas, M.I.; Casals, I. et al. (2006). Rapid High–Performance Liquid Chromatography-Electrospray Ionization Mass Spectrometry Method for Qualitative and Quantitative Analysis of Virgin Olive Oil Phenolic Metabolites in Human Low-Density Lipoproteins. *Journal of Chromatography A*, Vol. 1116, No. 1-2, (May 2006), pp. 69-75, ISSN 0021-9673

De la Torre-Carbot, K.; Chavez-Servin, J.L.; Jáuregui, O.; Castellote, A.I.; Lamuela-Raventos, R.M.; Fito, M., et al. (2007). Presence of Virgin Olive Oil Phenolic Metabolites in Human Low Density Lipoprotein Fraction: Determination by High–Performance Liquid Chromatography-Electrospray Ionization Tandem Mass Spectrometry. *Analytica Chimica Acta*, Vol. 583, No. 2, (February 2007), pp. 402-410 ISSN 0003-2670

De la Torre, R. (2008). Bioavailability of Olive Oil Phenolic Compounds in Humans. *Inflammopharmacology*, Vol. 16 (September 2008), pp. 245-247, ISSN 0925-4692

De la Torre-Carbot, K.; Chávez-Servín, J.L.; Jaúregui, O.; Castellote, A.I.; Lamuela-Raventós, R.M.; Nurmi, T. et al. (2010). Elevated Circulating LDL Phenol Levels in Men who Consumed Virgin rather than Refined Olive Oil are Associated with Less Oxidation of Plasma LDL. *The Journal of Nutrition*, Vol. 140, No. 3, (March 2010), pp. 501-508, ISSN 0022-3166

Del Boccio, P.; Di Deo, A.; De Curtis, A.; Celli, N.; Iacoviello, L. & Rotilio, D. (2003). Liquid Chromatography–Tandem Mass Spectrometry Analysis of Oleuropein and its Metabolite Hydroxytyrosol in Rat Plasma and Urine after Oral Administration. *Journal of Chromatography B*, Vol. 785, No. 1, (February 2003), pp. 47-56, ISSN 1570-0232

Edgecombe, S.C.; Stretch, G.L. & Hayball, P.J., (2000). Oleuropein, an Antioxidant Polyphenol from Olive Oil, Is Poorly Absorbed from Isolated Perfused Rat

Intestine. *The Journal of Nutrition*, Vol. 130, No. 12, (December 2000), pp. 2996-3002, ISSN 0022-3166

Food and Agricultural Organization [FAO], (2000). Food Balance Sheets, 1999. Rome.

Fitó, M.; de la Torre, R.; Farré-Albadalejo, M.; Khymenets, O.; Marrugat, J. & Covas, M.I. (2007). Bioavailability and Antioxidant Effects of Olive Oil Phenolic Compounds in Humans: A Review. *Annali dell'Istituto Superiore di Sanità*, Vol. 43, No. 4, (n.d.), pp. 375-381 ISSN 0021-2571

García-Villalba, R.; Carrasco-Pancorbo, A.; Nevedomskaya, E.; Mayboroda O.A,; Deelder, A.M.; Segura-Carretero, A. et al. (2010). Exploratory Analysis of Human Urine by LC-ESI-TOF MS after High Intake of Olive Oil: Understanding the Metabolism of Polyphenols. *Analytical and Bioanalytical Chemistry,* Vol. 398, No. 1, (September 2010), pp. 463-75, ISSN 1618-2642

Gimeno, E.; Fito, M.; Lamuela-Raventos, R.M.; Castellote, A.I.; Covas, M.; Farre, M. et al. (2002). Effect of Ingestion of Virgin Olive Oil on Human Low Density Lipoprotein Composition. *European Journal of Clinical Nutrition*, Vol. 56, No. 2, (February 2002), pp. 114-120, ISSN 0954-3007

