Dietary EVOO Polyphenols and Gut Microbiota Interaction

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Accumulating evidence indicates that regular consumption of extra virgin olive oil (EVOO), the main source of fat in the Mediterranean diet, is associated with beneficial health effects and a reduced risk of developing chronic degenerative disorders. The beneficial effects of EVOO can be attributed to its unique composition in monounsaturated fats and phenolic compounds that provide important antioxidant, anti-inflammatory, and immune-modulating activities. On the other hand, it is well known that the gut microbiota has several important roles in normal human physiology, and its composition can be influenced by a multitude of environmental and lifestyle factors, among which dietary components play a relevant role.

Keywords: extra virgin olive oil ; polyphenols ; gut microbiota ; sex ; gender ; diet

1. Introduction

The beneficial effects of polyphenols contained in extra virgin olive oil (EVOO) have been recognized by the European Food Safety Authority, which recommends a daily consumption of about 20 g of EVOO, containing at least 5 mg of hydroxytyrosol (HT) and its derivatives, to prevent the onset of cardiovascular disease (CVD) and inflammation and to counteract oxidative stress caused by free radicals [1]. Encouraging findings indicate that obesity, metabolic and digestive disorders, liver and neurological diseases, and cancer can also benefit from EVOO polyphenol ingestion [2], as demonstrated by the increasing number of clinical trials designed to understand and validate the benefits of EVOO and its polyphenols in human diseases, as seen in the public web archive of ClinicalTrials.gov: https://clinicaltrials.gov/ (accessed on 30 April 2022).

EVOO polyphenols exert their well-known health benefits by interacting with fundamental cell signaling and gene regulation pathways in target cells and tissues. These compounds, after ingestion, undergo biotransformation in the gut by the gut microbiota (GM) [3], now considered an essential 'organ' that contributes to the health status or, when altered (dysbiosis), to the onset and progression of diseases in humans [4][5]. The GM contains more than 1000 bacterial species and, to a lesser extent, viruses and archaea that participate in maintaining host homeostasis, in regulating digestion, metabolism, and immunity, and in the protection against pathogens [4]. Accumulating evidence indicates that GM composition can be modulated by dietary polyphenols, thus highlighting a two-way interaction between dietary polyphenols and GM in which host characteristics (sex, age, genetics and ethnicity) and external environmental factors (diet, lifestyle, antibiotics and drugs) can influence each other through complex mechanisms not yet fully elucidated [5][6].

However, although several data evidence that consumption of an EVOO-rich Mediterranean diet can have positive effects on GM and associated microbial metabolites [2][7], only a few human studies have evaluated the effect of EVOO polyphenols on the intestinal homeostasis. Additionally, the increasing awareness that sex (i.e., the sum of biological attributes such as chromosomes, gene expression, hormone levels, and function) and gender (i.e., the socially constructed roles, behaviors, lifestyle, expressions and identities strongly influenced by sociocultural factors) [8] influence body homeostasis and disease susceptibility [9], along with the interindividual variability in response to polyphenols intake [10], strongly suggests a sex/gender-specific approach in moving toward a science-based personalized nutrition.

2. EVOO Composition and Characteristics

Extra virgin olive oil is universally recognized as a symbol of the Mediterranean diet, and its effects on human health have been amply demonstrated by recent relevant intervention studies [11][12][13][14].

The credit for the beneficial properties of EVOO is due to its composition; EVOO contains high levels of monounsaturated acids (63–83%), mainly oleic acid, associated with a lower cardiovascular risk, and other valuable components such as phenols, phytosterols, tocopherols, and squalene, which albeit present in low percentages (1–2%) exert beneficial effects on health [15].

The lipid profile, a well-balanced ω6/ω3 ratio, and the presence of bioactive compounds have been linked to protective effects on coronary, autoimmune, and inflammatory disorders, as well as anti-thrombotic and regulatory effects of blood pressure [16].

