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Antioxidant and Pro-Oxidant Effects of Polyphenolic Compounds and Structure-Activity Relationship Evidence

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1. Introduction

Polyphenolic compounds are bioactive substances widely distributed in the vegetable kingdom. They act as natural antioxidants and their presence contributes to the color, flavor and aroma of food. Therefore, they are considered dietary antioxidants with interesting benefits to health.

The research and characterization of new bioactive substances, for the new design of functional foods, nutraceuticals, or drugs, has been intensified. Several studies showing controversial results of exogenous antioxidants, debating that the type, dosage and matrix of these antioxidants may be determining factors impacting the balance between beneficial and deleterious effects of these natural compounds (Bouayed & Bohn, 2010). There are also some proofs that they act as pro-oxidants, under certain conditions, such as high doses or the presence of metal ions (Decker, 1997; Raza & John, 2005; Watjen et al., 2005). The antioxidant or pro-oxidant activity intimately depends on their concentration (Bouayed & Bohn, 2010). The consequences of pro-oxidant activity could be the possible damage to the biomolecules such as DNA, proteins and lipids, and the consequent cellular death (Aruoma, 2003).

The relationship between the chemical structure and the anti-oxidant/pro-oxidant activities has been the main focus of important studies in the nineteenth century. Nevertheless, in general it was carried out without the use of bioinformatics. It was only observed in the last years that different research groups started to use quantitative structure-activity relationships (QSAR) methodologies, using different molecular descriptors.

In this chapter, the principal aim is to describe and analyze the potentialities of the QSAR methods, which has already been evaluated in the pharmaceutical sciences. These methodologies are going to be useful tools for the research and characterization of bioactive compounds, especially polyphenols, which can be used as functional foods in food science.

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The possibilities of the *in silico* studies in a structural level are going to be discussed, since many of the antioxidant compounds have a dual behaviour by also displaying pro-oxidant activity.

2. Polyphenolic compounds and their presence in food items

2.1 Description of principal polyphenols, their presence in foods and the functions that they may play

Phenolic or polyphenolic compounds are plant metabolites widely spread throughout the plant kingdom. Phenolic compounds are essential for the growth and reproduction of plants, and are produced as a response for defending plants against pathogens and stress in general. Chemically, they are compounds with an aromatic ring linked to one or more hydroxyl groups. They are an important group with numerous substances, including structures from different moieties. They include simple compounds, such as phenolic acids and also more complex molecules such as hydrolysable and condensed tannins (Fig.1). The most prevalent group is the flavonoid group, including anthocyanins, flavonols, flavones, chalcones, dihydrochalcones, isoflavones and flavan-3-ols. They are composed of two aromatic rings (A and B) linked by an oxygenated heterocycle (C). Different subclasses depend on the degree of hydrogenation and substitution of the heterocycle (Fig.2). Another important subgroup is the one that include the phenylpropanoids, e.g. hydroxycinnamic acids (caffeic, ferulic and *p*-coumaric acids). Also important are the stilbenoids (resveratrol and piceatannol) and the benzoic acid derivatives (gallic and ellagic acids).

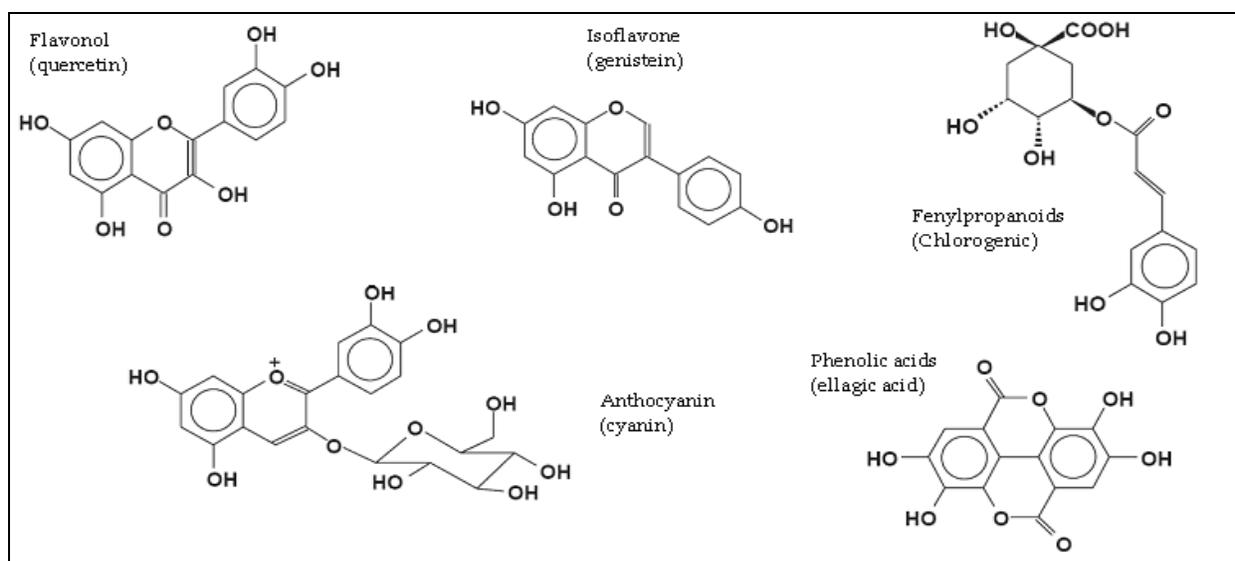


Fig. 1. Families and examples of polyphenols. Adapted from (Espín & Tomás-Barberán, 2005)

These compounds are present in important amounts in fruit and vegetables (Table 1) (Manach et al., 2004). They are considered as bioactive non-nutritional compounds, due to their properties, including antioxidant functions. The importance of antioxidant activities of phenolic compounds and their possible usage in processed foods as natural antioxidants have reached a new role in recent years.

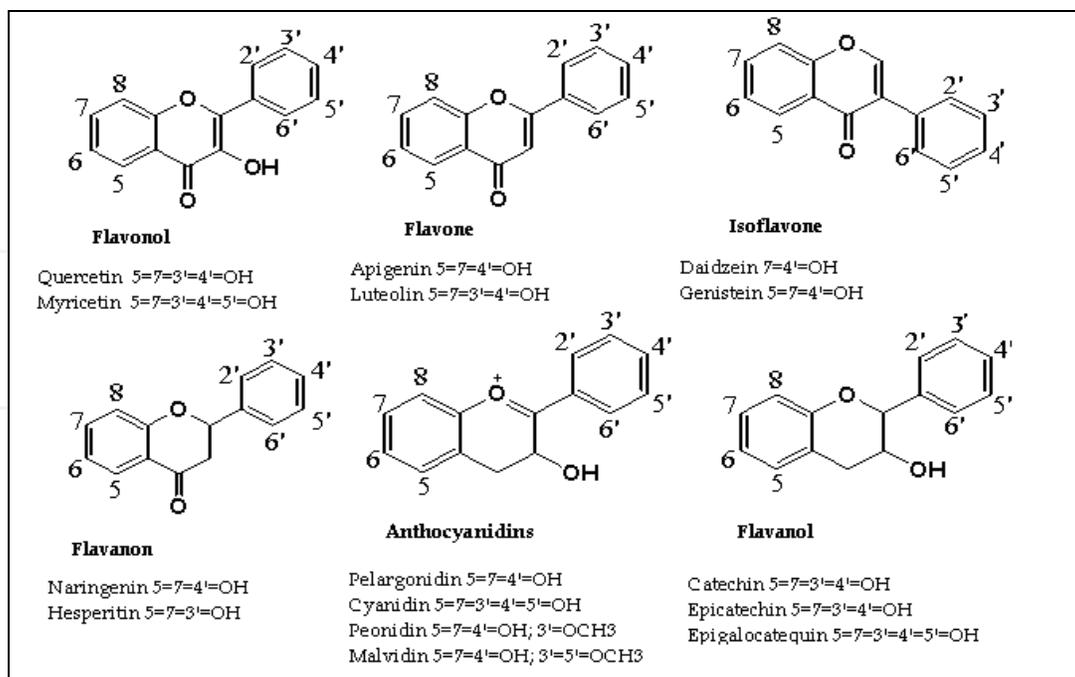


Fig. 2. Skeleton and some subclasses of flavonoids.

