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Antioxidant properties of plant polyphenols in the counteraction of alcohol-abuse induced damage: Impact on the Mediterranean diet

Marco Fiore[a,*], Marisa Patrizia Messina[b], Carla Petrella[a], Alessio D'Angelo[b], Antonio Greco[c], Massimo Ralli[c], Giampiero Ferraguti[d], Luigi Tarani[e], Mario Vitali[f], Mauro Ceccanti[g]

[a] Institute of Biochemistry and Cell Biology, IBBC-CNR, Rome, Italy
[b] Department of Gynecology, Obstetrics and Urology, Sapienza University of Rome, Italy
[c] Department of Sense Organ, Sapienza University of Rome, Italy
[d] Department of Cellular Biotechnologies and Hematology, Sapienza University Hospital of Rome, Italy
[e] Department of Pediatrics, Medical Faculty, Sapienza University of Rome, Italy
[f] ASUR Marche-AV4, Italy
[g] Centro Riferimento Alcologico Regione Lazio, ASL ROMA 1, Rome, Italy

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ABSTRACT

Polyphenols are antioxidants contained in plants as olive and grape. As part of the Mediterranean diet, they may decrease the risk of cancer, of chronic and neurodegenerative diseases. Alcohol consumption plays a detrimental effect on health, causing tissue damage and disrupting the metabolism of Neurotrophins (NTs). NTs are crucial proteins for the life cycle of neuronal and non-neuronal cells. Alcohol abuse elicits changes in NTs levels in the brain and in other target organs, however, it was observed minor damage in animals early exposed to red wine, probably due to the antioxidant effects of polyphenols. Indeed, data show that resveratrol or other polyphenols extracted from the olive can effectively counteract serum free radicals' formation caused by chronic alcohol intake, contrasting also alcohol-induced NTs liver elevation. The aim of the present review is to update pieces of evidences about the antioxidant properties of polyphenols and their role in counteracting alcohol-induced damage.

1. Introduction

Polyphenols are a structural class of more than five thousand chemicals, including organic but also synthetical and semi-synthetical components. Their molecules are characterized by multiples phenolic structures that contribute to their functional activity. Polyphenols can be found in a large variety of plants, including foods like fruits, vegetables, cereals, tea, coffee, olive oil and red wine (Pandey & Rizvi, 2009) which are part of the Mediterranean diet (Da Silva et al., 2009).

The Mediterranean diet was inspired by the traditional dietary patterns of populations living around the Mediterranean Basin, like Italians and Greeks, in the middle of the last century. This diet includes both local products and food imported from Eastern, Arabic and American areas. It was firstly described by Keys et al. (1966, 1970) who observed that mortality rate and incidence of cancer and cardiovascular diseases were significantly lower in the Italian and Greek populations (Rodríguez-Morató et al., 2015).

The diet is characterized by a high intake of plant-based foods (fruit, vegetables, nuts and cereals), extra-virgin olive oil, a moderate intake of fish and poultry, a low intake of dairy products (principally yogurt and cheese), red meat, wine, processed meats and sweets (for which fresh fruit is often substituted). Social and cultural factors closely associated with the traditional Mediterranean diet, including shared eating practices, post-meal naps and longer mealtimes, are also thought to contribute to the attributed positive health effects recorded in the Mediterranean region (WHO Europe, 2018). In has been shown that effects of the Mediterranean diet on a long-term basis can lower the risk of developing cardiovascular diseases, hypertension, diabetes and even Parkinson's and Alzheimer's diseases (Carito et al., 2016). It has been proposed that the intake of extra-virgin olive oil, walnuts and wine in elderly people can significantly reduce the risk of age-related cognitive decline (Valls-Pedret et al., 2012). Protective effects of red wine moderate consumption in diabetes have been also shown from human studies (Martin, Goya, & Ramos, 2017). It should be noted that most of

* Corresponding author at: Institute of Biochemistry and Cell Biology, IBBC-CNR, Section of Neurobiology, c/o Department of Sense Organ, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome, Italy.
E-mail address: marco.fiore@cnr.it (M. Fiore).