From the fruit of the olive tree *Olea europaea* L., family Oleaceae, an oil is produced in which more than 30 hydrophilic phenolic compounds have been identified that contribute to the oil's distinctive characteristic smell and flavor [17]. However, the content of these compounds depends on several factors, such as the olive cultivar, the stage of ripeness, certain environmental factors related to soil and cultivation practices, extraction conditions (heating, addition of water, and extraction systems used to separate the oil from the olive paste), and storage methods [18][19].

The cultivar, i.e., the variety of the olive, is the main differentiating factor in the quality of oils. Each cultivar has a specific organoleptic profile characterized by aromatic substances, number and contents of polyphenols, and specific composition of sterols [20]. Each cultivar also records differences in fatty acid composition. Furthermore, the production process of EVOO strongly influences the polyphenol content. Thus, this process plays a key role in the quality of the final product, giving final EVOO products with different concentrations of polyphenols ranging between 50 and 1000 mg/kg [16], most commonly between 100 and 300 mg/kg [21].

2.1. EVOO Polyphenols

Polyphenols are organic compounds that have aroused great interest for nutritional issues in recent decades. Several classes of polyphenols can be identified, namely, flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans, which differ in their chemical structure [22]. The classes of polyphenols are contained in different percentages in foods of plant origin, including EVOO [23].

In EVOO, the most abundant class is represented by secoiridoids that are present exclusively in plants belonging to the Oleaceae family and include oleuropein and ligstroside, as well as several isomers of oleuropein and ligstroside aglycons, such as the dialdehydic form of decarboxymethyl oleuropein aglycone (oleacein) and the dialdehydic form of decarboxymethyl ligstroside aglycone (oleocanthal). Lignans represent, after secoiridoids, another abundant class of phenolic compounds in EVOO; the most common representatives are pinoresinol and 1-acetoxypinoresinol. Another relevant class is that of phenolic acids, namely, hydroxybenzoic acid derivatives (such as gallic and protocatechuic acids) and hydroxycinnamic acid derivatives (such as caffeic and coumaric acids), and phenyl-alcohols, such as HT and tyrosol (Tyr). Flavonoids, luteolin and apigenin, are present in much lower levels than other phenols [24][25][26][27][28][29][30].

2.2. EVOO Polyphenols and Health

The scientific literature has provided evidence that polyphenols in EVOO contribute to the maintenance of human health by modulating metabolic processes, immune function, and cell proliferation [31][32]. The biological activity of polyphenols is strongly related to their antioxidant and anti-inflammatory properties, since they can improve the activity of the endogenous antioxidant system, reduce the pool of reactive oxygen species (ROS), neutralize potentially carcinogenic metabolites, and counteract the inflammatory processes associated with the onset of several pathological conditions [33][34][35]. For all these reasons, polyphenols, particularly EVOO polyphenols, have been considered as preventive and/or therapeutic agents against noncommunicable diseases (NCDs), such as CVD, type 2 diabetes, neurodegenerative disorders, and cancer, as well as obesity, a main risk factor for NCDs [31][32][36].

Several biological activities of polyphenols are closely linked to the antioxidant action they can exert at the level of cells and organs of the body. Oxidative stress, in fact, represents a common factor in the pathogenesis of several diseases [31][37][38]. However, emerging results suggest several mechanisms of action of EVOO polyphenols against oxidative stress that go beyond the conventional and direct free-radical-scavenging properties. In fact, EVOO polyphenols appear to be able to interact with cellular signals and influence gene expression, inducing an endogenous response to oxidative stress driven by modulation of different enzymatic activities [39][40].

Several studies have demonstrated that EVOO polyphenols are able to interact with the human immune system, influencing both the proliferation and the activity of lymphocytes and monocytes regulating the balance between anti- and pro-inflammatory cytokines, thus playing a role in inflammatory process control [41]. In particular, it has been suggested that the polyphenolic compounds in EVOO, once metabolized, can counteract the local and systemic inflammatory environment typical of immune-mediated inflammatory diseases) [33][42][43][44].

2.3. Biological Properties and Mechanisms of Action of Main EVOO Polyphenols in Preclinical Models

Among the EVOO polyphenols HT, Tyr, oleuropein, and oleocanthal have attracted great interest as a number of studies in preclinical models have demonstrated their protective power in various diseases including cardiovascular [27][45] and metabolic diseases [46].

