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Modulation of intestinal epithelium homeostasis by extra virgin olive oil phenolic compounds

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1 **Abstract**

2 Dietary habits have been strongly linked to the maintenance of intestinal epithelium homeostasis,
3 whose alteration may contribute to the pathogenesis of inflammatory diseases and cancer.
4 Polyphenols are among those dietary components suggested to be beneficial for gut health. Within a
5 balanced Mediterranean type diet, a good portion of ingested polyphenols comes from olives and
6 extra virgin olive oil (EVOO). Most of them reach the intestine, where they may be directly
7 absorbed or metabolized under absorption. Others undergo an extensive gastrointestinal
8 biotransformation, originating various metabolites that retain the potential beneficial effect of the
9 parent compounds, or exert a more efficient biological action themselves. Ingested EVOO
10 polyphenols (EVOOP) and their metabolites will be particularly concentrated in the intestinal
11 lumen, where they might exert a significant local action. In this review we summarize the few
12 studies that investigated the effect of EVOOP at intestinal level, focusing on the possible
13 mechanism of action in relation to their interaction with the microbiota, and their ability to
14 potentially modulate the oxidative status of the intestinal epithelial layer, inflammation and immune
15 response.

16

17 **Abbreviation:** extra virgin olive oil, EVOO; extra virgin olive oil polyphenols, EVOOP;
18 hydroxytyrosol, HT; tyrosol, TYR; oleuropein, OL; homovanillic acid, HVA; homovanillyl
19 alcohol, HVAlc

20 1. Introduction

21 The intestinal epithelium is a physical and biochemical barrier with a huge surface area, and defines
22 the boundary between intestinal tissues and the external environment. The intestinal epithelium is
23 specialized for nutrient and water absorption, and intestinal homeostasis depends on complex
24 interactions among the intestinal epithelium, local and systemic immune factors, and the microbial
25 content of the gut.

26 A deregulation of this equilibrium may contribute to the pathogenesis of inflammatory diseases and
27 cancer. Dietary components strongly influence intestinal epithelium homeostasis; the “western diet”
28 has been associated to an elevated risk of developing intestinal diseases, as it alters intestinal
29 microbiota, increases intestinal permeability and promotes inflammation. Other dietary components,
30 as those characteristic of the Mediterranean diet, whole-grain foods, fruits, vegetables and derived
31 products as wine and extra virgin olive oil (EVOO), have been proved to be beneficial for gut health
32 ¹. They are rich in bioactive compounds such as polyphenols, potentially able to exert antioxidant,
33 anti-inflammatory and prebiotic effects at intestinal level ². The average intake of polyphenols is
34 approximately 1g/day ³. Most of them are poorly absorbed and directly or through the bile reach the
35 colon, where they concentrate up to several hundred μM ³, in the parental form or partly
36 metabolized. Thus, as suggested years ago by Halliwell ⁴, it is likely that in this site they exert a
37 significant local action. Although the concentration of polyphenols is higher in the intestine than
38 elsewhere, the number of studies that investigate their effect at intestinal level is quite limited.

39 Even more limited are studies regarding specifically EVOOP. Only few human studies have
40 evaluated the effect of EVOOP on the intestinal homeostasis; most have been performed on
41 intestinal cell lines and on experimental colitis animal models. Therefore, there is limited *in vivo*
42 evidence showing a beneficial effect of EVOOP in humans at intestinal level, and we may only
43 speculate on a protective role based on what suggested by experimental models and observational
44 trials.

45 2. Extra virgin olive oil polyphenols

46 EVOO is obtained solely through physical means by mechanical or direct pressing of the olives. It
47 is not subjected to any treatment except washing, decantation, centrifugation and filtration. The oil
48 produced from this first press is known as EVOO; it is of the highest quality and it contains also the
49 highest levels of beneficial constituents⁵⁻⁶. The olive oil chemical composition consists of major
50 components (triacylglycerol) that represent about 98-99% of the total oil weight, mainly oleic acid
51 (MUFA) much higher (55-83%) than that of the other fatty acids (linoleic, palmitic, or stearic
52 acids), which ranges between 3% and 21%. Minor components are present in small amounts (about
53 2% of oil weight) and include more than 230 chemical compounds such as hydrocarbons
54 (squalene), phytosterols (β -sitosterol, stigmasterol, and campesterol), tocopherols (α -tocopherol),
55 carotenoids (β -carotene), coloring pigments (chlorophylls), aliphatic and triterpenic alcohols,
56 volatile compounds and phenolics, such as tyrosol (TYR) and hydroxytyrosol (HT)⁷⁻⁹.
57 The phenolic fraction of EVOO is heterogeneous, with at least 36 structurally distinct phenolic
58 compounds identified that can be grouped into the following classes:

- 59 • Phenolic acids. They can be divided into three subgroups, hydroxybenzoic acids, such as,
60 gallic, protocatechuic, and 4-hydroxybenzoic acids, hydroxycinnamic acids, such as caffeic,
61 vanillin, syringic, p- coumaric, and o-coumaric acids and other phenolic acids and derivatives.
62 These compounds are generally present in small amounts (<10 mg per kg of oil)¹⁰.
- 63 • Phenolic alcohols. These compounds possess a hydroxyl group attached to an aromatic
64 hydrocarbon group, HT (3,4-dihydroxyphenyl-ethanol or 3,4-DHPEA,) and TYR (p-
65 hydroxyphenyl-ethanol or p-HPEA). Their concentration is usually low in fresh oils but increases
66 during oil storage due to the hydrolysis of EVOO secoiridoids (ranging from 0 to 70 mg per Kg of
67 oil)¹⁰⁻¹².
- 68 • Secoiridoids. This phenolic group is characterized by the presence of either elenolic acid or
69 elenolic acid derivatives in their molecular structure^{11, 13}. The most abundant are the dialdehydic
70 form of decarboxymethyl elenolic acid linked to HT (3,4-DHPEA) or TYR (p-HPEA) (3,4-
71 DHPEA-EDA or p-HPEA-EDA), oleuropein (OL), its isomer, OL aglycon (HT linked to elenolic

72 acid) (3,4-DHPEA-EA), and ligstroside aglycon (TYR linked to elenolic acid) (p-HPEA-EA). p-
73 HPEA-derivates and dialdehydic forms of OL and ligstroside aglycon were also detected as minor
74 hydrophilic phenols of EVOO ¹⁴.

75 • Hydroxy-isocromans. This is a class of phenolic compounds recently characterized of
76 EVOO and the presence of 1-phenyl-6,7- dihydroxy-isochroman and 1-(39-methoxy-49-hydroxy)
77 phenyl-6, 7-dihydroxy- isochroman has been shown in several samples ¹⁵.

78 • Flavonoids: These polyphenolic compounds contain two benzene rings joined by a linear
79 three carbon chain and apigenine, luteoline, and (+)- taxifoline are the most concentrated. The
80 amount of these compounds in EVOO is very low and generally ranges between 0 and 10 mg/kg of
81 oil ¹⁶.

82 • Lignans: The exact structure of this type of phenolic is not well understood but it is based on
83 aromatic aldehydes condensation. (+)-1-pinoresinol, (+)-1-acetoxypinoresinol and
84 hydroxypinoresinol were characterized as the most concentrated lignans in EVOO ¹⁷. These
85 compounds are present in the pulp and in the woody portion of the seed ¹⁸.

86 TYR, HT, and their secoiridoid derivatives make up around 90 % of the total phenolic content of
87 EVOO ¹⁹. Not all phenolics are present in every EVOO and considerable variation has been noted
88 in the concentration of such phenolic compounds (50 to 1000 mg/kg) ^{5, 20-21}.

89 The EVOO phenolic content is determined by several factors such as olive variety (cultivar),
90 growing area, fruit ripening, cultivation techniques, processing and storage conditions ²²⁻²⁴.

91

92 **3. Metabolism and bioavailability**

93 The metabolic fate of phenolic compounds after ingestion has been the subject of several studies by
94 the scientific community to find out the mechanisms through which they exert their activity into the
95 organism. Indeed, bioavailability of EVOOP is the key in achieving an effect in specific tissues or
96 organs ²⁵⁻²⁶.

97 Most of the studies regarding the bioavailability of these compounds have focused on the two most
98 abundant EVOO simple phenolics: HT and TYR, amongst a few others²⁷. After ingestion, EVOOP
99 can be partially modified in the acidic environment of the stomach. The effect of such environment
100 on aglycone secoiridoids has been examined *in vitro* by incubating the compounds at 37 °C in
101 simulated gastric pH conditions (pH 2.0) and during normal physiological time frames (up to 4 h)
102²⁸⁻²⁹. Although hydrolysis takes place releasing free phenolic alcohols, a significant amount remains
103 intact and thus, enters the small intestine un-hydrolyzed. However, OL aglycone and its dialdehydic
104 form, are likely not absorbed as such in the small intestine; in fact, the major metabolites detected
105 using a perfused rat intestinal model were the glucuronide conjugates of the reduced form of both
106 compounds²⁹. In contrast, if the ingested secoiridoid is glucosylated it appears not to be subjected
107 to gastric hydrolysis³⁰, meaning that phenolics such as the glucosides of OL enter the small
108 intestine unmodified, along with high amounts of free HT and TYR and remaining secoiridoid
109 aglycones.

110 Research evidence demonstrates that EVOOP are significantly absorbed (~40%–95%) in a dose-
111 dependent manner in humans³⁰⁻³⁷ and the major site for the absorption of these compounds is the
112 small intestine^{30, 32, 38-40}.

113 There are different mechanisms by which absorption occurs with regards to EVOOP. The different
114 polarities of the various phenolics has been postulated to play a role in the absorption of these
115 compounds³⁰. For instance, TYR and HT are polar compounds and their absorption has been
116 shown to occur by a bidirectional passive diffusion mechanism across the membrane of the human
117 enterocytes⁴¹. Other EVOOP, such as p-coumaric acid, pinoreosinol, luteolin²⁵ and HT acetate⁴²
118 have shown the same mechanism of transport.

119 Larger compounds may be absorbed via a different mechanism to TYR and HT. It has been
120 proposed that the polar but larger OL-glycoside may diffuse through the lipid bilayer of the
121 epithelial cell membrane and be absorbed via a glucose transporter, but, potentially also via the
122 paracellular route or transcellular passive diffusion⁴³. Despite being well absorbed, the

123 bioavailability of EVOOP is scarce due to an extensive pre-systemic first-pass metabolism in the
124 gut and liver²⁷.

125 Once absorbed, EVOOP are, in fact, subjected to three main types of conjugation: methylation,
126 glucuronidation and sulfation, through the respective action of catechol-O-methyl transferases
127 (COMT), uridine-5'-diphosphate glucuronosyltransferases (UDPGT) and sulfotransferases (SULT)
128⁴⁴.

129 Different studies showed that HT and TYR can be metabolized to O-glucuronidated conjugates³¹,
130^{33, 40, 45-46}, but HT also undergoes O-methylation, and both homovanillic acid (HVA) and
131 homovanillyl alcohol (HVAlc) have been detected in human and animal plasma and urine after oral
132 administration of either EVOO or pure HT and TYR^{34, 40, 47-49}.

133 The urinary excretion of HVAlc and HVA in humans was reported for the first time by Caruso et al.
134⁴⁵ after the intake of different EVOOs (the lowest administered dose was 7 mg of total HT/50 mL
135 oil, and the max provided about 23 mg/50 mL oil). HVAlc contributes to 22% of the total excretion
136 of HT and its metabolites, and HVA 56%. The excretion of both metabolites correlated with the
137 administered dose of HT. Even at low doses, HVAlc and HVA were excreted. In a later study,
138 Miró-Casas et al.³⁹ observed how urinary amounts of HT and HVAlc increased in response to
139 EVOO ingestion, reaching the maximum peak at 0-2 h. Urinary recovery 12 h after olive oil
140 ingestion showed that 65% of HT was in its glucuronoconjugated form and 35% in other conjugated
141 forms.

142 Urinary concentrations and excretion rates of glucuronides of EVOOP were also successfully
143 estimated in a study carried out by Khymenets et al.⁴⁶, using a dietary dose of EVOO (50 mL).
144 About 13% of the consumed EVOOP were recovered in 24-h urine, where 75% of them were in the
145 form of glucuronides (30- and 40-O-HT glucuronides, 40-O-glucuronides of TYR) and 25% as free
146 compounds.