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these findings derive from epidemiological studies with no causal relationship. However, a clinical trial involving 7447 participants (55–80 years of age, 57% women) who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, assessing the effects of extra-virgin olive oil or nuts consumption in the Mediterranean diet on the cardiovascular risk revealed that the incidence of major cardiovascular events was lower among those people assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet (Estruch et al., 2018).

However, the quite toxic effects of alcohol abuse on health shouldn't be downrated: alcohol consumption may cause various kinds of tissue damage in several regions of the body as the brain, liver, kidney, endocrine glands and its intake can disrupt the synthesis and functionality of neurotrophins, proteins that play an important role in nerve cells development and growth (Chao, Rajagopal, & Lee, 2006; Ciafrè et al., 2018), immune and endocrine functions (D'Angelo et al., 2020; Fiore, Chaldakov, & Aloe, 2009) and also in the fine tuning of memory and learning processes (Cunha, Brambilla, & Thomas, 2010; De Nicoló et al., 2013). It has been shown that the antioxidant properties of polyphenols can play a pivotal role in counteracting alcohol-induced damage, especially during alcohol withdrawal (Attilia et al., 2018; Ceccanti et al., 2015).

The objective of the present review is to shortly summarize pieces of evidences about the antioxidant properties of polyphenols and their role in contrasting alcohol-induced damages.

2. Study selection

References included in the present narrative review were found searching PubMed between January and February 2020 with keywords "polyphenols", "olive oil", "alcohol" and "alcohol damage". Studies on humans, animals and plants models were all included. References were also included a thorough manual search in other websites. The final number of references included is 121.

3. Polyphenols in olive oil

Olive oil is extracted by olives, fruits of the olive tree (*Olea europea*), and it is largely used in the Mediterranean cuisine as source of vegetal fats. The Harvard TH Chan School of Public Health (Chan, 2011) indicates olive oil as an healthy choice instead of animal-derived fats and the reference intake levels of nutrients for the Italian population (LARN) recommend a daily consumption of 1 tablespoon of olive oil (approximately 10 mL) (Italiana, 2014) to prevent cardiovascular diseases and reduce inflammation caused by free radicals (Carito et al., 2015).

Olive oil is mainly composed of two groups of compounds: 99% of saponifiable lipids and a little fraction of unsaponifiable such as hydrocarbons, terpene compounds, sterols, phenolic compounds and aliphatic alcohol. Phenolic compounds include among others: oleuropein, tyrosol, hydroxytyrosol, polyphenols, secoiridoids and ligands (Boskou, Blekas, & Tsimidou, 1996) (Fig. 2).

Table 1 summarizes different commercial forms of olive oil and their characteristics as codified by European Commission Regulation EEC no 2568/91.

Extra virgin olive oil may contain more than 36 different phenolic compounds (Bendini et al., 2007) with a prevalence of tyrosol and hydroxytyrosol. Oleuropein is more represented in the olive tree leaves (Carito et al., 2014).

However, olive oil coming from different regions displays a great variety in composition and concentration of phenolic components based on place of cultivation, maturation, climate, extraction techniques, storage ext. (Baiano, Gambacorta, Terracone, Previtali, & Lamacchia, 2009;74.).

Hydroxytyrosol is the main polyphenolic compound found in both leaves and fruits of the olive tree and it has been shown to be one of the most powerful antioxidants among all olive-derived polyphenols (Visioli, Bellomo, & Galli, 1998). Although it can be assumed as part of the diet, hydroxytyrosol can also be synthesized by humans as a product of dopamine oxidative metabolism known as 3,4-dihydroxyphenylethanol (DOPET) (Rodríguez-Morató et al., 2015). Although hydroxytyrosol absorption is dose-dependent from olive oil intake (Visioli et al., 2000), it is poorly bioavailable (Rodríguez-Morató et al., 2015). Great attention has been recently given to the waste remaining after the production of olive oil (olive pomace) known to contain significant amounts of phenolic compounds that exert different types of biological activities, primarily acting as antioxidants (Nocella et al., 2017; Piroddi et al., 2017; Santangelo et al., 2017). Indeed, many studies have been published in animal models and humans using polyphenols extracted from the olive pomace (Carito et al., 2017, 2015, 2016; Ceccanti et al., 2015; Conterno et al., 2019).