Antioxidant compounds are described as chemical structures that prevent the oxidation of a substrate at low concentrations (Halliwell, 1990). The type of substrates susceptible to this activity includes structures such as proteins, lipids, carbohydrates and DNA (Aruoma & Halliwell, 1995). They are also defined as compounds that protect the cellular system from potentially harmful processes that can cause excessive oxidation (Duthie et al., 2000).

Many phenolic compounds are responsible for some of the sensorial properties of food and therefore are important for their quality (Manach et al., 2004; Tomás-Barberán & Espín, 2001). There are bitter polyphenols, such as certain citrus flavanones (naringin from grapefruit and neohesperidine from the bitter oranges) or oleuropein present in olives. Among the polyphenols, there are pigments such as anthocyanins, responsible for the red, blue and violet characteristics of many fruits (strawberries, plums, grapes, etc.), vegetables (eggplant, red cabbage, radish, etc.) and red wine, or flavonols, with a cream-yellowish hue, which are found principally in the outer parts of fruits and vegetables (Tomás-Barberán et al., 2000). Proanthocyanidins (condensed tannins) and hydrolysable tannins confer astringency to fruits, and some simple phenols are important for the aroma of certain fruits, such as eugenol in bananas. Hydroxycinnamic acid derivatives such as caffeic, ferulic and sinapic acids are present in a number of fruits and vegetables and food products, cereals, and in some cases are the major polyphenols. Although they have not a direct impact on the organoleptic characteristics of foods containing them, they may indirectly negatively affect the quality if they are oxidized by oxidative enzymes found naturally in plant tissues. This leads to the formation of brown polymers (Tomás-Barberán & Espín, 2001).

The most relevant, in terms of abundance in the diet and due to their biological activity, are stilbenoids, hydroxytyrosol, ellagic acid and flavonoids (flavonols, flavan-3-ols and isoflavones). They are usually found in the form of glycosides. However, the human body cannot produce any of the polyphenols, therefore they must be obtained through the diet.

Chemical skeleton	Class	Example for each class	Sources
C6	Simple phenols	Hydroquinone	Gayuba
C6-C1	Benzoic acids	<i>p</i> -hydroxybenzoic acid	Coconut shell, white wine
C6-C3	Hydroxycinnamic acids	Caffeic acid	Apple, pear, red wine
C6-C3	Coumarins	Scopoletin	Cinnamon, mulberry from India, green tea
C6-C4	Naftoquinones	Vitamin K1	Spinach, cabbage, cereals
C6-C2-C6	Stilbenoids	<i>Trans</i> -resveratrol	Grapes, peanuts
C6-C3-C6	Flavonoids	Luteolin	Olive, grapes
(C6-C3-C6)	Condensed tannins	Procyanidins	Grapes, red wine, cherries

Table 1. Classification of the phenolic compounds in relation to the number of carbon atoms and examples of their sources.

2.2 Food sources of flavonoids and phenolic acids

Flavonoids are widely distributed in plants, fruits and vegetables and represent substantial components, without significant contribution to the human diet (Aherne & O'Brien, 2002). Apart from being found in fruits and vegetables, they are present in seeds and flowers, as well as wine, green tea, black tea and soy, which are usually consumed in the human diet. Beer also contains significant amounts of flavonoids, mainly polyhydroxyflavanes (catechin and epicatechin), anthocyanidins (leucocyanidins or leucopelargonidine) and flavonols. Today more than 5.000 flavonoids have been identified (Ross & Kasum, 2002), among which are especially:

1. Citrus flavonoids: Quercetin, hesperidin, rutin, naranjin and limonene. Quercetin is a flavonoid present in green-yellow onions, apples, broccoli, cherries, grapes and red cabbage. Hesperidin is found in the peels of oranges and lemons. Naranjin results in the bitter taste of many fruits such as orange, lemon and grapefruit. Limonene has been isolated from lemon and lime.
2. Flavonoids from soy or isoflavones (genistein and daidzein): they are present in soy foods such as beans, tofu, tempeh, soy milk, textured vegetable protein, flour and miso.
3. Anthocyanidins: they are plant pigments responsible for the colour of red and bluish-red cherries.
4. Proanthocyanidins are found in grape seed, red wine and pine bark sea extract.
5. Ellagic acid: it is a flavonoid found in fruits, such as grapes, and vegetables.
6. Catechins: green and black tea are good sources.
7. Kaempferol: is abundant in leek, broccoli, radish, endive and red beets.

Recently, the United States Department of Agriculture (USDA) published a "Database for the Flavonoid Content of Selected Foods". This database contains values for 385 food items with five subclasses of flavonoids: flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins (United States Department of Agriculture [USDA], 2007). Another

important database is the “Phenol-Explorer” version 1.5.7 (database on polyphenol content in foods) (INRA & Wishart Research Group, 2009). It contains more than 35.000 content values for 500 different polyphenols in more than 400 foods. These data derive from the systematic collection of more than 60.000 original content values in more than 1.300 scientific publications. Data have been critically evaluated before inclusion in the database.

Phenolic acids, in general, describe phenols that possess a carboxylic acid function. However, when describing them as metabolites of the plant, they are referred to a different group of organic acids. These phenolic acids are distinguished according to two underlying structural compounds: the cinnamic and benzoic acids (Fig. 3). While for the rest of the phenolic acids the basic scheme is the same, the number and positions of hydroxyl and methoxy groups on the aromatic ring create variety. Hydroxybenzoic acids have a general structure C6-C1 (Macheix et al., 1990).

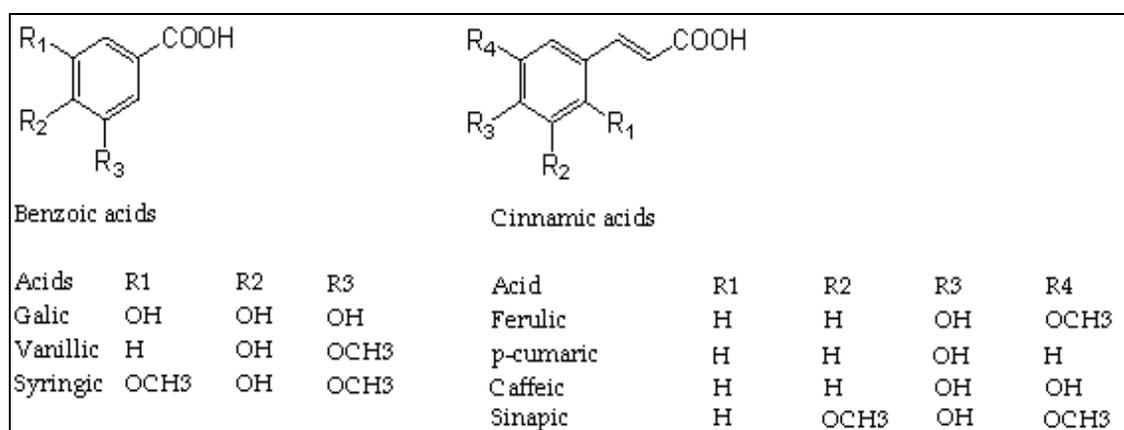


Fig. 3. Basic structure of benzoic and cinnamic acid derivatives.