147 A study conducted by Corona et al.²⁸ about absorption, metabolism and microflora-dependent
148 transformation of HT, TYR and their conjugated forms (e.g. OL) also showed similar results; both

149 HT and TYR, transferred across human Caco-2 cell monolayers and rat segments of jejunum and
150 ileum, were subject to classic phase I/II biotransformation. The major gastrointestinal metabolites
151 identified were an O-methylated derivative of HT, glucuronides of HT and TYR and a novel
152 glutathionylated conjugate of HT (HT-GSH). In contrast, there was no absorption of OL in either
153 model ²⁸.

154 On the other hand, sulfation can occur after gastrointestinal absorption, in fact in different studies
155 conducted testing phenol-enriched virgin olive oils ^{37, 50-51}, sulfation was the main conjugation
156 pathway for EVOOP, whereas the glucuronidated forms were not detected. The main phenolic
157 metabolites detected in plasma samples after ingestion of EVOO were, HT sulfate, HT acetate
158 sulfate, HVA and HVA sulfate. HT sulfate appears to be a good biomarker for monitoring
159 compliance of EVOO intake and a very recent study using pure HT ⁵² seems to reinforce this
160 notion. In this last study, quantitatively, the total amount of HT recovered in the urine was minimal
161 and accounted for 0.02% (only for the 25 mg dose). For the metabolites, they observed a dose-
162 dependent increase in their excretion. And the major metabolite detected was HT 3-sulphate, which
163 accounted for 23.1% (for the 5 mg dose) and 16.6% (for the 25 mg dose) of the administered HT,
164 followed by HT 3-O-glucuronide with 2.78% (for the 5 mg dose) and 2.87% (for the 25 mg dose).

165 Suárez et al. ⁵³ considered for the first time the absorption and disposition of flavonoids and lignans
166 after the ingestion of EVOO. Besides the presence of those EVOOP in their conjugated forms, an
167 important variability in the concentrations was observed between the plasma samples obtained from
168 different volunteers. This variability may be attributed to differences in the expression of
169 metabolizing enzymes due to genetic variability within the population ⁵³.

170 Also De Bock et al. noted a large inter-individual variation in absorption and metabolism of
171 phenolic compounds in a study with olive leaf extracts administration in humans, possibly resulting
172 from differences in human enzymatic activity. For example, males may be more efficient at
173 conjugating OL, which would explain their lower area under the curve (AUC) for OL but higher
174 AUC for HT metabolites ⁵⁴.

175 The most comprehensive study regarding the identification of metabolites in human urine of most
176 of the EVOOP (i.e. secoiridoids, flavanoids and phenolic alcohols) was reported by Garcia-Villalba
177 et al.⁵⁵. These authors were able to achieve the tentative identification of 60 metabolites. Phenolic
178 compounds were subjected to various phase I and phase II reactions, mainly methylation and
179 glucuronidation. For instance, the largest number of metabolites was produced from HT, OL
180 aglycone and oleocanthal, indicating significant post-absorption metabolism of these compounds.
181 Conversely, the lowest number of metabolites came from TYR, luteolin, apigenin, pinoresinol and
182 acetoxypinoresinol, suggesting that these compounds may have been excreted in faeces, destroyed
183 in the gastrointestinal tract, excreted through another metabolic pathway or poorly absorbed⁵⁵. A
184 recent paper by De la Torre et al. further confirmed the presence of HT and its major methylated
185 metabolite, 3-O-methyl-hydroxytyrosol or HVA1c, in urine following EVOO consumption in a high
186 risk of CVD subjects, where HVA1c concentration was predictive of CVD⁵⁶.
187 In the case of poorly absorbed phenolic compounds, it has been suggested that these components
188 may exert a local protective action in the large intestine, and this assumption is supported by
189 research demonstrating, for instance, the free radical scavenging capacity of EVOOP in both the
190 faecal matrix and intestinal epithelial cells¹⁹.

191 4. Interaction with the microbiota

192 EVOOP can likely influence the gut microbial balance since, as reviewed in the previous paragraph,
193 most of them are not completely absorbed into the upper parts of the gastrointestinal tract and reach
194 the colon, where the different microbial species that inhabits the intestine reach the highest
195 concentration⁵⁷. The complex interaction between dietary polyphenols and the microbiota has been
196 extensively studied, being recognized as one of the factor contributing to the beneficial effect of
197 polyphenols consumption, although the mechanisms are still poorly understood.

198 Colon bacteria substantially contribute to the biotransformation of the polyphenols, breaking down
199 unabsorbed compounds into a wide range of metabolites, which may be absorbed or excreted.
200 Bacteria may also further modify enterocytes-derived metabolites⁵⁸. On the other hand, dietary

201 polyphenols and their metabolites may strongly influence microbiota composition, inhibiting the
202 growth of harmful bacteria and exerting prebiotic-like effects towards beneficial bacteria, as nicely
203 reviewed by Cardona et al.⁵⁸.

204 However, studies specifically regarding the impact of dietary intake of olives or EVOO polyphenols
205 on the microbiota are scarce. One of the first studies on the biotransformation of ingested EVOOP
206 by colonic microflora, was the in vitro study conducted by Corona et al.²⁸ cited above. The authors,
207 using human fecal microbiota and a perfused rat intestinal model, demonstrated that these phenolic
208 compounds undergo an extensive metabolisation in the passage through the gastrointestinal tract
209 and are mainly absorbed as simple phenols in the small intestine. However, OL reaches the large
210 intestine as an unmodified compounds and it is rapidly degraded in this site by the microflora to
211 yield mainly HT. Using the same in vitro experimental model, Mosele et al.⁵⁹ reported HT as the
212 main product of OL microbial metabolisation, together with a pool of phenolic acids resulting from
213 further metabolisation. HT, HT acetate and TYR, tested as individual phenols, also originated
214 phenolic acids, as phenylacetic acid, phenylpropionic acid and their hydroxylated derivatives.

215 A subsequent study determined in rat feces, after oral administration of OL, the presence of the
216 parent compound together with other metabolites, identified as HT, elenolic acid and HVA⁶⁰. In
217 human fecal samples, obtained before and after the sustained intake of a phenol-enriched olive oil,
218 free HT, phenylacetic acid, 2-(4'-hydroxyphenyl)acetic acid, 2-(3'-hydroxyphenyl)-acetic acid, 3-
219 (4'-hydroxyphenyl)-propionic acid were detected; neither OL nor HVA were present in human
220 feces, probably because of the differences in the gut metabolic responses between rat and human⁵⁹.

221 Microbial-derived phenolic acids have been reported to exert a significant biological activity at
222 local and systemic level⁶¹; phenylacetic and phenylpropionic acids, together with their variously
223 hydroxylated derivatives, are among the predominant structures in fecal water⁶² and have shown to
224 inhibit platelet aggregation⁶³ and the growth of intestinal pathogenic bacteria⁶⁴.

225 OL is likely to be preferentially degraded in vivo by lactic acid bacteria, as *Lactobacillus* and
226 *Bifidobacterium* species⁶⁵, which are involved in developing the spontaneous or started lactic

227 fermentation of table olives but also contribute, as probiotic bacteria, to maintain or improve
228 microbial balance in the gut⁶⁶. Thanks to the β -glucosidase and esterase activity⁶⁷, *L. plantarum*,
229 that is also found as natural inhabitant of the human gastrointestinal tract, is the most effective
230 bacteria converting OL into HT^{65, 68} and it is also able to metabolize some phenolic acids as
231 protocatechuic acid⁶⁹, ferulic, gallic and coumaric acids through inducible decarboxylase and
232 reductase enzymes (⁷⁰ and references therein). Thus, OL possess prebiotic properties, as
233 *Lactobacillus* and *Bifidobacterium* strains may utilize it as a carbon source, but others such as
234 *Clostridium* and *E. coli* cannot²⁸. Actually, it is assumed that EVOOP might influence the
235 composition of the microbiota also inhibiting the growth of pathogenic bacteria. The antimicrobial
236 activity of phenolic compounds from *Olea europaea* has been extensively studied since the early
237 1970s, although, depending on the experimental conditions, results have been contrasting. HT, for
238 example, has been shown to inhibit *E. coli* growth⁷¹, although culture media and the type of strain
239 remarkably affected the bacterial susceptibility to HT⁷². HT exhibited also a significant
240 antimicrobial activity against selected *Enterobacter* species⁷³. Similarly, OL was effective in *E.*
241 *coli* growth inhibition⁷⁴. In general, several experimental trials showed OL and HT to be the best
242 inhibitors of several gastrointestinal pathogens, as reported in the recent review of Thielmann et al.
243⁷⁵. However, this great amount of data arises from in vitro experiments that do not mimic the in vivo
244 conditions. To the best of our knowledge, there are only two recent reports by Martin-Pelaez et al.
245⁷⁶⁻⁷⁷ and one from Conterno et al.⁷⁸ on the modulation of microbiota by EVOOP in humans. Martin-
246 Pelaez's studies arise from the VOHF study, a randomized, controlled, double-blind, crossover
247 clinical trial with hypercholesterolemic subjects⁷⁹. In a subsample of 12 hypercholesterolemic
248 adults⁷⁶, changes in faecal microbial populations were evaluated following sustained consumption
249 of EVOOP, alone or in combination with thyme polyphenols; the study reported a slight HT
250 modification in microbial composition following EVOOP intake, depending on the dosage, as
251 confirmed by the parallel study in another subsample of 10 subjects⁷⁷. A significant increase of
252 *Bifidobacterium* group numbers was detected instead, when polyphenols from olive oil and thyme

253 were ingested in combination ⁷⁶. Among the microbial phenolic metabolites, dihydroxyphenyl and
254 hydroxyphenyl acetic acid, and a significant amount of protocatechuic acid and HT were detected in
255 faeces after dietary interventions with polyphenols. The ingestion of a mixture of olive oil and
256 thyme polyphenols exerted a cardio-protective effect in hypercholesterolemic subjects, mediated by
257 the specific growth stimulation of *Bifidobacteria*, together with the increases in microbial phenolic
258 metabolites with antioxidant activities such as protocatechuic acid and HT ⁷⁶. Conterno et al.
259 reported small changes within the composition of the gut microbiota, showing a small increase in
260 *Bifidobacteria*, and an up-regulation of microbial polyphenol biotransformation in the intestine,
261 following ingestion of olive pomace extract-enriched biscuits.⁷⁸

262 Although the complex interrelation between EVOOP and human microbiota is still far from being
263 exhaustively investigated, data collected so far clearly suggest a concentration dependent impact of
264 phenolic compounds and metabolites on bacterial growth and on the associated metabolic
265 consequences at local and systemic level.

266

267 **5. Antioxidant and anti-inflammatory effect at intestinal level**

268 Dietary polyphenols have been claimed to exert both a protective and therapeutic effect in the
269 management of gastro intestinal disorders, mainly those strictly linked to oxidative stress and
270 chronic inflammation, as IBD. Being particularly concentrated in the intestinal tract, dietary
271 polyphenols, now undoubtedly associated with scientifically validated antioxidant and anti-
272 inflammatory properties, may act locally reducing oxidative stress and inflammatory response ^{2, 80}.

273 **5.1 Antioxidant effect**

274 The gut lumen is likely to be the only site where EVOOP, together with their active metabolites,
275 may reach a concentration high enough to enable them to act as direct antioxidants, scavenging
276 ROS; once absorbed, they may also modulate the expression of genes linked to antioxidant cellular
277 defenses via molecular targets. The phenolic fraction of EVOO has been shown to protect intestinal
278 Caco-2 cells against the alteration of cellular redox status and oxidative damage to the membrane

279 lipid fraction, due to the pro-oxidant action of oxidized lipids and this effect has been correlated to
280 the activity of the most abundant phenolic compounds present in the tested fraction, HT, TYR and
281 OL⁸¹. As reviewed in the first paragraph, HT, TYR and OL, together with their metabolites, are the
282 major phenols found at intestinal level, following ingestion of EVOO, and, due to their high local
283 concentrations, they might exert a relevant antioxidant effect. HT has been recognized as the most
284 efficient free radical scavenger and radical chain breaker, and its catecholic structure is also able to
285 prevent reactive species formation through metal chelation features⁸²⁻⁸³. It has been shown to
286 protect Caco-2 cells against oxidative injury⁸⁴⁻⁸⁶, because of its scavenging properties, and its major
287 metabolites, sulfates and glucuronides, showed an efficiency in protecting Caco-2 cells⁸⁷, as well as
288 renal cells⁸⁸ and erythrocytes⁸⁹, comparable or even better than that of the parent compound. TYR
289 has also been shown to be effective in protecting Caco-2 cells against the cytostatic and cytotoxic
290 effects produced by oxidized LDL⁹⁰ and to possess scavenging effects on peroxy radicals^{84,91}, O₂⁻
291⁹² and ONOO⁻⁹³. Although there are no studies regarding specifically the intestinal compartment,
292 trials in animal models and cell cultures demonstrated that HT is able to increase the endogenous
293 defense system, through the modulation of related gene expression.

