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Review

Bioavailability of olive oil phenolic compounds in humans

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Abstract. Olive oil is a functional food, which in addition to having a high level of monounsaturated fatty acids (MUFA), also contains multiple minor components, among them several phenolic compounds. Oleuropeine and its glycoside are the main sources of a simple phenol hydroxytyrosol with a strong antioxidant activity. Hydroxytyrosol is well absorbed in the gastrointestinal tract but its bioavailability is poor because an important first past metabolism both in gut and liver, leading to the formation of sulphate and glucuronide conjugates, to the extent that concentrations in body fluids of its free form are almost undetectable. This is a major drawback in our understanding of the antioxidant activity of this compound *in vivo* and the potential health benefits derived from its consumption. The picture is further compounded by the fact that hydroxytyrosol is also a dopamine metabolite and body fluids concentrations combine exogenous and endogenous sources.

Key words: Olive oil – Polyphenols – Bioavailability – hydroxytyrosol – Ethanol – dopamine metabolism.

Introduction

A lower incidence of coronary heart disease and certain cancers in the European Mediterranean regions when compared to those observed in the Northern ones or other Western countries has been attributed to the high consumption of olive oil in the Mediterranean diet (Trichopoulou et al., 2003). Olive oil is a functional food, which in addition to having a high level of monounsaturated fatty acids (MUFA), also contains multiple minor components with biological properties. The minor components of virgin olive oil are classified into two types: the unsaponifiable fraction, defined as the fraction extracted with solvents after the saponification of the oil, and the soluble fraction, which includes the phenolic compounds.

Olive oil phenolic compounds

Olive oil contains several phenolic compounds with antioxidant activity. Major phenolic compounds in olive oil are: 1) simple phenols (e. g, hydroxytyrosol, tyrosol, vanillic acid); 2) secoiridoids (e. g., oleuropein glucoside), and the aglycone form of oleuropein and ligstroside; and 3) polyphenols, which are lignans and flavonols. Tyrosol, hydroxytyrosol, and their secoiridoid derivatives make up around 90 % of the total phenolic content of virgin olive oil (De la Torre K et al., 2005). Hydroxytyrosol is the most potent phenolic antioxidant of olive oil and olive mill waste water which biological activities have stimulated research on its potential role in cardiovascular protection (Owen et al., 2000).

In animal models both *in-vitro* and *ex-vivo* hydroxytyrosol has shown its antioxidant capacity to prevent the oxidation of lipids (Rietjens et al., 2007) and DNA (Nousis et al., 2005). It has the capacity to prevent also endothelial dysfunction (Carluccio et al., 2003), to inhibit platelet aggregation (Dell'agli et al., 2007) and to promote gene expression of enzymes related to glutathione (Masella et al., 2004). These activities are relevant for the prevention of cardiovascular diseases and have been confirmed indirectly in humans after olive oil administration with varying concentrations of polyphenols (Weinbrenner et al., 2004; Covas et al., 2006).

Dietary intake of olive oil polyphenols has been estimated to be around 9 mg, within 25–50 mL of olive oil per day, where at least 1 mg of them is derived from free HT and T, and 8 mg are related to their elenolic esters and also to the oleuropein- and ligstroside-aglycons.

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Bioavailability and metabolic disposition of olive oil phenolic compounds in humans

It has been suggested that non-absorbable phenolic compounds may display local antioxidant activities in the gastrointestinal tract. This idea is supported by the capacity of isolated phenolic compounds to scavenge both the free radicals generated by the fecal matrix (Owen et al., 2000) and those induced in epithelial cells of the intestine (Manna et al., 1996). However, one of the prerequisites for assessing the physiological significance of olive oil phenolic compounds in human beings is the ability to determine their bioavailability. Several clinical and animal studies have provided evidence that phenolic compounds are absorbed, and exert their biological effects, in a dose-dependent manner.

Tyrosol and hydroxytyrosol are absorbed by humans in a dose-dependent manner with the phenolic content of the olive oil administered (Visioli et al., 2000). Even from moderate doses (25 mL/d), which are lower than the traditional daily dietary intake in Mediterranean countries, (Weinbrenner et al., 2004; Marrugat et al., 2004) around 98 % of these phenolics are present in plasma and urine in conjugated forms, mainly glucuronides and sulphate conjugates, (Miró-Casas et al., 2003). A minor metabolic pathway of hydroxytyrosol gives rise to the formation of 3-hydroxy-4-methoxyphenylethanol (homovanyl alcohol) in a reaction regulated by catecholmethyltransferase (COMT). Homovanyl alcohol is also found in biological fluids as its 3-O-glucuronide conjugate (Fig. 1). Therefore, in the process of crossing epithelial cells of the GI tract, phenolic compounds from olive oil are subject to a classic phase I/II biotransformation, and subjected to an important first pass metabolism. This process is very relevant, to the extent that polyphenols in its free form are deemed undetectable in biological matrices. It is not surprising that some authors caution that the attained concentrations after their ingestion are too low to explain the observed biological activities in *in vitro* and *in vivo* models at higher doses/concentrations (Vissers et al., 2004).

Several hypotheses have been postulated to explain discrepancies between nutritional intervention clinical trials where effects on secondary biomarkers of oxidation are dose dependently related to polyphenols content of olive oil and the poor bioavailability of polyphenols. Among them some authors postulate that glucuronide and/or sulfate conjugates of polyphenols are biologically active (Tuck et al., 2002). Alternatively it has been also proposed that polyphenol conjugates may act as a depot form and that polyphenols are freed from glucuronide and/or sulphate moieties intracellularly (Santner et al., 1984). Several reports have provided evidence that phenolic compounds and their metabolites after olive oil ingestion are incorporated in lipoproteins and this may explain their protecting antioxidant effects (Lamuela-Raventós et al., 1999). Globally none of these hypotheses has been fully corroborated experimentally.

Hydroxytyrosol and dopamine metabolism

A major unresolved drawback in the evaluation of the disposition of hydroxytyrosol is the fact that after strict dietary control, as well as after hours of fasting, it is not possible to minimize hydroxytyrosol concentration in biological fluids. One explanation could be that hydroxytyrosol is also known as DOPET (3,4-dihydroxyphenylethanol), a well-known metabolite of dopamine (Fig. 2). In fact, homovanillic acid, one of the main metabolites of dopamine, has also been reported as a major metabolite of hydroxytyrosol (Caruso et al., 2001).

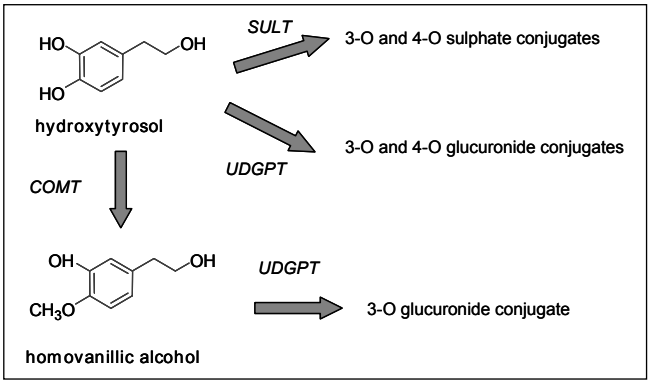

Fig. 1. Biotransformation of hydroxytyrosol
SULT = sulphotransferase; UGDPT = uridine diphospho-glucuronosyltransferase COMT = cathecolmethyltransferase

Dopamine is inactivated from the synaptic cleft after is intracellular reuptake via the dopamine transporter and its further biotransformation by catechol-methyltransferase (COMT) and monoaminooxidase (MAO). MAO A and B regulate dopamine deamination to 3,4-dihydroxyphenyl acetaldehyde (DOPAL). DOPAL is converted to 3,4-dihydroxyphenylacetic acid (DOPAC), a biomarker of dopaminergic activity in the body by the action of the aldehyde deshydrogenase (ALDH). A minor pathway of DOPAL biotransformation consists on its conversion to DOPET via alcohol deshydrogenase or the aldehyde/aldose reductase (Marchitti et al., 2007).

In a recent study, the pharmacokinetics of hydroxytyrosol from two clinical trials, designed to assess the short-term and postprandial effects of moderate doses of wine and olive oil in healthy volunteers, were compared. Despite a five-fold difference in the doses of hydroxytyrosol administered (0.35 mg for red wine and 1.7 mg for olive oil), urinary recoveries of hydroxytyrosol were higher after red wine administration. An interaction between ethanol and dopamine after red wine ingestion leading to the formation of hydroxytyrosol was observed (de la Torre et al., 2006). Biological effects after red wine ingestion should be re-examined on the basis of combined hydroxytyrosol concentrations from red wine and dopamine turnover. Studies in animal models show that ethanol alters dopamine metabolism in a way that 3,4-dihydroxyphenilacetic acid (DOPAC) is no longer the major metabolite but 3,4-dihydroxyphenyl ethanol (DOPET, hydroxytyrosol). While in the absence of ethanol the ratio DOPAC/DOPET is around 10, in the presence of ethanol is 0.25 (Tank et al., 1979), thus confirming findings in humans. Overall these observations indicate that outside clinical trials where olive oil and ethanol (e. g. wine) ingestion are controlled, recoveries of hydroxytyrosol in biological fluids are the sum of the consumption of both foods (directly in case of olive oil and indirectly in the case of ethanol via dopamine metabolism).

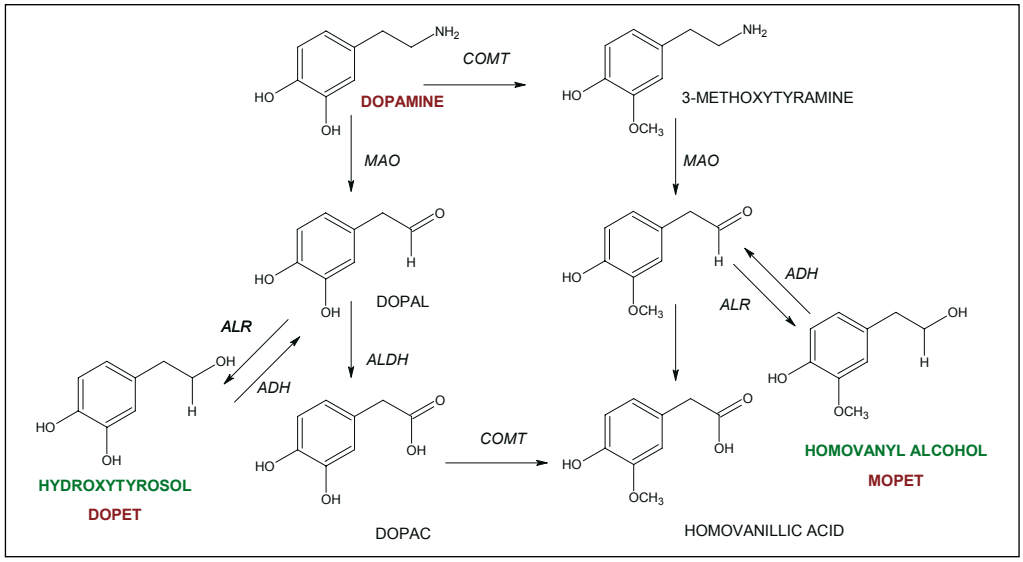

Fig. 2. Biotransformation of dopamine.
COMT = catechol methyltransferase; MAO = monoaminoxidase; ALDH = aldehyde deshydrogenase; ADH=alcohol deshydrogenase; ALR = aldehyde/aldose reductase; DOPET = 3,4-dihydroxyphenylethanol (hydroxytyrosol); DOPAL = 3,4-dihydroxyphenylacetaldehyde; MOPET = 3-hydroxy-4-methoxyphenylethanol (homovanyl alcohol); DOPAC = 3,4-dihydroxyphenyl acetic acid

Conclusion

In conclusion despite compelling evidences of the good absorption of polyphenols, their poor bioavailability is a major drawback in our understanding of the antioxidant activity of these compounds *in vivo* and the potential health benefits derived from their consumption. Circulating concentrations of hydroxytyrosol, the main polyphenol present in olive oil because its biological activities as antioxidant, may be the result not only of olive oil ingestion but also the result of dietary ethanol consumption via its interaction with the oxidative metabolism of dopamine.

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