Gimeno, E.; de la Torre-Carbot, K.; Lamuela-Raventós, R.M.; Castellote, A.I.; Fitó, M.; de la Torre, R. et al. (2007). Changes in the Phenolic Content of Low Density Lipoprotein after Olive Oil Consumption in Men. A Randomized Crossover Controlled Trial. *British Journal of Nutrition,* Vol. 98, No. 6, (December 2007), pp. 1243-1250, ISSN 0007-1145

Hillestrom, P.R.; Covas, M.I. & Poulsen, H.E. (2006). Effect of Dietary Virgin Oil on Urinary Excretion of Etheno-DNA Adducts. *Free Radical Biology & Medicine*, Vol. 41, No. 7, (October 2006), pp. 1133-1138, ISSN 0891-5849

Khymenets, O.; Farré, M.; Pujadas, M.; Ortiz, E; Joglar, J.; Covas, M.I et al. (2011). Direct Analysis of Glucuronidated Metabolites of Main Olive Oil Phenols in Human Urine after Dietary Consumption of Virgin Olive Oil. *Food Chemistry*, Vol. 126, No. 1, (May 2011), pp. 306-314, ISSN 0308-8146

Kroon, P.A.; Clifford, M.N.; Crozier, A.; Day, A.J.; Donovan, J.L.; Manach, C. et al. (2004). How Should we Asses the Effects of Exposure to Dietary Polyphenols *In Vitro*? *The American Journal of Clinical Nutrition*, Vol. 80 No. 1, (July 2004), pp. 15-21, ISSN 0002-9165

Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C. & Jiménez, L. (2004). Polyphenols: Food Sources and Bioavailability. *The American Journal of Clinical Nutrition*, Vol. 79, No. 5, (May 2004), pp. 727-747, ISSN 0002-9165

Manach, C.; Hubert, J.; Llorach, R. & Scalbert, A. (2009). The Complex Links between Dietary Phytochemicals and Human Health Deciphered by Metabolomics. *Molecular Nutrition & Food Research*, Vol. 53, No. 10, (October 2009), pp. 1303-1315, ISSN 1613-4125

Manna, C.; Galletti, P.; Maisto, G.; Cucciolla, V.; D'Angelo, S. & Zappia, V. (2000). Transport Mechanism and Metabolism of Olive Oil Hydroxytyrosol in Caco-2 Cells. *FEBS Letters*, Vol. 470, No. 3, (March 2000), pp. 341-344, ISSN 0014-5793

Marrugat, J.; Covas, M.I.; Fito, M.; Schroder, H.; Miró-Casas, E.; Gimeno, E. et al. (2004). Effects of Differing Phenolic Content in Dietary Olive Oils on Lipids and LDL Oxidation--A Randomized Controlled Trial. *European Journal of Nutrition*, Vol. 43, No. 3, (2004), pp. 140-147, ISSN 1436-6207

Mateos, R.; Goya, L. & Bravo, L. (2005). Metabolism of the Olive Oil Phenols Hydroxytyrosol, Tyrosol, and Hydroxytyrosyl Acetate by Human Hepatoma HepG2 Cells. *Journal of Agricultural and Food Chemistry*, Vol.53, No. 26, (December 2005), pp. 9897-9905, ISSN 0021-8561

Mateos, R.; Pereira-Caro, G.; Saha, S.; Cert, R.; Redondo-Horcajo, M.; Bravo, L. et al. (2011). Acetylation of Hydroxytyrosol Enhances its Transport across Differentiated Caco-2 Cell Monolayers. *Food Chemistry*, Vol. 125, No. 3, (April 2011), pp. 865-872, ISSN 0308-8146

Miró-Casas, E.; Farre-Albaladejo, M.; Covas-Planells, M.I.; Fito-Colomer, M.; Lamuela-Raventos, R.M. & de la Torre-Fornell, R. (2001a). Tyrosol Bioavailability in Humans after Ingestion of Virgin Olive Oil. *Clinical Chemistry*, Vol. 47, No. 2, (February 2001), pp. 341-343, ISSN 0009-9147