Common benzoic acids are vanillic, *p*-hydroxybenzoic, syringic, protocatechuic, salicylic and gallic acids. They may be present in soluble form, conjugated with sugars or organic acids. Gallic acid is a trihydroxylic derivative, involved in the formation of gallotannins hydrolysates. The four cinnamic acid derivatives widely distributed in fruits are: *p*-coumaric, caffeic, ferulic and sinapic acids (Macheix et al., 1990). Cinnamic acid derivatives are mainly found in several conjugated forms, mainly esters of hydroxyl acids such as tartaric acid and sugar derivatives (Shahidi & Nacsk, 1995). Chlorogenic acid (5-caffeoylquinic acid) is one of the most important derivatives of cinnamic acid found in fruits, being sometimes the predominant phenolic compound. The wide distribution and high concentration of cinnamic acids in fruits may be due, in part, to the key role that they play in the biosynthesis of more complicated phenolic compounds such as shikimate and phenylpropanoid (Robards et al., 1999).

Plants contain a wide variety of phenolic compounds depending on the species (Bravo, 1998; Saraji & Mousavi, 2010). In general, plants of the *Solanaceae* family provide both chlorogenic acid and other hydroxycinnamic acids. In fruits, the content of hydroxybenzoic acid is generally low, with the exception of grapes, raspberries and strawberries. Usually, the content of hydroxycinnamic acid is higher. Caffeic acid is the predominant cinnamic acid in many fruits, constituting up to 75 % of phenolic acids. It is found in pears, apples, cherries and blueberries (Manach et al., 2004). However, *p*-coumaric acid is the major component

within the cinnamic acid group of citrus and pineapple (Macheix et al., 1990). The presence of chlorogenic acid in fruits has also been widely studied (Martínez- Valverde et al., 2000).

Cinnamic acid derivatives are usually more abundant in fruits and vegetables than those of benzoic acid. Derivatives of cinnamic acid exist in all fruit parts, but concentrations are higher in the outer parts of ripe fruit. Concentrations generally decrease during the course of ripening, but total quantities increase as the size of the fruit increases (Hakkinen, 2000).

The content of polyphenols in fruit juices is generally between 2 and 500mg/L (Bravo, 1998). The highest concentrations were found in the pulp of oranges, with values around 31mg/100g of fresh weight (Justesen et al., 1998). Wine is a much studied source of phenolic compounds, especially of phenolic acids, anthocyanins, tannins and flavonoids. Within these food groups, the phenolic compounds of interest are the hydroxycinnamic (Buiarelli et al., 2010) and benzoic acids, along with flavan-3-ols and flavan-3-diols, anthocyanins, anthocyanidins, flavonols, flavones and condensed tannins. There are differences between the content of phenolic compounds in white wine and red wine. First, total content is lower for white wine. The average content of phenolic compounds in a typical white wine is about 250mg/L, although some types may contain up to 2000mg/L. By contrast, the content of total phenolic compounds in red wine typically ranges between 1000 and 4000mg/L. *p*-Coumaric, protocatechuic, syringic and caffeic acids are among the most abundant polyphenols in wines (Benassi & Cecchi, 1998).

Beer contains vanillic, *p*-coumaric and caffeic acids (Lunte et al., 1988). Tea is a beverage with a high content of phenolic compounds, noted for its high concentration of catechins, which constitute over 30 % of the dry weight of the leaf, and additional flavonols (quercetin, kaempferol and their glycosides), flavones and phenolic acids (gallic and chlorogenic acids).

In legumes and cereals, the main phenolic compounds are flavonoids, phenolic acids and tannins. Rice flour contains up to 86mg/100g of phenolic acids. This content is similar to those in wheat flour and oats. In both rice and wheat flour, the main phenolic component is ferulic acid, constituting at least 89 % of total phenolic acids (Sun et al., 2001). In addition, ferulic, sinapic, vanillic and syringic acids are among the most frequently found polyphenols in cereals (Lempereur et al., 1997).

3. Evidence for health benefits

The information linking diet to chronic diseases comes mainly from epidemiological studies and controlled assays in humans. These diseases are predominantly cardiac and vascular pathologies, cancer, atherosclerosis, diabetes type 2, Alzheimer's disease, hypertension, obesity, osteoporosis, chronic liver disease, nephritis or chronic renal and gastrointestinal diseases. These diseases are potentially preventable and are related to inappropriate lifestyles (Pasinetti, 2007).

According to WHO, in the early twentieth century around 20 % of the deaths were caused by cardiovascular or malignant tumors. The loss of quality of life becomes more critical in those over sixty years old, in whom these conditions predominate as causes of morbidity and mortality. There is an increasing epidemiological evidence associating diets rich in fruits and vegetables with lower rates of mortality from cardiovascular disease and some cancers. More limited evidences suggest that such diets may decrease the incidence of other chronic diseases, including diabetes, cataracts, macular degeneration, rheumatoid arthritis,

neurodegenerative diseases and hypertension. Thus, the scientific community's attention has been focussing on the antioxidant components, which may provide protection against chronic diseases by decreasing oxidative damage in tissues. However, these antioxidant components are also involved in other cellular mechanisms such as apoptosis and have an important impact on intracellular signalling and gene regulation.

The so-called "antioxidant hypothesis" has been suggested based on the oxidative damage resulting from the action of reactive oxygen species (ROS) and nitrogen radicals, which are formed naturally in the body. ROS are known to be involved in pathogenic processes of numerous diseases described before (Diplock, 1994; Sies, 1997). When antioxidant defenses are insufficient, DNA, lipids, proteins and other molecules may be oxidatively damaged. Oxidation effects could be reduced by dietary antioxidants (e.g. polyphenolic compounds) (Ferrari & Torres, 2003). Fortunately, in the human body, there is a balance between oxidant and antioxidant species generation. When this equilibrium is broken, oxidative stress (OS) results. The balance between oxidation and antioxidation (redox balance) is critical in maintaining a healthy biological system (Bouayed, 2010; Bouayed & Bohn, 2010; Bouayed et al., 2009; Valko et al., 2007). However, despite that the role of the antioxidant defense mechanisms is to neutralize oxidant species, oxidative damages to proteins, lipids and DNA related to undetoxified ROS occur and accumulate during life, promoting aging process.

3.1 Cardiovascular and cerebrovascular disease prevention

In the last decades, several epidemiological studies have shown that dietary intake of foods rich in natural antioxidants was correlated with reduced risk of coronary heart disease. Particularly, a negative association between the consumption of polyphenol-rich foods and cardiovascular diseases has been demonstrated (Pokorny et al., 2001). This association has been partially explained based on the fact that polyphenols interrupt lipid peroxidation induced by ROS.

Epidemiological evidence for the importance of flavonoids in reducing mortality from coronary heart disease was provided by the Zutphen Elderly study (Anandh Babu & Liu, 2008; Hertog et al., 1993). These authors proved that the ingestion of flavonoids and other phenolic substances was inversely associated with mortality from myocardial infarction (Hertog et al., 1995).

Prospective studies have been conducted in order to analyze the effects of diet on heart disease on populations in the Netherlands (Hertog et al., 1993), USA (Rimm et al., 1996), UK (Hertog et al., 1997) and Finland (Knekt et al., 1996) and also on cerebrovascular disease in the Netherlands (Keli et al., 1996). In some of these studies there has been found a strong protective effect of flavonoids, from the group of polyphenols, against these diseases. However, in other studies the effect was less significant or even negative, as in the case of the British study (Hertog et al., 1997). These discrepancies may be due, among other factors, to defects in the evaluation methods of the ingestion of flavonoids and other polyphenols, the varieties of fruit and vegetable consumed, and differences postharvest such as cooking treatment effects, bioavailability and metabolism by colonic bacteria, and so on (Tomás-Barberán et al., 2000).

Knekt (2002) confirmed that people with higher intake of quercetin (a flavonol abundant in onions, apples, tea, wine and other fruits and vegetables) have lower myocardial infarction

mortality rates. Also, cerebrovascular disease incidence was lower in those with higher intake of kaempferol, naringenin and hesperetin (very abundant in citrus) (Knekt et al., 2002). However, evidence on the role of flavonoids in the prevention of cardiovascular diseases is still a matter of discordance.

The oxidative modification of low density lipoprotein (LDL) is believed to have a crucial role in atherogenesis, and epidemiological studies have shown that consumption of fruits and vegetables and regular or moderate consumption of red wine is correlated with a reduced risk of cardiovascular disease (Renaud & Lorgeril, 1992). Other epidemiological studies have shown a direct relationship between tea consumption and cardiovascular disease. They hypothesized that the antioxidant effects of tea flavonoids may include prevention of oxidative damage to LDL (Kris-Etherton & Keen, 2002). Geleijnse et al. (2002) studied the association between intake of flavonoids in tea and the incidence of myocardial infarction in the Dutch population. The results indicated that the intake of flavonoids (quercetin + kaempferol + myricetin) was inversely associated with fatal myocardial infarction, when comparing individuals with higher compared to lower intake (Geleijnse et al., 2002).

3.2 Cancer prevention

Some of the most compelling evidence of a protective effect of diets against cancer, in recent years, is the evidence on the intake of fruits and vegetables (Block et al., 1992). A review of more than 160 epidemiological studies by Steinmetz & Potter (1996) showed that an increased consumption of fruits and vegetables was associated with a lower incidence of certain cancers, among which were the stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas and colon (Steinmetz & Potter, 1996). This showed that the most important vegetables involved in this protective effect would be the ones consumed raw, followed by garlic and onions, cabbages, cauliflowers and broccoli, tomatoes and fruits in general. Among other protective components, the polyphenols have been generally cited. For example, it has been suggested that quercetin play an important role in the anticarcinogenicity effects of plant foods such as apples and onions (Knekt et al., 1997) owing to its chemopreventive activity against carcinogens *in vitro* (Obermeier et al., 1995) and *in vivo* as suggested by animal studies (Deschner et al., 1991). EPIC is an important study that indicates that these retrospectively obtained results, at least respecting to cancer, might have been somewhat overestimated, however, still a significant reduction of consumption of fruits and vegetables on e.g. colorectal cancer was found (Bouayed & Bohn, 2010, van Duijnhoven et al., 2009).

Polyphenols can further act by inhibiting cell proliferation, which is deregulated in cancer. This inhibition has been demonstrated *in vitro* in many tumor cell lines. For example, Kuo (1996) published the antiproliferative effect of flavonoids on colon carcinoma cells through mechanisms of apoptosis induction (Kuo, 1996). Although the antiproliferative effects of polyphenols in general and in particular of flavonoids and isoflavonoids in cell cultures seems well established, there are relatively few data regarding the *in vivo* antiproliferative activity, and virtually nothing is known about the clinical relevance of this bioactivity (Birt et al., 2001). This antiproliferative effect suggests that polyphenols may have an effect via regulating the cell cycle or inducing apoptosis in tumor cells. In fact, many studies have shown the effect of polyphenols on the cell cycle of tumor cells in cultures in *in vitro* assays.

This has been demonstrated in cells of several types of leukemia, stomach cancer, lung, colon, bladder and prostate (Birt et al., 2001).

Polyphenols can also protect against cancer through their inhibition of oxidative DNA damage (Omenn, 1995). A mechanism of oxidation appears to be a major cause of mutations that could potentially be reduced by dietary antioxidants. Polyphenols, because of their amply demonstrated *in vitro* antioxidant activity, could prevent this oxidation if reaching those tissues where these oxidations occur. Again, relatively few data have been published about their role *in vivo*.

It has been suggested that flavonoids (flavones and isoflavones) can prevent cancer because they can be found in many plant foods that are associated with reduced cancer rates. In this sense, studies such as one following 10,054 people in Finland (Knekt et al., 2002) have shown that men with higher quercetin intake had a lower incidence of lung cancer and those who took more myricetin had a lower incidence of prostate cancer. Among the possible mechanisms of action were mentioned estrogenic/antiestrogenic activities, antiproliferative effects, induction of cell cycle block of cancer cells in a special phase and apoptosis, preventing oxidation, induction of detoxification enzymes (phase I enzymes and phase II), immune system regulation and changes in cell signalling (Birt et al., 2001). Recently, Banerjee et al. (2008) analyzed the use of genistein for cancer therapy (Banerjee et al., 2008), an isoflavonoid with potential estrogenic activity.

3.3 Neurodegenerative disease prevention

Neurodegenerative diseases are becoming increasingly prevalent with the aging of the general population. The twentieth century witnessed a significant demographic change in the human population of the industrialized world that is currently followed by a similar shift of life expectancy toward higher age ranges in Asia, Africa, and Middle and South America. Thus, neurodegenerative diseases are presently amongst the major contributors to disability and disease in human populations. Alzheimer's disease is the most prevalent of the neurodegenerative diseases followed by Parkinson's disease. Free radicals have been implicated in the development of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, among other multifactorial diseases such as diabetes, rheumatoid arthritis and chronic obstructive pulmonary diseases (Diplock, 1994; Diplock et al., 1998; Sies, 1997). These age-related diseases may, therefore, be beneficially influenced by antioxidant consumption. However, few epidemiological data exists on the association of antioxidants with the risk for these diseases (Diplock et al., 1998).

For instance studies suggest that OS may contribute to the pathogenesis of Alzheimer's disease. Although the etiology of this disease is not completely understood, deposits of aberrant proteins, namely β -amyloid ($A\beta$) and τ -protein, OS dyshomeostasis of biometals and low levels of acetylcholine (ACh) seem to play significant roles. Monoamine oxidase B (MAO-B) activity is also increased in association with gliosis, which can result in higher levels of H_2O_2 and oxidative free radicals which are a possible source of OS for vulnerable neurons affected by Alzheimer's disease. The risk of this disease could be reduced by the consumption of antioxidants that counteract the negative effects of OS. Epidemiological studies have been carried out, such as the "Rotterdam Study", to evaluate the effect of diet on the prevention of neurodegenerative diseases and dementia. In this case, 5395 persons

were followed during the nineties and it had been studied whether there was any relationship between diet and the development of Alzheimer's disease, especially following the consumption of antioxidants such as vitamins C and E, β -carotene and flavonoids. In this study, higher intakes of vitamins C and E were associated with a lower risk for developing Alzheimer's disease. This relationship was even more pronounced in the case of smokers, and was also observed in the case of β -carotene and flavonoids (Engelhart et al., 2002). However, epidemiological studies conducted in the USA found that only vitamin E, but not C or β -carotene may be associated with reduced risk of Alzheimer's disease (Morris et al., 2002). More research is needed regarding these data in order to demonstrate whether antioxidants in the diet can have an impact for the prevention of neurodegenerative diseases.

4. Polyphenolic compounds with antioxidant/pro-oxidant activities

In recent years, studies of natural antioxidants that are part of plant foods have become the focus of increased interest. Flavonoids and phenolic acids are receiving increased attention as potential antioxidants, primarily due to their wide presence in a large number of widely consumed foods. Different experimental methods developed for this purpose represent a major critical factor when it comes to strategies for developing fortified foods, or the characterization of a functional food and/or the formulation of an antioxidant supplement (Antolovich et al., 2002). There is a great diversity of variants and experimental assays designed for these studies (León et al., 2005).