4. Polyphenols in wine

Since ancient times, wine has always been part of the Mediterranean diet and it is considered among the sacred foods both in ancient and modern religions (Amor, Châlons, Aires, & Delmas, 2018). Wine consumption and production have recently involved non-Mediterranean countries like China, Argentina and Brazil but also the USA and Japan (Amor et al., 2018).

Despite the harmful effects of alcohol assumption are clearly stated in the literature, numerous scientific evidences are underlying the benefits of moderate wine intake, as part of a healthy diet, in the prevention of relevant chronic diseases like coronary diseases (Goldberg, Soleas, & Levesque, 1999). This observation is known as the controversial *"French Paradox"* and it was highlighted by the "MONICA Project" run by WHO (Parodi, 1997). It was proved that in France, as compared with other western countries, the incidence of coronary heart diseases was lower and it may be partly attributed to the moderate consumption of red wine (Ferrières, 2004; Renaud & de Lorgeril, 1992). Therefore, several various case–control studies have demonstrated the antitumoral potential of wine phenols, such as resveratrol and quercetin, showing that a moderate red wine consumption may exert a protective effect on colorectal cancer in both men and women (Crockett et al., 2011; Kontou et al., 2012). Data also show that a moderate red wine consumption may modulate the onset of diabetes-associated effects (Golan et al., 2017, 2018; Martin et al., 2017). While the effects of chronic ethanol drinking on liver and other organs have been well investigated, its effect on the cardiovascular system is bimodal (Lakshman et al., 2010). Indeed, moderate drinking in many population studies is associated with lower incidence of coronary artery disease. By contrast, heavy drinking relates with higher occurrence of coronary artery disease. In several other studies of cardiovascular mortalities, abstainers and heavy drinkers are at higher risk than light or moderate drinkers (Lakshman et al., 2010). Significantly, apart from its ethanol content, red wine also contains polyphenols such as resveratrol and quercetin known to possess cardioprotective effects. The French Paradox is an statement of a low incidence of ischemic heart disorder, with high consumptions of saturated fats, a fact accredited to the intake of red wine. Although many epidemiological studies have supported this opinion, others have attributed it to other alcoholic beverages suggesting that the drink kind is not essential (Haseeb, Alexander, & Baranchuk, 2017). Although alcohol abuse is commonly regarded to be damaging to cardiovascular health, there is a strong argue as to whether light-to-moderate drinking could be cardioprotective. Although there is wide epidemiological support for this drinking pattern, a agreement has not been gotten. (Haseeb et al., 2017)

Red wine contains a range of biologically active polyphenols, including phenolic acids, trihydroxystilbenes, and flavonoids (Fig. 1). In previous studies, it has been shown that a mixture of polyphenol extract from vine shoots elicits antiproliferative activity on colon cancer cells than resveratrol alone, due to the synergic action of polyphenols (Colin

