NorCal Open Access Publications
Recent Advancement in Food Science and Nutrition Research
Volume 1; Issue 1
Ricci A et al.

Review Article

The Nutraceutical Impact of Polyphenolic Composition in Commonly Consumed Green Tea, Green Coffee and Red Wine Beverages: A Review

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Received Date: 27 July, 2017; **Accepted Date:** 17 January, 2018; **Published Date:** 28 March, 2018

Abstract

Commonly consumed beverages, e.g., green tea, green coffee, and red wine, have gained a prominent role in food science due to their nutraceutical value. The high content in bioactive compounds, particularly polyphenols, able to scavenge free radicals and other reactive species, has led to considerable interest in assessing the impact of their consumption in human diet. *In vitro* and *in vivo* tests have highlighted the multiple reaction mechanisms involved in the protective role of polyphenols; nevertheless, the variability of chemical structures of phenolic compounds, their reactivity and side-effects, and their availability to the human metabolism are key issues to increase awareness on the use of functional beverages as diet supplements. This review aims to provide chemical and nutraceutical bases to establish the healthy effects induced by green tea, green coffee and red wine polyphenols intake in human diet.

Keywords

Antioxidant Activity; Green Coffee; Green Tea; Nutraceutical Beverages; Polyphenols; Red Wine

Introduction

Polyphenols are ubiquitous compounds in plants, produced by plant metabolism and stored in leaves, wood, roots, stems, seeds, and fruits to protect tissues against pathogens [1]. Most of these compounds are readily available in derived food products, extracted during alcoholic fermentations, hot water infusions, roasting processes; the extraction of polyphenolic compounds from their botanical sources has a long tradition in the food industry, and it is reaching an increasing interest due to their unique bioactive properties and beneficial health effects [2-5]. Polyphenolic compounds range structurally from low-weight monomeric and dimeric compounds (as in the case of castalagin, vescalagin, and roburin ellagitannins) up to high molecular weight polyphenols, obtained via addition or condensation reactions between monomers (tannic acid, proanthocyanidins); every subclass is characterised by specific mechanisms of action (radical scavenging, reduction and/or complexation of catalytic metal ions) [6]. Flavonoids and other plant polyphenols exhibit a strong antioxidant activity related to the individual structure and number of hydroxyl groups; a consistent number of i*n vitro* and *in vivo* studies have supported the theoretical antioxidant capacity of polyphenolic compounds against free radicals, and there is an increasing evidence that consumption of phenolic compounds in food may protect against a variety of health disorders [7-9]. Moreover, the presence of food phenolic compounds extends shelf-life and improves the quality of food products, limiting both the oxidation of organic substrates and the formation of toxic or potentially harmful by-products, thus contributing to the conservation of nutritional properties. A correct balance in polyphenolic compounds enables the limitation or the replacement of synthetic antioxidants, which is desiderable for the consumer's health, since synthetic additives constitute a source of allergens or are potentially toxic when used at high dosages [10,11].

Beverages has have a long tradition within the functional foods, and several commonly consumed beverages are rich in polyphenolic compounds: the intake of leaves, roots, flowers and fruit

infusions and the moderate consumption of alcoholic beverages like red wine are considered as an effective dietary practice to guarantee the correct polyphenolic intake for human nutritional needs. Regardless the variability related to the botanical source and to the bioavailability of polyphenols extracted from plants tissues, average polyphenolic content obtained for standard serving conditions have been investigated and aggregate values have been reported as follows: a cup of black coffee contains between 200 and 550 mg polyphenols, a cup of tea (either white, green or black) between 150 and 200 mg, a glass of wine-including red and white varietals-between 200 and 800 mg, as red wine is generally richer in polyphenols [12-14].

The aim of this review is to summarize recent advances in the study of the polyphenolic content and related nutraceutical effects of selected commonly consumed beverages: green tea, green coffee and red wine.

Coffee and tea trade is an important sector of the global food market, according to the worldwide distribution of these products; more specifically, green tea and green coffee are greatly appreciated by consumers who are interested in healthy and highly nutritional products.

Green tea leaves are rich in flavonoid derivatives of (epi)catechin, gallo(epi)catechins and especially (epi)gallocatechin gallates, readily extracted in hot water infusion [15]. The manufacture of black tea leads to the modification of this specific polyphenolic profile as a consequence of the enzyme-catalyzed oxidation of catechin-based structures that results in the formation of reactive catechin-based quinones and further complex flavonoid - based structures (mainly theaflavins and thearubigins) having weaker antioxidant capacity. A comparative study of Rababah et al., concluded that regardless the content in total polyphenolic compounds (59.8 mg of Catechin Equivalent (CAE)/g Dry Weight (DW) for green tea and 59.3 mg of CAE/g DW for black tea) the antioxidant activity is enhanced in green tea approx. 70.1% against 52.0% in black tea (as calculated using the Conjugated Diene Method) [16]. Accordingly, the antioxidant activity of unfermented green tea and related polyphenolic active components have been extensively studied, in view of their exploitation as dietary supplements.

Green coffee has been recently introduced in the food market, despite the widespread long-term tradition characterising the roasted product. Green coffee bean mass varies between 100 and 200 mg, according to the geographical origin and to the water available to the bushes. The most representative bioactive compounds in fresh coffee are hydroxycinnamic acids that confer unique antioxidant properties to the beans and are readily extractable in hot water. The common practice of roasting coffee markedly affects on the original polyphenolic profile, although providing black coffee its pleasant taste and aroma. Roasting could reach pyrolytic peaks ranging from 190°-210°C; at these temperatures, a fraction of dry matter (approx. 10%) and water (approx. 25%) is lost during the process, and Maillard and other side-reactions occur, producing lactones (caffeoyl quinides) and phenylindans from chlorogenic acids (Figure 1) [17]. In order to both preserve the polyphenolic composition of coffee and take advantage of sensory improvement induced by roasting, the impact of reducing roasting times has been investigated, to obtain a satisfactory compromise for the industrial needs; nevertheless, a study of Daglia et al., has highlighted a nonlinear effect between roasting degree and change of *in vitro* antioxidant activity of the polyphenolic fraction of *Coffea arabica* and *Coffea robusta* species from different countries, discouraging a forecasting approach [18]. Fresh beans and roasted coffee have therefore maintained distinct identities in the food industry and green coffee production is currently encouraged for the preparation of nutritional supplements, mainly infusions and dry extracts [19,20].

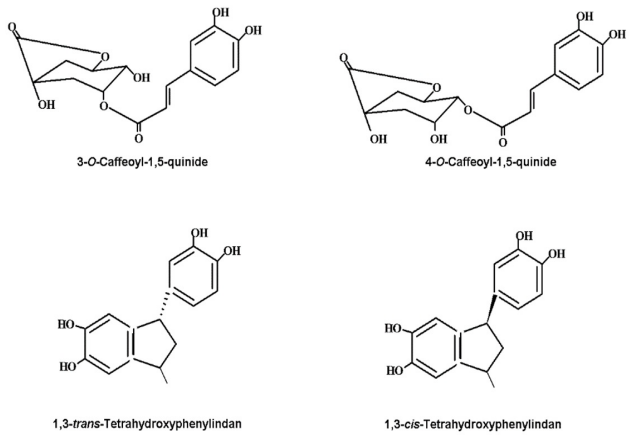

Figure 1: Chlorogenic acid derivatives obtained in coffee beans following the roasting process.

Grape berries contain a variety of antioxidants, in particular flavonoid compounds located in the grape seeds and skin and gradually released in wine as a consequence of alcoholic extraction following the production of ethanol by fermentation. Aggregate values for the polyphenolic composition in red and white wines have been reported, showing that non-flavonoid polyphenols could reach values up to 500 mg/L, while flavonoids could exceed 1000 mg/L; the higher content in polyphenolic compounds in red wine accounts not only from the composition of the red grape varieties, which are enriched in flavonoid and anthocyanins, but also from the winemaking practices, involving a prolonged contact with grape skins during the maceration process [21]. Regardless the impact of flavonoid compounds and other polyphenols released during aging in oak barrel in the physico-chemical and sensory properties of wine, the high content of polyphenolic antioxidant in red wine encourages its moderate consumption despite its significant alcoholic content; epidemiological studies have confirmed that the consumption of wine, particularly red wine varietals, reduces the incidence of coronary heart diseases, and the cardioprotective effect has been attributed to the specific polyphenolic profile and content. This has given rise to the so-called "*French paradox*", showing how the toxic effect provided by alcohol is offset by the massive presence of protective compounds [22-24]. Nowadays, wine has a worldwide distribution, both in production and consumption terms, and the effect of moderate red wine consumption in the human health is gaining an increasing interest in food sciences, being an integral

part of the diet for most of the world's human communities.

The selected beverages are discussed in detail as sources of bioactive compounds in the following review's sections, investigating their polyphenolic composition and disclosing the physicochemistry behind their antioxidant capacity. In addition, the potential impact of bioavailability and human metabolism in the beneficial effect of beverages consumption is been debated.

The Chemistry of Bioactive Polyphenols

The wide chemical class of phenolic compounds comprises natural substances of plant origin characterized by the presence of at least one phenolic function and a marked antioxidant activity. In order of increasing complexity, this class includes hydroxystilbenes, simple benzoic acids, monomeric flavonoid compounds, hydroxycinnamic acids, oligomeric compounds based on catechol structures and caffeic acid moieties (rosmarinic acid, salvianolic acids), anthocyanins monomeric pigments (flavonoid-based structures) and their derivatives, up to more complex structures, including high-molecular weight monomeric, oligomeric and polymeric tannins, tannin adducts and polymeric pigments. Due to the high number and complexity of polyphenolic compounds, in the context of this review we will focus on the most representative compounds contained in selected beverages; in more detail, both flavonoids and flavan-3-ols are major polyphenols of green tea leaves, grape seeds and skin and thus present in green tea infusion and red wine, while the hydroxycinnamic acids, based on cinnamates, chlorogenic acids and their esters, are mainly responsible for the antioxidant activity of green coffee beverages. A further class of compounds, gallotannins and ellagitannins present in oak barrels, will be discussed due to their ability of being leached into wine during barrique aging, since they play an important role as antioxidants with a double action: preserving the integrity of wine and increasing the antioxidant capacity of wine itself [25].

Nutraceutical and clinical studies in food polyphenols have confirmed the existence of Structure-Activity Relationships (SAR) as a basis for the main antioxidant mechanisms; studies showed the induction of oxidative stress in analytical standards and food matrices by external activators as oxidase enzymes, transition metals, addition of synthetic radicals or physical stress conditions (pressure, temperature) capable to generate Reactive Oxygen Species (ROS), and offered a reasonable predictions of the influence of antioxidant compounds chemical structures in radical scavenging, catalysts inactivation and oxidases conversion into harmless compounds [26-29]. Now we are aware that multiple mechanisms contribute to overall antioxidant effect (neturalization of free radicals through hydrogen or electron transfer mechanisms, chelation of transitions metals which are natural catalysts of the fenton or fenton-like reactions, inactivation of oxidase enzymes through the subtraction of binding sites and reduction of the subtraction of binding sites) and polyphenolic compounds can be classified on an effectiveness basis [30-33]. Based on these premises, the most important antioxidant mechanisms for the polyphenolic classes of interest are schematically represented in figure 2 and will be discussed in more details in the next sections (2.1 -2.3).