Miró-Casas, E.; Farre-Albaladejo, M.; Covas, M.I.; Ortuno-Rodriguez, J.O.; Colomer, E.; Lamuela-Raventos, R.M. et al. (2001b). Capillary Gas Chromatography-Mass Spectrometry Quantitative Determination of Hydroxytyrosol and Tyrosol in Human Urine after Olive Oil Intake. *Analytical Biochemistry*, Vol. 294 No. 1, (July 2001), pp. 63-72, ISSN 0003-2697

Miró-Casas, E.; Covas, M.I.; Fitó, M.; Farre-Albaladejo, M.; Marrugat, J. & de la Torre, R. (2003a). Tyrosol and Hydroxytyrosol are Absorbed from Moderate and Sustained Doses of Virgin Olive Oil in Humans. *European Journal of Clinical Nutrition*, Vol. 57, No. 1, (January 2003), pp. 186-190, ISSN 0954-3007

Miró-Casas, E.; Covas, M.I.; Farre, M.; Fito, M.; Ortuno, J.; Weinbrenner, T. et al. (2003b). Hydroxytyrosol Disposition in Humans. *Clinical Chemistry*, Vol. 49, No. 6, (June 2003), pp. 945-952, ISSN 0009-9147

Murkovic, M. ; Lechner, S. ; Pietzka, A. ; Bratakos, M. & Katzogiannos, M. (2004). Analysis of Minor Constituents in olive Oil, *Journal of Biochemical and Biophysical Methods*, Vol. 61, No. 1-2, (October 2004), pp. 155-160, ISSN 0165-022X

Pinto, J.; Paiva-Martins, F.; Corona, G.; Debnam, E.S.; Oruna-Concha, J.M.; Vauzour, D. et al. (2011). Absorption and Metabolism of Olive Oil Secoiridoids in the Small Intestine. *British Journal of Nutrition,* Vol. 105, No. 11, (June 2011), pp. 1607-1618, ISSN 0007-1145

Romero, M.P.; Tovar, M.J.; Girona, J. & Motilva, M.J. (2002). Changes in the HPLC Phenolic Profile of Virgin Olive Oil from Young Trees (*Olea europaea* L. cv Arbequina) Grown Under Different Deficit Irrigation Strategies. *Journal of Agricultural and Food Chemistry*, Vol. 50, No. 19, (September 2002), pp. 5349-5354, ISSN 0021-8561

Ruiz-Gutiérrez, V.; Juan, M.E.; Cert, A. & Planas, M. (2000). Determination of Hydroxytyrosol in Plasma by HPLC. *Analytical Chemistry*, Vol. 72, No. 18, (September 2000), pp. 4458–4461, ISSN 0003-2700

Scalbert, A. & Williamson, G. (2000). Dietary Intake and Bioavailability of Polyphenols. *The Journal of Nutrition*, Vol. 130, No. 8 Suppl., (August 2000), pp.2073S-2085S, ISSN 0022-3166

Servili, M. & Montedoro, G., (2002). Contribution of Phenolic Compounds to Virgin Olive Oil Quality. *European Journal of Lipid Science and Technology*, Vol. 104, No. 9-10, (October 2002), pp. 602-613, ISSN 1438-7697

Servili, M.; Selvaggini, R.; Esposto, S.; Taticchi, A.; Montedoro, G. & Morozzi. G. (2004). Health and Sensory Properties of Virgin Olive Oil Hydrophilic Phenols: Agronomic

and Technological Aspects of Production that Affect Their Occurrence in the Oil. *Journal of Chromatography A,* Vol. 1054, No. 1-2, (October 2004), pp. 113-127, ISSN 0021-9673

Soler, A.; Romero, M.P.; Macià, A.; Saha, S.; Furniss, C.S.S.; Kroon, P.A. et al. (2010). Digestion Stability and Evaluation of the Metabolism and Transport of Olive Oil Phenols in the Human Small-Intestinal Epithelial Caco-2/TC7 Cell Line. *Food Chemistry*, Vol. 119, No. 2, (March 2010), pp. 703-714, ISSN 0308-8146