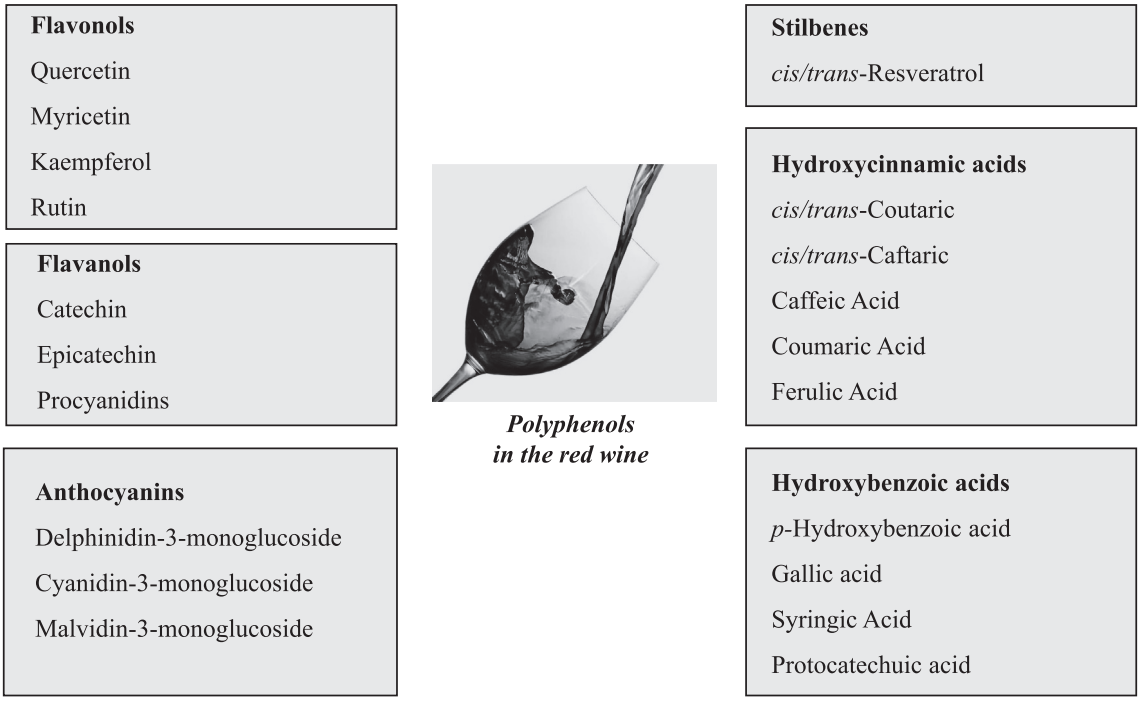

Fig. 1. Schematic representation of the main polyphenols present in the red wine.

et al., 2009), and that a relevant role was played by quantity and quality of polyphenols present in the wine.

Wine composition is resulted by a complex and unique blend of various factors depending on the vine, climate, weather, soil composition, year of cultivation and agronomic techniques (Van Leeuwen, 2010).

Although the amount of polyphenols in wine can vary significantly, it was estimated to be around 190–290 mg/L in white wines and 900–2500 mg/L in red wines (Cueva et al., 2017; German & Walzem, 2000). This variability of the phenolic composition seems very important in determining its effects. Mazué et al. (Mazué et al., 2014) demonstrated (Mazué et al., 2014) that longer periods of maceration enriched the polyphenol composition of red wine. In comparison with red wine extracts, whose maceration time was shorter and whose

Table 1
Commercial forms of olive oil and their characteristics as codified by EEC no. 2568/91.

Category	Acidity (%)	Fatty acid ethyl esters (mg/kg)
Extra-virgin olive oil	≤0.8	≤35
Virgin olive oil	≤2.0	—
Lampante olive oil	> 2.0	—
Refined olive oil	≤0.3	—
Olive oil composed of refined and virgin olive oils	≤1.0	—
Crude olive–pomace oil	—	—
Refined olive–pomace oil	≤0.3	—
Olive-pomace oil	≤1.0	—