Flavonoid compounds

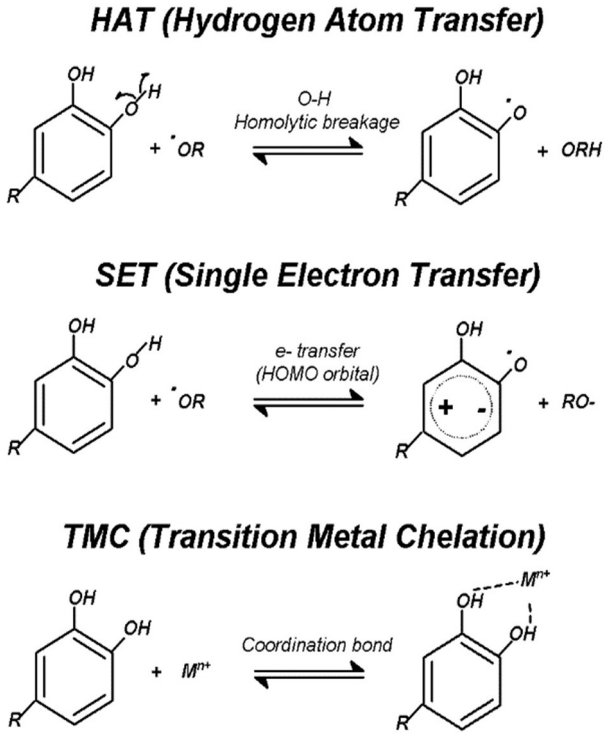

Figure 2: Key mechanisms for the antioxidant activity of polyphenolic compounds.

HOMO: Highest Occupied Molecular Orbital

Chemical structure: The most important flavonoids in green tea and red wine are flavan-3-ols and flavonols-based compounds. Flavonoids all share the same basic skeleton, the flavan nucleus composed by fifteen carbons, where two aromatic rings commonly labelled ring A (resorcinol moiety) and B (catechol moiety) are interconnected by an oxygenated three-carbons heterocycle, ring C (Figure 3).

The number and nature of substituents, the degree of polymer-

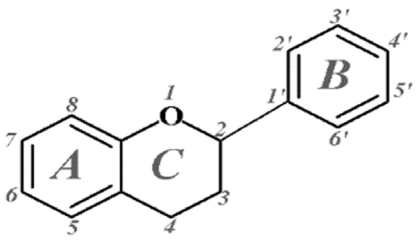

Figure 3: Schematic representation of a flavonoid compound.

isation and the extent of glycosylation affect the activity of flavonoids. Dietary flavonoids show high variability according to hydroxylation pattern, extent of conjugation, glycosylation and methoxylation. Condensation of different nuclear structures yields to a variety of polymeric structures and adduct species

occurring in both red wine and green tea. On a chemical perspective, the structures responsible for antioxidant capacity of flavonoids are: *ortho*-3,4-dihydroxyl group (catechol) or 3,4,5-trihydroxyl group in the B-ring (gallocatechol), a galloylated moiety at the position 3 of the C-ring (flavonoid gallate compound), unsaturation and oxo-group in the C-ring (furan) and hydroxyl substitutions at positions 5 and 7 of the A-ring (resorcinol); all these structures contribute to the formation of intra-molecular H-bonding and to the electron delocalization from the B-ring [26].

Structure-activity relationship: Farkas et al., have conducted structure-activity investigations on the antioxidant properties of well-known flavonoids, showing that a major contribution arises from the number and position of hydroxyl groups [34]. The free radical scavenging activity of flavonoids is primarily attributed to the reactivity of hydroxy-substituted benzene ring; in particular, the B-ring configuration plays a key role in ROS scavenging. The specific electron resonance induced by orto di- and tri- substitutions enhances the hydrogen or electron-donor capability, which are diffusion-controlled mechanisms, and constitute the basis for deactivation of hydroxyl, peroxyl radicals and other reactive species. Catechol and pyrogallol moieties are able to neutralize the exceeding energy gap between the ground state and the $^1\Delta$ excited state of molecular oxygen, which was estimated in 937.2 kJ according to Bradley & Min (1992), through a single H or electron donation [35]; the resulting products are neutral oxygen species and a relatively stable flavonoid radical, characterised by lower stabilisation energies (≈ 387.7 kcal/mol for (+)-catechin radical) [36].

The number of ortho-hydroxy substituents has a major effect on the antiradical effect; this is related to the rearrangement of electronic configuration that affects the availability of protons in transfer processes. The 3,4-catechol structure of the B-ring strongly enhances the inhibition of peroxidation; as an example, luteolin overcomes kaempferol in antiradical ability, although having the same basic structure (flavonol compound), and mechanistic studies under similar experimental conditions have demonstrated that this is related to the lack of catechol ring in the kaempferol molecule [36]. The role of the A ring and of the heterocycle to the total antioxidant capacity was investigated; it was observed that the resorcinol-like moieties have a minor correlation with redox and antiradical activities [37], even though a 5-OH substitution seemed to contribute to the radical scavenging effect [38]. The C-heterocycle contributes to antiradical activity by extending the conjugation between A and B rings, thus increasing electron displacement, through a planar, free 3-OH (flavan-3-ols, flavonols), 2,3-unsaturation (flavonols) and the presence of 4-oxo function (flavonols). The superior antiradical action of flavonols could be ascribed to the combined presence of these two molecular features; in particular the 3-OH substitution promotes a planar molecular geometry through the formation of intramolecular hydrogen bonds, increasing the availability of active sites [26,36,39]. The presence of glycosylation or methylation at the position 3 of the heterocycle induces the suppression of the antiradical activity and this effect has particularly been observed in flavonol monomeric compounds [39]. The occurrence of condensed structures (proanthocyanidins, prodelphinidins) has a positive effect on the total antioxidant capacity, however not correlated with an increase in the number of monomeric units. The mechanism of action behind this non-linear effect is poorly understood; it has been postulated that the spatial arrangement of complex polymeric structures is responsible for this apparent contradictory trend. Briefly, the non-planar geometry of condensed polymers inactivates some hidden hydrowyls, as in diffusion-controlled mechanisms the proximity of reaction sites is a crucial condition for reactivity [5]. It was further observed that procyanidins dimers and trimers have both an additional antiradical effect with respect to the number of monomers, but little difference has been observed between dimers-trimers and trimers-tetramers couples; reversely, a significantly enhanced bioactivity is observed between hexamers and tetramers [40]. The most claimed theory is that higher polymers take advantage of a consistent number of C4-C8 condensation linkages, increasing the stability of the polymeric flavonoid radicals formed during the radical chain-breaking reactions [41].

The flavonoid compounds are essential components in green tea and red wine beverages and their nutraceutical impact will be further discussed in sections 5 and 6.

Bioactivity: Much of the literature refers to the flavonoids as a case study for the benefit nutraceutical and biological properties of polyphenols, due to their enhanced antioxidant and antiradical activities and their peculiar ability to regenerate their original structure during oxidative reactions [26]. The flavonoid compounds are widely available from several plant foods, in fruits, berries, nuts, leaves, woody parts, and for this reason they are widespread in the industry of nutraceutical beverages and diet supplements [13]. Several experiments have focused on the flavonoid composition of beverages derived from natural sources, investigating the extent of the antioxidant and antiradical contributions [12,14,15]. Lakenbrink et al., have reviewed the activity of commercial tea bag and other drinks derived from the same plant and intended as food supplements [14]; according to this study, flavonoid accounted for 93-94% (average value) of the total polyphenols content in selected commercial products, and such composition remained constant after 2 minutes brewing; it was also demonstrated that the flavonols and flavons compounds were more effectively extracted when compared to other phenolic, flavonoids and theaflavines (whose extraction yields ranged 35-55%), and efficiency of the extraction was comparable with caffeine (extraction yields ranging 55-90%) [14].

The availability of flavonoid and their efficient extraction from natural sources is the main reason for the high antioxidant level of derived beverages, as determined by *in vitro* and *in vivo* studies [26,27]. Flavonoid showed antiradical activities when using the DPPH as the model radical; a work investigating the activity of selected flavonoids, including catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, myricetin, quercetin, apigenin, kaempferol, and luteolin, toward 1,1-Diphenyl-2 Picryl-Hydrazyl [DPPH] radical, provided the activity of such compounds in aqueous systems, also enabling a classification based on the effectiveness (in terms of amount of radical scavenged after 20 minutes incubation); it resulted that the epi-

gallocatechin gallate was the most effective antiradical, showing the lowest concentration needed to scavenge 50% of DPPH• radical (IC_{50}, 1.06 μM). Contrariwise, luteolin needed the highest concentration to scavenge the same amount of radical (IC_{50}, >15 μM), and kaempferol was also less effective (IC_{50}, 5.93 μM). When excluding Kaempferol and luteolin, selected flavonoid showed low IC_{50} values (range 1.06 - 3.99 μM), confirming their pronounced ability to neutralize radicals in solution [32].

Flavonoid-rich plant extracts are gaining an increasing interest in their application as food supplements or additives. A recent review has focused on the activity of natural sources of proanthocyanidins like pine bark and grape seeds, studying the antioxidant capacity of extracts obtained and intended for the food supplements industry. Large ranges in antioxidant potency were found in the formulations commercially available, ranging from 16 to 8392 μmol TE/g as measured using the TEAC assay; this is a consequence of the quality of the botanical source and the efficiency of the extraction methods used, together with the potential adulterations. The authors highlighted the need for defining a detailed quality control procedure, especially in the United States market were the herbal supplements are not regulated as drugs, but generically labeled as food "supplements" [4].

Proanthocyanin sources such as pine bark and grape seed extracts had antioxidant capacities ranging from 16 to 8392 μmol TE/g. The finding of these wide ranges in the antioxidant potency of the products assayed underscores the need for quality control of these herbal supplements. This need is especially important in the United States because herbal supplements are not regulated as drugs, but are instead sold as "food supplements" [4]. In the same work, it was also highlighted that the absence of anthocyanins in grape seeds and pine bark sources negatively affected the antioxidant activity levels of the extracts when compared to berry-based products bilberry, cranberry, chokeberry, and elderberry, which showed systematically higher antioxidant capacities determined using the ORAC assay [4].

The impact of the flavonoid profile on the nutraceutical properties of green tea and red wine will be described in more detail in the sections 5 and 6 of this review.

Hydroxycinnamic acids

Chemical structure: Hydroxycinnamic acids and their derivatives also called hydroxycinnamates, are dietary non-flavonoid polyphenols largely present in fruits, vegetables, and commonly consumed beverages: Radtke et al., have estimated a daily intake of 206 mg hydroxycinnamates in habitual coffee drinkers [42]. Hydroxycinnamic acids are basically composed by a benzene ring with a three-carbon chain substituent, structure that is referred to as C6-C3 (Figure 4); they are generally classified as phenylpropanoid compounds. On a nutritional point of view, the prominent compounds are Caffeic Acid (CaA), Chlorogenic Acid (ChA), Sinapic Acid (SA), Ferulic Acid (FA), p-Coumaric (pCU) Monomers, and their bound, conjugated and esterified forms.

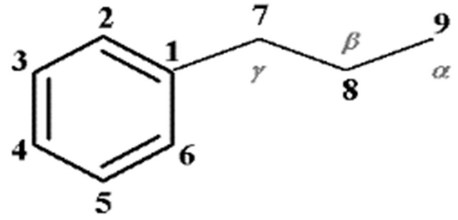

Figure 4: Representation of the basic chemical structure for a hydroxycinnamic acid-based compound. Specific compounds are classified on the basis of number and position of substituents and hydroxylation patterns.

Structure-activity relationship: Several studies have recognized the antioxidant activity of hydroxycinnamic acids, as well as the beneficial secondary effects of reducing the intestinal absorption of glucose and modulating the hormonal secretions; accordingly, they have been qualified as dietary supplements for the management of oxidative stress-related diseases [43-45]. The antioxidant capacity of this class of compounds is related to the ability to scavenge radicals, bind proteins, and chelate metals, along with their enhanced reducing power. The reduction of transition metal ions like Fe^{3+} and Cu^{2+} is considered the basis for their dose-dependent antioxidant or prooxidant effects; when reducing iron and copper ions they subtract catalysts for Fenton or Fenton-like reactions, which are the basic reactions for the formation of ROS; nevertheless, a high Fe^{3+} to Fe^{2+} (or Cu^{2+} to Cu^{+}) conversion rate is responsible for the regeneration of Fenton's catalysts [46]. Despite this dual effect could discourages a massive consumption of hydroxycinnamates and of phenolic compounds characterised by similar reactivity, it was earlier proposed that the prooxidant action of hydroxycinnamic acids under controlled conditions may also be the key mechanism for their anticancer and apoptosis-inducing properties [47].

In general, the presence of a second hydroxyl group in the *ortho-* or *para-* positions was observed to increase antioxidant activity due to electron resonance stabilization and formation of related quinones; this observation can be extended to the whole class of polyphenolic compounds [26,48]. In the specific case of hydroxycinnamates, the number and distribution of hydroxyl groups showed a critical role in the discrimination of compounds based on their antioxidant capacity: it follows that the Total Antioxidant Capacity (TAC) of caffeic acid and related phenethyl ester are greater than those of ferulic acid and its derivates, and that caffeic acid dimer (rosmarinic acid) has an increased activity compared to the related monomer. Hydroxicinnamic acids generally have a lower activity against ROS than other polyphenolic classes [49]; nevertheless, clinical studies have highlighted the specific ability of caffeic acid and its derivatives to inhibit human Low-Density Lipoprotein (LDL) oxidation, and a ranking of single cinnamates on an effectiveness scale basis has been attempted by several authors [50-52]. In the study of Nardini et al., caffeic, ferulic, and *p*-coumaric acids were assayed for the inhibition of *in vitro* LDL oxidation, using Cu^{2+} as catalyst. At the minimum assayed concentration (5 μM), only caffeic acid protected LDL from oxidative stress, and it remained the prominent antiradical at higher concentrations, confirming the previous observations on the relationship between activity and structural properties of

hydroxy-substituted compounds. Moreover, the formation of a caffeic acid:copper complex responsible for a transient chelating activity was elucidated using UV-Vis spectroscopy; the same authors stated that the superior antioxidant activity observed for caffeic acid in the specific analytical conditions could be ascribed to a combination of both radical chain-breaking and metal chelation mechanisms [50]. Cheng et al., have ranked the monomeric cinnamates of nutritional interest according to the lipoprotein protective effect. The selected monomers were classified as follows: caffeic acid > chlorogenic acid > sinapic acid > ferulic acid > *p*-coumaric acid when using the water-soluble 2,2′ -azo-bis(2-amidinopropane hydrochloride) as reactive initiator and the same ranking was obtained when using the cupric ion Cu^{2+} as oxidation catalyst [52]. We can generally conclude that hydroxycinnamic acids bearing *ortho*-dihydroxyl or 4-hydroxy-3-methoxyl groups possess significantly higher antioxidant activity; it has been proposed that the activity of *p*-coumaric and ferulic acids-based compounds against LDL oxidation could also be enhanced through tartaric acid esterification and subsequent binding to apolipoprotein B functions [51].

Bioactivity: The hydroxycinnamic acid derivatives are largely present in the human diet, distributed between fruits, vegetables, beverages; the average daily uptake of caffeic acid in a habitual coffee drinker was estimated in 206 mg [52]. Most generally, hydroxycinnamic in the diet are largely derived from fruits, grains, and coffee; in fruits, p-coumaric, caffeic, and ferulic acids are the most representative and predominantly occur in esterified form with quinic acid or glucose, hydroxycinnamoylquinic acids are mainly obtained from pome and stone fruits consumption (with chlorogenic acid being predominant in apples, pears, and peaches and neochlorogenic acid dominating in plums) [51]. The antioxidant activity of hydroxycinnamic acid derivatives was investigated in model systems, especially about their ability to inhibit the oxidation of Low-Density Lipoproteins (LDL), showing an enhanced inhibitory effect against peroxidation [51,52]. In a work after Nardini et al., the effect of caffeic, ferulic and p-cumaric acids in inhibiting LDL oxidative modification induced by oxidant systems in aqueous phase was tested, and it was demonstrated that the peculiar structure of caffeic acid, bearing two phenolic hydroxy group was able to enhance the inhibitory activity against oxidation, following a dose-dependent trend [50]. To further investigate the effect of different hydroxycinnamic acid structures in the antioxidant capacity, selection of compounds which are systematically found in fruits were tested in *in vitro* studies, showing that the o-dihydroxy caffeic, caftaric, chlorogenic, and neochlorogenic acids inhibited the oxidation of LDL from 86 to 97% in a 5 μM concentration, and that the activity of p-cumaric and ferulic acids was improved following esterification of tartaric acid; the latter mechanisms was possibly due to the binding of apolipoprotein B in the LDL particle, and it is likely to occur in *in vivo* systems like fruits [51].

The previous works highlighted that an improved understanding of antioxidant mechanisms for the inhibition of radical formations and LDL oxidation might enhance the contribution of *in vitro* observation in defining the optimal dietary intake of hydroxycinnamic compounds in the human diet, also supporting the selection of their most valuable dietary sources. The present review will account for the dietary uptake of hydroxycinnamic acid by means of green coffee consumption, and this topic will be discussed in more detail in section 6.

Ellagitannins and gallotannins

Chemical structure: Phenolic enzymatic coupling and galloylation of the sugar ring in plant tissues are responsible for the formation of high molecular weight compounds like ellagitannins and gallotannins; these molecules are generally classified as hydrolysable tannins, referring to their specific ability to decompose in water, with which they react to form water-soluble substances [53]. Hydrolysable tannins are mainly included in wood and woody part of plants: pentagalloyl glucose and galloyl glucose chain fragments usually arises from degradation of lignin during the extraction process [2]. Galloyl moieties could undergo dehydrogenation between 2-4 and 3-6 gallates forming ellagic acid, Hexahydroxydiphenic Acid Dimers (HHDP) and low-weight polymers, which are the basic structures for ellagitannin compounds [54]. Ellagic acid is the main wood polyphenol in its monomeric, oligomeric and polymerized forms; it is also present in rasperries, strawberries, walnuts, black currants and, in a minor extent, in grape; it is also the main phenolic constituent in distilled beverages, while its presence in wine (especially red wine) could be ascribed to aging in barrels or to the addition of powdered tannins, wood chips and staves during wine fining.

Structure-activity relationship: It has been observed that the prolonged contact of wine with wood contributes to the release of ellagic acid-based compounds, being soluble in hydro-alcoholic systems, with a beneficial effect on wine conservability and sensory profile [55,56]. A significant role in total antioxidant activity of aged wines is played by hydrolysable compounds, mainly castalagin and vescalagin deriving from castalin and vescalin precursors, roburin dimers and polygalloylglucose fragments, which are major phenolic components of oak, chestnut and cherry woods used for cooperage [54,57,58]. The role of hydrolysable tannins in antioxidant activity is controversial: Vivas and Glories have demonstrated that ellagitannins are partially involved in wine oxidation processes, due to their tendensy to absorb dissolved oxygen, thus enhancing the hydroperoxidation of wine constituents [59]; it follows that a wrong dosage could affect the quality and shelf-life of wine. In contrast, the ability of hydrolysable extracts to react quickly with oxygen is the origin for color stabilisation of red wines by generating alternative reaction paths with stable intermediates [60-62]. This is the reason for the double beneficial effect of the presence of oak-derived compounds in wine; on one hand, they prevent wine from chemical oxidation and on the other hand they increase the healty impact of moderate wine consumption [25]. Antiradical activity of hydrolysable tannins has been evaluated through the *in vitro* test of the 1,1-Diphenyl-2-Picryl-Hydrazyl (DPPH•) stable azo radical; results showed that ellagitannins have a protective effect against superoxide radical, hydroxyl radical and inhibit LDL oxidation in model systems [63-65]. In the study of Romani et al., the antiradical properties of myrtle and pomegranate, typical sources of both hydrolysable and condensed tannins, have been compared with the antioxidant capacity of chestnut barks and of a commercial extract from grapes, which are typically rich in hydro-

lyzable tannins and condensed tannins, respectively. According to EC_{50} values calculated using the DPPH• assay, extracts were ranked in the following order from best to worst: 0.586 μmol L^{-1} for chestnut bark (based on hydrolysable structures), 0.667 μmol L^{-1} for myrtle leaves (mainly composed of hydrolysable gallotannins and some flavonoid compounds), 1.347 μmol L^{-1} for pomegranate peels (mainly having predominant ellagitannin structures), 1.675 μmol L^{-1} for grape seeds (rich in proanthocyanidins and gallic acid). It was concluded that the simultaneous presence of gallotannins and ellagitannins or flavonoids enhances the antiradical activity of botanical extracts; contrariwise, the EC_{50} of pomegranate peel extract and the EC_{50} of grape seeds, while missing this combination, decreased the radical scavenging activity of 2-3 times. The same conclusion was drawn when comparing the inhibition of LDL oxidation by ellagitannins and flavonoid compounds; it was found a generally higher activity for hydrolysable structures, with the exception of (-)-epigallocatechin gallate (the main component of so-called green tea tannin) that showed comparable results with respect to ellagic and gallotannins [62]. An additional effect of reduction of metallic catalysts like Cu^{2+} and Fe^{3+} was observed in the presence of tannins at room temperatures. Hydrolysable polyphenols have a low oxidation potential [37] and this is the basis for their ability to reduce and chelate transition metal ions.

Bioactivity: Ellagitannins are common dietary polyphenols, and their antioxidant and chemopreventive activities have been reviewed in the scientific literature [25,62,63]. Different valuable sources of ellagitannins have been detected, mainly strawberries, red raspberries, myrtle, and pomegranate berries, myrtle leaves, walnuts, and oak-aged red wine, and metabolomics studies have enabled the identification of microbial metabolite urolithin B as a biomarker of the gastrointestinal activity when assimilating dietary ellagitannins [25]. Isolation and structural determination of ellagitannin structures occurring in dietary sources, coupled to the determination of biological activities of the same compounds in model solutions have enabled the discussion of the nutritional value of tannins on the basis of their structural differences.

A review by Okuda et al., have focused on this aspect, showing that the different chemical arrangements provided within this class of compounds have different potential applications in the prevention of degenerative diseases, due to differential reactivity and bioavailability; in particular, oligomeric compounds have been recognized for their enhanced antitumor and anti-HIV activities when compared to monomeric and highly-polymerized compounds of the same chemical class, and in a more general perspective, the inhibitory activity against LDL peroxidation is generally stronger by ellagitannins than by the other tannin compounds [62]. In the same study, it was reported that the ellagitannins showed a promising ability to inhibit peroxidation in physiological conditions, as determined through the monitoring of radical species by Electron Spin Resonance (ESR) spectroscopy measurements [62]. In more recent times, Romani et al., have confirmed the superior antiradical mechanisms of ellagitannins dietary sources (myrtle and pomegranate food-grade extracts) when compared to dietary sources of condensed tannins, like chestnut bark and grape seeds; the ability to scavenge the DPPH radical was assayed and expressed as EC_{50} value (concentration of the compound giving half-maximal response, μM), obtaining the following values: 0.586 μM for chestnut bark, 1.675 μM for grape seeds, 0.667 μM for myrtle leaves, 1.347 μM for pomegranate peels. It was concluded that the chestnut and myrtle extracts exhibited the higher antiradical activity due to the simultaneous presence of gallotannins and ellagitannins, followed by pomegranate peel extract that was mainly composed by ellagitannins; the grape seed extract, which contained exclusively condensed tannins, exhibited the lowest antiradical activity of the series [63]. The superior antiradical activity of extracts containing gallotannins, ellagitannins, or mixtures of them was also confirmed by Ricci et al., comparing with grape seed and skin extracts which are mostly constituted by condensed tannins [2].

The data collected in literature about ellagitannins bioactivity suggest their use as nutraceutical and functional ingredients for their important antioxidant properties; a more detailed investigation will be requested through the investigation of their bioavailability and efficiency when considering *in vivo* systems, and their enhanced efficiency when used in combination with other bioactive compounds like phenolic acids and gallotannins. In this review, the availability of ellagitannins in wine following storage in oak barrels and the nutraceutical implication in human diet will be discussed in section 7.

Green Tea: Chemistry and Bioactivity

Tea is a widely consumed beverage, probably the most worldwide consumed after water. Among the multiple tea types which are traditionally consumed, the unfermented green tea contains a major concentration of active catechins, minerals and vitamins, conferring a high nutraceutical value [66]. The use of green tea in medicine has a long tradition, being developed in China as a healthy beverage few millennia ago. Nowadays, the interest on green tea beverage and supplements is mainly driven by clinical evidences on its contribution to reducing the risk of cardiovascular diseases and some forms of cancer, together with its beneficial action on hypertension control, body weight control, its antibacterial and antivirasic activity, its neuroprotective power, to cite some examples. However, despite the multiple beneficial effects, the consumption of green tea in Western countries is somehow limited and sporadic, and there is a need to raise awareness among consumers on the benefit impact of tea in humans diet [67].

The main consequences in human health deriving from the activity of green tea flavonoid and polyphenols could be summarized as follow: radical chain breaking, inhibition of DNA oxidative modification induced by Tetradecanoylphorbol Acetate (TPA), inhibition of low-density lipoprotein oxidation, inhibition of tert-butil peroxidation and inactivation of reactive species derived from cooked meal [68].

The fresh and dry tea leaves show the following general composition: polyphenols (10-35%) caffeine (approximately 3.5%), theobromine (0.15-0.2%), theophylline and other methylxanthines (0.02-0.04%), lignin (6.5%), organic acids (1.5%), pigments, mainly chlorophyll (0.5%), theanine (4%), free amino acids (1-

5.5%), in addition to numerous flavour compounds [69,70]. Several carbohydrates, alkaloids, minerals, vitamins and enzymes are also present as minor constituents [71]. Catechins are ubiquitously distributed in the tea leaf tissues, where they are prevented from contact with oxidase enzymes by specific membranes; during the processing, which provides withering and rolling of fresh leaves, the structure of the leaf is disrupted and the oxidases come into contact with the catechins inducing oxidation. To limit the oxidative effect the green tea leaves are typically *st*eamed or pan-fired to induce enzymatic inactivation, and subsequently the condensation reactions are inhibited; for this reason, 60 to 80% of the total flavonoids in green tea are catechin monomers. The green tea dried leaves preserve a significant content in flavan-3-ol active monomers, mainly Epigallocatechin-3-Gallate (EGCG) and Epicatechin-3-Gallate (ECG); minor components are (-)-Epicatechin (EC) and Epigallocatechin (EGC) [72]. EGCG, characterized by a strong antioxidant activity (section 4.1) is the most abundant flavan-3-ol monomer in tea leaves, contained in green tea in a concentration ranging from 30 to 130 mg/cup [73].

Most of the flavan-3-ol-based compounds which could be identified in a green tea extract are reported in figure 5. A minor concentration of condensed polymers were reported for green tea polyphenols, induced by partial oxidation processes occurring at the withering stage [15]. This finding was in apparent contradiction with a study of Ricci et al., showing that the polymerized compounds constituted almost half (47.6%) of the total polyphenolic fraction in a food-grade lyophilized green tea. Nevertheless, the same authors have concluded that high variability is expected in the composition of botanical food-grade additives, according to extraction procedures, processing, and storage [2].

The early evidence of EGCG bioactivity has arisen from clinical studies showing inhibition of soybean lipoxygenase, using the IC_{50} 10-20 μM Trolox Equivalent (TE) as reference values. The green tea, considered as the main natural source of galloflavonol gallates, was then compared with other plant species having a high antioxidant activity but lower EGCG content: results showed that oxygen radical absorbance capacity of green tea was enhanced comparing to brussel sprouts, garlic, kale and spinach extracts [68].

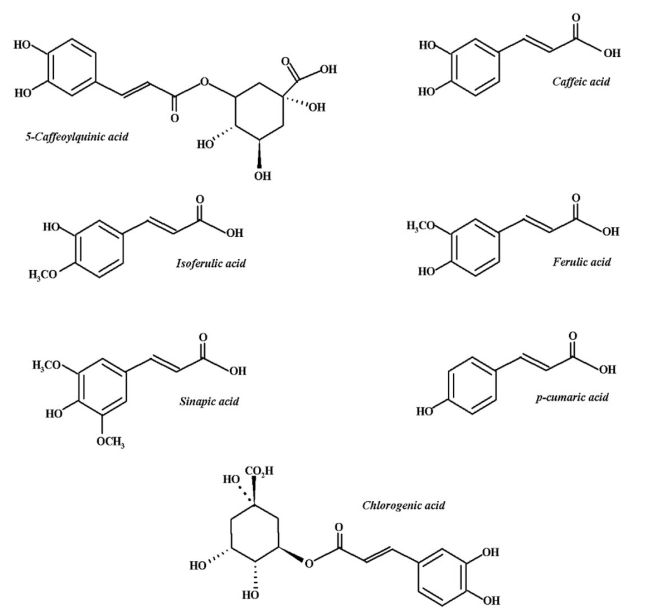

Figure 5: Structure of some major hydroxycinnamic acids detected in fresh coffee leaves.

The incidence of both galloylated substitution and gallate function in the antiradical activity flavan-3-ol-based monomers was further confirmed in a study of Heim et al. In this study, antioxidant capacity was evaluated as Trolox Equivalent Antioxidant Capacity (TEAC), showing that the activity of EGCG (4.75 mM TE) is more than double compared to EC (2.5 mM TE) and catechin (C, 2.4 mM TE) monomeric compounds; on the opposite, it is comparable to the activity of quercetin (4.7 mM TE), which is recognized as a strong flavonoid antioxidant [74].

Green tea also has a noticeable variety of flavonol structures, mainly flavonol-derived glycosides and rutinosides; Ricci et al., have listed several flavonol structures elucidated by MALDI-ToF of a food-grade green tea lyophilized extract, including kaempferol, myricetin, quercetin, kaempferol-3-glycoside, quercetin-3-glycoside, myricetin-3-glycoside, quercetin-3-rutinoside, kaempferol-3-rutinoside and quercetin-3-rutinoside [2]. In the same study, the total polyphenolic content and bioactivity of green tea (GTP) lyophilized extract was compared with grape seeds (SEP) and skin (SKP) extracts, all assumed to be mainly composed by flavonoid compounds; the aim was to highlight how the occurrence of specific flavan-3-ol structures (regardless their concentration) has a major impact in the antioxidant capacity, according to chemical mechanisms elucidated in section 4.1. When dissolving 1 g/L of lyophilized products into an hydro-alcoholic solution, the folllowing contents in flavonoids were found: SKP (2.83 mM catechin-equivalents, CE) > GTP (2.11 mM CE) > SEP (1.62 mM CE). A high correlation between total polyphenolic content and antioxidant activity has often been generally observed in previous works when studying samples from similar botanical matrices [75-77], but the correlation is lost when comparing different botanical sources [2]. In more detail, the antioxidant capacity of commercial extract per g of dried material decreased in the following order: GTP (0.42 mM TE) > SEP (0.26 mM TE) > SKP (0.24 mM TE). It follows that the quality of the polyphenolic profile has a major influence on the bioactivity and, in particular, the antioxidant activity follows the same trend as the content in galloylated gallocatechins, being the main functional components in green tea and not present at all in grape skin [2]. These conclusions were supported by previous literature showing the prominence of EGCG-derived compounds in the bioactivity and bioavailability of green tea polyphenols [78-80].

Green Coffee: Chemistry and Bioactivity

Coffee mainly contains hydroxycinnamic acids with their concentration depending on the type of beans (green or roasted). The roasting process affects the bioactivity of coffee beverages (section 1) as confirmed by del Castillo et al., who found that the antiradical activity evaluated by the ABTS•+ assay decreases in light-, medium- and dark-roasted samples of Colombian *Coffea arabica*, due to progressive degradation of chlorogenic acid and formation of high and low molecular mass by-products.

Among them, the stronger activity against ABTS•+ radical was found in the low molecular fraction, mainly observed in medium-roasted beans [81].

The fresh beans are major sources of bioavailable caffeoyl and dicaffeoylquinic acids derivatives [82] with biological effects mostly related to antioxidant and antiinflammatory activities. Coffee has high concentrations of chlorogenic, caffeic, ferulic, p-coumaric acids and other chlorogenic-acid derivatives, formed by esterification of the former with (-)-quinic acid (Figure 6); in more detail, the concentration of highly bioactive chlorogenic acids ranges between 5-12 g/100g dry weight [83]. The antioxidant activity of these compounds is well recognized in the literature [51,84,85], and their radical scavenging activity was assessed in previous works with pure standards in hydro-alcoholic solutions (20 μM concentration) by the DPPH• assay; the results ing inhibition percentage values were 51.5% (caffeic acid), 36.3% (chlorogenic acid) and 24.8% (ferulic acid), respectively [86]. Nevertheless, the effective bioactives made available consuming green coffee on a daily basis has been rarely investigated. A study conducted on ten healthy adults evaluated the bioavailability of chlorogenic acids in human plasma and urine for 8 h after the consumption of a green coffee supplement containing 170 mg (Dry Weight) of the same compounds [87]. Results showed that the concentration of chlorogenic acids and related metabolites recovered in human plasma was higher than 33.1±23.1%, with peak levels from 0.5 to 8 h following ingestion, and only 5.5±10.6% of cinnamic and quinic acids were overall highly absorbed in urine over the same period; elevated standard deviations reported in this work are associated to the clinical nature of the experimental setup. It was concluded that chlorogenic acids provided by green coffee are highly absorbed and metabolized [87], although the same authors had previously highlighted a large inter-individual variation in the absorption and metabolism of chlorogenic compounds in humans [88].

The interest on green coffee consumption in human diet arises from recent clinical studies; it was demonstrated that the ability of humans to absorb bioactive polyphenols contained in coffee beans has a positive impact in antihypertensive effects, vasoreactivity, inhibition of fat accumulation and body weight regulation, modulation of glucose metabolism [89-92]. The clinical impact of green coffee consumption is mainly driven by the strong antiradical and reducing capacity of the polyphenolic fraction. In a study of Naidu et al., food-grade extracts were prepared from the green coffee beans of *Coffea arabica* and *Coffea robusta* by flaking (hydrothermal treatment followed by drum drying), powdering and solvent extraction, and the antioxidant capacity of extracts was assayed. When dissolving the powdered extract at a concentration of 200 mg/L in water, the total polyphenols content ranged between 31.7% and 32.2% for the two coffee species, with chlorogenic acid as the major polyphenolic compound in both cases. The antioxidant capacity was exceptionally high, 92% for *Coffea arabica* and 88% for *Coffea robusta* varieties; percentages are expressed in terms of synthetic DPPH• radical scavenged [93].

Iwai et al., have investigated the composition of low-grade (immature) and commercial-grade green coffee beans by Mass Spectrometry (MS), Magnetic Nuclear Resonance (^{1}H NMR), and High-Performance Liquid Chromatography (HPLC) methods; they were able to identify and quantify seven distinctive

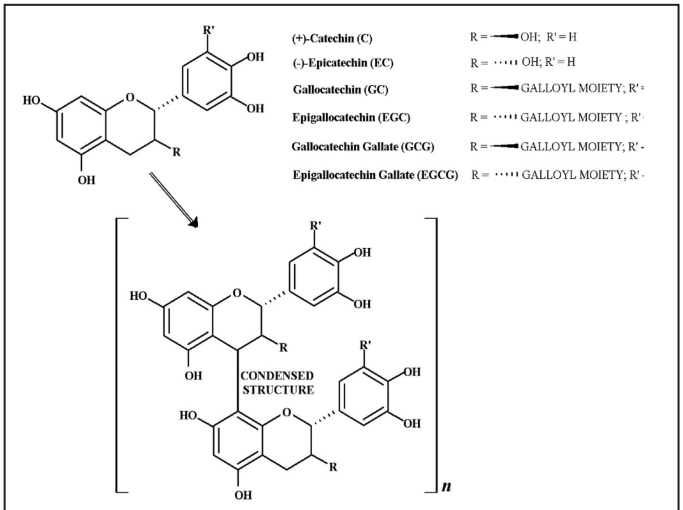

Figure 6: Structure of some major flavan-3-ol compounds.

hydroxycinnamic acid derivatives, namely 3-Caffeoylquinic Acid (3-CQA), 4-Caffeolyquinic Acid (4-CQA), 5-Caffeoylquinic Acid (5-CQA), 5-Feruloylquinic Acid (5-FQA), 3,4-di-Caffeoylquinic Acid (3,4-diCQA), 3,5-diCaffeoylquinic Acid (3,5-diCQA) and 4,5-diCaffoylquinic Acid (4,5-diCQA). Chlorogenic acid isomers constituted 10.4% of the total dry weight of commercial product, with 5-CQA being the main compound. The polyphenolic fraction was then analyzed in terms of antiradical activity, using the DPPH• free radical and superoxide anion radicals generated by xanthine-oxidase methods; comparison with reference standards and previous literature showed that the chlorogenic acids of green coffee were from 1.0 to 1.8 times stronger than common antioxidants such as α-to1 copherol and ascorbic acid. Moreover, between the chlorogenic acid subclasses, the activities of the dicaffeoylquinic acids were generally twice stronger than caffeoylquinic acids and 4 times more active than 5-FQA [94].

We can generally conclude that the content in phenolics and chlorogenic acids in coffee at the pre-roasting stage makes the green coffee bean a source of natural antioxidants and a valuable ingredient for human supplements. However, some authors have noted that regardless the promising results in matter of bioactivity of green coffee bean extracts, their exploitation as supplement or incorporation into food systems may require further studies involving toxicological effect, dosage level and carry-through effect possibly induced by occasional contaminants [95-98].

Red Wine: Chemistry and Bioactivity

The phenolic composition of wines is characterized by a certain variability, depending on grape species and cultivar, climatic conditions (mean day temperature, sunlight exposure), soil characteristics and soil management history [99-102], and

then, on the winemaking conditions: fermented yeasts, maceration time, use of additives, fining and aging conditions, among others [103-105]. Wine is an hydroalcoholic solution (generally 10-16% v/v), enriched with organic and inorganic components: aldehydes (70 mg/L on average, mainly acetaldehyde), glycerol (7000 mg/L on average), higher alcohols (500 mg/L on average), sorbitol and mannitol (300 mg/L on average), sulfites (80 mg/L on average), fixed acids (6000 mg/L on average), amino acids (550 mg/L on average), esters (60 mg/L on average), minerals (1200 mg/L on average), sugars (750 mg/L on average), volatile acids (400 mg/L on average) and polyphenols (1800 mg/L on average) [106]. In general, the average composition of red and white wines is substantially different in terms of polyphenolic compounds, with the former being richer in flavonoid polyphenols and tannins and also including anthocyanins and pigmented polymeric compounds [107,108]. The extraction of phenolics from grape is a critical issue for winemakers, since technological properties like color, flavor, astringency and bitterness are related to their amount and molecular structure [109-111]; moreover, they are mainly responsible for the antioxidant power, and their simultaneous presence provides a synergistic effect on antioxidant activity [112-114].

A study of de Beer et al., has reviewed the average polyphenolic contents reported in previous works; the total polyphenolic content for red wines ranged between 700 and 4 059 mg/L with an average of 1686.4 mg/L. Red wine mainly contains flavonoid compounds (range 700-1060 mg/L), distributed among flavan-3-ol monomers (catechin and epicatechin), oligomers and polymers (proanthocyanidins or condensed tannins), whose main structures are shown in figure 5, anthocyanins (malvidin-3-O-glucoside, mainly) and flavonols (quercetin, myricetin and kaempferol and their glycosides) [115].

The abundance of polyphenols in red wine is responsible for its health benefits; nevertheless, as noted by German and Walzem (2000), the disclosure of effective nutritional properties of red wine is a challenging task, due to the high variability of involved phenolic structures (estimated over 200 different molecules) and to the simultaneous presence of ethanol, which is toxic for the human beings above a certain threshold. A further limitation in clinical and nutraceutical studies arises from slowly developing diseases for which validated biomarkers are rare; this complicates the correlation between the potential protective effects of red wine polyphenols and recommended nutritional dosages [21]. Numerous epidemiologic studies, involving human groups characterised by different geographical origin and traditions, reveal that daily moderate wine consumption statistically reduces cardiovascular diseases when compared with individuals who abstain or who drink excess alcohol [116-118].

In nutraceutical terms, when limiting the ethanol intake, two main mechanisms are responsible for the healthy effect of wine: (i) the improvement of lipoprotrein metabolism as a consequence of a controlled ethanol intake [119-120] and (ii) the radical chain action induced by polyphenolic compounds present in wine, particularly flavonoid compounds, which limit the Low Density Lipoprotein (LDL) oxidation and subsequent detrimental mutagenicity of the cells, also correlated to the development of cancers and other degenerative diseases [121-123]. Further, the combined effect of alcohol and polyphenols was investigated, to detect biomarkers of specific diseases, allowing to detect them and enabling their prevention [124-126]. The hypothesis of a combined effect is related to the evidence that the bioavailability of wine flavonoids in human beings is very low; although the bioavailability data for these compounds are still sparse, gut absorption of flavonoids seems to be inversely correlated with their degree of polymerization: absorption is higher for dimeric and trimeric procyanidins than for higher order polymers [127]. Moreover, due to the limitation in wine dose recommended by FAO to avoid diseases induced by an excessive alcohol intake, the concentrations of flavan-3-ols and anthocyanins that could occur in plasma under a realistic dietary supply range from nano-moles to micro-moles [128,129]. This assumption makes unlikely a relevant contribution of polyphenols themselves to the putative healthy effects associated to wine consumption. The recent work of Boto-Ordóñez et al., in particular, has evidenced that the beneficial effects on blood pressure and inflammatory parameters in cardiopathic subjects may be attributed to metabolites formed by the intestinal microbiota from flavonoids present in ingested food, more than the polyphenolic precursors originally present in red wine.

An additional source of polyphenols arises from the barrel aging processing step, which is a common practice in red winemaking, besides the use of additives like powdered tannins, chips and staves. Oak wood has been traditionally used for red wine aging due to its technological properties and to the sensory impact in terms of flavors and aroma and it is characterized by a high content of benzoic acid monomers and extractable ellagitannins, which are easily released in hydro-alcoholic solutions like wine (Figure 7). In particular, Jourdes et al., have identified oak-derived C-glucoside ellagitannins in red wines aged in oak wood barrels and put in contact with oak wood chips, as well as condensed compounds as the β-1-O-ethylvescalagin and flavano-ellagitannins, acutissimin and epiacutissimin, togheter with galloylated and glycosylated fragments derived from hemicellulose and lignin degradation [130]. The impact of hydrolysable tannins derived from oak aging in wine has been studied in a work of Cerda et al. In this study, forty volunteers were divided into four groups and each group was supplied with a dose of foodstuff containing high levels of ellagitannins: strawberries (250 g), red raspberries (225 g), walnuts (35 g) and oak-aged red wine (300 mL). Urine samples were collected for each group after ingestion and they showed a very low concentration of hydrolysable tannin structures, associated with the presence of the specific metabolite 3-hydroxybenzo[c]chromen-6-one (urolithin B) conjugated with glucuronic acid. Moreover, large variations in absorption capacity were denoted among individuals, resulting in a large concentration range of this specific metabolite in urines. The study showed that the ellagitannins are easily made available in humans by hydrolysis and metabolism by specific gastric microflora, despite the corresponding metabolism was not fully elucidated [25]; the same authors have suggested to focus on the bioactivity of the urolithin B derivatives and on the variability of human gastric microflora for a better elucidation of mechanisms of the antioxidant activity. Several studies have

demonstrated the additional healthy effect of urolithin B as hyaluronidase inhibitors and antiangiogenic agents [131-133].

The controversial role of resveratrol in the nutraceutical properties of red wine

Resveratrol (3,5,4′′ -trihydroxystilbene) is the parent compound of the family of viniferin molecules, which is present in significant amounts in vines, peanuts, and pines; its synthesis from p-coumaroyl and malonyl acids is induced for protective purposes by plants, and the whole class of resveratrol-derived molecules is classified as phytoalexin anti-fungicides, inhibiting the progress of fungal infection and conferring resistance toward the attack of several plant pathogens. The resveratrol was first identified in its free form and as a β-glucoside (polydatin or piceid) in the root of Polygonum cuspidatum, with the trans form as the main isomeric configuration. The plant preparation is the main ingredient of the Japanese medicine Ko-jo-kon, an herbal preparation used to treat inflammatory and fungal diseases, heart and blood vessels [134]. The interest in resveratrol as a putative bioactive compound contained in plant-derived beverages and extracts raised at the beginning of 90ties, in particular in 1992 a study by Siemann and Creasy reported the presence of trans-resveratrol in wine, postulating the potential impact of a moderate red wine consumption in the resveratrol dietary intake [135]; the study was supported by the growing interest in the impact of wine consumption on limiting chronic cardiovascular diseases, and several epidemiological studies were devoted to the correlation between the bioactive compounds occurring in wine, the toxic effects induced by alcohol, and the beneficial/detrimental effect balance among them [136]. Most of the studies were focused on the antioxidant capacity of red wine and the putative beneficial effects associated to its consumption, and at a first stage, a key role for this property was attributed to the original presence of trans-resveratrol in the vine. Nevertheless, the studies conducted over the following years made some important contributions to this preliminary assessment; a research undertaken in vitro by the University of California, Davis, aimed to compare the antioxidant effect of white and red wines, showing that the phenolic constituent of red wine prevented oxidative stress in a larger extent than those contained in white wine. Pure quercetin, (-)-epicatechin and trans-resveratrol were assessed as major phenolic constituents of red wines, considering the average concentrations of these compounds expected in red wines; nevertheless, the resveratrol showed to produce only a minor contribution on the overall antioxidant capacity [137]. Further studies were conducted to assess the ability of the same compounds to inhibit the LDL oxidation; results confirmed the previous findings, showing a strong correlation between the content in gallic acid, (+)-catechin, myricetin, quercetin, caftaric acid and their inhibitory effect against pro-oxidant, while any correlation was found between the inhibitory effect and the content in trans-resveratrol [138].

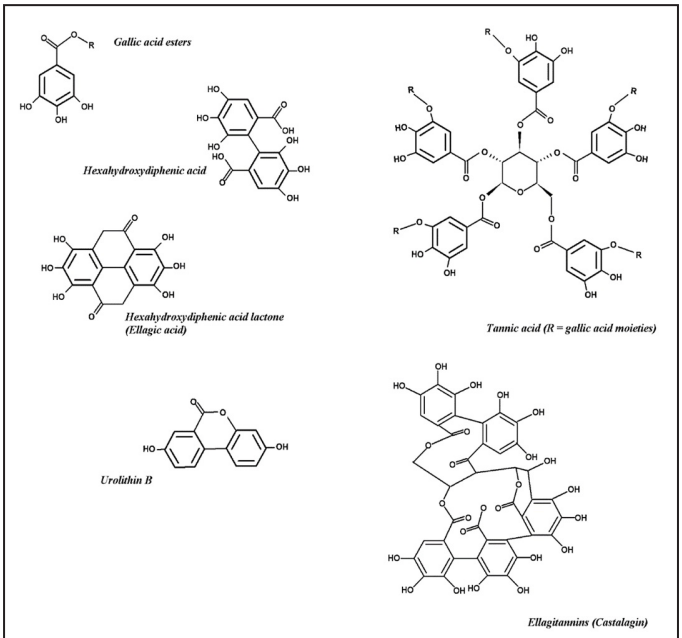

Figure 6: Structure of some representatives of benzoic and ellagic acids-based structures that can be released in red wine during the fining process using oak wood.

The role of resveratrol in the beneficial effect of red wine consumption was debated up to a decade, involving intense researches devoted to the analytical characterization, bioactivity measurement applied to in vitro and in vivo systems, and identification of the factors which are likely to promote its enrichment in wine. At the state of art, a conclusive evidence for its beneficial effect on human metabolism is lacking, and it is questionable that the in vitro bioactivity of trans-resveratrol can be reproduced through a moderate red wine consumption. The main concern regarding the effect of assuming red wine as a dietary source of resveratrol is the low content of this compound occurring in wine, and the competitive activity of other polyphenolic compounds which are present in a larger extent [134]. In spite of the interest initially raised, since the end of the 1990s studies on trans-resveratrol in red wine have been practically interrupted, supplanted by a more in-depth study of simple phenolic compounds, tannins, and of the mechanisms involving their antioxidant capacity.

Putative Toxicological Effects and Epidemiological Effect of Biomedical Strategies Based on Polyphenols Consumption

The regular and massive consumption of fruits and vegetables and their derivatives, which are sources of bioactive compounds (vitamins, mineral elements, polyphenols, among others) have been considered for a long time a preventive approach against major degenerative diseases, including cancer. Nutraceutical studies listed in the previous paragraphs suggest the potential nutraceutical impact arising from the consumption of polyphenolic-rich beverages; nevertheless, it is worthy of notice that further extensive clinical studies have been conducted on dietary sources of bioactive compounds and neither epidemiological nor experimental evidence have been found confirming this assumption. A recent, systematic study of the chemopreventive effect induced by non-polyphenolic bioactives has alerted about the excessive trust placed in the beneficial effect of individual compounds rather than in the planning of a balanced and complete diet [139]. Further studies have paid attention in dietary sources of polyphenolic compounds commonly recognized as bioactive foods; in particular, the chemopreventive ability of nutraceutical

food has been tested in humans and rats in case study, planning a daily diet restricted to the consumption of selected fruit and vegetables. A recent study by Bonamassa et al., included black grape among diet supplements that were administered to laboratory mice, alone or in combination with lyophilized onion, tomato, peach, and lettuce; ten days post-treatment, the following parameters were monitored: phase-I/II xenobiotic metabolizing and antioxidant enzyme activities, protein and mRNA levels; moreover, the occurrence and level of hydroperoxides were investigated in rat serum samples as a marker of oxidative stress. Noticeably, the systematic consumption of randomly-blended selected food, being lyophilized onion, tomato, peach, lettuce and black grape, on a daily basis, induced a down-regulation of the catalytic activity, protein and mRNA levels of a cohort of hepatic metabolizing enzymes, reducing their activity upon exposure to ubiquitous carcinogens; the latter observation was further confirmed by the boost in systemic hydroperoxide levels, as a consequence of the impairment of antioxidant enzymes. The authors of this study have concluded that a proper dietary guidance should rely on a "daily diversification" of fruit and vegetables dietary sources, to avoid the systemic stress induced by the repeated assumption of the same food [140]. In a previous work, Sapone et al., also noted that the concept of chemopreventive action of fruits and vegetables, being foods rich in nutrients and phytochemicals, have been drastically simplified by applying dietary experimental approaches based on the use of single bioactive components both as a single supplement or in functional foods; this approach fails to take into account the outcomes of enzyme modulators and their effects on immunosystemic responses. In particular, the study has highlighted that a regular long-term administration of isolated nutrients and other chemicals derived from food plants is not sufficient to manipulate the activity of specific catalysts; reversely, a healthy diet is likely to reduce mutagenesis risk, showing that dietary patterns with high nutraceutical value are more effective than isolated nutraceutical compounds [141].

Conclusion

Commonly consumed beverages, green tea, green coffee and red wine, have been discussed in terms of general composition and described in relation to their content in phenolic compounds. Green tea, green coffee and red wine have been reported as major sources of antioxidant polyphenols; polyphenols are well-known antioxidants, and the specific classes of phenolic compounds involved: flavonoid compounds, hydroxycinnamic acids, hydrolysable tannins, have been detailed in terms of their chemical structure and reactivity, to support the evaluation of potential nutraceutical impact of beverages containing high concentrations of these bioactives. The most recent literature on the nutraceutical impact of selected beverages was reported leading to the following general conclusions: (i) Green coffee, green tea and (moderate) red wine consumption has a positive nutraceutical impact due to their polyphenolic content, both in qualitative and quantitative terms; structure-activity relationship have been demonstrated based on specific chemical and biological reactivities. (ii) Although the strong antioxidant activity and associated mechanisms of action have been demonstrated by in vitro studies and briefly summarized in this review, a nutraceutical approach requires a more detailed study of the biosynthesis of specific metabolites produced by human microbiota during digestion, because metabolism significantly changes the biochemical characteristics of the precursors. Promising studies have been carried out from this perspective, highlighting differential absorption capacity of subclasses of phenolic compounds; a further cause of variability should be attributed to the specific microflora among individuals. Based on these premises, a significant contribution would arise from systematic in vivo studies in a representative samples series; the combination of existing scientific evidences and new experimental approaches would improve the consumer awareness on the consumption of green tea, green coffee, red wine, as pleasing drinks and dietary supplements.

References

1. Haslam E (1998) Practical Polyphenolics: From Structure to Molecular Recognition and Physiological Action. Cambridge University Press, New York, USA. Pg no: 422.
2. Ricci A, Parpinello GP, Palma AS, Teslić N, Brilli C, et al. (2017) Analytical profiling of food-grade extracts from grape (*Vitis vinifera* sp.) seeds and skins, green tea (*Camellia sinensis*) leaves and Limousin oak (*Quercus robur*) heartwood using MALDI-TOF-MS, ICP-MS and spectrophotometric methods. J Food Compos Anal 59: 95-104.
3. Versari A, du Toit W, Parpinello GP (2013) Oenological tannins: a review. Aust J Grape Wine Res 19: 1-10.
4. Prior RL, Cao G, Prior RL, Cao G (2000) Analysis of botanicals and dietary supplements for antioxidant capacity: A review. J AOAC Int 83: 950-956.
5. Ricci A, Olejar KJ, Parpinello GP, Mattioli AU, Teslić N, et al. (2016) Antioxidant activity of commercial food grade tannins exemplified in a wine model. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 33: 1761-1774.
6. Quideau S, Deffieux D, Douat-Casassus C, Pouysegu L (2011) Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Ed Engl 50: 586-621.
7. Visioli F, Lastra CADL, Andres-Lacueva C, Aviram M, Calhau C, et al. (2011) Polyphenols and human health: a prospectus. Crit Rev Food Sci Nutr 51: 524-546.
8. Scalbert A, Johnson IT, Saltmarsh M (2005) Polyphenols: antioxidants and beyond. Am J Clin Nutr 81: 215-217.
9. Bors W, Michel C (2002) Chemistry of the antioxidant effect of polyphenols. Ann NY Acad Sci 957: 57-69.
10. Murcia MA, Egea I, Romojaro F, Parras P, Jiménez AM, et al. (2004) Antioxidant evaluation in dessert spices compared with common food additives. Influence of irradiation procedure. J Agr Food Chem 52: 1872-1881.
11. Carocho M, Barreiro MF, Morales P, Ferreira ICFR (2014) Adding molecules to food, pros and cons: A review on synthetic and natural food additives. Compr Rev Food Sci Food Saf 13: 377-399.
12. Richelle M, Tavazzi I, Offord E (2001) Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. J Agr Food Chem 49: 3438-3442.
13. Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 56: 317-333.
14. Lakenbrink C, Lapczynski S, Maiwald B, Engelhardt UH (2000) Flavonoids and other polyphenols in consumer brews of tea and other caffeinated beverages. J Agr Food Chem 48: 2848-2852.
15. Balentine DA, Wiseman SA, Bouwens LC (1997) The chemistry of tea flavonoids. Crit Rev Food Sci Nutr 37: 693-704.
16. Rababah TM, Hettiarachchy NS, Horax R (2004) Total phenolics

and antioxidant activities of fenugreek, green tea, black tea, grape seed, ginger, rosemary, gotu kola, and ginkgo extracts, vitamin E, and tert-butylhydroquinone. J Agr Food Chem 52: 5183-5186.

17. Clifford MN (1985) Chemical and physical aspects of green coffee and coffee products. In: Clifford MN, Willson KC (ed.). Coffee, Springer, Boston, MA, USA. Pg no: 305-374.

18. Daglia M, Papetti A, Gregotti C, Bertè F, Gazzani G (2000) *In vitro* antioxidant and *ex vivo* protective activities of green and roasted coffee. J Agr Food Chem 48: 1449-1454.

19. Dziki D, Gawlik-Dziki U, Pecio Ł, Różyło R, Świeca M, et al. (2015) Ground green coffee beans as a functional food supplement-preliminary study. Food Sci Technol 63: 691-699.

20. Watanabe T, Arai Y, Mitsui Y, Kusaura T, Okawa W, et al. (2006) The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. Clin Exp Hypertens 28: 439-449.

21. German JB, Walzem RL (2000) The health benefits of wine. Annu Rev Nutr 20: 561-593.

22. Renaud Sd, de Lorgeril M (1992) Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 339: 1523-1526.

23. Vidavalur R, Otani H, Singal PK, Maulik N (2006) Significance of wine and resveratrol in cardiovascular disease: French paradox revisited. Exp Clin Cardiol 11: 217-225.

24. Sun AY, Simonyi A, Sun GY (2002) The "French paradox" and beyond: neuroprotective effects of polyphenols. Free Radic Biol Med 32: 314-318.

25. Cerdá B, Tomás-Barberán FA, Espín JC (2005) Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: identification of biomarkers and individual variability. J Agr Food Chem 53: 227-235.

26. Rice-Evans CA, Miller NJ, Paganga G (1996) Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 20: 933-956.

27. Chen L, Teng H, Xie Z, Cao H, Cheang WS, et al. (2016) Modifications of dietary flavonoids towards improved bioactivity: an update on sructure-activity relationship. Crit Rev Food Sci Nutr 20: 1-15.

28. Gonzales GB, Smagghe G, Grootaert C, Zotti M, Raes K, et al. (2015) Flavonoid interactions during digestion, absorption, distribution and metabolism: a sequential structure-activity/property relationship-based approach in the study of bioavailability and bioactivity. Drug Metab Rev 47: 175-190.

29. de Queiroz Ferreira R, Greco SJ, Delarmelina M, Weber KC (2015) Electrochemical quantification of the structure/antioxidant activity relationship of flavonoids. Electrochim Acta 163: 161-166.

30. Ferrali M, Signorini C, Caciotti B, Sugherini L, Ciccoli L, et al. (1997) Protection against oxidative damage of erythrocyte membrane by the flavonoid quercetin and its relation to iron chelating activity. FEBS Lett 416: 123-129.

31. Elliott AJ, Scheiber SA, Thomas C, Pardini RS (1992) Inhibition of glutathione reductase by flavonoids. A structure-activity study. Biochem Pharmacol 44: 1603-1608.

32. Hirano R, Sasamoto W, Matsumoto A, Itakura H, Igarashi O, et al. (2001) Antioxidant ability of various flavonoids against DPPH radicals and LDL oxidation. J Nutr Sci Vitaminol 47: 357-362.

33. Cos P, Ying L, Calomme M, Hu JP, Cimanga K, et al. (1998) Structure-activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J Nat Prod 61: 71-76.

34. Farkas O, Jakus J, Héberger K (2004) Quantitative structure-antioxidant activity relationships of flavonoid compounds. Molecules 9: 1079-1088.

35. Bradley DG, Min DB (1992) Singlet oxygen oxidation of foods. Crit Rev Food Sci Nutr 31: 211-236.

36. van Acker SA, de Groot MJ, van den Berg DJ, Tromp MN, Donné-Op den Kelder G, et al. (1996) A quantum chemical explanation of the antioxidant activity of flavonoids. Chem Res Toxicol 9: 1305-1312.

37. Kilmartin PA, Zou H, Waterhouse AL (2001) A cyclic voltammetry method suitable for characterizing antioxidant properties of wine and wine phenolics. J Agr Food Chem 49: 1957-1965.

38. Cholbi M, Paya M, Alcaraz M (1991) Inhibitory effects of phenolic compounds on CCl 4-induced microsomal lipid peroxidation. Cell Mol Life Sci 47: 195-199.

39. Burda S, Oleszek W (2001) Antioxidant and antiradical activities of flavonoids. J Agr Food Chem 49: 2774-2779.

40. Vennat B, Bos M, Pourrat A, Bastide P (1994) Procyanidins from tormentil: fractionation and study of the anti-radical activity towards superoxide anion. Biol Pharm Bull 17: 1613-1615.

41. Castillo J, Benavente-Garcia O, Lorente J, Alcaraz M, Redondo A, et al. (2000) Antioxidant activity and radioprotective effects against chromosomal damage induced *in vivo* by X-rays of flavan-3-ols (Procyanidins) from grape seeds (*Vitis vinifera*): comparative study versus other phenolic and organic compounds. J Agr Food Chem 48: 1738-1745.

42. Radtke J, Linseisen J, Wolfram G (1998) Phenolic acid intake of adults in a Bavarian subgroup of the national food consumption survey. Z Ernahrungswiss 37: 190-197.

43. Dykes L, Rooney L (2007) Phenolic compounds in cereal grains and their health benefits. Cereal Foods World 52: 105-111.

44. Beattie J, Crozier A, Duthie GG (2005) Potential health benefits of berries. Curr Nutr Food Sci 1: 71-86.

45. Liu RH (2013) Health-promoting components of fruits and vegetables in the diet. Adv Nutr 4: 384-392.

46. Maurya DK, Devasagayam TPA (2010) Antioxidant and prooxidant nature of hydroxycinnamic acid derivatives ferulic and caffeic acids. Food Chem Toxicol 48: 3369-3373.

47. Hadi SM, Asad SF, Singh S, Ahmad A (2000) Putative mechanism for anticancer and apoptosis-inducing properties of plant□derived polyphenolic compounds. IUBMB Life 50: 167-171.

48. Cuvelier M-E, Richard H, Berset C (1992) Comparison of the antioxidative activity of some acid-phenols: structure-activity relationship. Biosci Biotechnol Biochem 56: 324-325.

49. Sroka Z, Cisowski W (2003) Hydrogen peroxide scavenging, antioxidant and anti-radical activity of some phenolic acids. Food Chem Toxicol 41: 753-758.

50. Nardini M, D'Aquino M, Tomassi G, Gentili V, Di Felice M, et al. (1995) Inhibition of human low-density lipoprotein oxidation by caffeic acid and other hydroxycinnamic acid derivatives. Free Radic Biol Med 19: 541-552.

51. Meyer AS, Donovan JL, Pearson DA, Waterhouse AL, Frankel EN (1998) Fruit hydroxycinnamic acids inhibit human low-density lipoprotein oxidation *in vitro*. J Agr Food Chem 46: 1783-1787.

52. Cheng JC, Dai F, Zhou B, Yang L, Liu ZL (2007) Antioxidant activity of hydroxycinnamic acid derivatives in human low-density lipoprotein: mechanism and structure-activity relationship. Food Chem 104: 132-139.

53. Hagerman AE (2011) Hydrolyzable tannin structural chemistry. In: Hagerman AE (ed.). The Tannin Handbook. 3rdedn, Miami University, Oxford, OH, USA. Pg no: 1-5.

54. Ricci A, Lagel MC, Parpinello GP, Pizzi A, Kilmartin PA, et al. (2016) Spectroscopy analysis of phenolic and sugar patterns in a food grade chestnut tannin. Food Chem 203: 425-429.

55. Garde-Cerdán T, Ancín-Azpilicueta C (2006) Review of quality fac-

tors on wine ageing in oak barrels. Trends Food Sci Technol 17: 438-447.

56. Cerdán TG, Mozaz SR, Azpilicueta CA (2002) Volatile composition of aged wine in used barrels of French oak and of American oak. Food Res Int 35: 603-610.

57. Puech J-L, Feuillat F, Mosedale J (1999) The Tannins of Oak Heartwood: Structure, Properties, and Their Influence on Wine Flavor. Am J Enol Vitic 50: 469-478.

58. De Rosso M, Panighel A, Dalla Vedova A, Stella L, Flamini R (2009) Changes in chemical composition of a red wine aged in acacia, cherry, chestnut, mulberry, and oak wood barrels. J Agr Food Chem 57: 1915-1920.

59. Vivas N, Glories Y (1996) Role of oak wood ellagitannins in the oxidation process of red wines during aging. Am J Enol Vitic 47: 103-107.

60. Bautista-Ortín AB, Martínez-Cutillas A, Ros-García JM, López-Roca JM, Gómez-Plaza E (2005) Improving colour extraction and stability in red wines: the use of maceration enzymes and enological tannins. Int J Food Sci Tech 40: 867-878.

61. Escribano-Bailon MT, Santos-Buelga C (2012) Anthocyanin copigmentation-evaluation, mechanisms and implications for the colour of red wines. Curr Org Chem 16: 715-723.

62. Okuda T, Yoshida T, Hatano T (1989) Ellagitannins as active constituents of medicinal plants. Planta Med 55: 117-122.

63. Romani A, Campo M, Pinelli P (2012) HPLC/DAD/ESI-MS analyses and anti-radical activity of hydrolyzable tannins from different vegetal species. Food Chem 130: 214-221.

64. Baratto MC, Tattini M, Galardi C, Pinelli P, Romani A, et al. (2003) Antioxidant activity of galloyl quinic derivatives isolated from P. lentiscus leaves. Free Radic Res 37: 405-412.

65. Heimler D, Vignolini P, Dini MG, Vincieri FF, Romani A (2006) Antiradical activity and polyphenol composition of local *Brassicaceae* edible varieties. Food Chem 99: 464-469.

66. Cabrera C, Artacho R, Giménez R (2006) Beneficial effects of green tea-a review. J Am Coll Nutr 25: 79-99.

67. Sinija VR, Mishra HN (2008) Green tea: health benefits. J Nutr Environ Med 17: 232-242.

68. Cao G, Sofic E, Prior RL (1996) Antioxidant capacity of tea and common vegetables. J Agr Food Chem 44: 3426-3431.

69. Graham HN (1992) Green tea composition, consumption, and polyphenol chemistry. Prev Med 21: 334-350.

70. Pan X, Niu G, Liu H (2003) Microwave-assisted extraction of tea polyphenols and tea caffeine from green tea leaves. Chem Eng Process 42: 129-133.

71. Chaturvedula VSP, Prakash I (2011) The aroma, taste, colour and bioactive constituents of tea. J Med Plant Res 5: 2110-2124.

72. Senanayake SN (2013) Green tea extract: chemistry, antioxidant properties and food applications-A review. J Funct Foods 5: 1529-1541.

73. Balentine D, aetau-Robinson I (2000) Tea as a source of dietary antioxidants. In: Mazza G, Oomah BD (eds.). Herbs, Botanicals and Teas. CRC Press, USA. Pg no: 265-287.

74. Heim KE, Tagliaferro AR, Bobilya DJ (2002) Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. J Nutr Biochem 13: 572-584.

75. Ivanova-Petropulos V, Ricci A, Nedelkovski D, Dimovska V, Parpinello GP, et al. (2015) Targeted analysis of bioactive phenolic compounds and antioxidant activity of Macedonian red wines. Food Chem 171: 412-420.

76. Alonso ÁM, Guillén DA, Barroso CG, Puertas B, García A (2002). Determination of antioxidant activity of wine byproducts and its correlation with polyphenolic content. J Agr Food Chem 50: 5832-5836.

77. Paśko P, Bartoń H, Zagrodzki P, Gorinstein S, Fołta M, et al. (2009) Anthocyanins, total polyphenols and antioxidant activity in amaranth and quinoa seeds and sprouts during their growth. Food Chem 115: 994-998.

78. Singh BN, Shankar S, Srivastava RK (2011) Green tea catechin, Epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol 82: 1807-1821.

79. Nie G, Cao Y, Zhao B (2002) Protective effects of green tea polyphenols and their major component, (-)-Epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells. Redox Rep 7: 171-177.

80. Du GJ, Zhang Z, Wen XD, Yu C, Calway T, et al. (2012) Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. Nutrients 4: 1679-1691.

81. del Castillo MD, Ames JM, Gordon MH (2002) Effect of roasting on the antioxidant activity of coffee brews. J Agr Food Chem 50: 3698-3703.

82. Clifford MN (1986) Coffee bean dicaffeoylquinic acids. Phytochemistry 25: 1767-1769.

83. Farah A, Donangelo CM (2006) Phenolic compounds in coffee. Braz J Plant Physiol 18: 23-36.

84. Gülçin İ (2006) Antioxidant activity of caffeic acid (3, 4-dihydroxycinnamic acid). Toxicology 217: 213-220.

85. Kikuzaki H, Hisamoto M, Hirose K, Akiyama K, Taniguchi H (2002) Antioxidant properties of ferulic acid and its related compounds. J Agr Food Chem 50: 2161-2168.

86. Chen JH, Ho CT (1997) Antioxidant activities of caffeic acid and its related hydroxycinnamic acid compounds. J Agr Food Chem 45: 2374-2378.

87. Farah A, Monteiro M, Donangelo CM, Lafay S (2008). Chlorogenic acids from green coffee extract are highly bioavailable in humans. J Nutr 138: 2309-2315.

88. Monteiro M, Farah A, Perrone D, Trugo LC, Donangelo C (2007) Chlorogenic acid compounds from coffee are differentially absorbed and metabolized in humans. J Nutr 137: 2196-2201.

89. Kozuma K, Tsuchiya S, Kohori J, Hase T, Tokimitsu I (2005) Antihypertensive effect of green coffee bean extract on mildly hypertensive subjects. Hypertens Res 28: 711-718.

90. Ochiai R, Jokura H, Suzuki A, Tokimitsu I, Ohishi M, et al. (2004) Green coffee bean extract improves human vasoreactivity. Hypertens Res 27: 731-737.

91. Dellalibera O, Lemaire B, Lafay S (2006) Le Svetol®, un extrait de café vert décaféiné, induit une perte de poids et augmente le ratio masse maigre sur masse grasse chez des volontaires en surcharge pondérale. Phytotherapie 4: 194-197.

92. Blum J, Lemaire B, Lafay S (2007) Effect of a green decaffeinated coffee extract on glycaemia. NUTRAFoods 6: 13-17.

93. Naidu MM, Sulochanamma G, Sampathu SR, Srinivas P (2008) Studies on extraction and antioxidant potential of green coffee. Food Chem 107: 377-384.

94. Iwai K, Kishimoto N, Kakino Y, Mochida K, Fujita T (2004) *In vitro* antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. J Agr Food Chem 52: 4893-4898.

95. Ramalakshmi K, Rao LJM, Takano-Ishikawa Y, Goto M (2009) Bioactivities of low-grade green coffee and spent coffee in different *in vitro* model systems. Food Chem 115: 79-85.

96. Romani S, Sacchetti G, Chaves López C, Pinnavaia GG, Dalla Rosa M (2000) Screening on the occurrence of ochratoxin A in green coffee beans of different origins and types. J Agr Food Chem 48: 3616-3619.

97. Waters DM, Arendt EK, Moroni AV (2017) Overview on the mechanisms of coffee germination and fermentation and their significance for coffee and coffee beverage quality. Crit Rev Food Sci Nutr 57: 259-274.

98. Şemen S, Mercan S, Yayla M, Açıkkol M (2017) Elemental composition of green coffee and its contribution to dietary intake. Food Chem 215: 92-100.

99. Parpinello GP, Rombolà AD, Simoni M, Versari, A (2015) Chemical and sensory characterisation of Sangiovese red wines: comparison between biodynamic and organic management. Food Chem 167: 145-152.

100. Granato D, de Magalhães Carrapeiro M, Fogliano V, van Ruth SM (2016) Effects of geographical origin, varietal and farming system on the chemical composition and functional properties of purple grape juices: a review. Trends Food Sci Technol 52: 31-48.

101. Teslić N, Zinzani G, Parpinello GP, Versari A (2016) Climate change trends, grape production, and potential alcohol concentration in wine from the "Romagna Sangiovese" appellation area (Italy). Theor Appl Climatol 1-11.

102. Pérez-Magariño S, González-San José ML (2006) Polyphenols and colour variability of red wines made from grapes harvested at different ripeness grade. Food Chem 96: 197-208.

103. Fulcrand H, Dueñas M, Salas E, Cheynier V (2006) Phenolic reactions during winemaking and aging. Am J Enol Vitic 57: 289-297.

104. Guadalupe Z, Martínez L, Ayestarán B (2010) Yeast mannoproteins in red winemaking: effect on polysaccharide, polyphenolic, and color composition. Am J Enol Vitic 61: 191-200.

105. Ducasse MA, Canal-Llauberes RM, de Lumley M, Williams P, Souquet JM, et al. (2010). Effect of macerating enzyme treatment on the polyphenol and polysaccharide composition of red wines. Food Chem 118: 369-376.

106. Waterhouse AL, Sacks GL, Jeffery DW (2016) Understanding Wine Chemistry: John Wiley & Sons. New Jersey, USA.

107. Kammerer D, Claus A, Carle R, Schieber A (2004) Polyphenol screening of pomace from red and white grape varieties (*Vitis vinifera L.*) by HPLC-DAD-MS/MS. J Agr Food Chem 52: 4360-4367.

108. Versari AV, Parpinello GP, Mattioli AU (2016) Characterisation of colour components and polymeric pigments of commercial red wines by using selected UV-Vis spectrophotometric methods. S Afr J Enol Vitic 28: 6-10.

109. Boulton R (2001) The copigmentation of anthocyanins and its role in the color of red wine: a critical review. Am J Enol Vitic 52: 67-87.

110. Brossaud F, Cheynier V, Noble AC (2001) Bitterness and astringency of grape and wine polyphenols. Aust J Grape Wine Res 7: 33-39.

111. Versari A, Boulton RB, Parpinello GP (2008) A comparison of analytical methods for measuring the color components of red wines. Food Chem 106: 397-402.

112. Saucier CT, Waterhouse AL (1999) Synergetic activity of catechin and other antioxidants. J Agr Food Chem 47: 4491-4494.

113. Waterhouse AL (2002) Wine phenolics. Ann N Y Acad Sci 957: 21-36.

114. Versari A, Parpinello GP, Scazzina F, Del Rio D (2010) Prediction of total antioxidant capacity of red wine by Fourier transform infrared spectroscopy. Food Control 21: 786-789.

115. De Beer D, Joubert E, Gelderblom WCA, Manley M (2017) Phenolic compounds: a review of their possible role as *in vivo* antioxidants of wine. S Afr J Enol Vitic 23: 48-61.

116. Vidot DC, Stoutenberg M, Gellman M, Arheart KL, Teng Y, et al. (2016) Alcohol consumption and metabolic syndrome among hispanics/latinos: the hispanic community health study/study of latinos. Metab Syndr Relat Disord 14: 354-362.

117. Barrett-Connor E, de Gaetano G, Djoussé L, Ellison RC, Estruch R, et al. (2016) Comments on moderate alcohol consumption and mortality. J Stud Alcohol Drugs 77: 834-836.

118. Chang KJ, Thach ML, Olsen J (2016) Wine and health perceptions: exploring the impact of gender, age and ethnicity on consumer perceptions of wine and health. Wine Economics and Policy 5: 105-113.

119. Krenz M, Korthuis RJ (2012) Moderate ethanol ingestion and cardiovascular protection: from epidemiologic associations to cellular mechanisms. J Mol Cell Cardiol 52: 93-104.

120. Hagström H, Nasr P, Ekstedt M, Kechagias S, Önnerhag K, et al. (2017) Low to moderate lifetime alcohol consumption is associated with less advanced stages of fibrosis in non-alcoholic fatty liver disease. Scand J Gastroenterol 52: 159-165.

121. Golan R, Shelef I, Shemesh E, Henkin Y, Schwarzfuchs D, et al. (2017) Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. Public Health Nutr 20: 549-555.

122. Khymenets O, Vázquez-Fresno R, Palau-Rodriguez M, Llorach R, Urpí-Sardà M, et al. (2016) Metabolomic approaches in the study of wine benefits in human health. In: Moreno-Arribas MV, Suáldea BB (eds.). Wine Safety, Consumer Preference, and Human Health. Springer International Publishing, NewYork, USA Pg no: 293-317.

123. C Zuniga-Lopez M, Felipe Laurie V, Barriga-Gonzalez G, Folch-Cano C, Fuentes J, et al. (2017) Chemical and biological properties of phenolics in wine: analytical determinations and health benefits. Curr Org Chem 21: 357-367.

124. Lippi G, Franchini M, Favaloro EJ, Targher G (2010) Moderate red wine consumption and cardiovascular disease risk: beyond the "French paradox". Semin Thromb Hemost 31: 59-70.

125. Wollin SD Jones PJ (2001) Alcohol, red wine and cardiovascular disease. J Nutr 131: 1401-1404.

126. Boban M, Stockley C, Teissedre PL, Restani P, Fradera U, et al. (2016) Drinking pattern of wine and effects on human health: why should we drink moderately and with meals? Food Funct 7: 2937-2942.

127. Smeriglio A, Barreca D, Bellocco E, Trombetta D (2016) Proanthocyanidins and hydrolysable tannins: occurrence, dietary intake and pharmacological effects. Br J Pharmacol 174: 1244-1262.

128. Boto-Ordóñez M, Urpi-Sarda M, Queipo-Ortuño MI, Corella D, Tinahones FJ, et al. (2013) Microbial metabolomic fingerprinting in urine after regular dealcoholized red wine consumption in humans. J Agr Food Chem 61: 9166-9175.

129. Cueva C, Gil-Sánchez I, Ayuda-Durán B, González-Manzano S, González-Paramás AM, et al. (2017) An integrated view of the effects of wine polyphenols and their relevant metabolites on gut and host health. Molecules 22: 99-114.

130. Jourdes M, Michel J, Saucier C, Quideau S, Teissedre PL (2011) Identification, amounts, and kinetics of extraction of C-glucosidic ellagitannins during wine aging in oak barrels or in stainless steel tanks with oak chips. Anal Bioanal Chem 401: 1531-1539.

131. Jeong SJ, Kim NY, Kim DH, Kang TH, Ahn NH, et al. (2000) Hyaluronidase inhibitory active 6H-dibenzo [b, d] pyran-6-ones from the feces of Trogopterus xanthipes. Planta Med 66: 76-77.

132. Larrosa M, González-Sarrías A, Yáñez-Gascón MJ, Selma MV, Azorín-Ortuño M, et al. (2010) Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. The J Nutr Biochem 21: 717-725.

133. Qiu Z, Zhou B, Jin L, Yu H, Liu L, et al. (2013) *In vitro* antioxidant and antiproliferative effects of ellagic acid and its colonic metabolite, urolithins, on human bladder cancer T24 cells. Food Chem Toxicol 59: 428-437.

134. Soleas GJ, Diamandis EP, Goldberg DM (1997) Resveratrol: a molecule whose time has come? And gone? Clin Biochem 30: 91-113.

135. Siemann EH, Creasy LL (1992) Concentration of the phytoalexin resveratrol in wine. Am J Enol Vitic 43: 49-52.

136. Goldberg DM, Hahn SE, Parkes JG (1995) Beyond alcohol: beverage consumption and cardiovascular mortality. Clin Chim Acta 237: 155-187.

137. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE (1993) Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. The Lancet 341: 454-457.

138. Frankel EN, Waterhouse AL, Teissedre PL (1995) Principal phenolic phytochemicals in selected California wines and their antioxidant activity in inhibiting oxidation of human low-density lipoproteins. J Agr Food Chem 43: 890-894.

139. Potter JD (2014) The failure of cancer chemoprevention. Carcinogenesis 35: 974-982.

140. Bonamassa B, Canistro D, Sapone A, Vivarelli F, Vornoli A, et al. (2016) Harmful effects behind the daily supplementation of a fixed vegetarian blend in the rat model. Food Chem Toxicol 97: 367-374.

141. Sapone A, Canistro D, Melega S, Moles R, Vivarelli F, et al. (2012) On enzyme-based anticancer molecular dietary manipulations. J Biomed Biotechnol 2012: 790987.