Chapter 6
The French Paradox at Tea Time: From Antioxidant Flavonoids and Stilbenes Toward Bio-inspired Synthetic Derivatives

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Keywords Epicatechin • Flavonoids • Frenchparadox • Resveratrol • Stilbenes

1 Introduction

Nowadays, science has become more immerged into daily life. Who has not heard or at least observed the word 'antioxidant', which is frequently advertised on many beverages and dairy products of the supermarket? Although most people ignore the real significance of an antioxidant, many of them do use the term 'antioxidant' while discussing nutrition, food, and health; hence, the question must be posed "What is an antioxidant?"

In a general aspect, an antioxidant is a substance able to prevent the oxidation reaction mainly caused by oxygen. A concrete example is commonly observed in the well-known phenomena of metal corrosion. Iron is oxidized by oxygen from the air. Anticorrosive agents, which in fact are antioxidants, are used to protect metallic surfaces from corrosive damage. From a chemical point of view, the oxidation reaction is a redox reaction involving electron transfer from a substance toward the oxidant agent. This reaction can produce free radicals that are highly reactive species that attack molecules by capturing electrons, thus modifying their molecular structures. In other words, any substance that reduces the oxidative damage due to oxygen (and/or free radicals) is called an 'antioxidant'. It is therefore capable to stop the destructive oxidation process by reacting with free radicals and stopping their activity (Valko et al. 2007; Hermes-Lima 2005). These antioxidant properties are encountered in specific families of natural and synthetic organic compounds; the most common are phenolic compounds.

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In biology, despite the crucial role of oxidation reactions for metabolism and organism functioning, they can also be highly destructive. A biological paradox is eventually noticed for most beings (animals and plants) requiring oxygen to ensure life, while this molecule is extremely reactive and able to induce degradation for many organisms. Under such circumstances, antioxidation systems are set up in the form of antioxidant agents acting together with enzymes to prevent the formation of highly reactive species or even to eliminate them just before they damage cell-components, like DNA, lipids, and proteins. Plants and animals utilize and produce various antioxidants to protect themselves, such as glutathione, vitamin C, and vitamin E, or enzymes like catalase, peroxidase, and superoxide dismutase. Similarly, our body itself produces, involving the amino acid cysteine, a powerful antioxidant, α-lipoic acid. A deficiency or total absence of antioxidants causes oxidative stress that can damage or destroy cells. Oxidative stress has been implicated in the pathogenesis of many human diseases, mainly cancer. So far, the application of antioxidants in pharmacology has been studied in order to treat several pathologies namely cardio, cerebral, vascular, atherosclerosis, neoplasia, and neurodegenerative diseases. However, it still remains unclear whether oxidative stress is the cause or the consequence of these diseases (Valko et al. 2007).

Great attention was focused on the naturally occurring antioxidant phytochemicals as possible therapy for cardiovascular diseases. These natural occurring components are considered as important nutritional ingredients acting as protectors for the health maintenance and preventing certain diseases like cancer or heart failure. Although studies suggest that nutritional antioxidants are beneficial to health, extensive clinical trials did not reveal a very clear *in vivo* biological action on humans and have even suggested that excessive intake of these substances could sometimes have negative effects (Barbosa 2007; Galati and O'Brien 2004; Gerhaeuser 2001).

A huge amount of organic compounds from both natural and synthetic sources are recognized as potent antioxidant agents. The flavonoid family, widespread in the plant kingdom is associated with antioxidant capacities, especially flavones. Great attention is due to the stilbene family in which resveratrol, the main grape skin and red wine active component, is the chief leader of this family, displaying a broad spectrum of biological effects, also followed by a queue of numerous biological active synthetic analogs.

This chapter deals with a brief structural introduction to the flavonoid and the stilbene compounds. A word is given on the chemistry behind the drive to synthesize more effective derivatives of the previously mentioned natural products, including flavones, 2-styrylchromones, and stilbenes. A discussion on nutritional polyphenols is presented emphasizing some biologically impactful molecules mainly from the flavonoid and stilbene families. Flavonoids such as quercetin, anthocyanins, catechins, and resveratrol, along with other small phenolic molecules constitute the subject of this chapter. These compounds are frequently encountered in vegetables, fruits, and beverages. Red wine, tea, especially green, and chocolate are, without any doubt, the most fascinating examples considered in people's eating habits and most important sources of the above highlighted

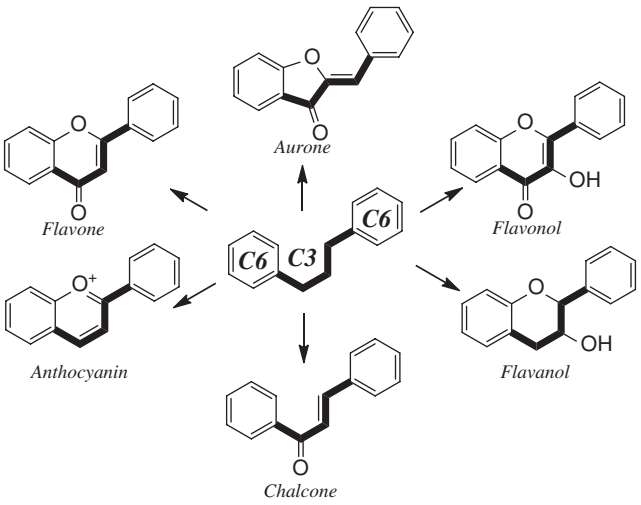


Fig. 1 Flavonoid main basic structures

nutritional polyphenols. We will revisit the French Paradox which relates the observation that mortality rates due to coronary heart disease are relatively low in some regions of France despite a diet rich in saturated fats. A similar concept will be treated regarding tea drinks and their potential cancer prevention. Chocolate is a tasty source of polyphenols which is taking part in our survey on food-nutrients and health effects. Aspects of biology, recent evidences on beneficial effects, *in vitro*, *in vivo* and clinical trials, for antioxidant assays of these polyphenol-rich foods are outlined. Some social circumstances end up with different opinions on whether these foods are with or without risk for human health.

2 Flavonoids and Related Compounds

Flavonoids form a family of phenolic secondary metabolites of plants. All the classes of this family of compounds share the same basic structure formed by two aromatic rings attached together via a three carbon chain giving rise to a C_6–C_3–C_6 system. Usually their structure contains a pyrano- or furano-heterocycle with a ketone function. They constitute one of the most numerous and widespread families of natural plant phytoconstituents with more than 4,000 structures identified, and categorized into several classes, namely the six member containing form (pyrano-) including flavones, flavanols (catechins), flavanones, flavonols, isoflavones, anthocyanins, and procyanidins; the five member containing form (furano-) is represented by aurones. In addition to the open forms like chalcones and dihydrochalcones exist (Fig. 1) (Harborne and Grayer 1993; Andersen and Markham 2006).

Flavonoids are low-molecular-weight substances extracted from plants by various methods (Harborne and Grayer 1993; Andersen and Markham 2006). They have primarily been identified as pigments responsible for the autumnal shades (yellow, orange, and red) of many kinds of flowers and plants. Flavonols (quercetin, myricetin, and kaempferol) and flavones (apigenin and luteolin) are the most common phenolics in plant-based foods. Quercetin is a predominant component in onions, apples, and berries (Tereschuk et al. 2004). Flavonoids like the colorful anthocyanins are found in vegetables and fruits, such as red cabbage (McDougall et al. 2007) and red grapes (Orak 2007). They are also found in red wine phytochemicals (Perez-Magarino and Gonzalez-San Jose 2006; Cliff et al. 2007; Crozier et al. 2010). More colorful flavonoids are prominent components of citrus fruits and other food sources. Flavanones, like narrigin are typically present in citrus fruits, and flavanols, particularly catechin, are present as catechin gallate in beverages such as green or black tea (Amarowicz and Shahidi 1996; Armoskaite et al. 2011; Atoui et al. 2005; Gao et al. 2008) and red wine (Rosenkranz et al. 2002).

Flavonoids not only give to food its colors but play a crucial protective role in human health. Consequently, many structures are established as potential biologically active nutrients (Harborne and Grayer 1993; Andersen and Markham 2006; Martino 2000). They have also been credited with many diverse key functions in plant growth and development, including stress protection, reproduction, signaling, and protection from insect and mammalian consumption (Harborne and Grayer 1993; Andersen and Markham 2006). The daily intake of flavonoids in humans can reach an approximate value of 25 mg/day, an average amount which qualifies a pharmacological level to human body fluids and tissues, guaranteeing a good absorption from the gastrointestinal tract. In 1938, Szent-Gÿorgyi has first initiated the biological activity of flavonoids, in his study on citrus peel flavonoids which provide an efficient activity in preventing the capillary bleeding and fragility associated with scurvy (Tereschuk et al. 2004). Certain individual members of the flavonoid family displayed a multiplicity of biological activities, and therefore this most promising family of biologically active compounds becomes the key title of several recent research works. Among the authors, Morton et al. (2000) has published a review on distribution, bioavailability, and biological activity of the flavonoid compounds suggesting that they may have a physiological role as antioxidants.

Actually, it is accepted that natural flavonoids present in fruits and plant-derived-foods are relevant, not only for technological reasons and organoleptic properties, but also because of their potential health-promoting effects, as suggested by the available experimental and epidemiological data. Human trials on the antioxidant effects of beverages rich in such polyphenolic compounds, like red wine, fruit juice, and tea, have been limited and results are, at present, inconclusive. This fact is particularly due to poor inconvincible methodologies available to measure oxidative damage *in vivo*, and that is why still further research efforts are being required. The use of appropriate biomarkers of oxidant damage *in vivo* measure is primordial in order to prove that these compounds can be conclusively considered as dietary antioxidants with nutritional benefit. In contrast, the beneficial biological effects of these food components may be depicted by two of their characteristic properties, their

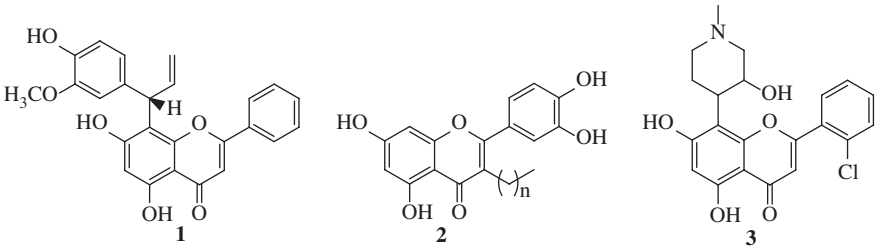


Fig. 2 Molecular structures of (7″*R*)-8-[1-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-yl]galangin **1**, 3-alkyl-3′,4′,5,7-tetrahydroxyflavones **2**, flavopiridol [2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-chromen-4-one] **3**

affinity for proteins and their antioxidant activity. Over the last 15 years, numerous publications have demonstrated that besides their *in vitro* antioxidant capacity (measured by DPPH, ORAC, and other techniques) (Salucci et al. 2002) and *in vivo* evaluation (Dai et al. 2004), certain flavonoids, such as anthocyanins, catechins, proanthocyanidins encountered in our daily food, may regulate different signaling pathways involved in cell survival, growth, and differentiation. These compounds act differently and selectively in various models as far as their antioxidant capacity is concerned, suggesting that multi-models should be utilized in order to evaluate an antioxidant from natural sources (de Pascual-Teresa et al. 2010).