Stahl, W.; Van Den Berg, H.; Arthur, J.; Bast, A.; Dainty, J.; Faulks, R.M. et al. (2002). Bioavailability and Metabolism. *Molecular Aspects of Medicine,* Vol. 23, (February 2002), pp.39-100, ISSN 0098-2997

Stark, A.H. & Madar, Z. (2002). Olive Oil as a Functional Food: Epidemiology and Nutritional Approaches. *Nutrition Reviews,* Vol. 60, No. 6, (June 2002), pp. 170-176, ISSN 0029-6643

Suárez, M.; Romero, M.P.; Macià, A.; Valls, R.M.; Fernández, S.; Solà, R. et al. (2009). Improved Method for Identifying and Quantifying Olive Oil Phenolic Compounds and Their Metabolites in Human Plasma by Microelution Solid-Phase Extraction Plate and Liquid Chromatography-Tandem Mass Spectrometry. *Journal of Chromatography B*, Vol. 877, No. 32, (December 2009), pp. 4097-4106, ISSN 1570-0232

Tan, H.-W.; Tuck, K.L.; Stupans, I. & Hayball, P.J. (2003). Simultaneous Determination of Oleuropein and Hydroxytyrosol in Rat Plasma Using Liquid Chromatography with Fluorescence Detection. *Journal of Chromatography B*, Vol. 785, No. 1, (February 2003), pp. 187-191, ISSN 1570-0232

Tovar, M.J.; Motilva, M.J. & Romero, M.P. (2001). Changes in the Phenolic Composition of Virgin Olive Oil from Young Trees (*Olea europaea* L. cv Arbequina) Grown Under Linear Irrigation Strategies. *Journal of Agricultural and Food Chemistry*, Vol. 49, No. 11, (November 2001), pp. 5502-5508, ISSN 0021-8561

Tuck, K.L.; Freeman, M.P.; Hayball, P.J.; Stretch, G.L. & Stupans, I. (2001). The *In Vivo* Fate of Hydroxytyrosol and Tyrosol, Antioxidant Phenolic Constituents of Olive Oil, after Intravenous and Oral Dosing of Labeled Compounds to Rats. *The Journal of Nutrition,* Vol. 131, No. 7, (July 2001), pp. 1993–1996, ISSN 0022-3166

Tuck, L.K. & Hayball, P.J. (2002). Major Phenolic Compounds in Olive Oil: Metabolism and Health Effects. *Journal of Nutritional Biochemistry*, Vol. 13, No. 11, (July 2002), pp. 636-644, ISSN 0955-2863

Tuck, K.L.; Hayball, P.J. & Stupans, I. (2002). Structural Characterization of the Metabolites of Hydroxytyrosol, the Principal Phenolic Component in Olive Oil, in Rats. *Journal of Agriculture and Food Chemistry*, Vol. 50, No. 8, (April 2002), pp. 2404–2409, ISSN 0021-8561

Uceda, M.; Hermoso, M.; García-Ortiz, A.; Jiménez, A. & Beltran, G. (1999). Intraspecific Variation of Oil Contents and the Characteristics of Oils in Olive Cultivars. *Acta Horticulturae (ISHS)*, Vol. 474, No. 2, (April 1999), pp. 659–652, ISSN 0567-7572

Visioli, F.; Bellomo, G.; Montedoro, G. & Galli, C. (1995). Low Density Lipoprotein Oxidation is Inhibited In Vitro by Olive Oil Constituents. *Atherosclerosis*, Vol. 117, No. 1, (September 1995), pp. 25-32, ISSN 0021-9150

Visioli, F.; Galli, C.; Bornet, F.; Mattei, A.; Patelli, R.; Galli, G. et al. (2000). Olive Oil Phenolics are Dose-Dependently Absorbed in Humans, *FEBS Letters*, Vol. 468, No. 2-3, (February 2000), pp. 159-160, ISSN 0014-5793