294 In human HepG2 cells HT enhanced the expression and the activity of the glutathione related
295 enzymes, glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione S-transferase
296 (GST)⁹⁴. The modulating activity of HT on the glutathione antioxidant network has been also
297 demonstrated in the adipose tissue of mice fed an HT-supplemented diet⁹⁵ and in the liver of obese
298 mice after 17 weeks supplementation⁹⁶. HT has been shown to be a potent inducer of phase II
299 detoxifying enzymes in retinal pigment epithelial cells⁹⁷ and to increase the expression and activity
300 of SOD and CAT in rats fed a cholesterol-rich diet⁹⁸. The effect of HT on the cellular antioxidant
301 enzymes has been linked to its ability to increase the translocation of Nrf2^{94,97} to the nucleus, thus
302 promoting the expression of genes related to the antioxidant defense system and contributing to the
303 protection of cells against oxidative stress. However, this hypothesis has never been proven in

304 humans; indeed, a pilot study on humans demonstrated that HT administration did not significantly
305 modify phase II enzyme expression in peripheral blood mononuclear cells⁹⁹.

306 Recent studies showed the ability of TYR and its sulfate metabolite to induce the GPx activity in
307 Caco-2 cells⁸⁷ and, together with its glucuronide metabolite, to restore GSH level and related
308 antioxidant enzymes in TNF- α treated human endothelial cells¹⁰⁰, as previously demonstrated in
309 macrophages, where TYR preserved cellular antioxidant defenses against the pro-oxidant effect of
310 oxidized LDL¹⁰¹. In a mouse model of lipopolysaccharide (LPS)-induced acute lung injury, TYR
311 pretreatment attenuated the inflammatory response and improved expression of the antioxidant
312 enzymes, through the activation of Nrf2¹⁰².

313 OL possesses well-documented pharmacological properties, including a potent antioxidant activity
314 mainly due to the presence of hydroxyl groups in its chemical structure. Its free radical scavenging
315 and metal-chelating activities enable OL to inhibit the production of a wide range of ROS and RNS
316 in in vitro cell-free systems, as well as in cultured cells, as reported in the Hassen et al. extensive
317 review¹⁰³. There are also evidence for the stimulatory effect of OL on the expression of the
318 intracellular antioxidant enzymes in free endothelial progenitor cells, via the activation of Nrf2¹⁰⁴,
319 and in normal human liver cells¹⁰⁵. In vivo data confirm the ability of OL to increase the level and
320 activities of enzymatic antioxidants in rats fed a cholesterol rich diet¹⁰⁶, in acute arsenic exposed
321 rats¹⁰⁷, in the hypothalamus of hypertensive rats¹⁰⁸, in the substantia nigra of aged rats¹⁰⁹ and to
322 enhance the level of non enzymatic antioxidants such as glutathione, α -tocopherol, ascorbic acid
323 and β -carotene in alloxan-diabetic rabbits¹¹⁰.

324 **5.2 Anti-inflammatory effect**

325 A large body of studies carried out in cell cultures, animal models and humans provides solid
326 evidence that EVOOP are able to inhibit the inflammatory process, through the modulation of
327 different signaling pathways regulating immune cells response, activation of pro-inflammatory
328 enzymes and release of inflammatory mediators¹¹¹.

329 There are few studies focusing on the anti-inflammatory action of EVOOP at intestinal level. In
330 cultured Caco-2 cells stimulated with LPS or IL-1 β , EVOOP are able to regulate IL-8 expression by
331 transcriptional or posttranscriptional mechanisms, depending on the stage of inflammation ¹¹². We
332 recently demonstrated that EVOOP may also counteract oxysterols-induced redox imbalance and
333 pro-inflammatory response in Caco-2 cells, inhibiting cytokines and NO release, through the
334 modulation of the MAPK-NF- κ B pathway ¹¹³.

335 Studies in animal models show that an EVOO diet enriched with phenolic compounds mitigate the
336 severity of DSS-induced colitis in mice, attenuating clinical and histological signs of damage of
337 colonic segments, suppressing oxidative events and inhibiting pro-inflammatory protein expression
338 ¹¹⁴⁻¹¹⁶.

339 The anti-inflammatory activity of the phenolic fraction is likely to be dependent on the active
340 constituents OL, HT and oleocanthal, whose anti-inflammatory effect has been clearly
341 demonstrated in vitro. In the same mice model of DSS-induced colitis, oral administration of OL
342 attenuated the extent and severity of acute colitis, reducing pro-inflammatory cytokine, IL-1 β , IL-6,
343 TNF- α and NO production and enhancing anti-inflammatory cytokine levels, IL-10, in the colonic
344 tissue. The molecular mechanism of its protective action seems at least in part linked to the down-
345 regulation of COX-2 and iNOS proteins gene expression and to the up-regulation of annexin A1,
346 which may mediate the suppression of p38 MAPK phosphorylation and NF- κ B translocation to the
347 nucleus ¹¹⁶⁻¹¹⁷. A subsequent investigation by the same group confirmed the ability of OL to
348 modulate intestinal immune response in DSS acute model, inhibiting Th17 response and the release
349 of Th17-related cytokines, and, down regulating inflammatory mediators, to inhibit the
350 development of the connected colorectal cancer ¹¹⁸.

351 A recent study conducted in colonic biopsies obtained from patients with ulcerative colitis
352 demonstrated the ability of OL to ameliorate the inflammatory damage and reduce infiltration of
353 CD3, CD4, and CD20 cells, while increasing CD68 numbers. In the colonic biopsies treated with

354 LPS and OL the expression of COX-2 and IL-17 were significantly lower compared with those
355 treated with LPS alone ¹¹⁹.

356 HT also demonstrated an anti-inflammatory effect in vivo, when locally applied in TNBS-induced
357 colitic rats ¹²⁰, and when administered within HT supplemented EVOO-diet to DSS-induced colitic
358 mice. This anti-inflammatory effect has been related to the ability to modulate cytokines secretion
359 and to reduce COX-2 and iNOS expression in colonic mucosa, by down regulating p38 MAPK
360 pathway ¹²¹. These observations agree with the study of Corona et al.¹²² in Caco-2 cells which
361 demonstrates that inhibition of p38 significantly reduces COX-2 expression.

362 A significant beneficial effect in chronic DSS-induced colitis was also exerted by HT acetate,
363 sharing the same mechanism of action as HT ¹²³. There is strong evidence in vitro that also
364 oleocanthal is an effective anti-inflammatory agent. In fact, it can efficiently inhibit COX-2 enzyme
365 expression and activity, which is implicated in the pathogenesis of several cancers ¹²⁴.

366 The findings of these few studies suggest that EVOOP have the potential to exert anti-inflammatory
367 effects in the human gastrointestinal mucosa, however, no human studies, up to now, have
368 specifically dealt with this issue.

369

370 **6. Anti-carcinogenic effect at intestinal level**

371 Over the past decades, epidemiological studies have indicated an inverse correlation between
372 EVOO consumption and the incidence of different type of cancers, although the scientific evidence
373 in support of this correlation is still limited ¹²⁵. It has been shown that the Mediterranean diet, and
374 EVOO seem to be protective against colon cancer ¹²⁶⁻¹²⁷. A systematic review and meta-analysis
375 analyzed 19 case-control studies (13800 cancer patients and 23340 controls) and found that high
376 olive oil consumption was associated with lower odds of having any type of cancer ¹²⁸. Moreover,
377 high olive oil consumption was associated with lower odds of developing breast cancer (logOR = -
378 0,45 95% CI -0.78 to -0.12), and a cancer of the digestive system (logOR = -0,36 95% CI -0.50 to -
379 0.21), compared with the lowest intake ¹²⁸. In addition, another systematic review and meta-analysis

380 included 25 studies, and concluded that high olive oil consumption decreased the risk of upper
381 digestive and respiratory tract neoplasms, breast and, possibly, colorectal and other cancer sites ¹²⁵.
382 More recently, a systematic review reported the association between EVOOP and other
383 Mediterranean diet components with a reduction of colorectal cancer initiation, promotion and
384 progression ¹²⁹. Several nutrients play a significant role in colorectal cancer development, and the
385 importance of monounsaturated fatty acids has been highlighted ¹³⁰.
386 In addition, EVOOP, including phenolic alcohols, lignans and secoiridoids, are thought to be, in
387 part, responsible for EVOO reported anti-carcinogenic effects ¹³¹. EVOOP have been shown to
388 influence carcinogenesis and tumor development at various levels ¹³²⁻¹³⁴: by exerting antioxidant
389 activities ¹³⁵⁻¹³⁶, by modulating detoxification enzyme systems ¹³⁷, and the immune system ¹³⁸, by
390 reacting with activated carcinogens and mutagens ¹³⁹⁻¹⁴⁰, and by exerting actions on proteins
391 controlling cell cycle progression ^{122, 141-142}, and gene expression ¹⁴³⁻¹⁴⁴.
392 The ability of EVOO to inhibit colon cancer development has been demonstrated in large intestinal
393 cancer cell models ^{122, 144-145}, in animals ^{140, 146} and in humans ^{131, 147}. In experimental models, olive
394 oil consumption has been shown to prevent benzo(a)pyrene [B(a)P]-induced colon carcinogenesis
395 in Apc(Min) mice ¹⁴⁰, reduce the incidence of aberrant crypt foci in azoxymethane-treated rats ¹⁴⁶
396 and dimethyl-benz(a)anthracene-induced mammary carcinogenesis ¹⁴⁸, and has been shown to induce
397 significant levels of apoptosis in large intestinal cancer cells ^{136, 145}. In animal models, n9 fatty acids
398 present in olive oil have been able to prevent the development of aberrant crypt foci and colon
399 carcinomas ¹⁴⁶. Thus, EVOOP have also been shown to play an important role, due to their ability to
400 inhibit the initiation, promotion and metastasis of the carcinogenetic process in human colon
401 adenocarcinoma cells ¹⁴⁹⁻¹⁵⁰. Furthermore, EVOO has been shown to down-regulate the expression
402 of COX-2 and Bcl-2 proteins that have a crucial role in colorectal carcinogenesis ¹⁴⁵.
403 A study conducted using different colon cancer cell lines (p53 proficient, mutant and knocked out),
404 demonstrated that a pinoresinol-rich olive oil extract was capable of reducing cancer cell viability
405 (particularly in p53-proficient cells), inducing apoptosis, inducing a G2/M cell cycle block and

406 causing the up-regulating of ATM and a parallel decrease of cyclin B/cdc2¹⁵¹. Similar experiments
407 conducted with purified pinosresinol resulted in similar effects, although higher concentrations were
408 required, indicating a possible synergistic effect between pinosresinol and other polyphenols in
409 EVOO¹⁵¹.

410 The cellular mechanism by which EVOOP exert anticancer effects can also be linked to the
411 modulation of MAPK kinases and COX-2¹²². COX-2 is over-expressed in colorectal cancer, and its
412 over-expression has a strong association with colorectal neoplasia, by promoting cell survival, cell
413 growth, migration, invasion and angiogenesis¹⁵². An efficient inhibitor of COX-2, oleocanthal,
414 repressed cell viability and induced apoptosis in human colon carcinoma HT-29 cells, via AMPK
415 activation and COX-2 suppression¹⁵³, and it has also been proven to reduce proliferation and
416 migration in different cancer cells, deactivating the activity of various mediators in addition to
417 COX-2, which result in tumorigenesis¹²⁴.