Currently, the exogenous antioxidants, including polyphenols were considered "double-edged swords" in the cellular redox state. Several studies of exogenous antioxidants showed controversial results, especially when administered at high doses. The type, dosage and matrix of exogenous antioxidants may be determining factors impacting the balance between beneficial or deleterious effects of these natural compounds (Bouayed & Bohn, 2010). From epidemiological and dietary intervention studies, it appears, however, that exogenous antioxidants at physiologic (nutritional) doses play an important role in the maintenance or re-establishment of redox homeostasis, an essential state in maintaining healthy biological systems (Bouayed & Bohn, 2010; Valko et al., 2007).

4.1 Mechanisms involved in the antioxidant activity

The role of antioxidants in nutrition and health, as well as their mechanisms of action, have been extensively researched (Serafini, 2006). Although the biological functions of polyphenols and/or metabolism in the human body are not completely established, there is a consensus that the antioxidant activity of flavonoids could be a combination of metal chelating properties and free radical scavengers (Bohm et al., 1998; Bravo, 1998). Other authors also refer to the inhibition of oxidases, such as lipoxygenase (LO), cyclooxygenase (CO), myeloperoxidase (MPO), NADPH oxidase and xanthine oxidase (XO) (Groot & Rauen, 1998), as important mechanisms for avoiding the generation of higher amounts of ROS *in vivo*, as well as organic hydroperoxides. Moreover, they have been also known to inhibit enzymes indirectly involved in the oxidative processes, such as phospholipase A2 (FLA2) (Lindahl & Tagesson, 1997), while they stimulate others with recognized antioxidant activity, such as catalase (CAT) and superoxide dismutase (SOD) (Sudheesh et al., 1999). Therefore, the flavonoids interfere with the propagation reactions of free radicals and the radical formation itself (Van Acquire et al., 1996).

The chemical structure of polyphenols gives them the ability to act as free radical scavengers. The type of compound, the degree of methoxylation and the number of hydroxyl groups are some of the parameters that determine the antioxidant activity. As for phenolic acids, the oxidation inhibition is related to the chelation of metal ions via the *ortho*-dihydroxy phenolic structure, the scavenging of alkoxy and peroxy radicals, and the regeneration of α -tocopherol through reduction of the tocopheryl radical (Bors et al., 1990).

The structural features that have been associated with antioxidant activity are: a) a catechol group on the B-ring, which confers high stability to the radical formed after the capture reaction of the free radical, b) the 2,3-double bond in conjugation with a 4-oxofunction of a carbonyl group in the C-ring and c) the presence of hydroxyl groups at the 3 and 5 position (Fig. 4) (Bourne & Rice-Evans, 1998).

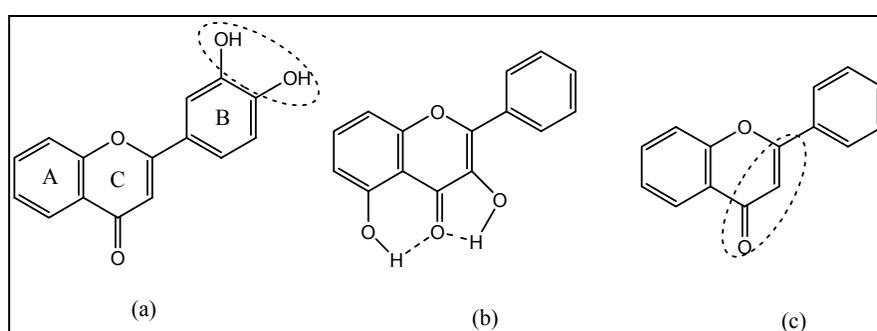


Fig. 4. Antioxidant activity-structure relationship of flavonoids. (a) a catechol moiety of the B-ring, (b) presence of hydroxyl groups at the 3 and 5 position, (c) the 2,3-double bond in conjugation with a 4-oxofunction of a carbonyl group in the C-ring.

Current studies on their metabolism established that flavonoids are located in the membrane at the interface lipid/water, being the first to react with the ROS formed in these areas. The type of conjugation during biotransformation and their location in the body, determines the ability of enzyme inhibition and antioxidant capacity. As part of this, they can act directly as "scavengers" of free radicals, by hydrogen or electron donation, leading to other more stable compounds, or compounds that can stabilize compounds obtained from free radicals or may have an additive effect on the endogenous antioxidant defense system by increasing or maintaining this antioxidant defence. These mechanisms are also the same for phenolic acids.

4.2 Evidence of pro-oxidant activity of polyphenols

4.2.1 Flavonoids and phenolic acids as pro-oxidant compounds

The need to clarify the safety aspects (McKevith et al., 2003), structure-activity (Yordi, 2010), bioavailability and metabolism of compounds with antioxidant activity when they become part of functional foods or nutraceuticals has been suggested (Fundación Española para la Ciencia y la Tecnología [FECYT], 2005). This is because many of the study results are inconclusive and sometimes contradictory. Examples of this are reported below, showing that some polyphenol antioxidants may have pro-oxidant activity under certain conditions such as at high doses or in the presence of metal ions (Azam et al., 2004; Bouayed & Bohn, 2010; Decker, 1997; Raza & John, 2005; Watjen et al., 2005) (Table 2).

Polyphenols and particularly flavonoids are examples of substances with such dual *in vitro* behaviour (Fukumoto & Mazza, 2000; Pérez-Trueba, 2003; Pérez-Trueba & Martínez, 2001; Sakihama et al., 2002). We recently published a list of such compounds and their dietary sources (Yordi, 2010). Phenolic acids have also been reported as pro-oxidants (Fukumoto & Mazza, 2000; Maurya & Devasagayam, 2010; Mozuraityte et al., 2009; Sakihama et al., 2002; Simiã et al., 2007) (Table 2).

It is noteworthy that some of the most abundant flavonoids and phenolic acids present in foods were reported to act as pro-oxidants: quercetin, myricetin, kaempferol and caffeic, chlorogenic and ferulic acids (see Table 2). In the 2.2 section, some examples of the main food sources for these two groups of polyphenols are shown.

No.	Phenolic acids	CAS* Numbers	Pro-oxidant reference
1	<i>o</i> -coumaric acid	614-60-8	(Simiã et al., 2007)
2	<i>p</i> -coumaric acid	501-98-4	(Fukumoto & Mazza, 2000; Mozuraityte et al., 2009; Simiã et al., 2007)
3	<i>m</i> -coumaric acid	14755-02-03	(Simiã et al., 2007)
4	ferulic acid	537-98-4	(Fukumoto & Mazza, 2000; Maurya & Devasagayam, 2010; Mozuraityte et al., 2009)
5	caffeic acid	331-39-5	(Fukumoto & Mazza, 2000; Maurya & Devasagayam, 2010; Mozuraityte et al., 2009)
6	salicylic acid	69-72-7	(Simiã et al., 2007)
7	<i>p</i> -hydroxybenzoic acid	99-96-7	(Simiã et al., 2007)
8	vanillic acid	306-08-1	(Fukumoto & Mazza, 2000) (Simiã et al., 2007)
9	syringic acid	530-57-4	(Simiã et al., 2007)
10	protocatechuic acid	99-50-3	(Fukumoto & Mazza, 2000)
11	gallic acid	149-91-7	(Fukumoto & Mazza, 2000)
12	chlorogenic acid	327-97-9	(Fukumoto & Mazza, 2000; Sakihama et al., 2002)
13	<i>m</i> -hydroxybenzoic acid	99-06-09	(Simiã et al., 2007)
14	ellagic acid	476-66-4	(Fukumoto & Mazza, 2000)

* Chemical Abstracts Service

Table 2. Pro-oxidant activity of phenolic acids (benzoic and cinnamic acids derivatives).

4.2.2 New challenges in pro-oxidant activity

It is known that antioxidants should be present in the body in sufficient concentrations to prevent the accumulation of pro-oxidants (state of oxidative stress) (Sies & Jones, 2007). The human body has mechanisms that protect against the harmful effects of ROS that are continually being formed. These defense systems are antioxidant in nature and stabilize highly reactive compounds. The fact that some substances in foods have pro-oxidant activity is particularly interesting. Although there are few studies, this is due to the fact that OS can be induced from the pro-oxidant agents, either through the creation of ROS or inhibition of antioxidant systems (Puglia & Powell, 1984). This can generate oxidative damage to

biomolecules such as proteins, DNA and lipids and eventually cells and tissues (Aruoma, 1999, 2003; James et al., 2003). It is recognized that the development of many chronic diseases may be due to OS (Espín & Tomás-Barberán, 2005; Halliwell & Whiteman, 2004), where an antioxidant/pro-oxidant balance is not achieved, resulting in a pathological process. The pro-oxidants catalyze then oxidative reactions of biomolecules, which may lead to cellular dysfunction, ending with cell death (Aruoma, 2003).

It is now recognized that the pro-oxidant action, of natural polyphenols, unlike their antioxidant properties, has a more specific preference against certain cellular targets, since it appears to play an important role in the prevention of certain types of cancer (Lambert & Elias, 2010). In a recent review, the pro-oxidant activity of individual dietary polyphenols and their ability to induce mitochondrial dysfunction and consequently apoptosis has been suggested as a possible anticancer mechanism (Galati & O'Brien, 2004). Also, it was recently reported that dietary polyphenols could mobilize endogenous copper in humans, leading to oxidative DNA damage that could be responsible for inducing anti-cancer properties (Azmi et al., 2005).

We think it is interesting to predict, from the standpoint of polyphenolic structure-activity, the DNA damage leading to pro-oxidant substances (Yordi et al., 2011). Aruoma (2003) described that oxidative modifications to DNA are very important. These represent an early stage of carcinogenesis and may provide important OS biomarkers (Aruoma, 2003). It is known that one of the endpoints of the oxidation of this biomolecule are chromosomal aberrations (CA) which are changes in chromosome structure, visible by light microscopy (Astley & Lindsay, 2002). Physical or chemical agents capable of inducing these mechanisms are called clastogens (Bender et al., 1974; Galloway, 1994; Ishidate et al., 1988). The clastogen prediction, starting from a structural analysis, has been postulated by Estrada et al. (2006). These authors developed a quantitative structure-activity relationship (QSAR) model that allows the prediction of clastogens. They identified that one of the structural alerts which characterized clastogenic activity was the diphenylpyran group present in flavonoids (Estrada & Molina, 2006). These methodologies are going to be useful tools for the research and characterization of bioactive compounds, especially polyphenols, which can be used as functional foods, nutraceuticals or drugs. In the following section the possibilities of the *in silico* studies are going to be discussed.

5. Potentialities of bioinformatic methods approaches, such as QSAR studies, in structure-activity relationship studies

QSAR/QSPR (Quantitative structure-property relationship) methods are computational methods based on the physical, physicochemical, chemical and biological properties of organic compounds, depending ultimately on the molecular structure (Randic, 1998). This technique makes it possible to predict activities of new candidate compounds which are bioactive. These predictive methods require the existence of an experimental data set of chemicals, including activity/property relationship results. This allows for the development of mathematical models describing structure-activity/property relationships. This cheminformatics employs multivariate linear regression (MLR) and discriminant linear analysis (DLA) or nonlinear including neural networks. One advantage of these is to help identify the optimal structures for a given activity.

Chemical information of each molecule is encoded by molecular descriptors. These molecular descriptors such as CoMFA (Comparative Molecular Field Analysis) and graph-

theoretic descriptors have become an interesting option for the generation of QSAR models (Devillers & Balaban, 1999). Nowadays, the number of papers in which graph-theoretic molecular descriptors are used in QSAR studies is increasing, especially the so-called topological indices. However, there are some misunderstandings on the role of such molecular descriptors in chemistry and drug investigation. These misunderstandings have produced severe criticisms to their use in QSAR, and sometimes excluded them from the pool of descriptors, which are traditionally used in structure-property-activity studies (Kubinyi, 1993).

The first serious attempt to establish an order in the definition of graph theoretical molecular descriptors was carried out by Randic in 1991 (Randic, 1991). This author gave a series of desired attributes that the topological indices need to have to be considered as useful molecular descriptors. In a more recent study, Milne in 1997 analyzed some aspects concerning the applications of graph theoretical molecular descriptors (Milne, 1997).

5.1 QSAR studies and antioxidant/pro-oxidant activities

Several studies of structure-activity relationship of polyphenolic compounds have been made on the basis of non-congeneric structures and empirically, which relate chemical structure with experimental results obtained, without using such graph-theoretic molecular descriptors or another topologic descriptor. In this sense, it is important to cite the paper by Cao et al. (1997) entitled "Antioxidant and pro-oxidant behavior of flavonoids: structure-activity relationships". An analysis by Fukumoto and Mazza (2000) related the antioxidant/pro-oxidant activities of phenolic compounds, comparing the results obtained by different established methods such as β -carotene bleaching and HPLC methods. For example these methods were used to assess activity of selected phenolic compounds, including several phenolic acids, flavonols, flavanols, flavanones, anthocyanidins/anthocyanins. Both pro-oxidant and antioxidant activities could be measured by the HPLC method. Comparisons in antioxidant activity of compounds with different structures could be made using the β -carotene bleaching and HPLC methods. Generally, antioxidant activity increased with an increase in hydroxyl groups and a decrease in glycosylation (Fukumoto & Mazza, 2000). Although these are no classical QSAR studies, they correlate the experimental results obtained with the chemical structure of compounds with antioxidant activity. Another more detailed analysis, but with the same characteristics, which established the relationship between the structure-antioxidant activity of polyphenolic compounds particularizing on possible mechanisms of action, was described by Perez-Trueba (2001) (Pérez-Trueba & Martínez, 2001). Regarding the analysis of the relationship between structure and pro-oxidant activity, there are few reports, among one of them the research by Gaspar et al. (1996) about flavonoid compounds with different hydroxyl substitutions.

Research teams such as Sergediene et al. (1999) have started to do QSAR studies, using different molecular descriptors, relating the influence of certain physical properties of polyphenols with pro-oxidant activity. The cytotoxicity of 13 polyhydroxybenzenes was described by the QSAR models created by Nemeikaitė-Čėnienė et al. (2005). The correlations obtained quantitatively confirmed the parallelism between the polyphenol cytotoxicity and the rates of their single-electron oxidation, and point to the leading role of formation of the reactive oxygen species in their cytotoxicity. Depending on the examined system, this parallelism may be distorted due to the cytochrome P-450 and COMT-catalyzed transformation of polyphenols (Nemeikaitė-Čėnienė et al., 2005). Selassie et al. (2005)

developed another QSAR study of phenolic compounds, based on physical properties such as hydrophobicity, partition coefficient *o/w*, etc., and the biological activities with respect to apoptosis and cytotoxicity in the cell line L1210, demonstrating the importance of hydrophobicity for these activities (Selassie et al., 2005). Later & Nandi (2007), developed another QSAR study using statistical techniques such as neural networks. More recently, Yuanqiang et al. (2010) related the measured caspase apoptotic activity of L1210 cell line analogues of phenolic compounds, obtaining good predictability from three dimension (3D), topographic descriptors used.

Studies have been focussing on the relationship between the chemical structure and the antioxidant activity of flavonoid compounds. These studies showed that the position of the hydroxyl groups, the dipole moment magnitude and the shape of the molecule play an important role in the inhibition of lipid peroxidation (Bakhtiyor et al., 2005). Amic, et al. (2007) created a more efficient model for the design of new flavonoids with antioxidant activity. More recently, Om & Kim (2008) focused their attention on the radical scavenging activity of flavonoids using 3D QSAR methods.

The understanding of the relationship between chemical structure and activity, and the ability to predict this, is a great advantage of such methods. We believe that these methods can be useful for predicting a specific activity of new polyphenolic compounds and/or synthesizing polyphenols with desired properties (Yordi et al., 2011).

5.2 QSAR studies under TOPS-MODE approach

In the last decade we have developed an approach to QSAR/QSPR and molecular design. It is known as the TOPS-MODE approach, which is the acronym for topological substructural molecular descriptors/design (Estrada, 1996; Estrada, 1998; Estrada & Uriarte, 2001; Estrada et al., 2000). The TOPS-MODE approach is based on the calculation of spectral moments of molecular bond matrices appropriately weighted to account for hydrophobic, electronic and steric molecular features. Spectral moments are the trace of the *k*th power of a matrix, i.e. the sum of all entries in the main diagonal of such matrices. The reader is referred to (Estrada, 1996; Estrada, 1998) to obtain full details of this method.

A bond matrix is a square symmetric matrix in which non-diagonal entries are ones or zeroes if the corresponding bonds have a common atom or not, respectively (Estrada, 1995). These matrices represent the molecular skeleton without taking into account hydrogen atoms. For example, in fig. 5 it is shown the molecular graph of the molecule 2,2-dimethylbutane and the adjacency matrix of corresponding link.

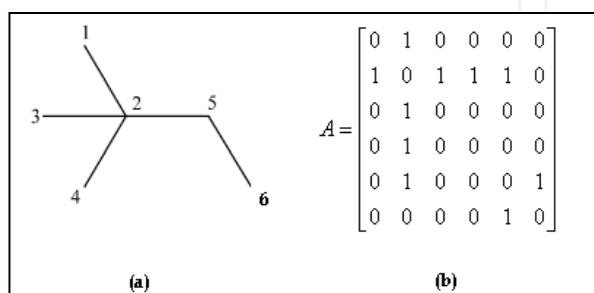


Fig. 5. Molecular graph (a) and its adjacency matrix link (b) corresponding to the 2,2-dimethylbutane molecule.

Bonds weights are placed as diagonal entries of such matrices and represent quantitative contributions to different physicochemical properties.

Among bond weights currently in use in our approach we have standard bond distance (SD), standard bond dipole moments (DM), hydrophobicity (H) (Wang et al., 2000), polar surface area (PS) (Ertl et al., 2000), polarizability (Pol) (Ghose & Crippen, 1987), molar refractivity (MR) (Ghose & Crippen, 1987), van der Waals radii (vdW) (Bondi, 1964), and Gasteiger-Marsilli charges (Ch) (Gasteiger & Marsilli, 1978).

The starting point for our approach is to calculate TOPS-MODE descriptors of the different types, e.g., H, PS, Pol, MR, vdW, and Ch, for the series of molecules under study. Then, we develop a quantitative model describing the property under study in terms of the spectral moments. In general this model can present the following form:

$$P = \sum_{j=1}^n b_j \mu_j + b_0 \quad (1)$$

where P is the property under study, b_j are the coefficients of the quantitative model (linear regression or discriminant analysis) and b_0 is the error.

The j th spectral moment of the bond matrix can be expressed as a sum of bond moments, which are simply the corresponding entries of the j th power of the bond matrix:

$$\mu_j = \sum_{i=1}^m \mu_j(i) \quad (2)$$

where $\mu_j(i)$ is the bond moment of the i th bond in a molecule with m bonds. Then, model (Trinajstić et al., 1986) can be written as:

$$P = \sum_{j=1}^L b_j \sum_{i=1}^m \mu_j(i) + b_0 = \sum_{i=1}^m \sum_{j=1}^L b_j \mu_j(i) + b_0 \quad (3)$$

where the right-hand side in (3) represents the contribution of bond i to the property P and is called the *bond contribution* and represented by $P(i)$:

$$P(i) = \sum_{j=1}^L b_j \mu_j(i) \quad (4)$$

and the property P can be expressed as an additive function of bond contributions:

$$P = \sum_{i=1}^m P(i) \quad (5)$$

5.2.1 Calculation of bond contributions

Bond contributions are numeric characterization of bonds which permit to identify some groups or regions of a molecular framework which can be responsible for a property/activity (Estrada & Molina, 2001). By carefully analyzing similar regions in different molecules we can obtain general rules about the contributions of molecular

fragments to a particular property/activity. They are based on the substructural nature of TOPS-MODE. This procedure consists in transforming a QSPR or QSAR model into a bond additive scheme in which a property can be calculated as the sum of bond contributions for a molecule. Readers interested in learning more about the procedure for calculating work can be found in (Estrada & Molina, 2006). Yordi et al. (2011) calculated the bond contribution to the clastogenic activity of compounds with reported pro-oxidant activity. **Figure 6** shows one example of the calculated bond fragment. The selected compound (morin) was “active” in the QSAR model predictions. The hydroxyl group contribution is positive when C3 appears in ring C, corroborating the alert analysis. The 5,7-hydroxyl groups in ring A have 0.172 and 0.153 fragment contributions, respectively, and are more than the hydroxyl groups in ring C. It can be concluded that 5,7-hydroxyl substitutions are very important for the activity, so the methoxyl and hydroxyl groups have similar bond contributions. The 2:3 double bond at ring C is an example of a negative fragment contribution -0.103 of the “active” molecules. Only one fragment does not determine the biologic activity. Also, the additional collaborative effect at the molecule is needed

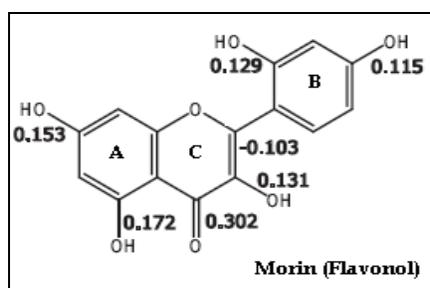


Fig. 6. Example of the Bond Contributions obtained from the TOPS-MODE classification model. Adapted from (Yordi et al., 2011).

5.2.2 Applications of the TOPS-MODE to the molecular design: MODESLAB

In recent years, the computer program TOPS-MODE (now called MODESLAB) was developed for Windows. This software facilitates the calculation of global spectral moments selecting any weight (weight) for different bonds in the molecule, while local spectral moments for single bonds or a defined fragment (contribution) in the molecule can be estimated in the same way after select the link/excerpt. The results are in file format, ready to be manipulated by statistical packages such as STATISTICA (StatSoft, 2001).

A novel application of TOPS-MODE was carried out for antibacterial drugs using computer-aided molecular design by Molina et al. in 2004. In this paper, the TOPS-MODE approach was largely probed to generate good predictive linear models in order to account for antimicrobial activity of a broader range of molecular structural patterns. Henceforth, we can assert that the TOPS-MODE approach may be used as an efficient alternative to massive screening of antimicrobial drugs (Molina et al., 2004).

This approach also allows formulating structural alert rules for chromosome aberration of organic compounds (Estrada & Molina, 2006). CA (clastogenic activity) are DNA changes generated by different repair mechanisms of DNA double strand breaks, which are microscopically visible. They are consequences of e.g. human exposure to ionising radiation or to mutagenic chemicals.

Speck et al. in 2009, used a mixed approach by employing atom-centered fragment, functional group counts, and TOPS-MODE descriptors in order to obtain fragment contributions that will provide a guide for the design of antituberculosis compounds (Speck et al., 2009).

Antytrypanosomal agents (compounds against a type of protozoa) were also studied. The model showed an accuracy of 100 % which means that the *in silico* methodology developed by our team is promising for the rational design of new antytrypanosomal drugs (Speck et al., 2009). In this sense, the molecules predicted can become or generate new leads for the development of more effective and less toxic compounds with antytrypanosomal activity. The methodology developed in this work provided in principle, the design, search and prediction of novel antytrypanosomal agents in a quantitative, rapid and easy way.

In this sense, the TOPS-MODE approach has been extended not only to the discovery of novel results but also toward the studying of the physicochemical and absorption properties of drugs (Cabrera et al., 2002; Estrada & González, 2003). On the other hand, most recently published papers in this area make use of reduced or homologous series of compounds to fit the QSAR for antimicrobial drug screening. This fact determines that these are not general models, which could be used to predict the biological activity of heterogeneous series of compounds. Approaches such as quantitative structure-activity relationships (QSAR) and molecular modeling are integrated with the study of complex networks to understand drug binding to human serum albumin (HSA) (Estrada & Molina, 2006). A topological substructural molecular design approach also has been used to formulate structural rules for binding of substrates of P-glycoprotein (P-gp). An important step in the development of any toxicological or metabolic activity of a chemical is the transport to the organs where the final effect takes place. One of the most important proteins in the transport of various molecules across extra- and intra-cellular membranes is P-glycoprotein (P comes from permeability) (Estrada et al., 2010).

The existence of a large number of polyphenols in different classes and the capacity to exercise different activities (estrogen, apoptotic, anti-depressant, anti-inflammatory, antioxidant, pro-oxidant etc) make this group of compounds very interesting to be studied using the TOPS-MODE approach, being able to predict not only the antioxidant activity, but any of the other properties mentioned. It is also possible to identify structural features and alerts that characterize a subclass of polyphenols that is likely to present a particular activity. It is also possible to do a substructural analysis, identifying how each fragment contributes to the activity. Allowing not only the selection of appropriate structures that are available but also the ability to synthesize, if they are not physically exist.

How does TOPS-MODE help in estimating antioxidant or another potential activity of polyphenols? For example, there are recent evidences about the potential use of dietary polyphenols as neuroprotective agents to reduce anxiety and to manage depression, analyzed by Bouayed (2010). In the paper "Polyphenols: A Potential New Strategy for the Prevention and Treatment of Anxiety and Depression" the pharmacological actions on the central nervous system of polyphenol compounds were analyzed (Bouayed, 2010). We can currently only imagine the possibilities offered by this approach in predicting antidepressant activity of polyphenol compounds. If we made a QSAR study using this approach, the first we need is to obtain a QSAR model. This model is building on a large

number of molecules of different nature, which have proved to be antidepressant in different experimental models. Once obtained, the robust and validated model using multivariate statistical techniques, a virtual screening of it can be performed. For this purpose, data (Espín & Tomás-Barberán, 2005) from polyphenolic compounds of unknown activities are selected. The chemical information is encoded, molecular descriptors are calculated and the results interpreted. Then, the prediction is validated using the data of polyphenols analyzed by Bouayed (2010). Depending on the objectives of this *in silico* study, it is possible to identify/design polyphenolic structures suitable for the activity. It is also possible to identify the fragments that contribute positively to the activity.

6. Conclusion

In summary, the approach that encloses the calculation of the spectral moments of the bond adjacency matrix is known as TOPS-MODE approach. This has been applied for the description of some physicochemical properties of organic compounds, in quantitative structure toxicity relationship (QSTR), and has also been reported for the modelling of pharmacological activities (Estrada & Molina, 2001). The TOPS-MODE approach has been extended not only to the discovery of novel recoveries but also to the study of the absorption properties of drugs (Cabrera et al., 2002; Estrada & González, 2003).

The QSAR method is a proposal to be considered for the design of functional foods and nutraceuticals, particularly when analyzing the activities of polyphenolic compounds, taking into account the high structural diversity (Yordi, 2010). They can allow for predictions about the toxicity, absorption, metabolism, distribution of these compounds, and they can help to understand the dual nature (antioxidant/pro-oxidant) of these compounds from different matrices (food, medicine).

Studies on antioxidants should focus on their bioavailability (absorption, metabolism and cellular and tissue distribution), establishing whether the *in vitro* effects are applicable to the situation *in vivo*. Human trials should focus on specific populations with low intake of these substances (Cooper, 2004). It is also necessary to clarify certain aspects of security, for example, antioxidants may act as pro-oxidants under certain circumstances (McKevith et al., 2003). Assuming the possibility that polyphenols exert positive health effects, their bioavailability should be investigated. Also, considering epidemiological studies and trials on humans, it is evident that the health benefits of phytochemicals were observed predominantly when being consumed within their natural food matrices (fruits, vegetables, grain, etc.) (Bouayed & Bohn, 2010). Because the antioxidants are not occurring isolated in food items, other constituents may influence their activity. It should also be noted that their metabolites may have more relevance *in vivo* assays than the molecule itself, in terms of concentration or biological activity (Buttriss et al., 2002).

7. Acknowledgment

We are grateful to the Xunta de Galicia (09CSA030203PR, PGIDIT07PXIB, 10PXIB203303PR) and Ministerio de Sanidad y Consumo (FISPI09/00501) for financial support. M. João Matos thanks Fundação de Ciência e Tecnologia for the fellowship.

The authors thank the creator of the MODESLAB software PhD Ernesto Estrada from the University of Strathclyde, Glasgow, U.K.

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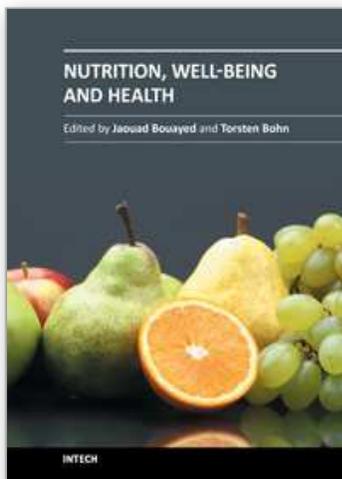
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Nutrition, Well-Being and Health

Edited by Dr. Jaouad Bouayed

ISBN 978-953-51-0125-3

Hard cover, 224 pages

Publisher InTech

Published online 23, February, 2012

Published in print edition February, 2012

In our modern society, expectations are high, also with respect to our daily diet. In addition to being merely "nutritious", i.e. supplying a variety of essential nutrients, including macro-nutrients such as proteins or micro-nutrients such as minerals and vitamins, it is almost expected that a good diet offers further advantages - especially well-being and health and the prevention of chronic diseases, which are, as we generally tend to grow older and older, becoming a burden to enjoying private life and to the entire society. These additional qualities are often sought in diets rich also in non-nutritive components, such as phytochemicals. In contrast to drugs, which are taken especially to cure or ameliorate diseases, it is expected that a healthy diet acts in particular on the side of prevention, allowing us to become old without feeling old. In the present book, rather than trying to give an exhaustive overview on nutritional aspects and their link to well-being and health, selected topics have been chosen, intended to address presently discussed key issues of nutrition for health, presenting a reasonable selection of the manifold topics around diet, well-being, and health: from the antioxidants polyphenols and carotenoids, aroma-active terpenoids, to calcium for bone health, back to traditional Chinese Medicine.

How to reference

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Estela Guardado Yordi, Enrique Molina Pérez, Maria João Matos and Eugenio Uriarte Villares (2012). Antioxidant and Pro-Oxidant Effects of Polyphenolic Compounds and Structure-Activity Relationship Evidence, Nutrition, Well-Being and Health, Dr. Jaouad Bouayed (Ed.), ISBN: 978-953-51-0125-3, InTech, Available from: <http://www.intechopen.com/books/nutrition-well-being-and-health/antioxidant-and-prooxidant-effect-of-polyphenol-compounds-and-structure-activity-relationship-eviden>

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