3. Bioavailability of Polyphenols and the Two-Way Interaction with Gut Microbiota

Polyphenols contained in foods are generally conjugated with sugars or organic acids or are present as unconjugated oligomers. Following their ingestion, small amounts of polyphenols (about 5–10%) [47], mainly those with simple monomeric and dimeric structures, may be absorbed in the small intestine, via hydrolyzation of glycosides [22]. More complex polyphenols, especially with oligomeric and polymeric structures, cannot be absorbed in the small intestine; they, thus, reach the colon, where their structures are extensively modified. In particular, the intestinal microbiota first hydrolyzes glycosides into aglycones and then metabolizes them to simple phenolic acids [48][49]. Colon bacteria substantially contribute to the biotransformation of the polyphenols, breaking down unabsorbed compounds into a wide range of metabolites. Bacteria may also further modify enterocyte-derived metabolites [50].

This activity is of great importance for the biological action of these compounds, since it produces active metabolites. Prior to passage into the blood stream, the polyphenols, which are now simple aglycones, undergo conjugation processes [51]. Conjugation includes three different processes: methylation, sulfation, and glucuronidation. Then, polyphenols are distributed to organs and excreted into the urine [52].

Therefore, it is clear that the polyphenols are extensively modified after their ingestion, and any single polyphenol can generate several metabolites [53]; all these modifications deeply affect their biological activity [54][55]. It must be taken into account that the bioactive compounds present in cells and tissues are chemically, biologically, and functionally different from the ingested form.

Many studies suggest a two-way interaction between dietary polyphenols and the gut microbiota. It is well known that the GM has several important roles in normal human physiology. The composition of GM can be influenced by a multitude of environmental and lifestyle factors, among which diet [56][57][58], giving rise to dysbiosis, could play a key role in human disease progression.

Dietary polyphenols have been evidenced in numerous reports with health-promoting functions, but it has to be underlined that their beneficial effects are related to their bioavailability, which is dictated by the composition of the gut microbiota. Recent improvements in deep sequencing technologies and bioinformatics have enabled a more complex understanding of the reciprocal interactions of dietary polyphenols and gut microbiota, as well as their metabolic impact. This two-way interaction gives rise to two different phenomena. First, as previously described, the GM is able to metabolize polyphenols, yielding many active metabolites [59][60][61]. Polyphenols and their metabolites may act on metabolic pathways and confer health benefits [62][63]. Accordingly, the possible beneficial effects of polyphenols are related not only to their dietary intake, but also to the individual capacity of metabolizing them [61], clearly highlighting that a different composition of the GM will cause a different biotransformation of dietary polyphenols.

On the other hand, polyphenols may directly modulate the gut microbiota. Recent studies suggest a prebiotic-like effect of polyphenols. Prebiotics are defined as substrates selectively utilized by the host's microorganisms, resulting in benefits for metabolic health, gastrointestinal system, bone health, and mental health [64]. Polyphenols are indeed able to stimulate the growth of beneficial bacteria, such as the genera *Lactobacillus* spp. (Firmicutes phylum), *Bifidobacterium* spp., *Akkermansia* spp., *Roseburia* spp. and *Faecalibacterium* spp., which provide antipathogenic and anti-inflammatory effects and cardiovascular protection [65][66]. Moreover, they are also able to hamper the increase in pathogenic bacteria, such as *Clostridium* spp. (Firmicutes phylum) [67][68]. Human in vivo studies have confirmed that polyphenols are able to remarkably shift the ratio between beneficial and harmful bacteria in gut microbiota, increasing the beneficial bacterial strains [69][70].

In this context, EVOO and its phenolic compounds, acting as prebiotics, can stimulate the growth of beneficial bacteria, increase the production of microbial-produced SCFAs, and reduce the abundance of pathogenic bacteria [7]. Specifically, EVOO ingestion enhances the growth of *Lactobacillus* and *Bifidobacterium*, which are also SCFA-producing bacteria, associated with potential anti-obesity effects in humans [71][72].

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