418 The MAPK signaling pathway has long been viewed as an attractive pathway for anticancer
419 therapies, based on its central role in regulating the growth and survival of cells from a broad
420 spectrum of human cancers¹⁵⁴, and it also modulates the transcriptional and post-transcriptional
421 activation of COX-2¹⁵⁵.

422 An EVOO phenolic extract has been shown to exert a strong inhibitory effect on the growth of
423 colon adenocarcinoma cells through the inhibition of p38/CREB signaling, a decrease in COX-2
424 expression and the stimulation of a G2/M phase cell cycle block¹²². In contrast, HT exerts its anti-
425 proliferative effects via its ability to strongly inhibit ERK1/2 phosphorylation and downstream
426 cyclin D1 expression¹⁴². These findings are of particular relevance due to the high colonic
427 bioavailability of HT compared to the other EVOOP and may help explain the inverse link between
428 colon cancer and EVOO consumption.

429 Furthermore, HT inhibits colon cancer cell proliferation¹⁵⁶ and induces cancer cell apoptosis¹⁵⁷
430 through a mechanism of action linked to a prolonged stress of the endoplasmic reticulum (activation
431 of unfolded proteins) and over-expression of pro-apoptotic factors, such as Ser/thr phosphatase 2A,

432 a key protein involved in the induction of apoptosis in colon cancer cells ¹⁵⁷. TYR on the other
433 hand, has been found to reverse a number of effects induced by oxidized lipids, including ROS
434 overproduction, GSH depletion, the impairment in antioxidant enzyme activity and the increase in
435 the expression of p66Shc protein ^{101, 158-159}. All of these findings suggest that the ability of EVOOP
436 as intestinal anti-cancer agents should be reappraised, as it is clear that their actions on the process
437 of carcinogenesis are many-fold and involve more than simple antioxidant effect.

438

439 7. Conclusions

440 A large body of evidence suggests the potential for EVOOP to promote beneficial health effects in
441 the prevention and amelioration of several chronic diseases, mainly cardiovascular diseases,
442 neurodegenerative disorders and cancer, as recently outlined by Visioli et al., who critically
443 summarized the main reported findings on the effects of EVOO consumption on human health,
444 discussed in the last International Olive Council Conference ¹⁶⁰. Studies on the absorption and
445 metabolization of EVOOP show that some complex polyphenols reach the intestine, where they
446 may be directly absorbed or metabolized during absorption, while others undergo an extensive
447 gastrointestinal biotransformation. Therefore, a significant amount of bioactive compounds, mainly
448 simple phenols and metabolites, will be present in the small and large intestine, concentrating at this
449 site.

450 Considering that dietary intake of EVOOP in the Mediterranean area has been estimated to be
451 around 9 mg, based on 25 - 50 ml of EVOO daily consumption ¹⁹, EVOOP may significantly
452 contribute to preserve intestinal epithelium homeostasis. As suggested by the few studies
453 summarized in this review (Table 1), EVOOP may help to counteract oxidative stress and can
454 modulate intestinal inflammation, gut microbiota and immune response, thus helping to prevent the
455 onset or delay the progression of inflammatory/degenerative diseases. Although more studies are
456 necessary to validate the important role of EVOOP in the maintenance of intestinal homeostasis, the

457 regular consumption of EVOO should be highly promoted also in view of their possible role in
458 preventing intestinal diseases.

459

460 **Conflicts of interest**

461 No conflicts of interest.

462 **References**

463

- 464 1. J. A. Uranga, V. Lopez-Miranda, F. Lombo and R. Abalo, Food, nutrients and nutraceuticals affecting
465 the course of inflammatory bowel disease, *Pharmacol Rep*, 2016, **68**, 816-826.
- 466 2. A. Kaulmann and T. Bohn, Bioactivity of Polyphenols: Preventive and Adjuvant Strategies toward
467 Reducing Inflammatory Bowel Diseases-Promises, Perspectives, and Pitfalls, *Oxid Med Cell Longev*,
468 2016, **2016**, 9346470.
- 469 3. A. Scalbert and G. Williamson, Dietary intake and bioavailability of polyphenols, *J Nutr*, 2000, **130**,
470 2073S-2085S.
- 471 4. B. Halliwell, J. Rafter and A. Jenner, Health promotion by flavonoids, tocopherols, tocotrienols, and
472 other phenols: direct or indirect effects? Antioxidant or not?, *The American journal of clinical*
473 *nutrition*, 2005, **81**, 268S-276S.
- 474 5. L. Parkinson and S. Cicerale, The Health Benefiting Mechanisms of Virgin Olive Oil Phenolic
475 Compounds, *Molecules*, 2016, **21**.
- 476 6. R. Estruch, E. Ros, J. Salas-Salvado, M. I. Covas, D. Corella, F. Aros, E. Gomez-Gracia, V. Ruiz-
477 Gutierrez, M. Fiol, J. Lapetra, R. M. Lamuela-Raventos, L. Serra-Majem, X. Pinto, J. Basora, M. A.
478 Munoz, J. V. Sorli, J. A. Martinez and M. A. Martinez-Gonzalez, Primary prevention of cardiovascular
479 disease with a Mediterranean diet, *N Engl J Med*, 2013, **368**, 1279-1290.
- 480 7. R. Casas, R. Estruch and E. Sacanella, The Protective Effects of Extra Virgin Olive Oil on Immune-
481 mediated Inflammatory Responses, *Endocr Metab Immune Disord Drug Targets*, 2018, **18**, 23-35.
- 482 8. E. Bernardini and F. Visioli, High quality, good health: The case for olive oil, *European Journal of*
483 *Lipid Science and Technology*, 2017, **119**.
- 484 9. M. I. Covas, M. Fito and R. De la Torre, in *Olive and Olive Oil Bioactive Constituents*, AOCS Press,
485 2015, pp. 31-52.
- 486 10. L. Cerretani, T. Gallina Toschi and A. Bendini, in *Functional Plant Science and Biotechnology*, Global
487 Science Books, 2009.
- 488 11. T. Gallina-Toschi, L. Cerretani, A. Bendini, M. Bonoli-Carbognin and G. Lercker, Oxidative stability
489 and phenolic content of virgin olive oil: an analytical approach by traditional and high resolution
490 techniques, *J Sep Sci*, 2005, **28**, 859-870.
- 491 12. M. Saitta, F. Salvo, G. Di Bella, G. Dugo and G. La Torre, Minor compounds in the phenolic fraction
492 of virgin olive oils, *Food Chem*, 2009, **112**, 525-532.
- 493 13. V. Lavelli and L. Bondesan, Secoiridoids, tocopherols, and antioxidant activity of monovarietal extra
494 virgin olive oils extracted from destoned fruits, *J Agric Food Chem*, 2005, **53**, 1102-1107.
- 495 14. A. Cardeno, M. Sanchez-Hidalgo and C. Alarcon-de-la-Lastra, An up-date of olive oil phenols in
496 inflammation and cancer: molecular mechanisms and clinical implications, *Current medicinal*
497 *chemistry*, 2013, **20**, 4758-4776.
- 498 15. A. Bianco, F. Coccioli, M. Guiso and C. Marra, The occurrence in olive oil of a new class of phenolic
499 compounds: Hydroxy-isochromans, *Food Chem Toxicol*, 2001, **77**, 405-411.
- 500 16. P. Rovellini and N. Cortesi, Liquid chromatography-mass spectrometry in the study of oleuropein
501 and ligstroside aglycons in virgin olive oils: Aldehydic, dialdehydic forms and their oxidized
502 products., *Riv. Ital. Sostanze Grasse* 2002, **79**, 1-14.
- 503 17. R. W. Owen, W. Mier, A. Giacosa, W. E. Hull, B. Spiegelhalder and H. Bartsch, Phenolic compounds
504 and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple
505 phenols, secoiridoids, lignans and squalene, *Food Chem Toxicol*, 2000, **38**, 647-659.
- 506 18. M. Servili, R. Selvaggini, S. Esposto, A. Taticchi, G. Montedoro and G. Morozzi, Health and sensory
507 properties of virgin olive oil hydrophilic phenols: agronomic and technological aspects of
508 production that affect their occurrence in the oil, *Journal of chromatography*, 2004, **1054**, 113-127.
- 509 19. R. de la Torre, Bioavailability of olive oil phenolic compounds in humans, *Inflammopharmacology*,
510 2008, **16**, 245-247.
- 511 20. S. Cicerale, X. A. Conlan, A. J. Sinclair and R. S. Keast, Chemistry and health of olive oil phenolics,
512 *Critical reviews in food science and nutrition*, 2009, **49**, 218-236.

- 513 21. M. Gorzynik-Debicka, P. Przychodzen, F. Cappello, A. Kuban-Jankowska, A. Marino Gammazza, N.
514 Knap, M. Wozniak and M. Gorska-Ponikowska, Potential Health Benefits of Olive Oil and Plant
515 Polyphenols, *Int J Mol Sci*, 2018, **19**.
- 516 22. S. Cicerale, L. Lucas and R. Keast, Biological activities of phenolic compounds present in virgin olive
517 oil, *Int J Mol Sci*, 2010, **11**, 458-479.
- 518 23. G. Fregapane, A. Gomez-Rico, A. M. Inarejos and M. D. Salvador, Relevance of minor components
519 stability in commercial olive oil quality during the market period, *European Journal of Lipid Science
520 and Technology*, 2013, **115**, 541-548.
- 521 24. O. S. Jolayemi, F. Tokatli and B. Ozen, Effects of malaxation temperature and harvest time on the
522 chemical characteristics of olive oils, *Food Chem*, 2016, **211**, 776-783.
- 523 25. A. Soler, M. P. Romero, A. Macià, S. Saha, C. S. M. Furniss, P. A. Kroon and M. J. Motilva, Digestion
524 stability and evaluation of the metabolism and transport of olive oil phenols in the human small-
525 intestinal epithelial Caco-2/TC7 cell line, *Food Chemistry* 2010, **119**, 704-714.
- 526 26. S. Cicerale, L. J. Lucas and R. S. Keast, Antimicrobial, antioxidant and anti-inflammatory phenolic
527 activities in extra virgin olive oil, *Current opinion in biotechnology*, 2012, **23**, 129-135.
- 528 27. J. Rodriguez-Morato, A. Boronat, A. Kotronoulas, M. Pujadas, A. Pastor, E. Olesti, C. Perez-Mana, O.
529 Khymenets, M. Fito, M. Farre and R. de la Torre, Metabolic disposition and biological significance of
530 simple phenols of dietary origin: hydroxytyrosol and tyrosol, *Drug Metab Rev*, 2016, **48**, 218-236.
- 531 28. G. Corona, X. Tzounis, M. Assunta Dessi, M. Deiana, E. S. Debnam, F. Visioli and J. P. Spencer, The
532 fate of olive oil polyphenols in the gastrointestinal tract: implications of gastric and colonic
533 microflora-dependent biotransformation, *Free Radic Res*, 2006, **40**, 647-658.
- 534 29. J. Pinto, F. Paiva-Martins, G. Corona, E. S. Debnam, M. Jose Oruna-Concha, D. Vauzour, M. H.
535 Gordon and J. P. Spencer, Absorption and metabolism of olive oil secoiridoids in the small intestine,
536 *Br J Nutr*, 2011, **105**, 1607-1618.
- 537 30. M. N. Vissers, P. L. Zock, A. J. Roodenburg, R. Leenen and M. B. Katan, Olive oil phenols are
538 absorbed in humans, *J Nutr*, 2002, **132**, 409-417.
- 539 31. F. Visioli, C. Galli, E. Plasmati, S. Viappiani, A. Hernandez, C. Colombo and A. Sala, Olive phenol
540 hydroxytyrosol prevents passive smoking-induced oxidative stress, *Circulation*, 2000, **102**, 2169-
541 2171.
- 542 32. E. Miro-Casas, M. Farre Albaladejo, M. I. Covas, J. O. Rodriguez, E. Menoyo Colomer, R. M. Lamuela
543 Raventos and R. de la Torre, Capillary gas chromatography-mass spectrometry quantitative
544 determination of hydroxytyrosol and tyrosol in human urine after olive oil intake, *Analytical
545 biochemistry*, 2001, **294**, 63-72.
- 546 33. F. Visioli, D. Caruso, E. Plasmati, R. Patelli, N. Mulinacci, A. Romani, G. Galli and C. Galli,
547 Hydroxytyrosol, as a component of olive mill waste water, is dose- dependently absorbed and
548 increases the antioxidant capacity of rat plasma, *Free Radic Res*, 2001, **34**, 301-305.
- 549 34. K. L. Tuck and P. J. Hayball, Major phenolic compounds in olive oil: metabolism and health effects, *J
550 Nutr Biochem*, 2002, **13**, 636-644.
- 551 35. T. Weinbrenner, M. Fito, M. Farre Albaladejo, G. T. Saez, P. Rijken, C. Tormos, S. Coolen, R. De La
552 Torre and M. I. Covas, Bioavailability of phenolic compounds from olive oil and
553 oxidative/antioxidant status at postprandial state in healthy humans, *Drugs Exp Clin Res*, 2004, **30**,
554 207-212.
- 555 36. M. I. Covas, K. de la Torre, M. Farre-Albaladejo, J. Kaikkonen, M. Fito, C. Lopez-Sabater, M. A.
556 Pujadas-Bastardes, J. Joglar, T. Weinbrenner, R. M. Lamuela-Raventos and R. de la Torre,
557 Postprandial LDL phenolic content and LDL oxidation are modulated by olive oil phenolic
558 compounds in humans, *Free Radic Biol Med*, 2006, **40**, 608-616.
- 559 37. L. Rubio, A. Macia, A. Castell-Auvi, M. Pinent, M. T. Blay, A. Ardevol, M. P. Romero and M. J.
560 Motilva, Effect of the co-occurring olive oil and thyme extracts on the phenolic bioaccessibility and
561 bioavailability assessed by in vitro digestion and cell models, *Food Chem*, 2014, **149**, 277-284.
- 562 38. E. Miro Casas, M. Farre Albadalejo, M. I. Covas Planells, M. Fito Colomer, R. M. Lamuela Raventos
563 and R. de la Torre Fornell, Tyrosol bioavailability in humans after ingestion of virgin olive oil, *Clin
564 Chem*, 2001, **47**, 341-343.