Visioli, F.; Caruso, D.; Plasmati, E.; Patelli, C.; Mulinacci, N.; Romani, A. et al. (2001). Hydroxytyrosol, as a Component of Olive Mill Waste Water, is Dose-Dependently Absorbed and Increases the Antioxidant Capacity of Rat Plasma. *Free Radical Research*, Vol. 34, No. 3, (March 2001), pp. 301-305, ISSN 1071-5762

Visoli, F.; Galli, C.; Galli, G. & Caruso, D. (2002). Biological Activities and Metabolic Fate of Olive Oil Phenols. *European Journal of Lipid Science and Technology*, Vol. 104, No. 9-10, (October 2002), pp. 677-684, ISSN 1438-7697

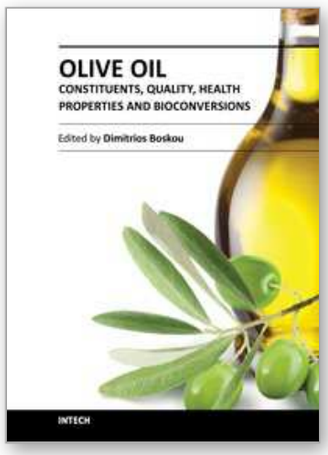
Visioli, F.; Galli, C.; Grande, S.; Colonnelli, K.; Patelli, C.; Galli, G. et al. (2003). Hydroxytyrosol Excretion Differs Between Rats and Humans and Depends on the Vehicle of Administration. *The Journal of Nutrition,* Vol. 133, No. 8, (August 2003), pp. 2612-2615, ISSN 0022-3166

Visioli, F. & Bernardini, E. (2011). Extra Virgin Olive Oil's Polyphenols: Biological Activities. *Current Pharmaceutical Design,* Vol. 17, No. 8, (n.d.), pp. 786-804, ISSN 1381-6128

Vissers, M.N.; Zock, P.L.; Roodenburg, A.J.C.; Leenen, R. & Katan, M.B. (2002). Olive Oil Phenols are absorbed in Humans? *The Journal of Nutrition,* Vol. 132, No. 3, (March 2002), pp. 409-417 ISSN 0022-3166

Vissers, M.N.; Zock, P.L. & Katan, M.B. (2004). Bioavailability and Antioxidant Effect of Olive Oil Phenols in Humans: A Review. *European Journal of Clinical Nutrition,* Vol. 58, No. 6, (June 2004), pp. 955-965, ISSN 0954-3007

Weinbrenner, T.; Fitó, M.; Farré-Albaladejo, M.; Saez, G.T.; Rijken, P.; Tormos, C. et al. (2004). Bioavailability of Olive Oil Phenolic Compounds from Olive Oil and Oxidative/Antioxidative Status at Postprandial State in Humans. *Drugs under Experimental and Clinical Research*, Vol. 30, No. 5-6, (n.d.), pp. 207-212, ISSN 0378-6501




**Olive Oil - Constituents, Quality, Health Properties and Bioconversions**

Edited by Dr. Dimitrios Boskou

ISBN 978-953-307-921-9
Hard cover, 510 pages
**Publisher** InTech
**Published online** 01, February, 2012
**Published in print edition** February, 2012

The health-promoting effects attributed to olive oil, and the development of the olive oil industry have intensified the quest for new information, stimulating wide areas of research. This book is a source of recently accumulated information. It covers a broad range of topics from chemistry, technology, and quality assessment, to bioavailability and function of important molecules, recovery of bioactive compounds, preparation of olive oil-based functional products, and identification of novel pharmacological targets for the prevention and treatment of certain diseases.

**How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

María Gómez-Romero, Rocío García-Villalba, Alegría Carrasco-Pancorbo and Alberto Fernández-Gutiérrez (2012). Metabolism and Bioavailability of Olive Oil Polyphenols, Olive Oil - Constituents, Quality, Health Properties and Bioconversions, Dr. Dimitrios Boskou (Ed.), ISBN: 978-953-307-921-9, InTech, Available from: http://www.intechopen.com/books/olive-oil-constituents-quality-health-properties-and-bioconversions/metabolism-and-bioavailability-of-olive-oil-polyphenols

INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen