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Anticarcinogenic compounds of olive oil and related biomarkers

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Abstract Olive oil, one of the oldest vegetable oils consumed without any refining, is associated with a reduced risk of a number of common cancers. Minor constituents of virgin olive oil have been suggested to be among the major chemopreventive components. A brief overview is presented of recent findings concerning the bioavailability of certain important olive oil minor components including efficient antioxidant polyphenols, the triterpene hydrocarbon squalene and β-sitosterol, considered as putative nutritional biomarkers, in relation to the incidence of cancer.

Key words olive oil – anticarcinogenic compounds – biomarkers

Introduction

Olive oil is an important ingredient of the Mediterranean diet. Epidemiological studies demonstrate rather conclusively that populations within Europe consuming this diet have a particularly low incidence of a number of common cancers [18, 23]. A plethora of minor constituents in olive oil have been identified as being effective agents mitigating against the initiation, promotion and progression of multistage carcinogenesis. These include tocopherol and carotenoid antioxidants that have been thoroughly studied, a number of simple and bound phenolics (tyrosol, hydroxytyrosol, secoiridoids and lignans), the triterpene hydrocarbon squalene and the phytosterol β-sitosterol [4, 18, 23]. The occurrence of these constituents also calls for the development of specific nutritional biomarkers that reflect the nutritional status of these dietary constituents with respect to their intake or metabolism and that can provide information useful for nutritional epidemiology regarding the links to disease processes that can occur [12].

Phenolic compounds

HPLC chromatography of the methanol extract of virgin olive oil reveals seven major polyphenol peaks corresponding to hydroxytyrosol, tyrosol, oleuropein, the aglycone of lingstroside, two secoiridoids (dialdehydes related to oleuropein and ligstroside but lacking the carboxymethyl group at C4), and a peak containing the lignans (+)-1-acetoxypinoresinol and (+)-pinoresinol [4, 18, 23] (Table 1; Fig. 1). Oleuropein and its metabolites tyrosol and hydroxytyrosol, which represent major antioxidants in olive oil, are dose-dependently absorbed in humans after the ingestion of realistic doses of virgin olive oil. When olive oil samples containing increasing amounts of a phenolic extract of olive oil were administered to human volunteers, a dose-dependent decrease in the urinary excretion of the F2-isoprostane 8-iso-PGF2α, a biomarker of in vivo lipid peroxidation processes, was observed. This indicates olive oil phenolics to maintain their antioxidant activities in vivo. It has also been shown that olive oil phenolics are excreted in the urine as glucuronide conjugates and that the urinary free

Table 1 Concentration of the major phenolic compounds found in virgin olive oil

Compounds	mg/kg
Tyrosol	27.45 [18], 2.65–4.75 [4]
Hydroxytyrosol	14.42 [18], 1.83–4.71 [4]
Oleuropein aglycone	103–205 [4]
Total secoiridoids	27.72 [18],
Lignans	41.53 [18], 38–65 [4]

References [18] and [4]

tyrosol concentration is responsive to the dietary intake of virgin olive oil. In addition, a statistically significant negative correlation has been found between homovanillyl alcohol (HValc, a major metabolite of hydroxytyrosol, together with homovanillic acid—HVA) and isoprostane excretion, the excretion

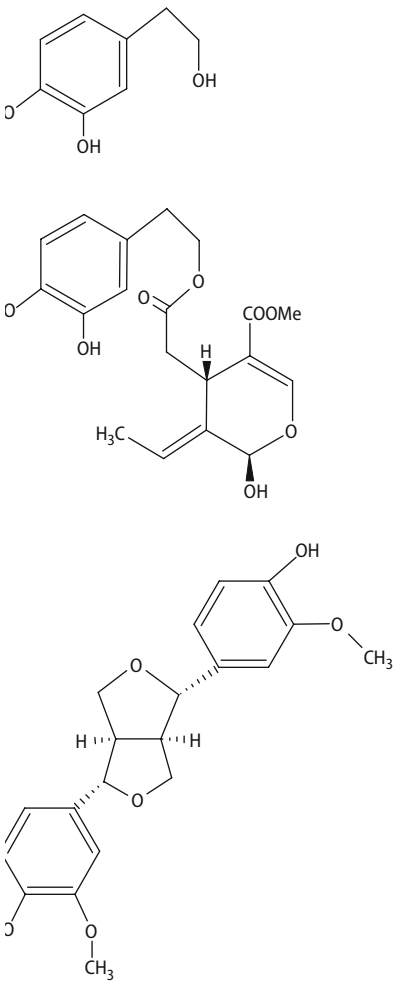

Fig. 1 Structures of certain phenolic compounds detected in olive oil. Hydroxytyrosol (**a**), oleuropein aglycone (**b**), (+)-pinoresinol (**c**)

of both HValc and HVA also being significantly correlated with the dose of administered hydroxytyrosol. Thus, HValc in urine reflects the in vivo concentration of hydroxytyrosol [2, 3, 14, 15, 25–27]. After the ingestion of olive oil of low phenolic content plasma glutathione peroxidase activity was found to decrease postprandially, but this was not observed after the intake of olive oils of moderate to high phenolic content [29]. An HPLC method for the simultaneous determination of oleuropein and of its metabolites hydroxytyrosol and tyrosol in human plasma has been developed [6, 24].

Recent findings suggest that olive oil may also affect the bioavailability of other food bioactive components with a chemopreventive potential. It was observed in this respect, that the concentration in human plasma of lycopene, a biomarker of the intake of tomato-rich food and hypothesized to be responsible for reducing the risk of various cancers, increased dramatically after the consumption of tomatoes cooked in olive oil, as compared to the consumption of tomatoes cooked without olive oil [5]. The consumption of tomato products prepared together with olive oil, but not with sunflower oil, was found to improve the antioxidant activity of plasma [10].

Lignans are plant compounds metabolized in the gut to produce the phytoestrogens enterolactone and enterodiol. Phytoestrogens have an anticarcinogenic potential through the anti-estrogenic, anti-angiogenic, proapoptotic and anti-oxidant mechanisms established for them [19, 28]. Recent findings suggest that enterolactone is more rapidly metabolized in human colon epithelial cells and/or excreted by them than enterodiol is, that the phase II metabolism of enterolactone and enterodiol already may take place during their uptake in the colon, and that the epithelial cells in the colon may be responsible for this metabolism [7]. Mean residence times and elimination half-lives that have been obtained indicate that enterolignans accumulate in the plasma when consumed two to three times a day, their reaching a steady state. Plasma enterolignan concentrations can thus be considered to be good biomarkers of dietary lignan exposure and be used to evaluate the effects of lignans [9]. A number of in vitro and animal studies support a role for lignan-rich foods and of purified lignans in the modulation of cancer events in the breast, the prostate and the colon, whereas the findings of epidemiological studies are controversial [28]. Nevertheless, a tendency for a lower risk of breast cancer to be associated with higher plasma concentrations of enterolactone, restricted almost entirely to estrogen-receptor alpha negative breast cancer has been found, suggesting that dietary lignans may be

important in the etiology of breast cancer, particularly in premenopausal women [13].

Squalene

It has been suggested that the lower risk of cancers of various types associated with high olive oil consumption (as compared with other human foods) may be due to the presence of squalene (reviewed in [23]). This triterpene hydrocarbon is found mainly in non edible shark liver oil, while virgin olive oil is a major source of phytosqualene, its content ranging from 800 to 12,000 mg/kg. If virgin olive oil were the sole source of dietary fat, the squalene intake would be more than 200 mg/d [16]. Nevertheless, very little is known concerning the postprandial metabolism of squalene. It has been observed that postprandial squalene metabolism is age dependent [20], and that the content of squalene in the whole plasma and in the lipoprotein fractions (where its ratio to cholesterol is highest in the VLDL and the intermediate density lipoproteins [8]) varies directly with the triglyceride content and is increased in hypertriglyceridemia, which expands the plasma pool of this metabolically active hydrocarbon [21]. Experiments in vitro and animal models suggest squalene to play a tumour-inhibiting role, which is most probably based on its strong inhibitory action on the catalytic activity of beta-hydroxy-beta-methylglutaryl-CoA reductase, leading to a reduced farnesyl pyrophosphate availability for prenylation of the ras oncogene [17]. Although animal studies have enhanced our understanding of the possible action of squalene in decreasing carcinogenesis, one should be cautious in extrapolating findings there to humans, both because of possible species differences and because the long-term effects of greater consumption of squalene are unknown. Several factors must be taken into account when examining the evidence for squalene's inhibition of carcinogenesis factors, such as the effective dose used and exposure time [22]. At present, therefore, its use as a nutritional biomarker is hardly to be considered.

Phytosterols

Phytosterols are plant sterols that are structurally similar to cholesterol and that possess anticarcinogenic properties [22]. Together with squalene, they represent markers of cholesterol synthesis and absorption and are transported together with cholesterol in serum lipoproteins [8]. β-Sitosterol, one of the most common phytosterols and the main olive oil sterol [23], together with campesterol are the two predominant phytosterols in the blood. It has been suggested that the high reproducibility and high reliability over time (consistency of the plasma phytosterol level over time) of the plasma measurements of these sterols makes them suitable for clinical and population-based studies of cancer prevention [11]. In recent years, functional foods high in phytosterol-ester content for lowering the cholesterol level have been developed. Although phytosterols act as immune modulators and anticancer agents in vitro [1], the protection (if any) that high concentrations of phytosterol provide against the development of cancer in humans has not been adequately examined, further study of this being needed.

Conclusions

Since the phenolic content of the olive oil consumed may account for the postprandial antioxidant activity in vivo after the ingestion of olive oils of moderate to high phenolic content, we suggest that these biomolecules, or certain polyphenol metabolites in human plasma and urine, may serve as practical biomarkers for olive oil consumption and as an alternative biomarker for future epidemiological studies in dietary cancer prevention and health promotion.

Conflict of Interest: None.

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