- 565 39. E. Miro-Casas, M. I. Covas, M. Farre, M. Fito, J. Ortuno, T. Weinbrenner, P. Roset and R. de la Torre,
566 Hydroxytyrosol disposition in humans, *Clin Chem*, 2003, **49**, 945-952.
- 567 40. E. Miro-Casas, M. I. Covas, M. Fito, M. Farre-Albadalejo, J. Marrugat and R. de la Torre, Tyrosol and
568 hydroxytyrosol are absorbed from moderate and sustained doses of virgin olive oil in humans, *Eur J*
569 *Clin Nutr*, 2003, **57**, 186-190.
- 570 41. C. Manna, P. Galletti, G. Maisto, V. Cucciolla, S. D'Angelo and V. Zappia, Transport mechanism and
571 metabolism of olive oil hydroxytyrosol in Caco-2 cells, *FEBS Lett*, 2000, **470**, 341-344.
- 572 42. R. Mateos, G. Pereira-Caro, S. Saha, R. Cert, M. Redondo-Horcajo and L. Bravo, Acetylation of
573 Hydroxytyrosol Enhances its Transport across Differentiated Caco-2 Cell Monolayers
574 *Food Chemistry*, 2011, **123**, 865-872.
- 575 43. S. C. Edgecombe, G. L. Stretch and P. J. Hayball, Oleuropein, an antioxidant polyphenol from olive
576 oil, is poorly absorbed from isolated perfused rat intestine, *J Nutr*, 2000, **130**, 2996-3002.
- 577 44. C. Manach, A. Scalbert, C. Morand, C. Remesy and L. Jimenez, Polyphenols: food sources and
578 bioavailability, *The American journal of clinical nutrition*, 2004, **79**, 727-747.
- 579 45. D. Caruso, F. Visioli, R. Patelli, C. Galli and G. Galli, Urinary excretion of olive oil phenols and their
580 metabolites in humans, *Metabolism*, 2001, **50**, 1426-1428.
- 581 46. O. Khymenets, M. Farré, M. Pujadas, E. Ortiz, J. Joglar, M. I. Covas and R. de la Torre, Direct analysis
582 of glucuronidated metabolites of main olive oil phenols in human urine after dietary consumption
583 of virgin olive oil, *Food Chemistry*, 2011, **126**, 306-314.
- 584 47. S. D'Angelo, C. Manna, V. Migliardi, O. Mazzoni, P. Morrica, G. Capasso, G. Pontoni, P. Galletti and
585 V. Zappia, Pharmacokinetics and metabolism of hydroxytyrosol, a natural antioxidant from olive oil,
586 *Drug Metab Dispos*, 2001, **29**, 1492-1498.
- 587 48. K. L. Tuck, M. P. Freeman, P. J. Hayball, G. L. Stretch and I. Stupans, The in vivo fate of
588 hydroxytyrosol and tyrosol, antioxidant phenolic constituents of olive oil, after intravenous and oral
589 dosing of labeled compounds to rats, *J Nutr*, 2001, **131**, 1993-1996.
- 590 49. F. Visioli, C. Galli, S. Grande, K. Colonnelli, C. Patelli, G. Galli and D. Caruso, Hydroxytyrosol excretion
591 differs between rats and humans and depends on the vehicle of administration, *J Nutr*, 2003, **133**,
592 2612-2615.
- 593 50. L. Rubio, R. M. Valls, A. Macia, A. Pedret, M. Giralt, M. P. Romero, R. de la Torre, M. I. Covas, R. Sola
594 and M. J. Motilva, Impact of olive oil phenolic concentration on human plasmatic phenolic
595 metabolites, *Food Chem*, 2012, **135**, 2922-2929.
- 596 51. M. Suarez, R. M. Valls, M. P. Romero, A. Macia, S. Fernandez, M. Giralt, R. Sola and M. J. Motilva,
597 Bioavailability of phenols from a phenol-enriched olive oil, *Br J Nutr*, 2011, **106**, 1691-1701.
- 598 52. O. Khymenets, M. C. Crespo, O. Dangles, N. Rakotomanomana, C. Andres-Lacueva and F. Visioli,
599 Human hydroxytyrosol's absorption and excretion from a nutraceutical, *Journal of Functional*
600 *Foods*, 2016, **23**, 278-282.
- 601 53. M. Suarez, M. P. Romero, A. Macia, R. M. Valls, S. Fernandez, R. Sola and M. J. Motilva, Improved
602 method for identifying and quantifying olive oil phenolic compounds and their metabolites in
603 human plasma by microelution solid-phase extraction plate and liquid chromatography-tandem
604 mass spectrometry, *J Chromatogr B Analyt Technol Biomed Life Sci*, 2009, **877**, 4097-4106.
- 605 54. M. de Bock, E. B. Thorstensen, J. G. Derraik, H. V. Henderson, P. L. Hofman and W. S. Cutfield,
606 Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (*Olea*
607 *europaea* L.) leaf extract, *Molecular nutrition & food research*, 2013, **57**, 2079-2085.
- 608 55. R. Garcia-Villalba, A. Carrasco-Pancorbo, E. Nevedomskaya, O. A. Mayboroda, A. M. Deelder, A.
609 Segura-Carretero and A. Fernandez-Gutierrez, Exploratory analysis of human urine by LC-ESI-TOF
610 MS after high intake of olive oil: understanding the metabolism of polyphenols, *Analytical and*
611 *bioanalytical chemistry*, 2010, **398**, 463-475.
- 612 56. R. De la Torre, D. Corella, O. Castaner, M. A. Martinez-Gonzalez, J. Salas-Salvador, J. Vila, R. Estruch,
613 J. V. Sorli, F. Aros, M. Fiol, E. Ros, L. Serra-Majem, X. Pinto, E. Gomez-Gracia, J. Lapetra, M. Ruiz-
614 Canela, J. Basora, E. M. Asensio, M. I. Covas and M. Fito, Protective effect of homovanillyl alcohol
615 on cardiovascular disease and total mortality: virgin olive oil, wine, and catechol-methylthion, *The*
616 *American journal of clinical nutrition*, 2017, **105**, 1297-1304.

- 617 57. G. P. Donaldson, S. M. Lee and S. K. Mazmanian, Gut biogeography of the bacterial microbiota, *Nat*
618 *Rev Microbiol*, 2016, **14**, 20-32.
- 619 58. F. Cardona, C. Andres-Lacueva, S. Tulipani, F. J. Tinahones and M. I. Queipo-Ortuno, Benefits of
620 polyphenols on gut microbiota and implications in human health, *J Nutr Biochem*, 2013, **24**, 1415-
621 1422.
- 622 59. J. I. Mosele, S. Martin-Pelaez, A. Macia, M. Farras, R. M. Valls, U. Catalan and M. J. Motilva, Faecal
623 microbial metabolism of olive oil phenolic compounds: in vitro and in vivo approaches, *Molecular*
624 *nutrition & food research*, 2014, **58**, 1809-1819.
- 625 60. P. Lin, W. Qian, X. Wang, L. Cao, S. Li and T. Qian, The biotransformation of oleuropein in rats,
626 *Biomed Chromatogr*, 2013, **27**, 1162-1167.
- 627 61. W. Russell and G. Duthie, Plant secondary metabolites and gut health: the case for phenolic acids, *P*
628 *Nutr Soc*, 2011, **70**, 389-396.
- 629 62. A. M. Jenner, J. Rafter and B. Halliwell, Human fecal water content of phenolics: The extent of
630 colonic exposure to aromatic compounds, *Free Radical Bio Med*, 2005, **38**, 763-772.
- 631 63. A. R. Rechner and C. Kroner, Anthocyanins and colonic metabolites of dietary polyphenols inhibit
632 platelet function, *Thromb Res*, 2005, **116**, 327-334.
- 633 64. C. Cueva, M. V. Moreno-Arribas, P. J. Martin-Alvarez, G. Bills, M. F. Vicente, A. Basilio, C. L. Rivas, T.
634 Requena, J. M. Rodriguez and B. Bartolome, Antimicrobial activity of phenolic acids against
635 commensal, probiotic and pathogenic bacteria, *Res Microbiol*, 2010, **161**, 372-382.
- 636 65. M. M. Santos, C. Piccirillo, P. M. L. Castro, N. Kalogerakis and M. E. Pintado, Bioconversion of
637 oleuropein to hydroxytyrosol by lactic acid bacteria, *World J Microb Biot*, 2012, **28**, 2435-2440.
- 638 66. M. Saarela, L. Lahteenmaki, R. Crittenden, S. Salminen and T. Mattila-Sandholm, Gut bacteria and
639 health foods - the European perspective, *Int J Food Microbiol*, 2002, **78**, 99-117.
- 640 67. M. Avila, M. Hidalgo, C. Sanchez-Moreno, C. Pelaez, T. Requena and S. de Pascual-Teresa,
641 Bioconversion of anthocyanin glycosides by Bifidobacteria and Lactobacillus, *Food Res Int*, 2009, **42**,
642 1453-1461.
- 643 68. V. Marsilio and B. Lanza, Characterisation of an oleuropein degrading strain of Lactobacillus
644 plantarum. Combined effects of compounds present in olive fermenting brines (phenols, glucose
645 and NaCl) on bacterial activity, *J Sci Food Agr*, 1998, **76**, 520-524.
- 646 69. J. M. Landete, J. A. Curiel, H. Rodriguez, B. de las Rivas and R. Munoz, Study of the inhibitory activity
647 of phenolic compounds found in olive products and their degradation by Lactobacillus plantarum
648 strains, *Food Chemistry*, 2008, **107**, 320-326.
- 649 70. H. Rodriguez, J. A. Curiel, J. M. Landete, B. de las Rivas, F. L. de Felipe, C. Gomez-Cordoves, J. M.
650 Mancheno and R. Munoz, Food phenolics and lactic acid bacteria, *Int J Food Microbiol*, 2009, **132**,
651 79-90.
- 652 71. A. Tafesh, N. Najami, J. Jadoun, F. Halahlih, H. Riepl and H. Azaizeh, Synergistic antibacterial effects
653 of polyphenolic compounds from olive mill wastewater, *Evid Based Complement Alternat Med*,
654 2011, **2011**, 431021.
- 655 72. M. S. Medina-Martinez, P. Truchado, I. Castro-Ibanez and A. Allende, Antimicrobial activity of
656 hydroxytyrosol: a current controversy, *Bioscience, biotechnology, and biochemistry*, 2016, **80**, 801-
657 810.
- 658 73. E. Medina, M. Brenes, C. Romero, A. Garcia and A. de Castro, Main antimicrobial compounds in
659 table olives, *J Agric Food Chem*, 2007, **55**, 9817-9823.
- 660 74. A. T. Serra, A. A. Matias, A. V. M. Nunes, M. C. Leitao, D. Brito, R. Bronze, S. Silva, A. Pires, M. T.
661 Crespo, M. V. S. Romao and C. M. Duarte, In vitro evaluation of olive- and grape-based natural
662 extracts as potential preservatives for food, *Innov Food Sci Emerg*, 2008, **9**, 311-319.
- 663 75. J. Thielmann, S. Kohnen and C. Hauser, Antimicrobial activity of Olea europaea Linne extracts and
664 their applicability as natural food preservative agents, *Int J Food Microbiol*, 2017, **251**, 48-66.
- 665 76. S. Martin-Pelaez, J. I. Mosele, N. Pizarro, M. Farras, R. de la Torre, I. Subirana, F. J. Perez-Cano, O.
666 Castaner, R. Sola, S. Fernandez-Castillejo, S. Heredia, M. Farre, M. J. Motilva and M. Fito, Effect of
667 virgin olive oil and thyme phenolic compounds on blood lipid profile: implications of human gut
668 microbiota, *European Journal of Nutrition*, 2017, **56**, 119-131.

- 669 77. S. Martin-Pelaez, O. Castaner, R. Sola, M. J. Motilva, M. Castell, F. J. Perez-Cano and M. Fito, Influence of Phenol-Enriched Olive Oils on Human Intestinal Immune Function, *Nutrients*, 2016, **8**.
- 670
- 671 78. L. Conterno, F. Martinelli, M. Tamburini, F. Fava, A. Mancini, M. Sordo, M. Pindo, S. Martens, D.
- 672 Masuero, U. Vrhovsek, C. Dal Lago, G. Ferrario, M. Morandini and K. Tuohy, Measuring the impact
- 673 of olive pomace enriched biscuits on the gut microbiota and its metabolic activity in mildly
- 674 hypercholesterolaemic subjects, *Eur J Nutr*, 2017.
- 675 79. M. Farras, O. Castaner, S. Martin-Pelaez, A. Hernaez, H. Schroder, I. Subirana, D. Munoz-Aguayo, S.
- 676 Gaixas, L. Torre Rde, M. Farre, L. Rubio, O. Diaz, S. Fernandez-Castillejo, R. Sola, M. J. Motilva and
- 677 M. Fito, Complementary phenol-enriched olive oil improves HDL characteristics in
- 678 hypercholesterolemic subjects. A randomized, double-blind, crossover, controlled trial. The VOHF
- 679 study, *Molecular nutrition & food research*, 2015, **59**, 1758-1770.
- 680 80. F. Biasi, M. Astegiano, M. Maina, G. Leonarduzzi and G. Poli, Polyphenol supplementation as a
- 681 complementary medicinal approach to treating inflammatory bowel disease, *Current medicinal*
- 682 *chemistry*, 2011, **18**, 4851-4865.
- 683 81. A. Incani, G. Serra, A. Atzeri, M. P. Melis, G. Serreli, G. Bandino, P. Sedda, M. Campus, C. I. Tuberoso
- 684 and M. Deiana, Extra virgin olive oil phenolic extracts counteract the pro-oxidant effect of dietary
- 685 oxidized lipids in human intestinal cells, *Food Chem Toxicol*, 2016, **90**, 171-180.
- 686 82. J. P. De La Cruz, M. I. Ruiz-Moreno, A. Guerrero, J. A. Lopez-Villodres, J. J. Reyes, J. L. Espartero, M.
- 687 T. Labajos and J. A. Gonzalez-Correa, Role of the catechol group in the antioxidant and
- 688 neuroprotective effects of virgin olive oil components in rat brain, *J Nutr Biochem*, 2015, **26**, 549-
- 689 555.
- 690 83. F. Visioli, A. Poli and C. Gall, Antioxidant and other biological activities of phenols from olives and
- 691 olive oil, *Medicinal research reviews*, 2002, **22**, 65-75.
- 692 84. M. Deiana, G. Corona, A. Incani, D. Loru, A. Rosa, A. Atzeri, M. P. Melis and M. A. Dessi, Protective
- 693 effect of simple phenols from extravirgin olive oil against lipid peroxidation in intestinal Caco-2
- 694 cells, *Food and Chemical Toxicology*, 2010, **48**, 3008-3016.
- 695 85. C. Manna, P. Galletti, V. Cucciolla, O. Moltedo, A. Leone and V. Zappia, The protective effect of the
- 696 olive oil polyphenol (3,4-dihydroxyphenyl)-ethanol counteracts reactive oxygen metabolite-induced
- 697 cytotoxicity in Caco-2 cells, *J Nutr*, 1997, **127**, 286-292.
- 698 86. I. Rodriguez-Ramiro, M. A. Martin, S. Ramos, L. Bravo and L. Goya, Olive oil hydroxytyrosol reduces
- 699 toxicity evoked by acrylamide in human Caco-2 cells by preventing oxidative stress, *Toxicology*,
- 700 2011, **288**, 43-48.
- 701 87. A. Atzeri, R. Lucas, A. Incani, P. Penalver, A. Zafra-Gomez, M. P. Melis, R. Pizzala, J. C. Morales and
- 702 M. Deiana, Hydroxytyrosol and tyrosol sulfate metabolites protect against the oxidized cholesterol
- 703 pro-oxidant effect in Caco-2 human enterocyte-like cells, *Food Funct*, 2016, **7**, 337-346.
- 704 88. M. Deiana, A. Incani, A. Rosa, A. Atzeri, D. Loru, B. Cabboi, M. Paola Melis, R. Lucas, J. C. Morales
- 705 and M. Assunta Dessi, Hydroxytyrosol glucuronides protect renal tubular epithelial cells against
- 706 H(2)O(2) induced oxidative damage, *Chemico-biological interactions*, 2011, **193**, 232-239.
- 707 89. F. Paiva-Martins, A. Silva, V. Almeida, M. Carvalheira, C. Serra, J. E. Rodrigues-Borges, J. Fernandes,
- 708 L. Belo and A. Santos-Silva, Protective activity of hydroxytyrosol metabolites on erythrocyte
- 709 oxidative-induced hemolysis, *J Agric Food Chem*, 2013, **61**, 6636-6642.
- 710 90. C. Giovannini, E. Straface, D. Modesti, E. Coni, A. Cantafora, M. De Vincenzi, W. Malorni and R.
- 711 Masella, Tyrosol, the major olive oil biophenol, protects against oxidized-LDL-induced injury in
- 712 Caco-2 cells, *J Nutr*, 1999, **129**, 1269-1277.
- 713 91. V. R. Gutierrez, R. de la Puerta and A. Catala, The effect of tyrosol, hydroxytyrosol and oleuropein
- 714 on the non-enzymatic lipid peroxidation of rat liver microsomes, *Mol Cell Biochem*, 2001, **217**, 35-
- 715 41.
- 716 92. A. A. Bertelli, M. Migliori, V. Panichi, B. Longoni, N. Origlia, A. Ferretti, M. G. Cuttano and L.
- 717 Giovannini, Oxidative stress and inflammatory reaction modulation by white wine, *Annals of the*
- 718 *New York Academy of Sciences*, 2002, **957**, 295-301.

- 719 93. R. de la Puerta, M. E. Martinez Dominguez, V. Ruiz-Gutierrez, J. A. Flavill and J. R. Hoult, Effects of
720 virgin olive oil phenolics on scavenging of reactive nitrogen species and upon nitregeric
721 neurotransmission, *Life Sci*, 2001, **69**, 1213-1222.
- 722 94. M. A. Martin, S. Ramos, A. B. Granado-Serrano, I. Rodriguez-Ramiro, M. Trujillo, L. Bravo and L.
723 Goya, Hydroxytyrosol induces antioxidant/detoxifcant enzymes and Nrf2 translocation via
724 extracellular regulated kinases and phosphatidylinositol-3-kinase/protein kinase B pathways in
725 HepG2 cells, *Molecular nutrition & food research*, 2010, **54**, 956-966.
- 726 95. E. Giordano, A. Davalos and F. Visioli, Chronic hydroxytyrosol feeding modulates glutathione-
727 mediated oxido-reduction pathways in adipose tissue: A nutrigenomic study, *Nutr Metab
728 Cardiovas*, 2014, **24**, 1144-1150.
- 729 96. K. Cao, J. Xu, X. Zou, Y. Li, C. Chen, A. Zheng, H. Li, I. M. Szeto, Y. Shi, J. Long, J. Liu and Z. Feng,
730 Hydroxytyrosol prevents diet-induced metabolic syndrome and attenuates mitochondrial
731 abnormalities in obese mice, *Free Radic Biol Med*, 2014, **67**, 396-407.
- 732 97. L. Zhu, Z. B. Liu, Z. H. Feng, J. J. Hao, W. L. Shen, X. S. Li, L. J. Sun, E. Sharman, Y. Wang, K. Wertz, P.
733 Weber, X. L. Shi and J. K. Liu, Hydroxytyrosol protects against oxidative damage by simultaneous
734 activation of mitochondrial biogenesis and phase II detoxifying enzyme systems in retinal pigment
735 epithelial cells, *Journal of Nutritional Biochemistry*, 2010, **21**, 1089-1098.
- 736 98. I. Fki, Z. Sahnoun and S. Sayadi, Hypocholesterolemic effects of phenolic extracts and purified
737 hydroxytyrosol recovered from olive mill wastewater in rats fed a cholesterol-rich diet, *J Agric Food
738 Chem*, 2007, **55**, 624-631.
- 739 99. M. C. Crespo, J. Tome-Carneiro, E. Burgos-Ramos, V. Loria Kohen, M. I. Espinosa, J. Herranz and F.
740 Visioli, One-week administration of hydroxytyrosol to humans does not activate Phase II enzymes,
741 *Pharmacol Res*, 2015, **95-96**, 132-137.
- 742 100. F. J. G. Muriana, S. Montserrat-de la Paz, R. Lucas, B. Bermudez, S. Jaramillo, J. C. Morales, R. Abia
743 and S. Lopez, Tyrosol and its metabolites as antioxidative and anti-inflammatory molecules in
744 human endothelial cells, *Food Funct*, 2017, **8**, 2905-2914.
- 745 101. R. Di Benedetto, R. Vari, B. Scazzocchio, C. Filesi, C. Santangelo, C. Giovannini, P. Matarrese, M.
746 D'Archivio and R. Masella, Tyrosol, the major extra virgin olive oil compound, restored intracellular
747 antioxidant defences in spite of its weak antioxidative effectiveness, *Nutr Metab Cardiovasc Dis*,
748 2007, **17**, 535-545.
- 749 102. W. C. Wang, Y. M. Xia, B. Yang, X. N. Su, J. K. Chen, W. Li and T. Jiang, Protective Effects of Tyrosol
750 against LPS-Induced Acute Lung Injury via Inhibiting NF-kappa B and AP-1 Activation and Activating
751 the HO-1/Nrf2 Pathways, *Biological & pharmaceutical bulletin*, 2017, **40**, 583-593.
- 752 103. I. Hassen, H. Casabianca and K. Hosni, Biological activities of the natural antioxidant oleuropein:
753 Exceeding the expectation - A mini-review, *J Funct Foods*, 2015, **18**, 926-940.
- 754 104. A. Parzonko, M. E. Czerwinska, A. K. Kiss and M. Naruszewicz, Oleuropein and oleacein may restore
755 biological functions of endothelial progenitor cells impaired by angiotensin II via activation of
756 Nrf2/heme oxygenase-1 pathway, *Phytomedicine*, 2013, **20**, 1088-1094.
- 757 105. C. Shi, X. Chen, Z. Liu, R. Meng, X. Zhao and N. Guo, Oleuropein protects L-02 cells against H2O2-
758 induced oxidative stress by increasing SOD1, GPx1 and CAT expression, *Biomedicine &
759 pharmacotherapy = Biomedecine & pharmacotherapie*, 2017, **85**, 740-748.
- 760 106. H. Jemai, M. Bouaziz, I. Fki, A. El Feki and S. Sayadi, Hypolipidimic and antioxidant activities of
761 oleuropein and its hydrolysis derivative-rich extracts from Chemlali olive leaves, *Chemico-biological
762 interactions*, 2008, **176**, 88-98.
- 763 107. D. Kotyzova, A. Hodkova and V. Eybl, The effect of olive oil phenolics - Hydroxytyrosol and
764 oleuropein on antioxidant defence status in acute arsenic exposed rats, *Toxicology Letters*, 2011,
765 **205**, S222-S222.
- 766 108. W. Sun, X. Wang, C. Hou, L. Yang, H. Li, J. Guo, C. Huo, M. Wang, Y. Miao, J. Liu and Y. Kang,
767 Oleuropein improves mitochondrial function to attenuate oxidative stress by activating the Nrf2
768 pathway in the hypothalamic paraventricular nucleus of spontaneously hypertensive rats,
769 *Neuropharmacology*, 2017, **113**, 556-566.

- 770 109. M. Sarbishegi, F. Mehraein and M. Soleimani, Antioxidant role of oleuropein on midbrain and
771 dopaminergic neurons of substantia nigra in aged rats, *Iran Biomed J*, 2014, **18**, 16-22.
- 772 110. H. F. Al-Azzawie and M. S. S. Alhamdani, Hypoglycemic and antioxidant effect of oleuropein in
773 alloxan-diabetic rabbits, *Life Sciences*, 2006, **78**, 1371-1377.
- 774 111. A. Cardeno, M. Sanchez-Hidalgo and C. Alarcon-de-la-Lastra, An up-date of olive oil phenols in
775 inflammation and cancer: molecular mechanisms and clinical implications, *Current medicinal*
776 *chemistry*, 2013, **20**, 4758-4776.
- 777 112. E. Muto, M. Dell'Agli, E. Sangiovanni, N. Mitro, M. Fumagalli, M. Crestani, E. De Fabiani and D.
778 Caruso, Olive oil phenolic extract regulates interleukin-8 expression by transcriptional and
779 posttranscriptional mechanisms in Caco-2 cells, *Molecular nutrition & food research*, 2015, **59**,
780 1217-1221.
- 781 113. G. Serra, A. Incani, G. Serreli, L. Porru, M. P. Melis, C. I. G. Tuberoso, D. Rossin, F. Biasi and M.
782 Deiana, Olive oil polyphenols reduce oxysterols -induced redox imbalance and pro-inflammatory
783 response in intestinal cells, *Redox Biol*, 2018, **17**, 348-354.
- 784 114. S. Sanchez-Fidalgo, A. Cardeno, M. Sanchez-Hidalgo, M. Aparicio-Soto and C. A. de la Lastra, Dietary
785 extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice, *J*
786 *Nutr Biochem*, 2013, **24**, 1401-1413.
- 787 115. S. Sanchez-Fidalgo, A. Cardeno, M. Sanchez-Hidalgo, M. Aparicio-Soto, I. Villegas, M. A. Rosillo and
788 C. A. de la Lastra, Dietary unsaponifiable fraction from extra virgin olive oil supplementation
789 attenuates acute ulcerative colitis in mice, *Eur J Pharm Sci*, 2013, **48**, 572-581.
- 790 116. E. Giner, I. Andujar, M. C. Recio, J. L. Rios, J. M. Cerda-Nicolas and R. M. Giner, Oleuropein
791 ameliorates acute colitis in mice, *J Agric Food Chem*, 2011, **59**, 12882-12892.
- 792 117. E. Giner, M. C. Recio, J. L. Rios and R. M. Giner, Oleuropein protects against dextran sodium sulfate-
793 induced chronic colitis in mice, *Journal of natural products*, 2013, **76**, 1113-1120.
- 794 118. E. Giner, M. C. Recio, J. L. Rios, J. M. Cerda-Nicolas and R. M. Giner, Chemopreventive effect of
795 oleuropein in colitis-associated colorectal cancer in c57bl/6 mice, *Molecular nutrition & food*
796 *research*, 2016, **60**, 242-255.
- 797 119. T. Larussa, M. Oliverio, E. Suraci, M. Greco, R. Placida, S. Gervasi, R. Marasco, M. Imeneo, D.
798 Paolino, L. Tucci, E. Gulletta, M. Fresta, A. Procopio and F. Lizza, Oleuropein Decreases
799 Cyclooxygenase-2 and Interleukin-17 Expression and Attenuates Inflammatory Damage in Colonic
800 Samples from Ulcerative Colitis Patients, *Nutrients*, 2017, **9**.
- 801 120. A. Voltes, A. Bermudez, G. Rodriguez-Gutierrez, M. L. Reyes, C. Olano, J. Fernandez-Bolanos and F.
802 Portilla, Anti-Inflammatory Local Effect of Hydroxytyrosol Combined with Pectin-Alginate and Olive
803 Oil on Trinitrobenzene Sulfonic Acid-Induced Colitis in Wistar Rats, *J Invest Surg*, 2018, 1-7.
- 804 121. S. Sanchez-Fidalgo, L. Sanchez de Ibarquen, A. Cardeno and C. Alarcon de la Lastra, Influence of
805 extra virgin olive oil diet enriched with hydroxytyrosol in a chronic DSS colitis model, *Eur J Nutr*,
806 2012, **51**, 497-506.
- 807 122. G. Corona, M. Deiana, A. Incani, D. Vauzour, M. A. Dessi and J. P. Spencer, Inhibition of p38/CREB
808 phosphorylation and COX-2 expression by olive oil polyphenols underlies their anti-proliferative
809 effects, *Biochem Biophys Res Commun*, 2007, **362**, 606-611.
- 810 123. S. Sanchez-Fidalgo, I. Villegas, M. Aparicio-Soto, A. Cardeno, M. A. Rosillo, A. Gonzalez-Benjumea, A.
811 Marset, O. Lopez, I. Maya, J. G. Fernandez-Bolanos and C. Alarcon de la Lastra, Effects of dietary
812 virgin olive oil polyphenols: hydroxytyrosyl acetate and 3, 4-dihydroxyphenylglycol on DSS-induced
813 acute colitis in mice, *J Nutr Biochem*, 2015, **26**, 513-520.
- 814 124. L. Parkinson and R. Keast, Oleocanthal, a phenolic derived from virgin olive oil: a review of the
815 beneficial effects on inflammatory disease, *Int J Mol Sci*, 2014, **15**, 12323-12334.
- 816 125. C. Pelucchi, C. Bosetti, E. Negri, L. Lipworth and C. La Vecchia, Olive oil and cancer risk: an update of
817 epidemiological findings through 2010, *Curr Pharm Des*, 2011, **17**, 805-812.
- 818 126. F. Levi, C. Pasche, C. La Vecchia, F. Lucchini and S. Franceschi, Food groups and colorectal cancer
819 risk, *British journal of cancer*, 1999, **79**, 1283-1287.

- 820 127. M. Stoneham, M. Goldacre, V. Seagroatt and L. Gill, Olive oil, diet and colorectal cancer: an
821 ecological study and a hypothesis, *Journal of epidemiology and community health*, 2000, **54**, 756-
822 760.
- 823 128. T. Psaltopoulou, R. I. Kostis, D. Haidopoulos, M. Dimopoulos and D. B. Panagiotakos, Olive oil intake
824 is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13800 patients
825 and 23340 controls in 19 observational studies, *Lipids in Health and Disease*, 2011, **10**.
- 826 129. A. Farinetti, V. Zurlo, A. Manenti, F. Coppi and A. V. Mattioli, Mediterranean diet and colorectal
827 cancer: A systematic review, *Nutrition (Burbank, Los Angeles County, Calif)*, 2017, **43-44**, 83-88.
- 828 130. J. A. Menendez and R. Lupu, Mediterranean dietary traditions for the molecular treatment of
829 human cancer: anti-oncogenic actions of the main olive oil's monounsaturated fatty acid oleic acid
830 (18:1n-9), *Curr Pharm Biotechnol*, 2006, **7**, 495-502.
- 831 131. R. W. Owen, A. Giacosa, W. E. Hull, R. Haubner, B. Spiegelhalder and H. Bartsch, The
832 antioxidant/anticancer potential of phenolic compounds isolated from olive oil, *Eur J Cancer*, 2000,
833 **36**, 1235-1247.
- 834 132. E. Middleton, Jr., C. Kandaswami and T. C. Theoharides, The effects of plant flavonoids on
835 mammalian cells: implications for inflammation, heart disease, and cancer, *Pharmacol Rev*, 2000,
836 **52**, 673-751.
- 837 133. G. Corona, J. P. Spencer and M. A. Dessi, Extra virgin olive oil phenolics: absorption, metabolism,
838 and biological activities in the GI tract, *Toxicol Ind Health*, 2009, **25**, 285-293.
- 839 134. I. Casaburi, F. Puoci, A. Chimento, R. Sirianni, C. Ruggiero, P. Avena and V. Pezzi, Potential of olive
840 oil phenols as chemopreventive and therapeutic agents against cancer: a review of in vitro studies,
841 *Molecular nutrition & food research*, 2013, **57**, 71-83.
- 842 135. S. J. Duthie and V. L. Dobson, Dietary flavonoids protect human colonocyte DNA from oxidative
843 attack in vitro, *Eur J Nutr*, 1999, **38**, 28-34.
- 844 136. L. Sun, C. Luo and J. Liu, Hydroxytyrosol induces apoptosis in human colon cancer cells through ROS
845 generation, *Food Funct*, 2014, **5**, 1909-1914.
- 846 137. J. O. Moskaug, H. Carlsen, M. C. Myhrstad and R. Blomhoff, Polyphenols and glutathione synthesis
847 regulation, *The American journal of clinical nutrition*, 2005, **81**, 277S-283S.
- 848 138. G. M. Safonova, Y. Shilov and A. B. Perevozchikov, Protective effects of plant polyphenols on the
849 immune system in acute stress, *Dokl Biol Sci*, 2001, **378**, 233-235.
- 850 139. M. Calomme, L. Pieters, A. Vlietinck and D. Vanden Berghe, Inhibition of bacterial mutagenesis by
851 Citrus flavonoids, *Planta medica*, 1996, **62**, 222-226.
- 852 140. L. D. Banks, P. Amoah, M. S. Niaz, M. K. Washington, S. E. Adunyah and A. Ramesh, Olive oil
853 prevents benzo(a)pyrene [B(a)P]-induced colon carcinogenesis through altered B(a)P metabolism
854 and decreased oxidative damage in Apc(Min) mouse model, *J Nutr Biochem*, 2016, **28**, 37-50.
- 855 141. B. Plaumann, M. Fritsche, H. Rimpler, G. Brandner and R. D. Hess, Flavonoids activate wild-type
856 p53, *Oncogene*, 1996, **13**, 1605-1614.
- 857 142. G. Corona, M. Deiana, A. Incani, D. Vauzour, M. A. Dessi and J. P. Spencer, Hydroxytyrosol inhibits
858 the proliferation of human colon adenocarcinoma cells through inhibition of ERK1/2 and cyclin D1,
859 *Molecular nutrition & food research*, 2009, **53**, 897-903.
- 860 143. M. J. van Erk, P. Roepman, T. R. van der Lende, R. H. Stierum, J. M. Aarts, P. J. van Bladeren and B.
861 van Ommen, Integrated assessment by multiple gene expression analysis of quercetin bioactivity
862 on anticancer-related mechanisms in colon cancer cells in vitro, *Eur J Nutr*, 2005, **44**, 143-156.
- 863 144. A. Di Francesco, A. Falconi, C. Di Germanio, M. V. Micioni Di Bonaventura, A. Costa, S. Caramuta, M.
864 Del Carlo, D. Compagnone, E. Dainese, C. Cifani, M. Maccarrone and C. D'Addario, Extravirgin olive
865 oil up-regulates CB(1) tumor suppressor gene in human colon cancer cells and in rat colon via
866 epigenetic mechanisms, *J Nutr Biochem*, 2015, **26**, 250-258.
- 867 145. X. Llor, E. Pons, A. Roca, M. Alvarez, J. Mane, F. Fernandez-Banares and M. A. Gassull, The effects of
868 fish oil, olive oil, oleic acid and linoleic acid on colorectal neoplastic processes, *Clin Nutr*, 2003, **22**,
869 71-79.

- 870 146. R. Bartoli, F. Fernandez-Banares, E. Navarro, E. Castella, J. Mane, M. Alvarez, C. Pastor, E. Cabre and
871 M. A. Gassull, Effect of olive oil on early and late events of colon carcinogenesis in rats: modulation
872 of arachidonic acid metabolism and local prostaglandin E(2) synthesis, *Gut*, 2000, **46**, 191-199.
- 873 147. S. Sieri, C. Agnoli, V. Pala, A. Mattiello, S. Panico, G. Masala, M. Assedi, R. Tumino, G. Frasca, C.
874 Sacerdote, P. Vineis and V. Krogh, [Dietary habits and cancer: the experience of EPIC-Italy],
875 *Epidemiol Prev*, 2015, **39**, 333-338.
- 876 148. M. Solanas, A. Hurtado, I. Costa, R. Moral, J. A. Menendez, R. Colomer and E. Escrich, Effects of a
877 high olive oil diet on the clinical behavior and histopathological features of rat DMBA-induced
878 mammary tumors compared with a high corn oil diet, *International journal of oncology*, 2002, **21**,
879 745-753.
- 880 149. C. I. Gill, A. Boyd, E. McDermott, M. McCann, M. Servili, R. Selvaggini, A. Taticchi, S. Esposto, G.
881 Montedoro, H. McGlynn and I. Rowland, Potential anti-cancer effects of virgin olive oil phenols on
882 colorectal carcinogenesis models in vitro, *Int J Cancer*, 2005, **117**, 1-7.
- 883 150. Y. Z. Hashim, I. R. Rowland, H. McGlynn, M. Servili, R. Selvaggini, A. Taticchi, S. Esposto, G.
884 Montedoro, L. Kaisalo, K. Wahala and C. I. Gill, Inhibitory effects of olive oil phenolics on invasion in
885 human colon adenocarcinoma cells in vitro, *Int J Cancer*, 2008, **122**, 495-500.
- 886 151. L. Fini, E. Hotchkiss, V. Fogliano, G. Graziani, M. Romano, E. B. De Vol, H. Qin, M. Selgrad, C. R.
887 Boland and L. Ricciardiello, Chemopreventive properties of pinoretinol-rich olive oil involve a
888 selective activation of the ATM-p53 cascade in colon cancer cell lines, *Carcinogenesis*, 2007.
- 889 152. S. Chell, A. Kadi, A. C. Williams and C. Paraskeva, Mediators of PGE2 synthesis and signalling
890 downstream of COX-2 represent potential targets for the prevention/treatment of colorectal
891 cancer, *Biochimica et biophysica acta*, 2006, **1766**, 104-119.
- 892 153. P. Khanal, W. K. Oh, H. J. Yun, G. M. Namgoong, S. G. Ahn, S. M. Kwon, H. K. Choi and H. S. Choi, p-
893 HPEA-EDA, a phenolic compound of virgin olive oil, activates AMP-activated protein kinase to
894 inhibit carcinogenesis, *Carcinogenesis*, 2011, **32**, 545-553.
- 895 154. J. S. Sebolt-Leopold and R. Herrera, Targeting the mitogen-activated protein kinase cascade to treat
896 cancer, *Nat Rev Cancer*, 2004, **4**, 937-947.
- 897 155. C. Tsatsanis, A. Androulidaki, M. Venihaki and A. N. Margioris, Signalling networks regulating
898 cyclooxygenase-2, *Int J Biochem Cell Biol*, 2006, **38**, 1654-1661.
- 899 156. R. Fabiani, A. De Bartolomeo, P. Rosignoli, M. Servili, G. F. Montedoro and G. Morozzi, Cancer
900 chemoprevention by hydroxytyrosol isolated from virgin olive oil through G1 cell cycle arrest and
901 apoptosis, *Eur J Cancer Prev*, 2002, **11**, 351-358.
- 902 157. C. Guichard, E. Pedrucci, M. Fay, J. C. Marie, F. Braut-Boucher, F. Daniel, A. Grodet, M. A. Gougerot-
903 Pocardalo, E. Chastre, L. Kotelevets, G. Lizard, A. Vandewalle, F. Driss and E. Ogier-Denis,
904 Dihydroxyphenylethanol induces apoptosis by activating serine/threonine protein phosphatase
905 PP2A and promotes the endoplasmic reticulum stress response in human colon carcinoma cells,
906 *Carcinogenesis*, 2006, **27**, 1812-1827.
- 907 158. C. Giovannini, B. Scazzocchio, P. Matarrese, R. Vari, M. D'Archivio, R. Di Benedetto, S. Casciani, M.
908 R. Dessi, E. Straface, W. Malorni and R. Masella, Apoptosis induced by oxidized lipids is associated
909 with up-regulation of p66Shc in intestinal Caco-2 cells: protective effects of phenolic compounds, *J*
910 *Nutr Biochem*, 2008, **19**, 118-128.
- 911 159. S. Purdom and Q. M. Chen, p66(Shc): at the crossroad of oxidative stress and the genetics of aging,
912 *Trends in molecular medicine*, 2003, **9**, 206-210.
- 913 160. F. Visioli, M. Franco, E. Toledo, J. Luchsinger, W. C. Willett, F. B. Hu and M. A. Martinez-Gonzalez,
914 Olive oil and prevention of chronic diseases: Summary of an International conference, *Nutr Metab*
915 *Cardiovasc Dis*, 2018, **28**, 649-656.
- 916
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Table 1. Overview of EVOOP actions at intestinal level

Compound	Experimental system	Mechanism	Ref.
<i>Interaction with microbiota</i>			
OL, HT, TYR	in vitro batch colonic fermentation/ perfused rat intestinal model	increase of bioactive phenolic metabolites	28
TYR, HT, HT acetate and OL/phenols-enriched OO	in vitro batch colonic fermentation/ human intervention study	increase of bioactive phenolic metabolites in faeces	59
OL	oral administration in rats	increase of bioactive phenolic metabolites in faeces	60
HT, TYR	broth dilution	growth inhibition of <i>E. coli</i> (ATCC no. 25922)	71
HT	broth dilution	growth inhibition of <i>E. coli</i> (CECT 533, 4972, and 679 grown in LB and <i>E. coli</i> 4972 grown in ISO)	72
HT	agar plates	growth inhibition of <i>E. coli</i> , <i>Enterobacter</i> and <i>Enterococcus</i> species	73
OL, HT/ phenolic extract	broth dilution	growth inhibition of <i>E. coli</i> (C7085L)	74
phenols-enriched OO/ phenols and thyme phenols-enriched OO	double-blind, cross-over human trial	increase of <i>Bifidobacteria</i> increase of bioactive phenolic metabolites in faeces	76 77
olive pomace enriched biscuits	double-blind, parallel dietary intervention in human subjects	increase of <i>Bifidobacteria</i>	78
<i>Antioxidant effect</i>			
HT, TYR, homovanillic alcohol	TBH treated human colon adenocarcinoma cells (Caco-2)	inhibition of oxidative modification of membrane lipid fraction	84
HT	H ₂ O ₂ or xanthine oxidase/xanthine treated Caco-2 cells	inhibition of lipid peroxidation and monolayer permeability changes	85
HT	acrylamide treated Caco-2 cells	prevention of ROS overproduction	86
HT, TYR and sulfate metabolites	oxydized cholesterol treated Caco-2 cells	inhibition of ROS and MDA production and GSH depletion	87
TYR	oxidized LDL treated Caco-2 cells	inhibition of morphological and functional alterations	90
phenolic extract	oxysterols treated Caco-2 cells	reduction of ROS production and GSH depletion	113
<i>Anti-inflammatory effect</i>			
phenolic extract	LPS or IL-1 β treated Caco-2 cells	prevention of IL-8 expression and secretion, regulation of IL-8 mRNA transcription and stability	112
phenolic extract	oxysterols treated Caco-2 cells	inhibition of IL-6, IL-8 and NO release, modulation of MAPK-NF-kB pathway	113

phenols-enriched EVOO	DSS-induced chronic colitis in mice	attenuated damage of colonic segments, PPAR γ up-regulation, NF- κ B, MAPK and downstream inflammatory cascade inhibition	114
EVOO unsaponifiable fraction	DSS-induced acute colitis in mice	attenuated damage of colonic segments, decreased MCP-1 and TNF- α levels, iNOS and COX-2 overexpression and p38 MAPK activation	115
OL	DSS-induced acute colitis in mice	reduction of neutrophil infiltration, NO, IL-1 β , IL-6, and TNF- α production, iNOS, COX-2, and MMP-9 expression	116
OL	DSS-induced chronic colitis in mice	attenuated colon damage, reduction of COX-2 and iNOS expression and IL-1 β and IL-6 release; increase of IL-10	117
OL	DSS-induced acute colitis in mice	inhibition of Th17 response and Th17-related cytokines release	118
OL	LPS treated colonic biopsies from UC patients	reduced expression of COX-2, IL-17 and infiltration of CD3, CD4 and CD20 cells	119
HT	TNBS- induced colitis in rats	reduced inflammatory infiltration	120
HT-enriched EVOO	DSS-induced chronic colitis in mice	attenuated colon damage, reduced TNF- α , COX-2 and iNOS expression, downregulation of p38 MAPK; increase of IL10	121
HT acetate	DSS-induced acute colitis in mice	improved histological damage, reduction of COX-2 and iNOS expression, inhibition of JNK MAPK and NF- κ B	123
<i>Anti-carcinogenic effect</i>			
phenolic extract	CaCo-2 cells	inhibition of cell proliferation, induction of G2/M phase cell cycle block, inhibition of p38 and CREB activation, reduction in COX-2 expression.	122
HT	adenocarcinoma cells (DLD1 cells)	ROS generation, apoptotic cell death, mitochondrial dysfunction, phosphoinositide 3-kinase/Akt pathway activation, FOXO3a phosphorylation, FOXO3a's target genes downregulation.	136
HT	CaCo-2 cells	inhibition of cell proliferation, induction of G2/M phase cell cycle block, inhibition of ERK1/2 activation, reduction of cyclin D1 expression.	142

EVOO, phenolic extract, HT	CaCo-2 cells, rat colon	up-regulation of CNR1 gene in CaCo-2 cells, reduced DNA methylation at CNR1 promoter in CaCo-2 cells, reduced cell proliferation; increase in CB(1) expression in rat colon, reduction of CpG methylation of rat Cnr1 promoter, miR23a and miR-301a	144
phenolic extract	colon cancer cells (HT-29), intestinal barrier function (CaCo-2 cell monolayers), matrigel invasion assay (HT115 cells)	reduction of DNA damage (HT-29), improved barrier function (CaCo-2), inhibition of HT115 invasion, inhibition of HT115 cell attachment	149
phenolic extract, HT, TYR, pinorelinol, caffeic acid	Matrigel invasion assay (HT115 cells)	anti-invasive effects, no cytotoxicity observed, no effects on cell attachment	150
pinorelinol-rich phenolic extract, oleocanthal-ric phenolic extract	p53 proficient (RKO and HCT116), and p53 knocked out (SW480 and HCT116 p53-/-) cell lines	reduction of cell viability, increased apoptosis, cell cycle arrest at G(2)/M, up-regulation of ATM signalling pathway, decrease of cyclin B/cdc2	151
HT	HT-29	inhibition of cell proliferation	156
HT	HT-29	induction of cell growth arrest, induction of apoptosis, prolonged stress of the endoplasmic reticulum (ER), activation of UPR, overexpression of CHOP/GADD153, activation of JNK, modulation of Akt/PKB, inhibition of TNF α -induced NF-kB	157

GRAPHICAL ABSTRACT

Extravirgin olive oil polyphenols concentrate at intestinal level and, modulating microbiota, oxidative status and inflammation, contribute to prevent the onset or delay the progression of inflammatory/degenerative diseases.