Flavones (2-arylchromones) are a group of flavonoids which gained great attention over the last decade due to their potential biological and medicinal utilities. These compounds can be characterized as 'privileged structures' for their ability to interact with a number of different receptors in the body, thereby precipitating a wide range of biological responses (Verma and Pratap 2010). Among the naturally occurring flavones and their synthetic analogs, several derivatives displayed important biological properties, such as anticancer (Cummings et al. 1989; Cardenas et al. 2006; Lin et al. 2007; Zhu et al. 2007), anti-inflammatory (Park et al. 1999; Nagaoka et al. 2003; Moscatelli et al. 2006) and antioxidant (Beyer and Melzig 2003; Vaya et al. 2003) activities. These first promising results explain the increasing interest in this class of the most abundant naturally occurring compounds and the continuous isolation of new biologically active derivatives, such as (7″*R*)-8-[1-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-yl]galangin **1** having a cytotoxic activity against PANC-1 human pancreatic cancer cells (Li et al. 2010). Considerable attention was paid to the synthesis of flavone derivatives especially those with biological activity predictions, for instance, we underline some molecules like 3-alkyl-3′,4′,5,7-tetrahydroxyflavones **2** proved as potent active antioxidant evaluated in various biological systems, including *in vitro* assays (Filipe et al. 2009; Gomes et al. 2009b). Flavopiridol **3** shows a cyclin-dependent kinase inhibitory effect which is actually under phase II clinical trials for a number of different malignancies (Fig. 2) (Murthi et al. 2000; Kosmider and Osiecka 2004; Teillet et al. 2008; Ahmadi et al. 2009; Diaz-Padilla et al. 2009; Hallek and Pflug 2011).

2-Styrylchromones constitute a further important biological active chromone-based structure, but very scarce as naturally occurring compounds (Gomes et al. 2010).

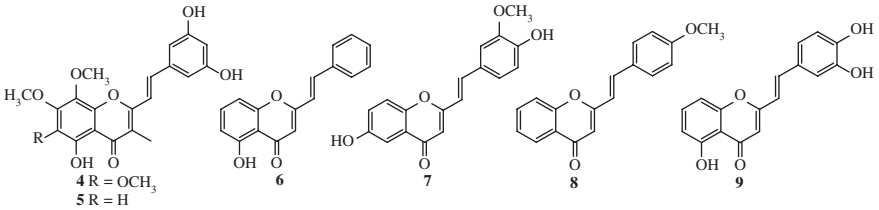
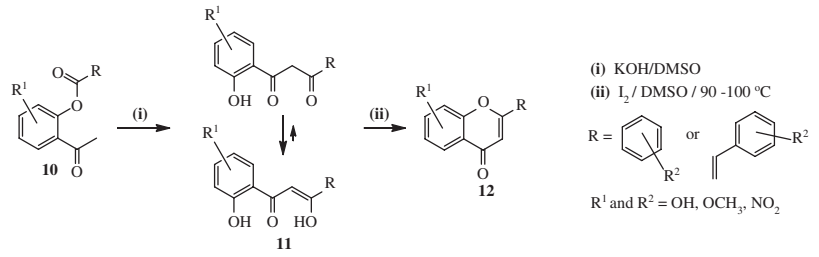


Fig. 3 Structures of hormothamnione **4**, 6-demethoxyhormothamnione **5**, (*E*)-5-hydroxy-2-styrylchromone **6**, (*E*)-6,4′-dihydroxy-3′-methoxy-2-styrylchromone **7**, (*E*)-3′methoxy-2-styrylchromone **8** and (*E*)-5,3′,4′-trihydroxy-2-styrylchromone **9**

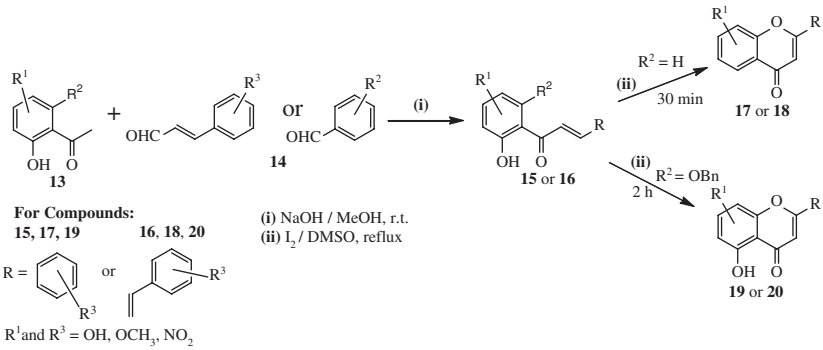
Only four derivatives have been isolated from nature, namely hormothamnione **4** and 6-demethoxyhormothamnione **5** from the marine blue-green algae *Chrysophaem taylori* (Gerwick et al. 1986; Gerwick 1989), (*E*)-5-hydroxy-2-styrylchromone **6** from the rhizomes of *Imperata cylindrical* (Yoon et al. 2006) and, more recently, (*E*)-6,4′-dihydroxy-3-methoxy-2-styrylchromone **7** isolated from the tree *Aquilaria sinensis* (Yang et al. 2012) (Fig. 3). Natural derivatives have only demonstrated cytotoxic activity against leukemia cells (Gerwick et al. 1986; Gerwick 1989) while a range of biological effects has been evidenced in synthetic derivatives, such as antiviral (Desideri et al. 2000), antitumor (Brion et al. 1991), antimitotic (Marinho et al. 2008), anti-inflammatory (Gomes et al. 2009a) and antioxidant (Gomes et al. 2007, 2008, 2010) activities. Some of the biologically active synthetic derivatives present simple structures; for example, the antimitotic (*E*)-4′-methoxy-2-styrylchromone **8** also considered as a potent anti-norovirus agent (Marinho et al. 2008), along with (*E*)-5-hydroxy-2-styrylchromone **6** (Rocha-Pereira et al. 2010). Moreover, 2-styrylchromones with a catechol pattern such as derivative **9**, present considerable anti-inflammatory and antioxidant activity (Fig. 3) (Gomes et al. 2007, 2008).

In light of the biological significance of the mentioned chromone-based compounds, many researchers dedicate their work to develop efficient synthetic methodologies for such compounds. The most used synthetic routes include the Baker–Venkataraman method and the cyclodehydrogenation of 2′-hydroxychalcones and 2′-hydroxycinnamylideneacetophenones.

The Baker–Venkataraman route is one of the oldest approaches drawn to the synthesis of flavone derivatives and still being one of the most used efficient routes for 2-styrylchromones production (Baker 1933; Mahal and Venkataraman 1934; Price et al. 1993; Silva et al. 2004; Pinto et al. 1998, 1999). It involves a three-step sequence where the final step consists in the cyclization of β-diketones **11** (obtained from ester **10** via Baker–Venkataraman rearrangement), which exists in equilibrium with its enolic form, into chromone derivatives **12**. Several conditions can be employed to perform this cyclization, mostly under acidic conditions. Extensive studies performed by Silva et al. indicate that molecular iodine leads to a successful manner of flavones and (*E*)-2-styrylchromones synthesis (Scheme 1) (Pinto et al. 2000a, b; Barros and Silva 2006, 2009).



Scheme 1 Synthesis of flavones (R = aryl) and (*E*)-2-styrylchromones (R = styryl) by the Baker–Venkataraman method



Scheme 2 Synthesis of flavones **17**, **19** and (*E*)-2-styrylchromones **18**, **20** by cyclodehydrogenation of the corresponding 2′-hydroxychalcones **15** and 2′-hydroxy-2-cinnamylideneacetophenones **16**

As mentioned previously, the oxidative ring closure of the appropriate 2′-hydroxychalcones and 2′-hydroxy-2-cinnamylideneacetophenones is another important well-documented approach toward flavones and (*E*)-2-styrylchromones synthesis. Various reagent systems are known for the oxidative cyclization of the 2′-hydroxychalcones **15** to the corresponding flavones **17**, namely disulfides (Hoshino et al. 1986), sodium periodate (Hans and Grover 1993), hypervalent iodine reagents (Gulacsi et al. 1998), DDQ (Chan et al. 2006), oxalic acid (Zambare et al. 2009), Wacker–Cook-related oxidation (Lorenz et al. 2010), and finally selenium dioxide (Gupta et al. 2000). Nevertheless, the use of molecular iodine/DMSO system seems to be more flexible for its lower toxicity and cost, leading to better yields and shorter reaction times. Further systematic studies have been conducted by Silva et al. disclosing scopes and limits of this method (Silva et al. 1997; Patonay et al. 1997). Yet, the most important aspect of their work was the successful application of this methodology to the synthesis of flavones **17** and (*E*)-2-styrylchromones **18**, via the oxidative ring closure of the 2′-hydroxychalcones **15** and 2′-hydroxy-2-cinnamylideneacetophenones **16** in 30 min. Also 5-hydroxyflavones **19** and (*E*)-5-hydroxy-2-styrylchromones **20** have been similarly produced but lasting a longer reaction time (Scheme 2) (Silva et al. 1994, 1998).

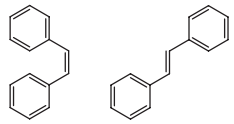
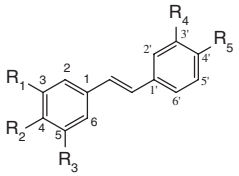


Fig. 4 Structures of stilbene diastereomers



21. $R^1 = R^3 = R^5 = OH$, $R^2 = R^4 = H$
22. $R^1 = R^3 = R^4 = R^5 = OH$, $R^2 = H$
23. $R^1 = R^4 = OH$, $R^2 = R^3 = R^5 = H$
24. $R^1 = R^2 = OH$, $R^3 = R^4 = R^5 = H$
25. $R^2 = R^5 = OH$, $R^1 = R^3 = R^4 = H$

Fig. 5 Resveratrol **21** and other biologically active synthetic stilbenes **22**–**25**

3 Stilbenes, Resveratrol, and More Active Synthetic Derivatives

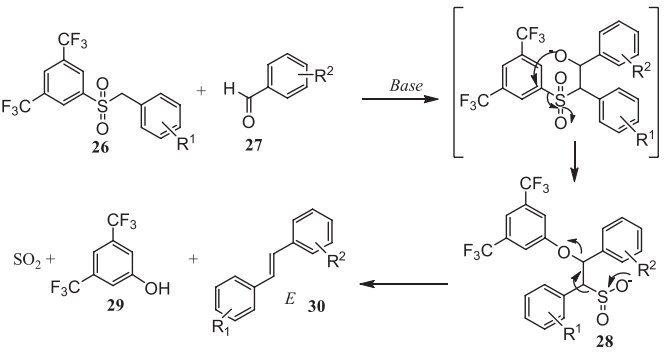
The stilbene skeleton consists in a C=C double bond linking two aromatic rings and presents two diastereomeric forms, *E*-1,2-diphenylethylene (*E*-stilbene) and *Z*-1,2-diphenylethylene (*Z*-stilbene) (Fig. 4). The name '*stilbene*' is also used to design the class of its poly-substituted hydroxy- and alkoxy-derivatives which are natural occurring phenolic compounds present in many families of plants. The most fascinating example is resveratrol **21** (Fig. 5), isolated from red fruits and different plants. Resveratrol (*Z*-3, 5, 4′-trihydroxystilbene) **21** is an abundant phytochemical of grape skins and therefore present in red wine (Likhtenshtein 2010). In the mid-1990s, resveratrol **21** was identified as one of the possible factors responsible for the "French Paradox". Numerous biomedical studies have been carried out on the pharmacological properties of **21** and its health benefits on humans. The discovery of David Sinclair's research group (Howitz et al. 2003; Wood et al. 2004) at Harvard University in 2003, that resveratrol **21** extends lifespan in yeast, was a step forward making resveratrol a sole biological active agent and chief leader of polyphenolic compounds. An overview of resveratrol **21** and its biological properties is presented in Sect. 4.1.4.

On the other side, the great attention devoted to resveratrol **21** due to its unique biological properties, does not really make it so exceptional because several of its synthetic analogs demonstrate better biological applications. Various operative challenges are faced in achieving the isolation of **21** in sufficient quantity from natural sources. Furthermore, its limited bioavailability in the blood circulation is seen as the main obstacle for therapeutic use. For such reasons, many researchers directed their attention toward the synthetic derivatives aiming the production of biologically more active agents. The elaboration of new stilbene derivatives was mainly based on modifying some structural features, for example, the number and position of the hydroxyl and other functional groups on the stilbene skeleton. Thakkar et al. was the first to describe the synthesis

of piceatannol **22** and other polyhydroxylated analogs, which presented antiproliferative action on leukemic cells. Other synthetic substituted (hydroxy, methoxy, fluoro) stilbenes have been evaluated on tumor cell lines [HCT-56 (colon), MDA-MB-468 (breast)], revealing better antiproliferative effect of the 3,3′-dihydroxystilbene **23** ($GI_{50} = 2.7$ μM) compared to resveratrol **21** ($GI_{50} = 41$ μM) (Fig. 5) (Thakkar et al. 1993). An established structure–antioxidant activity relationship of polyhydroxystilbenes showed great dependency on the number and relative position of their hydroxyl groups (Lion et al. 2005; Zhou and Liu 2005). Thus, 3,4-dihydroxystilbene **24** proves to have better antioxidant properties than *trans*-resveratrol **21**, however, in the stilbenes' case, the presence of a catechol moiety does not justify properly the antioxidant capacity of **24** since 4,4′-dihydroxystilbene **25** is even more powerful (Fig. 5). Besides, a clear observation was made on the presence of the *para*-hydroxyl function which greatly influences the antioxidant activity of stilbenes as confirmed by comparative results evaluated on the non-*para*-substituted derivatives (Fan et al. 2009; Petralia et al. 2004). Methoxy- and ethoxy-stilbenes have been tested on both NF-κB and TPA-induced activation of AP-1 pathways, revealing higher inhibitions than resveratrol **21**. In terms of structure–biological activity relationship, the absence of the *para*-hydroxyl function, in this case, does not explain the pro-apoptotic activity and its association with an inexistent antioxidant potential (Deck et al. 2008).

The construction of organic hybrids between resveratrol and other scaffolds consist of a new strategy toward new biological target design. As resveratrol **21** bioavailability is low in the organism and promptly metabolized, Hauss et al. (2007) focused on the increasing its presence in the blood circulation. Hence, the combination of the neuroregenerative properties of fatty alcohols with the neuroprotective properties of resveratrol **21** resulted in effective series of compounds with a dual biological activity and high metabolic resistance. The antiproliferative effects of phosphoric amino acids coupled to stilbenes were found 15 times more potent than **21**, as a result of CNE-1 and CNE-2 cell lines evaluation (Liu et al. 2008a). **21** was also functionalized by triphenylphosphonium iodide in order to confer a better solubility to the whole molecule in the mitochondrial medium and therefore a better inhibition of several tumor cell lines was observed (Biasutto et al. 2008). Resveratrol oligomers have been largely ignored despite their high biological activity. A recent report on a programmable, controlled, and potentially scalable synthesis of the resveratrol family via a three-stage design has been published (Snyder et al. 2011).

The C=C double bond of the stilbene skeleton is stabilized by conjugation electronic effects, making it more resistant to hydrolysis or other addition-type reaction and oxidative cleavages. Several strategies have been reported to build this relevant C=C double bond. The Julia olefination, for instance, is one of the C–C simple-bond formation reaction implicating the reaction of phenyl sulfones **26** with aldehydes (or ketones) **27** (Julia and Paris 1973). Under basic conditions, the obtained sulfinate **28** yield the alkene structure after a Smiles rearrangement and spontaneous reductive elimination of the phenolate **29** accompanied by sulfur



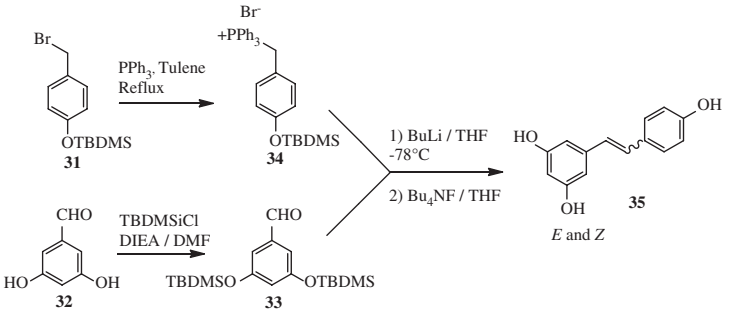
Scheme 3 Synthesis of stilbenes by the Julia olefination

dioxide release (Scheme 3). This transformation highly favors the formation of the *E*-alkene **30**. Thus different stilbenes have been diastereoselectively obtained by this method (Alonso et al. 2004).

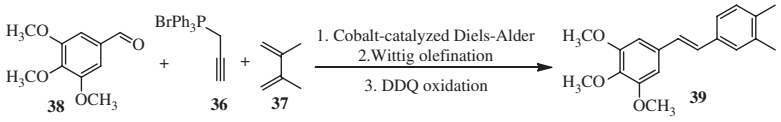
The Wittig reaction is largely known to produce a C=C double bond by coupling an aldehyde (or ketone) with a phosphorous ylide giving rise to an alkene and triphenylphosphine oxide. In this regard, stilbenes are usually synthesized via Wittig coupling reaction of aldehydes with substituted benzylic ylides, which tends to afford the thermodynamically stable *E*-products (Vedejs et al. 1993). The Wittig reaction is usually carried out in basic media, therefore, the presence of hydroxyl groups on both of the starting materials (aldehyde **33** and phosphine ylides **34**) can induce some problems due to the labile protons. In case of resveratrol **21** or similar bioactive polyhydroxylated derivatives (e.g., piceatannol **22**), the synthetic procedure start by an initial hydroxyl-protection step of the Wittig reaction partners **31**, **32** using appropriate protecting groups, such as methyl, trimethylsilyl, acetyl, etc. The required cleavage of these protecting groups at the end of the synthesis can cause some further problems. Pettit et al. have used *t*-butyldimethysilyl (TBDMS) as a protecting group (air-stable and easily cleaved with Bu_4NF) to achieve the production of a series of stilbenes **35** (mixture of separable *E* and *Z* isomers) (Scheme 4). These compounds have been assessed for their therapeutic effects in some cell line targets and allowed to establish a structure-activity relationship (Pettit et al. 1995, 2002). Interestingly, a set of antimicrobial resveratrol derivatives have also been elaborated using the Wittig olefination (Albert et al. 2011).

A multi-component strategy was developed by Hilt et al. involving a cobalt(I)-catalyzed Diels–Alder reaction of propargylic phosphonium salts **36** (or higher homologs) with 1,3-dienes **37** leading to dihydroaromatic phosphonium salt intermediates which underwent *in situ* a one-pot Wittig-type olefination reaction with aldehydes **38**. Subsequent oxidation led to stilbene-type products **39**. The semi-stabilized dihydroaromatic phosphonium ylides intermediates are predominantly leading to the *E*-configured products (Scheme 5) (Hilt and Hengst 2007).

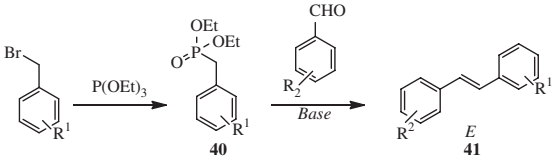
The Horner–Wadsworth–Emmons reaction is an alternative of the Wittig coupling reaction using stabilized phosphonate carbanions derived from **40** brought



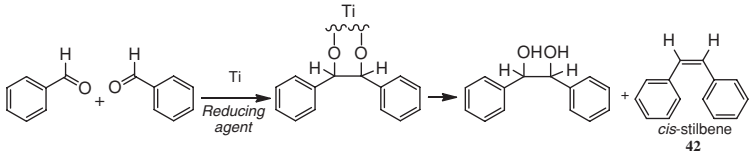
Scheme 4 Synthesis of stilbenes through the Wittig reaction



Scheme 5 A concise synthesis of substituted stilbenes by a cobalt(I)-catalyzed Diels-Alder/Wittig olefination reaction sequence starting from propargylic phosphonium salts



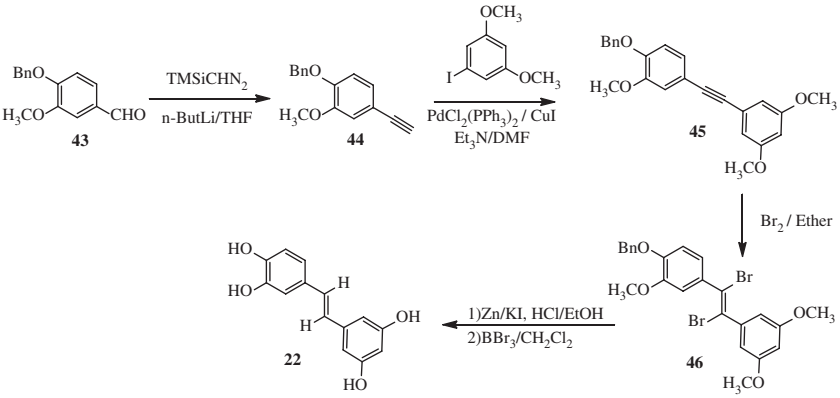
Scheme 6 Synthesis of stilbenes through the Horner–Wadsworth–Emmons reaction



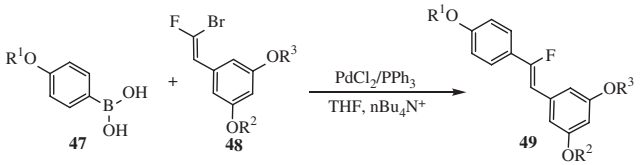
Scheme 7 Synthesis of stilbenes through the McMurry reaction

to react with aldehyde derivatives producing predominantly the *E*-alkenes **41** (Scheme 6). Due to this advantage, its application on the stilbene synthesis has been developed (Thakkar et al. 1993; Lion et al. 2005).

More C=C bond formation procedures have been used in the synthesis of stilbenes. In the McMurry reaction, two aromatic aldehydes or ketones are coupled to give the corresponding alkene using titanium(III) chloride and a reducing agent. The *Z*-stilbene skeleton **42** is predominantly obtained when coupling benzaldehyde derivatives using McMurry's conditions (Scheme 7) (McMurry and Fleming 1974; Rele et al. 2008).



Scheme 8 Synthesis of stilbenes involving a Sonogashira cross-coupling reaction

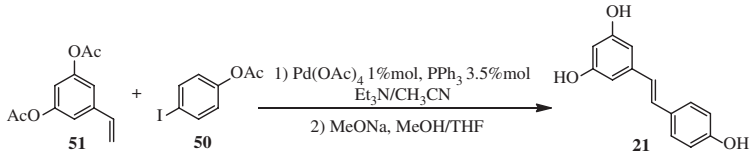


Scheme 9 Synthesis of stilbenes involving a Suzuki cross-coupling reaction

The Sonogashira cross-coupling reaction aims the formation of carbon–carbon bonds by the reaction of a terminal alkyne and an aryl or vinyl halide using a palladium catalyst. The resulting substituted alkyne is potential precursors for the synthesis of stilbenes. An example for the *E*-piceatannol **22** synthesis was described starting from vanillin. A one-step transformation of the *para*-protected-vanillin **43** to the corresponding terminal-alkyne **44**, was followed by the Sonogashira cross-coupling reaction with the appropriate 3,5-dimethoxyiodobenzene to afford the desired alkyne **45**. This latter compound was subjected to bromination to give selectively the *E*-dibromostilbene **46** and finally transformed to *E*-piceatannol **22** by a reductive debromination and deprotection of the phenolic functions (Scheme 8) (Han et al. 2008).

The Suzuki cross-coupling reaction is another palladium catalyzed transformation of aryl boronic acids **47** (or vinylboronic acids) into alkenes by reacting with vinyl halides **48** (or aryl halides). It is widely used to synthesize poly-olefins like styrenes **49** and substituted biphenyls, therefore, its application on the stilbene synthesis can be of a great interest. Some synthetic derivatives of resveratrol have been elaborated by this method (Scheme 9) (Eddarir et al. 2001).

The Heck reaction is another important synthetic access to substituted alkenes. It consists in the coupling of an aryl halide (or triflate) **50** with an alkene **51** catalyzed by palladium reagents under basic conditions. Comparing to the other



Scheme 10 Synthesis of stilbenes involving a Heck reaction

palladium-catalyzed cross-coupling reactions (Sonogashira and Suzuki), this reaction allows a concrete diastereoselective elaboration of resveratrol **21** (Scheme 10) (Guiso et al. 2002).

4 Nutritional Antioxidant Phenolic Compounds in Daily Life

Exceptive epidemiological studies agree that human diet rich in fruit, vegetables, and plant-derived foods decrease diseases incidence, like cardiovascular diseases (CVD) (Valko et al. 2007; de Pascual-Teresa et al. 2010; Loke et al. 2010; Berthelot-Garcias et al. 2009) diabetes (Ferruzzi 2010), cancer (Serafini 2004), and stroke (Bejot et al. 2009), which are the most common and the main worldwide death causes recorded in the past few years. According to some statistics of 2003, 44 % of worldwide deaths were related to acute myocardial infarction, 33 % to stroke, and 23 % to arterial hypertension or to other CVDs, such as pulmonary embolism and causes of heart failure. Age, male sex, smoking, increase in LDL-cholesterol, and type 2 diabetes, together with familial antecedents, lack of physical training, android obesity, and menopause are the main risk factors predisposed to CVD (Berthelot-Garcias et al. 2009).

Many reports associated the benefit of fruits, vegetables, and plants with their antioxidant polyphenolic content (Gerhaeuser 2001; Loke et al. 2010; Zloch 1996; Visioli et al. 2000). Polyphenolic compounds are ubiquitous in all plant organs and constitute, therefore, an integral part of the human diet. Despite their lifestyle and food fashion differences, most people have the tendency toward processed drinks and dairy products rather than taking raw fruits and vegetables. Many examples of our actual eating habits support this social observation, like the open day coffee or tea. Usually, lunch or dinner time is accompanied by wine, spirits, and beers, whereas at any time abnormal quantities of various attractive colored and tasty products are consumed like chocolates, cakes, and candies (Holdsworth 2008). In fact, although these products are submitted to food processing that definitely causes modifications in the initial raw material (for example, production of black tea, roasted coffee, matured wines, production of chocolate, jam, etc.,) (Ferruzzi 2010; Dominguez-Perles et al. 2011; Kaack and Christensen 2010; Nishiyama et al. 2010; Lee et al. 2008; Negukhula et al. 2011) they play an enormous role

as major human dietary polyphenolic sources. The daily intake of polyphenolic compounds (up to 1 g) has shown a relationship with reduced risk of CVDs and cancer prevention. Also, recent epidemiologic data further support the association of polyphenols to their antioxidant action but very restrictive and even without providing clear evidence of the contradictory properties of these compounds widely spread in our diet (Barbosa 2007; Galati and O'Brien 2004; Gerhaeuser 2001; Serafini 2004).

Polyphenolic compounds display multiple structure conditioned interactions with various biomolecules, namely the activity modulation of various enzyme systems. In the diet they act mostly as health promoting factors during various chemical and physical stresses of the organism. They are antiatherogenic and anticarcinogenic, on the principle of inhibition of oxidative destruction of various biological structures, inhibition of processes of bioactivation of carcinogens, blocking LDL oxidation, and stimulating the activity of antioxidant and detoxication enzymes. Some of them have shown some mutagenic properties in genotoxicity tests. However, results of animal experiments and epidemiological studies do not confirm the risk of neoplastic disease in subjects with a normal intake of these substances. The use of the health promoting properties of polyphenols isolated from plants and their administration in a pure state is not foreseen. However, under certain conditions it is desirable to increase the consumption of foods which are important sources of these substances (Zloch 1996).

Initially, the protective effect of dietary polyphenolic compounds was thought to be due to their antioxidant properties which result in a lowering of the free radicals levels within the body (Fernandez-Panchon et al. 2008). There is now emerging evidence that the metabolites of dietary polyphenolic compounds, which appear in the circulatory system in low concentrations, exert modulatory effects in cells through selective actions on different components of the intracellular signaling cascades vital for cellular functions, such as growth, proliferation, and apoptosis. In addition, the intracellular concentrations required to affect cell signaling pathways are considerably lower than those required to impact on antioxidant capacity (Crozier et al. 2009).

"An increased intake of dietary antioxidant polyphenols may protect against CVDs!" This possibility has always been considered in many research works due to the antioxidant property of polyphenols in one hand, and the oxidative events *in vivo* which may play a role in the pathogenesis of atherosclerosis in the other hand. In this regard, vitamins E and C are mostly known as potent antioxidant agents, while a slight to progressive knowledge has been reported about the similar antioxidant role of plant-derived polyphenolic compounds, especially, flavonoids and stilbenes. These two well-known families have been our previous case of discussion because of their bioavailability in our daily food. They are mostly reported to be members of red wines and teas compositions and therefore these common beverages should be exciting examples to be treated due to people's preferences. French Paradox at a relaxed tea time is a social circumstance that can be interpreted to a scientific dialogue on health promoting food and nutrition. The reader of this chapter can probably be without any tendency toward these two

popular beverages and, therefore, other tasty dietary sources are brought up in this subject in order to satisfy not only the food desire but also to enrich the scientific background.

4.1 A Red Wine Desire or in a Tea Mood?

At the pub, maybe the choice between ordering a cup of red wine or tea can be without great importance because this depends only on people's minds. However, in a bioanalytical laboratory, scientists cannot choose between them since both offer valuable phytochemical compositions taking into account their uncountable biological properties. In this part, a major discussion is presented on the French Paradox concept while having a relaxed tea time. These two popular beverages have been subjects of many recent works treating their health promotion and antioxidant effects, based on different new clinical trials and ancient epidemiological data. A knowledge update on the cardiovascular effects and cancer prevention of pure anthocyanins, proanthocyanidins, catechins, and stilbenes, as the main phytochemicals of red wine and tea, is being described. Basic information, some key molecule structures, *in vitro* and *in vivo* biological evaluation and clinical studies on both of the two beverages including their isolated phytochemicals are also indicated. The exceptional stilbene resveratrol **21** will take a great part of our discussion with an up-to-date overview on its biological manifestations contributing to the French Paradox explanation. Necessary data are mentioned in order to understand these polyphenols' role in reducing risk factors and preventing cardiovascular health problems through different aspects of their bioefficacy on vascular parameters such as platelet aggregation, atherosclerosis, antioxidant status (Sparwel et al. 2009; Cooper et al. 2004; de Lange et al. 2007) blood pressure (Kappagoda et al. 2000), inflammation, myocardial conditions, and whole-body metabolism (Dixon et al. 2002). Better designed clinical studies are strongly required to improve the current knowledge on the potential health benefits of these polyphenols on cardiovascular and metabolic health (Sun et al. 2002).

4.1.1 The French Paradox, History, and Actuality

An old friendship and cultural history are known between red wine and mankind dating back thousands of years. It was known and very common in many ancient civilizations having an important role in religions as well. For a long time, people admire drinking a lot of wine ignoring that its abuse has serious effects on physical and mental health and causes acute and chronic damage. But, in fact, light to moderate intake of red wine can be beneficial in healthy individuals, which was also observed in antiquity. Red wine was even used in ointments for its disinfectant effects and maybe due to its alcohol content (Feher et al. 2007). In the Muslim society, although drinking wine is absolutely inadmissible and considered a sin for

socio-religious reasons, a meaningful sentence in the Quran (the religious Islamic book) refers to its health effects on humans. The phenomena established in the French Paradox can also explain the positive effects of red wine, notably on high fatty diet French society. Behind these social, historical, and philosophical circumstances, enormous research efforts have been conducted toward a real scientific explanation.

The French Paradox was coined in the 1990s explaining the reason for the relatively low incidence of cardiovascular disease in the French population, despite a relatively high dietary intake of saturated fats. This was potentially attributable to moderate consumption of red wine (Lippi et al. 2010; Yoo et al. 2010). Statistical observations are leading to some explanations of the French Paradox (Bejot et al. 2009; Tunstall-Pedoe 2008). An evident inverse relationship between moderate wine consumption and coronary artery disease mortality was observed in France with an approximate mortality rate of 50 % compared to other European countries and the United States (Rosenkranz et al. 2002). Over the last 20 years, considerable amount of studies investigated the crucial biological actions and clinical associations of red wine consumption with cardiovascular disease and mortality. The putative cardioprotective effects of alcohol and other substances in alcoholic beverages have been discussed taking into account the French Paradox. Accordingly, our literature survey is quoting various hypotheses that explain the protective effects of moderate intake of red wine which offers a polyvalence of biological effects targeting all phases of the atherosclerotic process. Taking into account its polyphenolic profile, red wine favors a decrease of oxidative stress, enhance cholesterol efflux from vessel and inhibit lipoproteins LDL oxidation, macrophage cholesterol accumulation, and foam-cell formation (De Gaetano et al. 2005; Vidavalur et al. 2006; Zern and Fernandez 2005; Szmitko and Verma 2005; Raghava 1993; Howard et al. 2002; Shrikhande 2000) increase antioxidant capacity in humans (Logan et al. 2008; Pinzani et al. 2010; de Gaulejac et al. 1999) and reduce susceptibility of human plasma to lipid peroxidation (Barbaste et al. 2002; Belleville 2002). Red wine may also increase nitric oxide bioavailability, thereby antagonizing the development of endothelial dysfunction and improved endothelial function, decrease blood viscosity, improve insulin sensitivity, counteract platelet hyperactivity, inhibit platelet aggregation and platelet adhesion to fibrinogen-coated surfaces, and decrease plasma levels of von Willebrand factor, fibrinogen, and coagulation factor VII (Providencia 2006). Many reports also consider reactive oxygen species or free radical oxidations to be responsible for the accompanying disorders of most pathologies including CVDs, aging, and cancer. Hence, it is conceivable that natural plant metabolites such as polyphenols are likely to play an important role in ensuring this protection. Indeed, not only their presence, particularly high amounts and varieties in our daily food, especially in red wine, but also, their very potent antioxidant or radical scavenging properties are making polyphenols the best contributing for the paradoxical part of the French Paradox (Chong-Han 2010).

Some recent opinions are against the French Paradox concept since it was relatively observed that French coronary heart disease rates are not so low, nor

fat diet intake so high, nor the diet-heart concept so unique, as to support the French Paradox any further, except as cultural whimsy or a marketing stratagem (Ducimetière 2008). In fact, many other countries worldwide record low coronary heart disease rate as red wine consumption is not so popular. Overweight and increased cardiovascular mortality are some of the negative results attributed to red wine consumption and therefore, other opinions disagree totally with the idea of the healthy cup of red wine (Hu 2005). Of course, evidence is present for and against the French Paradox hypothesis, while strong epidemiological data favor the specific cardiovascular benefit of red wine which could at least explain it, while, epidemiological and mechanistic evidence proved that the alcohol intake is not without a degree of risk on healthy humans. More convincing evidence is that human studies with de-alcoholized red wine show short-term cardiovascular benefits. The specific components of the de-alcoholized wine that are active on cardiovascular endpoints are the polyphenols found in red wine (Vinson et al. 2001).

Further, Paradox states are linked to alcohol consumption, which, on one side, was associated with incidence of type 2 diabetes and cardiovascular disease in type 2 diabetes, while at the opposite side, a number of reports consistently suggest that the acute effect of alcohol induces a state of insulin resistance and improvement in insulin sensitivity (Zilkens and Puddey 2003). Difficulties are encountered to explain the effect of alcohol on risk factors associated with CVDs by a uniform biochemical mechanism. Moreover, its protective effects are counterbalanced by its addictive properties (Barbaste et al. 2002; Belleville 2002; Brenner et al. 2001; Iijima et al. 2000, 2002).

Although the majority of the scientific reports are in favor of beneficial cardiovascular effects related to the moderate red wine consumption, no one has yet considered the limit scale of red wine consumption for healthy individuals (Lippi et al. 2010). The limit line between ‘moderate’ and ‘excessive’ consumption is literary understandable but since red wine displays positive and negative effects, this limit line becomes a mathematical equation to be solved in order to determine whether or not one cup (or more, or less) is the appropriate amount for healthy people (Mudry 2010; Goldfinger 2003). In connection, Cordova et al. suggested to prescribe one or two drinks of red wine every day with meals for patients. This may translate to a longer, healthier, and better quality of life (Cordova and Sumpio 2009). This scientific prescription was based on the polyphenolic compounds responsible for these biological effects, including flavonoids and stilbenes, which are more abundant in red wine than in other beverages. However, this conclusion seems to be premature because no significant bioactive evidence of wine polyphenols has been shown in humans so far. Available data, justify the results of reduced cardiovascular risk and moderate consumption of red wine, but it was also associated with detrimental effects in pregnant women, in children, and in patients with various organic diseases, particularly hepatic, as well as in the case of regular administration of certain medicines (Feher et al. 2007; van de Wiel and de Lange 2008). International comparisons, starting from 1819, shows that a cup of red wine has a main role on individual’s health without ignoring that a bottle should not be healthier (Yoo et al. 2010;

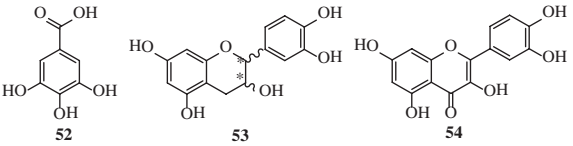


Fig. 6 Structure of gallic acid **52**, catechin base-structure **53**, and quercetin **54**

Chetreanu and Iliescu 2009). The French Paradox may have its basis within a milieu containing several key molecules exhibiting several biological actions coupled with probable or visible side effects. That is why its favorable cardiovascular benefits might be attributable to combined, additive, or perhaps synergistic effects of ethanol and other wine ingredients such as resveratrol **21**.

We have generalized the beneficial actions related to red wine as a whole beverage, but in fact a cup of red wine is composed of several individual components and each of the component display its specific biological role. *In vivo* evidences of red wine isolated and purified products have only been recently published consisting of a new background which may help to a better understanding of the French Paradox.

The oxidation of human Low Density Lipoproteins (or LDL) is responsible for atherosclerosis and arterial damage increase. In fact, molecules absorption through cell membrane (such as LDL and other proteins) has to be strictly regulated. This process known as endocytosis used by all cells of the body, can be enhanced in case of oxidised LDL which are not capable to pass through the hydrophobic plasma or cell membrane and cause accumulations in favor of atheroma and platelet aggregates formation. These are considered as primary risk factors of cardiovascular complications (Berthelot-Garcias et al. 2009; Zern and Fernandez 2005; Raghava 1993). Lectin-like oxidized LDL receptor-1 (LOX-1) is an endothelial receptor for oxidized LDL (ox-LDL) and plays multiple roles in the development of cardiovascular diseases. A chronic administration of purified oligomeric procyanidins from grapes and apples inhibit lipid accumulation in vascular wall in hypertensive rats fed with high fat diet. These results show the selective LOX-1 inhibition by procyanidins but not any other polyphenols (Howard et al. 2002; Nishizuka et al. 2011). This potent inhibition capacity can be particular evidence underlying the mechanism of the vascular action of red wine procyanidins as derived from red grapes.

Actual findings attribute the low incidence of cardiovascular disorders especially in Mediterranean countries to the antioxidant capacity of red wine polyphenols. Conceivably, other anti-inflammatory pathways may contribute to at least a similar extent to the atheroprotective activity of these polyphenols. Investigations have confirmed that gallic acid **52** (Fig. 6), an abundant red wine polyphenol, modulates the activity of P-selectin, an adhesion molecule that is critically involved in the recruitment of inflammatory cells to the vessel wall and thus in atherosclerosis, by binding and antagonizing this protein (Appeldoorn et al. 2005).

The protective effect of red wine on thrombosis is clinical evidence toward the concept of the French Paradox. Alcohol-free red wine supplementation almost completely reverted the prothrombotic effect of the cholesterol-rich-diet in

experimental animals, supporting the concept of the French Paradox that regular consumption of wine (rather than alcohol) was able to prevent arterial thrombosis associated with dietary-induced hypercholesterolemia, an effect mediated by down regulation of platelet function (De Curtis et al. 2005).

Rosenkranz et al., have comparatively demonstrated that pre-incubation of vascular smooth muscle cells (VSMCs) with red wine, but not white wine, inhibits ligand binding and the subsequent tyrosine phosphorylation of the platelet-derived growth factor beta receptor (beta-PDGFR), which plays a critical role in the pathogenesis of atherosclerosis. Analytical data revealed flavonoids of the catechin base-structure **53** (Fig. 6) as major constituents of red wine and potent inhibitors of beta-PDGFR signaling. Importantly, the concentrations of red wine/catechins necessary to inhibit the PDGFR *in vitro* correlate with the serum levels after red wine consumption in humans. It was then concluded that non-alcoholic constituents of red wine, which accumulate during the mash fermentation, inhibit beta-PDGFR activation and PDGF-dependent cellular responses in VSMCs. Hence, catechin-mediated inhibition of beta-PDGFR signaling constitutes one of the molecular explanations for the French Paradox (Rosenkranz et al. 2002).

Several animal and epidemiological studies suggest that red wine polyphenol constituents possess antioxidant activities that favor protection against cardiovascular and, probably, central nervous system disorders, such as Alzheimer's disease (AD) and ischemia. Bastianetto et al. studied the potential of the three major red wine derived-polyphenols resveratrol **21**, quercetin **54**, and (+)-catechin **53** to protect cultured rat hippocampus cells against toxicity induced by the nitric oxide free radical donors, sodium nitroprusside (SNP), and 3-morpholinosydnonimine (SIN-1) (Bastianetto et al. 2000). Among the phenolic compounds tested, only the flavonoids afforded significant protection against SIN-1-induced toxicity (5 mM). The effects of phenolic constituents were shared by Trolox (100 μM), a vitamin E analog, but not by selective inhibitors of cyclooxygenases (COX) and lipoxygenases (LOX). These results suggest that the neuroprotective abilities of quercetin **54**, resveratrol **21**, and (+)-catechin **53** result from their antioxidant properties rather than from their supposed inhibitory effects on intracellular enzymes such as COX, LOX, or nitric oxide synthase. Quercetin **54** (Fig. 6), however, may also act via protein kinase C (PKC) to produce its protective effects (Bastianetto et al. 2000; Rendig et al. 2001).

Rabai et al. (2010) showed that red wine and alcohol-free red wine have some beneficial effects on hemorheological parameters. These effects may play a role in the pathophysiology of the French Paradox regarding the cardiovascular protective impacts of red wine. The opening of mitochondrial KATP channels was obtained by a non-alcoholic red wine extract in guinea pigs, Therefore, this effect was prevented by the mitochondrial KATP channel blocker 5-hydroxydecanoate, confirming this subcellular mechanism as underlying the French Paradox (Aiello and Cingolani 2011).

A recent report demonstrated that red wine anthocyanins are rapidly absorbed in humans and affect monocyte chemoattractant protein 1 levels and antioxidant capacity of plasma (Garcia-Alonso et al. 2009). These interesting red wine phytochemicals have been previously proved to have a great participation in the whole antioxidant activity (Rivero-Perez et al. 2008).

4.1.2 The Tea Society

Diseases incidence and diet modes are geographically distributed in the world. We always focus on the diet mode of a population in order to explain certain low rate disease incidences in specific geographical parts. A similar situation, like in France, can be observed in countries like China, India, and most of Middle East Arabian countries, in which, the cancer incidence is relatively low comparing to the Europe and Western countries. If we want to mimic the French Paradox, in this case, the cup of tea replaces red wine. Tea drinks are diverse and very popular in the world, usually prepared by infusion of different tea herbs; green and black teas (*Camellia sinensis* family: (L.) Kuntze *Theaceae*) (Dominguez-Perles et al. 2011; Yao et al. 2006; Wang and Ho 2009). A wide occurrence of structurally diverse polyphenols is known throughout the plant kingdom. Recent interest on tea varieties from different geographical parts has increased greatly because of the antioxidant and free radical-scavenging abilities associated with some phenolics and their potential effects on human health (Armoskaite et al. 2011; Atoui et al. 2005; Black et al. 2011; Wu et al. 2010; Thuong et al. 2009; Terasawa and Yamazaki 2002; Viveros-Valdez et al. 2008; Jayasekera et al. 2011; Nuengchamnong et al. 2011; Omar et al. 2011; Wu et al. 2012; Etoh et al. 2004; Komes et al. 2010; Lee et al. 2006; Liu et al. 2009; Zhu et al. 2002; Unachukwu et al. 2010; Rechner et al. 2002; Rusak et al. 2008; Su et al. 2007; de Mejia et al. 2010; McKay and Blumberg 2006; Kulisic-Bilusic et al. 2008; Dominguez-Perles et al. 2012; Fale et al. 2011; Banerjee et al. 2010; AlGamdi et al. 2011; Ariffin et al. 2011; Bueyuekbalci and El 2008; Chen et al. 2012).

Catechins are the major class of polyphenols found in great amounts in green tea and, therefore, a scientific attention was paid to the regular consumption of green tea and its relation with atherosclerosis and cancer prevention (Salucci et al. 2002; de Mejia et al. 2010; Ishii et al. 2010; Carvalho et al. 2010). Green tea polyphenols have been proposed to exert protective effects against several types of cancer, based on preclinical and clinical trial data. Green tea extracts strongly inhibited the growth of renal carcinoma cell lines in a concentration-dependent manner. This is the first report showing that green tea is likely to be an effective anticancer agent for renal cell carcinoma (Carvalho et al. 2010). Tea catechins and tea catechin metabolites/catabolites are bioavailable in the systemic circulation after oral intake of green tea or green tea catechins. The metabolites/catabolites identified in humans include glucuronide/sulfate conjugates, methylated tea catechin conjugates, and microflora-mediated ring fission products and phenolic acid catabolites. Plasma levels of unchanged tea catechins in humans are mostly in the sub-μM or nM concentration range, which is much lower than the effective concentrations determined in most *in vitro* studies. However, some of the catechin metabolites/catabolites are present in the systemic circulation at levels much higher than those of the parent catechins. The contribution of catechin derived metabolites/catabolites to the biological effects associated with green tea is not yet defined. A limited number of chemoprevention trials of green tea or green tea catechins have been conducted to date and have shown potential preventive activity for oral, prostate, and colorectal cancer (Chow and Hakim 2011).

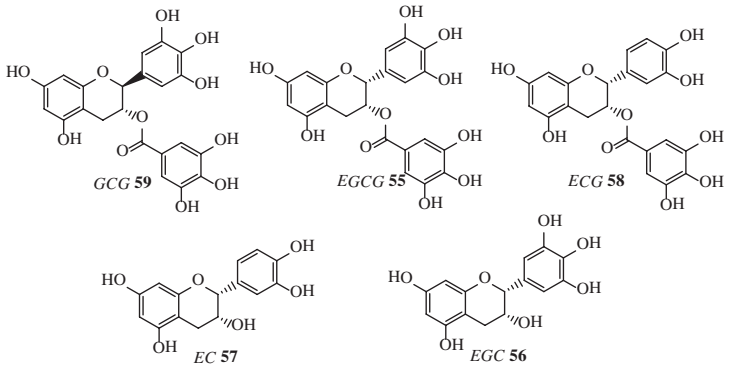


Fig. 7 Structures of catechin derivatives found in tea

The amounts of phenolics and flavonoid in the herbal green tea infusions were highly correlated with their anti-glycation activity (Bueyuekbalci and El 2008; Azevedo et al. 2011; Ho et al. 2010; Ankolekar et al. 2011). Thus, these compounds, like other that inhibit the formation of advanced glycation end-products, are supposed to have therapeutic potentials in patients with diabetes or age-related diseases.

Green tea might also be utilized as a natural antimicrobial agent to inactivate *Vibrio parahaemolyticus* in oysters and extend the shelf life during refrigeration storage (Xi et al. 2012). The green tea polyphenolic compounds treatment may be a useful method for preserving the human saphenous vein and could be exploited to craft strategies for the long-term preservation of other tissues under physiological conditions (Han et al. 2005). The ingestion of either green tea or black tea results in a major increase in the excretion of hippuric acid into urine (Mulder et al. 2005). Both black and green tea extracts may have synergistic or antagonistic effects on certain anti-streptococcal antibiotics. These effects are more prominent with black tea (Neyestani et al. 2007). Also, black tea extract has selective pro-inflammatory cytokine-suppressing effects on human peripheral blood mononuclear cells (Neyestani et al. 2009). Phytochemicals from Chinese herb teas showed antioxidant activity and inhibition of hepatoma cell proliferation *in vitro* assays, exhibiting a great potential as new nutraceutical agents (Li et al. 2009).

Besides their flavor fingerprint composed of terpenoids (Pripdeevech and Machan 2011) many kinds of teas display a variety of antioxidant flavonoids, especially, the flavanol subclass represented by catechins, namely epigallocatechin gallate (EGCG) **55**, epigallocatechin (EGC) **56**, epicatechin (EC) **57**, epicatechin gallate (ECG) **58**, and gallocatechin gallate (GCG) **59** (Fig. 7) (Amarowicz and Shahidi 1996; Williamson et al. 2011; Wu et al. 2011; Song et al. 2011; Dalluge and Nelson 2000; Karori et al. 2007; Kodama et al. 2010; Zuo et al. 2002; Zhu et al. 2009; Galati et al. 2006). According to a new phytochemical report on

Taiwan's teas (Wu et al. 2011; Wang et al. 2006) green tea drinks are found to contain the highest level of these major components comparing to other types, like oolong and black teas. The scavenging abilities against l,l-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radicals, used to determine the antioxidant potential of tea drinks, resulting in a higher free radical scavenging activity of the green tea. Total phenolics, total catechins, and EGC **56** of tea drinks were positively and significantly correlated ($r > 0.8$) to the scavenging abilities against DPPH and ABTS radicals (Wu et al. 2011). Total antioxidant capacities of herbal green tea extracts were further confirmed by other different assays including, trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) (Tsai et al. 2008). Complimentary studies suggest that iron may modify the antioxidant properties of phenolic compounds when adding to green tea, being noticed a decrease of its antioxidant capacity in rats after an oral dose of the mixture. However, further studies on the effect of iron on the bioavailability and the antioxidant capacity of phenolic compounds are required (Kapsokefalou et al. 2006).

Further recent knowledge was published on the antioxidant capability of green tea polyphenols, underlying the mechanism of antioxidant antagonism in peroxidising liposomes with β-carotene radical cation addition. The previously mentioned green tea catechins, including EC, EGC, ECG, and EGCG, all showed antioxidant effect in liposomes for lipid oxidation initiated in the lipid phase (antioxidant efficiency EC > EGCG > ECG > EGC) or in the aqueous phase (EC ≫ EGC > EGCG > ECG) as monitored by the formation of conjugated dienes. For initiation in the lipid phase, it is suggested that the β-carotene radical cation is rather reacting with the tea polyphenols through addition, in effect preventing regeneration of β-carotene as an active lipid phase antioxidant and leading to the observed antagonism with the polyphenols (EC > ECG > EGCG > EGC) (Song et al. 2011).

Tea phenolic acids along with the some previously highlighted catechins containing gallic acid moieties display further medical benefits. The cytotoxicity of these tea phenolic components toward isolated rat hepatocytes have been evaluated (epigallocatechin-3-gallate > propyl gallate > epicatechin-3-gallate > gallic acid, epigallocatechin > epicatechin). Using gallic acid as a model tea phenolic and comparing it with the tea catechins and gallic acid-derivative food supplements, the major cytotoxic mechanism found with hepatocytes was mitochondrial membrane potential collapse and ROS formation. Epigallocatechin-3-gallate was the most effective at collapsing the mitochondrial membrane potential and inducing ROS formation. Liver injury was also observed *in vivo* when these tea phenolics were administered into mice. In contrast, GSH conjugation, methylation, metabolism by NAD(P)H:quinone oxidoreductase 1, and formation of an iron complex were important in detoxifying the gallic acid (Galati et al. 2006).

Green and black tea have been considered as candidates for a chemopreventive evaluation in prostate cancer due to their valuable antioxidant activity. The polyphenol compositions of green and black tea are different due to post-harvest

processing. As far as green tea contains higher concentrations of monomeric polyphenols (catechins), it affects numerous intracellular signaling pathways involving prostate cancer (CaP) development. Black tea polymeric polyphenols, on the other hand, are poorly absorbed and are converted to phenolic acids by the colonic microflora. Therefore, after consumption of green tea, higher concentrations of polyphenols are found in the circulation, whereas in the case of black tea consumption, the phenolic acid levels in the circulation are higher. The majority of *in vitro* cell culture, *in vivo* animal, and clinical intervention tests of green tea extracts (or purified EGCG) on prostate carcinogenesis, provide strong evidence supporting a chemopreventive effect of green tea. While the evidence for a chemopreventive effect of black tea is much weaker, there are several animal black tea intervention studies demonstrating the inhibition of CaP growth (Henning et al. 2011).

Olech et al. (2012) demonstrated that *Rosa rugosa* Thunb. teas possess high antiradical activity and their polyphenols constituents showed a considerable impact in the anticancer activities against ovarian (TOV-112D), cervical (HeLa), breast (T47D), and lung cancer (A549) cell lines.

First convincing evidence showed that green tea polyphenols are effective in reducing tributyltin (TBT)-induced oxidative damage both *in vivo* and *in vitro*. The possible protective mechanism may be due to the powerful ability of polyphenols to scavenge ROS, nitric oxide and prevent DNA breaks (Liu et al. 2008b; Tsai et al. 2007). Thus, green tea could be an effective agent or food supplement to reduce the cytotoxicity of TBT (Liu et al. 2008b). Further studies reveal that tea polyphenols are able to act as pro-oxidants to cause a response to oxidative stress in yeasts under certain conditions (Maeta et al. 2007).

Anti-cholinesterase and antioxidant active constituents of *Plectranthus barbatus* Andrews (Indian coleus) aqueous extract were found in plasma of rats after its administration. The *Plectranthus barbatus* Andrews herbal tea extract components also inhibit lysozyme activity with IC_{50} values around 100 μM. This inhibition activity may be an additional mechanism for the anti-inflammatory activity of their polyphenolic constituents (Fale et al. 2011).

According to a recent pharmacokinetic study on healthy humans, a consumption of an average cup of green tea (200 mL) containing 112 mg of (−)-epigallocatechin gallate **55**, 51 mg of EGC **56** and 15 mg of EC **57**, gave rise to predicted C_{max} values (total free and sulfate/glucuronide conjugates) in plasma of 125, 181, and 76 nM, respectively, together with 94 nM methyl-EGC and 51 nM methyl-EC. Most studies with chlorogenic acids report a very low amount of intact molecules in plasma (Williamson et al. 2011).

Interestingly, the methanol extract of fresh tea leaves of *Camellia sinensis* (L.) Kuntze (Theaceae) inhibited enzymes with hydrolytic activity in snake [*Naja naja kaouthia* (L.) Kuntze (Elapidae) and *Calloselasma rhodostoma K.* (Viperidae)] venoms, by *in vitro* neutralization and *in vivo* inhibition of the hemorrhagic and the dermonecrotic activities. These snake venom enzymes are responsible for the early effects of envenomation, such as local tissue damage and inflammation. It is suggested that the inhibitory potential of the *Camellia*

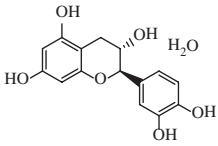


Fig. 8 Structure of catechin hydrate **60**

sinensis (L.) Kuntze extract against local tissue damage induced by snake venom may be attributed to complexation between the venom proteins and the phenolic contents of the extract (Pithayanukul et al. 2010).

4.1.3 Tea and Red Wine Common Factors

Several common biological activities approved for both red wine and tea may be due to their similar polyphenolic background. Catechin hydrate **60** (Fig. 8), a strong antioxidant that scavenges free radicals, is evidenced as an abundant phyto-constituent of both green tea and red wine. Catechin hydrate **60** possesses anticancer potential and effectively kills 100 % MCF-7 cells after 72 h of exposure, inducing apoptosis, which was confirmed by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) and real-time PCR assays. The induction of apoptosis by catechins hydrate is affected by its ability to increase the expression of pro-apoptotic genes such as caspase-3, -8, and -9 and TP53 (Alshatwi 2010).

Moreover, a comparative study shows that water extracts of black tea had the highest α-glucosidase inhibitory activity than several selected red wines. The α-glucosidase inhibitory activity of the examined teas and wines correlated with the phenolic content, antioxidant activity, and phenolic profile of the extracts (Kwon et al. 2008).

Dietary polyphenols in teas and wines have been associated with beneficial health effects. After ingestion, most polyphenols are metabolized by the colonic microbiota to a limited number of key metabolites. The metabolic profile depends on the individual and on the polyphenol sources. Varying metabolite pathways among individuals result in different metabolome profiles and therefore related health effects are hypothesized to differ between subjects (Gross et al. 2010; Roowi et al. 2010).

4.1.4 Resveratrol, the Difference Between Red Wine and Tea

Polyphenols, among them resveratrol **21**, have generated a great amount of scientific interests due to its *in vivo* and *in vitro* antioxidant capabilities. Since **21** has been evidenced in red wine, the birth of a new French Paradox key molecule has been noticed (Zhuang et al. 2003; Gusman et al. 2001; De Leiris and Boucher 2008; Das and Das 2007). The efficient *in vitro* cardioprotection effect and *in vivo*

on different animal models of **21** have been well documented (Zhuang et al. 2003; Liu et al. 2007). For the last few years, an outstanding focus on the therapeutic properties of **21** has been reported describing its antioxidant actions on one hand and its selectivity to some cell-targets on the other hand (Nikolova 2007; Poussier et al. 2005).

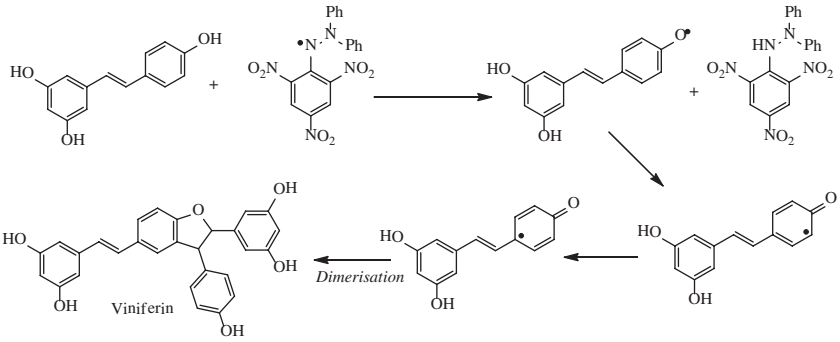
Resveratrol **21** is present in grapevine as constitutive compound of the woody organs, and as induced substance in leaves and fruit acting like phytoalexin in the mechanisms of grapevine resistance toward some pathogens (Bavaresco et al. 2000). As the main ingredient of red wine was thought to be its active principle involved in heart diseases prevention, it can reduce ischemic damage in heart ischemia reperfusion injury and also in brain ischemia/reperfusion in rodent models. Most of the protective biological actions associated with **21** have been associated with its intrinsic radical scavenger properties. It was shown that it exerts neuroprotective actions on primary neuronal cultures (Zhuang et al. 2003). It is a potent peroxidase-dependent mechanism-based inactivator of COX-1, a desired target for antiplatelet agents, but no similar effects have been noticed on COX-2. These findings imply that resveratrol **21** is not the sole agent responsible for the antiplatelet activity of red wine and suggest that all dietary meta-hydroquinones should be examined for cardioprotective effects (Szewczuk and Penning 2004).

A growing body of evidence supports the protecting role of resveratrol **21** in the cardiovascular system in a multidimensional way. The most important point is that at a very low concentration it inhibits apoptotic cell death, thereby providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis, and ventricular arrhythmias. **21** when used at higher doses facilitates apoptotic cell death and behaves as a chemopreventive alternative (Das and Das 2007).

In vivo animal tests of daily oral administration demonstrate that resveratrol **21** failed to protect against environmental tobacco smoke (ETS) exposure impaired endothelial function and increased oxidative stress, which was associated with pulmonary and systemic inflammation, in juvenile male pigs. However, it exerted a positive effect on left ventricular function which may help explain the French Paradox (Al-Dissi and Weber 2011).

A number of resveratrol **21** valuable properties have been attributed to its intrinsic antioxidant capabilities, although their potential level in the circulation is likely not enough to neutralize free radical scavenging. The brain and the heart are uniquely vulnerable to hypoxic conditions and oxidative stress injuries. Increased heme oxygenase activity, stimulated by resveratrol **21,** has led to significant protection against models of *in vitro* and *in vivo* oxidative stress injury (Dore 2005).

Resveratrol **21** acts as reactive oxygen species inhibitor, which together with the accumulation of the reactive oxygen intermediate (ROI) produced from cell antioxidant self-defense (enzymes), are also responsible for cell tissue damage, aging, and carcinogenesis. ROS and ROI lead to oxidative stress phenomena responsible for the development of cardiovascular diseases and oxidation of different macromolecules (DNA, lipids, and proteins) (Alcaraz et al. 2009). **21** is



Scheme 11 DPPH radical-induced dimerization of trans-resveratrol

transformed itself into a stabilized free radical upon reacting with DPPH radical leading to viniferin dimer (Scheme 11) (Wang et al. 1999).

Oxidative stress can also decrease the bioavailability of nitric oxide radical in vessels, which is highly associated with endothelial dysfunction. One of the mechanisms involved in beneficial effects of **21,** is its capacity to maintain sufficient nitric oxide radical bioavailability in vascular endothelium (Frombaum et al. 2012).

A huge amount of studies have shown that phenolic compounds contained in red wine inhibit the susceptibility of low-density lipoproteins (LDLs) to oxidation, thereby potentially reducing their atherogenicity (Iijima et al. 2000, 2002). The effects of **21** on isolated tissues or organs are well described and include molecular mechanisms leading to decrease arterial damage, decrease activity of angiotensin-II, increase nitric oxide, and decrease platelet aggregation. Anti-ischemic effects include stimulation of prosurvival paths, decrease LDL-oxidation, atheroma, and on the ischemic-beneficial metabolic changes. Most recently, the agonist effect of **21** on the anti-senescence factor sirtuin has lessened cell death in myocytes from failing hearts. Mechanistic feasibility strengthens the case for prospective therapeutic trials of alcohol *vs* red wine *vs* resveratrol, for example in those with heart failure (Opie and Lecour 2007).

Recently, **21** was discovered to be a putative activator of SIRT1 which can partially mimic the physiological effects of calorie restriction, such as the life span extension of model organisms. It is important to notice that SIRT1 activation is a promising new therapeutic approach for treating diseases of aging such as type 2 diabetes (Hu et al. 2011; Lekli et al. 2010).

4.2 Polyphenols from Other Tasty Sources

Few people do not like it, other few people like but avoid it, however most people adore chocolate. It was only recently published that cocoa-derived

products (dark chocolate, milk chocolate, and cocoa powder) are great sources of polyphenols particularly, catechins (flavan-3-ols), and procyanidins. However, the data vary remarkably due to the quantity of cocoa liquor used in the recipe of the cocoa products but also due to the analytical procedure employed. In 1994, the per head consumption of chocolate and chocolate confectionery in the European Union ranged from 1.3 kg/year in Portugal to 8.8 kg/year in Germany. In general, consumers in the northern countries consume on average more than people in the south. Thus, chocolate can be seen as a relevant source for phenolic antioxidants for some European populations. However, this alone does not imply that chocolate could be beneficial to human health. Some epidemiological evidence suggests a beneficial effect to human health by following a polyphenol-rich diet, namely rich in fruits and vegetables and to a less obvious extent an intake of tea and wine having a similar polyphenol composition as cocoa. In many experiments cellular targets have been identified and molecular mechanisms of disease prevention proposed, in particular for the prevention of cancer and cardiovascular diseases as well as for alleviating the response to inflammation reactions. However, it has to be demonstrated whether polyphenols exert these effects *in vivo*.

One prerequisite is that the polyphenols are absorbed from the diet. For monomeric flavonoids such as the catechins, there is increasing evidence for their absorption, while for complex phenols and tannins (procyanidins) these questions have to be addressed for the future. Another open question is related to polyphenol metabolism. For example, much effort has been invested to show antioxidant effects of free unbound polyphenols, especially of catechins and the flavonol quercetin. However, only a very small part can be found in plasma in the free form, but they occur as conjugated or even metabolized to several phenolic acids and other ring scission products. From the papers reviewed, it is too early to give an answer to the question, whether chocolate and/or other sources rich in catechins and procyanidins are beneficial to human health. Even though some data are promising and justify further research in the field, it has to be shown in future whether the intake of these functional compounds and/or their sources is related to measurable effects on human health and/or the development of diseases (Wollgast and Anklam 2000).

Flavanol-rich foods, i.e., wines, chocolates, and teas, and of purified flavonoids inhibited angiotensin converting enzyme (ACE) activity; red wines being more effective than white wine, and green tea more effective than black tea. When isolated polyphenols were assayed, procyanidins (dimer and hexamer) and epigallocatechin significantly inhibited enzyme activity. Similar concentrations of (+)-catechin (−)-epicatechin, gallic acid, chlorogenic acid, caffeic acid, quercetin, kaempferol, and resveratrol were ineffective. The ACE inhibition activity of rat kidney membranes in the presence of chocolate extracts or purified procyanidins depend on the chocolate content of flavanols and the number of flavanol units constituting the procyanidin. These experiments demonstrate that flavanols either isolated or present in foods could inhibit ACE activity. The occurrence of such inhibition *in vivo* needs to be determined, although it is

supported by the association between the consumption of flavanol-rich foods and reductions in blood pressure observed in several experimental models (Actis-Goretta et al. 2006).

Lee et al. prefer cocoa, not for the delicious taste of chocolate, but in fact, for its high phenolic content and higher antioxidant capacity than teas and red wine. A comparative report between phenolic and flavonoid contents and total antioxidant capacities of cocoa, black tea, green tea, and red wine revealed that the cocoa contained much higher levels of total phenolics and flavonoids. Cocoa exhibited the highest antioxidant activity, and the relative total antioxidant capacities were as follows in decreasing order: cocoa, red wine, green tea, black tea. The total antioxidant capacities were highly correlated with phenolic and flavonoid contents. These results suggest that cocoa is more beneficial to health than teas and red wine in terms of its higher antioxidant capacity (Lee et al. 2003).

5 Conclusions

The first part of the chapter focused on the move from the natural antioxidant nutrients to synthetic agents which are mostly bio-inspired from natural models like flavonoid-type compounds and stilbenes. The result of the chemistry laboratory demonstrated better activity of synthetic models. However nature remains the first supplier of nutritional dietary components while further research efforts are needed to prove the reliability of the synthetic ones. The second part of the chapter was devoted to some examples of people's eating habits according to their geographical and cultural belongings including, the so-called French Paradox or red wine in EU and USA, tea in Far East and Middle East, and finally chocolate, the worldwide tendency. By knowing the beneficial actions of each food, it was possible to establish a comprehensive relationship between health and nutrition mode underlying the limit of excessive intake and risk factors. The phytochemical knowledge of these daily consumed food is such important to assess their selective beneficial effects on humans and also some side effects almost related to an over intake. Individual biological evaluations of these food-isolated polyphenols provide a better understanding of the overall biological benefit and related negative effects. The case of resveratrol, catechins, quercetin, and other polyphenolic compounds is already quoted but further examinations are required for other key molecules and their metabolites. To sum up, natural or synthetic ingredients of our food should be promotable for our health but we always have to consider that the positive biological effect ensured by these phytochemicals and/or additive dietary synthetic chemicals can be transformed to negative effect after a certain limit line and therefore this is the line that has to be evaluated or at least estimated by scientists in order to avoid this negative side.

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Oualid Talhi (born 1985) received his first degree of graduate studies in Chemistry in 2007 at the University of Science and Technology Houari Boumediene (USTHB), Algiers, Algeria. Afterwards, he joined the laboratory of heterocyclic compounds and organic synthesis at USTHB to conduct his Master thesis research on solid catalysis and Knoevenagel reactions, successfully defending his Master thesis in 2009. In November 2009, he joined the laboratory of organic chemistry and natural products QOPNA at the University of Aveiro, Portugal, as an early stage researcher under the supervision of Prof. Artur Silva. He conducted his research project on natural-type polyphenols, their synthesis and biological applications within the European Initial Training Network "RedCat", obtaining a PhD degree in chemistry from the University of Aveiro by the end of 2012.

Oualid currently holds a postdoctoral position at the QOPNA group of the University of Aveiro, and is involved in organo-synthetic research aiming at new

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Diana C. G. A. Pinto studied chemistry at the University of Aveiro, Portugal, graduating from this university in Analytical Chemistry in 1991. In 1996 she received her PhD in Chemistry from Aveiro University. She then joined the Department of Chemistry at Aveiro University where she is currently Assistant Professor of Organic Chemistry.

Diana is an expert in organic synthesis, including the development of new strategies toward synthesis of nitrogen- and oxygen-containing heterocyclic compounds that can be used as new drugs. Over the years, her research has also focused on the application of environmentally friendly methodologies in organic synthesis, with a certain focus on the application of microwave irradiation. Besides her strong interest in organic synthesis, Diana is also developing an active research program in the isolation and characterization of natural products, focusing on medicinal plants.

Artur M. S. Silva is Full Professor at the University of Aveiro in Portugal. He obtained both his B.Sc. (1987) and PhD (1993) degrees from the University of Aveiro. He joined the Department of Chemistry of the same University in 1987 and was appointed to Auxiliary Professor in 1996, Associate Professor in 1999 and Full Professor in 2001. Artur has published over 410 SCI-listed papers and 15 book chapters and has delivered more than 30 lectures at scientific meetings. His research interests involve synthetic organic chemistry (especially the development of new synthetic methods for oxygen- and nitrogen-containing heterocyclic compounds and organo-catalyzed transformations), natural products identification, and structural characterization by NMR.