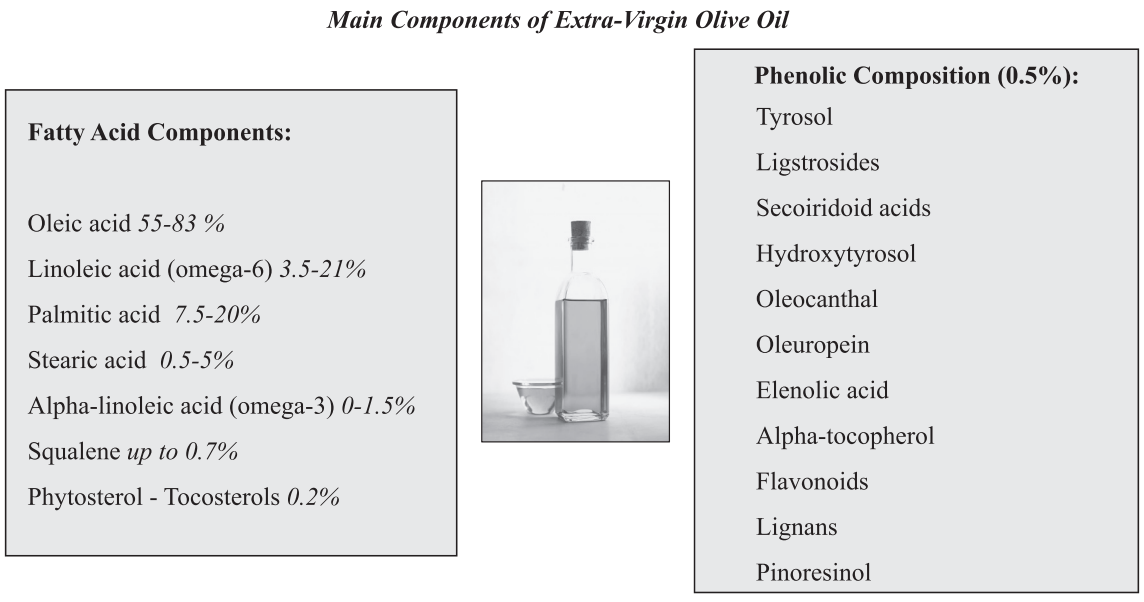

Fig. 2. Schematic representation of the main polyphenols present in the extra-virgin olive oil.

polyphenol composition was lower, the extract resulting from a longer maceration in red wine showed a more pronounced antiproliferative effect, with respect to the colonic cancer lines tested (Mazué et al., 2014).

5. Alcohol-related damages

Alcohol misuse can undoubtedly be considered one of the most relevant challenges in Western Countries (Attilia et al., 2018; Coriale, Fiorentino, Porrari et al., 2018; Coriale, Fiorentino, De Rosa et al., 2018; Mancinelli, Binetti, & Ceccanti, 2007). Indeed, around 2.3 billion people in the world drink alcoholic beverages (Istituto Superiore di Sanità, 2018) and more than 3 million people died as a result of the harmful use of alcohol in 2016 (WHO, 2014). Alcohol intake rates are particularly scaring among youngsters between 15 and 19 years old: 44% in Europe, 38% in America and 38% in the Pacific Ocean (Istituto Superiore di Sanità, 2018).

Alcohol intake can play a detrimental effect on health, causing a large variety of tissue damages. Most affected systems are the nervous system, digestive and cardiovascular systems (Global status report on alcohol and health 2018). The International Agency for Research on Cancer (IARC) has determined that alcohol consumption is causally related to the oral cavity, oropharyngeal, hypopharyngeal, oesophageal, colon, rectal, laryngeal, liver and intrahepatic bile duct, and breast cancers (Bagnardi et al., 2015; Hill, 2003; IARC, 2010, 2012). Chronic alcohol consumption has been observed to disrupt glucose homeostasis and to lead to insulin resistance, resulting in a higher risk of diabetes mellitus in heavy drinkers (Kim & Kim, 2012; Wan et al., 2005). Alcohol has a clear impact on haemorrhagic strokes, causing 9.5% of all haemorrhagic stroke deaths, hypertensive heart disease, causing 7.4% of all hypertension deaths, cardiomyopathy, causing 6.8% all cardiomyopathy deaths, and ischaemic heart disease, causing 2.7% of all ischaemic heart disease deaths (Who. , 2014). Alcohol is causally related to an increase in the risk of both liver cirrhosis and pancreatitis (Ceccanti et al., 2006; Rehm et al., 2017), causing an estimated 637 thousand digestive disease deaths in 2016. Within the burden of alcohol-attributable digestive diseases, alcohol-attributable liver cirrhosis caused 607 thousand deaths, while alcohol-attributable pancreatitis resulted in 30 thousand deaths (Who. , 2014). Moreover, alcohol can affect the innate and the acquired immune system and, thus, increase vulnerability to infectious diseases (Szabo & Saha, 2015;37.). Alcohol consumption may push people into adventurous sexual behavior and to increase the likelihood of unprotected sex, contributing to the spread of venereal diseases (Rehm et al., 2017; Steele & Josephs, 1990). There are also evidences that in the alcohol use disorder population, 50.3% of patients had psychiatric comorbidity during their lifetime (Ceccanti et al., 2015, 2018; Coriale et al., 2012, 2019; Ledda et al., 2019; Vitali et al., 2018; Vitali et al., 2018; Vitali et al., 2018).

Alcohol assumption during pregnancy is responsible for serious damage to fetuses causing a wide range of pathological conditions like miscarriage (Avalos, Roberts, Kaskutas, Block, & Li, 2014; Bailey & Sokol, 2011; Nybo Andersen, Kragh Andersen, Feodor Nilsson, & Strandberg-Larsen, 2014), stillbirth (Bailey & Sokol, 2011; Cornman-Homonoff et al., 2012), morphology (Ferraguti et al., 2017, 2019) and growth impairments (Strandberg-Larsen et al., 2017), premature birth (Bailey & Sokol, 2011; Cornman-Homonoff et al., 2012) and neonatal sequelae related to Fetal Alcohol Spectrum Disorders (FASD) (Coriale et al., 2013; Mamluk et al., 2017; Ruisch, Dietrich, Glennon, Buitelaar, & Hoekstra, 2018). This condition can result in physical abnormalities and neurodevelopmental impairments such as typical facial deformities (Denny, Coles, & Blitz, 2017), behavioral disorders (Hoyme et al., 2016), lowered functional IQ score (Streissguth, Barr, Kogan, & Bookstein, 1996) and poor performances at school (Lubbe, van Walbeek, & Vellios, 2017;14.). Fetal Alcohol Syndrome (FAS) is a completely avoidable form of developmental disability (Clarke & Gibbard, 2003) resulting from alcohol consumption during pregnancy. Data from our study group showed that even the father's alcohol assumption (Abel, 2004) is relevant in an animal model (Ceccanti et al., 2016). Nowadays, it is not possible to establish a safe threshold of alcohol consumption, therefore, the safest recommendation for pregnant women and couples that are looking for a pregnancy (Coriale et al., 2013; Ferraguti et al., 2017) is to totally avoid alcohol use during pregnancy (Ceccanti, Iannitelli, & Fiore, 2018) and breastfeeding (Gibson & Porter, 2018).

6. Alcohol effects on neurotrophins

Alcohol can also disrupt the metabolism of Neurotrophins (NTs) which are a family of proteins influencing the proliferation, differentiation, survival and death of neuronal and non-neuronal cells (Aloe, Alleva, & Fiore, 2002; Ciafre et al., 2020; Kim, Li, Hempstead, & Madri, 2004; Sornelli, Fiore, Chaldakov, & Aloe, 2007) which are also responsible for neuroprotection in mammals (Namiki, Kojima, & Tator, 2000). This family includes Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3) and Neurotrophin-4/5 (NT-4/5) (Barde, 1990; D'Angelo et al., 2020; Skaper, 2012). Gestational alcohol exposure's effects on neurotrophins are well known and many findings have been disclosed by animal model studies (Caldwell et al., 2008; Carito et al., 2019; Ceccanti et al., 2012, 2013, 2016; De Nicolò, Carito, Fiore, & Laviola, 2014; Fiore et al., 2009; Fiore et al., 2009). Indeed, both paternal and maternal alcohol exposure has been shown to affect the NTs' signaling pathways in the brain, as well as in target organs of ethanol intoxication. Such effects are not only caused by direct consequences of the action of ethanol and its derivatives on cell metabolism, but also by a cell reprograming through rearrangements of methylation of DNA and histone proteins (Carito et al., 2018; Ciafre' et al., 2019:). As for NTs, it has been shown that NGF and BDNF are molecules that not only playing a pivotal role in the survival, development and function of the peripheral and central nervous systems but also in the pathogenesis of developmental defects caused by alcohol exposure (Aloe & Tirassa, 1992; Carito et al., 2019; Ferraguti et al., 2019; Fiore et al., 2009). These findings suggest that the abnormal development of the central and peripheral nervous systems may be due to growth factors deregulation caused by preconceptual alcohol drinking (Carito et al., 2019).

7. Potential polyphenols role in counteracting alcohol damage

Disrupted levels of neurotrophins elicit neuronal injury and contribute to cause neurodegenerative diseases (Longo & Massa, 2013). In this framework, bioactive compounds, like polyphenols, capable of regulating the expression of neurotrophins or their receptors can be a promising tool in the management of neurodegenerative conditions (Carito et al., 2016). Indeed, in a mouse model, intraperitoneal administration of a blend of hydroxytyrosol and other polyphenols from olive pomace caused an increase in NGF, BDNF, TrkA and TrkB levels in the brain, especially in the hippocampus and olfactory lobes (De Nicoló et al., 2013). In fact, the olfactory bulbs are crucial brain areas as the olfaction is the key sense that allows rodents to exchange information with the surrounding environment (Sanchez-Andrade & Kendrick, 2009). Moreover, the olfactory system and dentate gyrus of the hippocampal formation are the two main areas to continue neurogenesis in adult mammals (Whitman & Greer, 2009). The same mouse model was used to measure the antioxidant abilities in vivo of olive polyphenols afterward chronic alcohol administration (Carito et al., 2017). Data showed that the elevation of reactive oxygen species induced by alcohol was completely neutralized by olive polyphenols administration.

However, other data (Carito et al., 2014) showed that intraperitoneal administration of polyphenols extracted from the olive leaves, containing mostly oleuropein, in adult male mice induced modifications of NGF and BDNF levels in the brain and serum approaching a toxic condition. Unlike polyphenols extracted from

pomace, polyphenols extracted from leaves induced a strong enhancement of NGF and BDNF serum level (Carito et al., 2014), which is a common finding in stressing situations like parachute jumping (Aloe et al., 1994). Alcohol addiction can disrupt neurotrophins pathways and functionalities, causing nerve outgrowth, impaired neuronal survival, limited ability to promote neuronal regeneration and alterations in the neurochemical phenotypes of selected cell lines (Heaton, Mitchell, Paiva, & Walker, 2000; Miller, King, Heaton, & Walker, 2002).

Several animal model studies investigated ethanol-induced toxicity in early ethanol or red wine exposure, administering an 11% ethanol solution or red wine with the same ethanol concentration. Quite interestingly, in this FASD mouse model, ethanol toxicity on NT's in the offspring resulted to be reduced if alcohol originated by red wine, neuroprotection probably due to the antioxidant abilities of the polyphenols present in the administered wine (Ceccanti et al., 2012, 2013; De Nicolò et al., 2014; Fiore et al., 2009; Fiore et al., 2009; Mattivi, Zulian, Nicolini, & Valenti, 2002; Opie & Lecour, 2007). Furthermore, other studies on red wine showed that i) red wine, but not port wine, protects rat hippocampal dentate gyrus against ethanol-induced neuronal damage (Carneiro, Assuncao, De Freitas, Paula-Barbosa, & Andrade, 2008): ii) red wine antioxidants protect rat hippocampal neurons against ethanol-induced damage (Assunção et al., 2007).

An abrupt cessation or reduction of alcohol intake can cause the alcohol withdrawal syndrome in people affected by alcohol use disorders which is considered a serious medical emergency (Attilia et al., 2018; Vitali et al., 2018). The alcohol withdrawal syndrome involves biochemical impairments including relevant oxidative stress (Parthasarathy, Kattimani, & Sridhar, 2015) by releasing free radicals (Ciafre et al., 2020). In this condition, the presence of serum neurotrophins may undergo significant changes (Heberlein et al., 2008, 2013; Jockers-Scherübl et al., 2007; Köhler, Klimke, Hellweg, & Lang, 2013). In particular, it has been shown that withdrawal may potentiate serum BDNF and NGF in alcoholics during the first week of withdrawal (Ceccanti et al., 2015) but in patients affected by alcohol use disorders treated with a blend of olive polyphenols (50 mg/day) the BDNF levels were significantly modulated up to normal values (Ceccanti et al., 2015).

In an animal model of alcohol addiction treated with oral resveratrol for two months (10 mg/kg/day), it was evaluated the oxidative stress by measuring serum free oxygen radicals defense (FORD) and free oxygen radicals (FORT) levels (Petrella et al., 2020). Data showed this prolonged consumption of a pharmacological dose of resveratrol strongly counteracted serum radical oxygen species formation caused by chronic alcohol intake. Moreover, resveratrol supplementation modulated the alcohol-induced BDNF elevation in the liver, the main target organ of alcohol-induced damage. Authors, according also to previous findings (Das, Mukherjee, Gupta, Rao, & Vasudevan, 2010; Tiwari & Chopra, 2013), suggested that the pharmacological supplementation of resveratrol through metabolite formation may play a protective role, by decreasing free radical formation, and by modulating BDNF involved in hepatic disruption induced by chronic alcohol consumption. However, it should be stressed the point that such dose of resveratrol supplementation cannot be reached by drinking red or white wine without eliciting the toxic effects of alcohol since resveratrol is present in the wine in low quantity (1.9 ± 1.7 mg/L (Stervbo, Vang, & Bonnesen, 2007). Authors also disclosed that supplemented resveratrol was present in the serum of treated animals in the form of its metabolites (resveratrol sulfate, dihydroresveratrol glucuronide, dihydroresveratrol sulfate) but not as resveratrol per se (Petrella et al., 2020) suggesting also that these metabolites contributed to the beneficial effects of the resveratrol supplementation.

Resveratrol prevents also alcohol-induced cognitive deficits and brain damage by blocking inflammatory signaling and cell death cascade in neonatal rat brain (Tiwari & Chopra, 2011) and attenuates ethanol-induced oxidative stress in rat liver (Kasdallah-Grissa et al., 2007).

As for the metabolism and bioavailability of polyphenols, the quantity of polyphenols or their metabolites found in the brain could be limited due to metabolization on liver and the blood–brain barrier. However, there are strong evidences of the effective capacity of polyphenols to reach the brain and exert neuroprotection (Figueira, Menezes, Macedo, Costa, & dos Santos, 2016). Indeed, several animal studies also indicate that polyphenols are able to cross the blood–brain barrier and co-localize within the brain tissues independently of their route of administration (Figueira et al., 2016). Thus, the brain neurotrophins potentiation associated with the pharmacological administration of olive polyphenols (De Nicoló et al., 2013) could be related to the tight relationship between oxidative stress and the physiology of neurotrophins as NGF and BDNF (Espinet, Gonzalo, Fleitas, Menal, & Egea, 2015).

8. Conclusions

The Mediterranean diet is globally known as the dietary pattern that provides the greatest number of positive effects on health because using food and drinking rich in polyphenols as vegetables, fruits, extra-virgin olive oil and a moderate intake of wine. Thus, the detrimental effects of ethanol contained in alcoholic beverages seem to be partly counterbalanced by the presence of polyphenols in the foods and extra-virgin olive oil which yield an important antioxidant action. However, further studies on humans will be necessary to fully disclose if and how it will be possible to include polyphenols supplementation in the treatment of patients affected by alcohol use disorders and in the management of abstinence.

Ethical statement

This research did not include any human subjects and animal experiments.

CRediT authorship contribution statement

Marco Fiore: Conceptualization, Methodology, Funding acquisition, Visualization, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Marisa Patrizia Messina:** . **Carla Petrella:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Alessio D'Angelo:** Writing - original draft, Writing - review & editing. **Antonio Greco:** Funding acquisition, Visualization, Supervision, Project administration. **Massimo Ralli:** Funding acquisition, Visualization, Supervision, Project administration. **Giampiero Ferraguti:** Conceptualization, Methodology, Funding acquisition, Visualization, Supervision, Project administration. **Luigi Tarani:** Funding acquisition, Visualization, Supervision, Project administration. **Mario Vitali:** Funding acquisition, Visualization, Supervision, Project administration. **Mauro Ceccanti:** Conceptualization, Methodology, Funding acquisition, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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